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Case report

Successful resolution of left ventricular thrombus with apixaban treatment

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ABSTRACT

A 68 years old male patient with history of dyslipidemia and smoking was admitted to our emergency department with complaint of dyspnea. He was transferred to the coronary care unit with the pre-diagnosis of acute coronary syndrome. In his transthoracic echocardiography, we detected anterior, anterior septal and apical wall akinesia with an LV ejection fraction (EF) of 25%, moderate mitral regurgitation and 13 × 6 mm sized thrombus in the LV. Apixaban treatment 5 mg po bid was started. In the second month transthoracic echocardiograpy, the thrombus in LV was found to have disappeared. In this report we present a patient whose LV thrombus was successfully treated after myocardial infarction by apixaban.

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Introduction

Left ventricular thrombus is usually seen in situations with reduced left ventricular (LV) function including dilated cardiomyopathy and LV aneurysms or after myocardial infarction (MI).[1] In observational studies and meta-analyses, anticoagulant therapy is recommended in order to minimize embolization risk.[2,3] An oral vitamin K antagonist, warfarin, has been being used as an anticoagulant for this purpose for a long period of time. New oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban, etc.) were found to be non-inferior or superior compared to warfarin in prevention of thromboembolism in patients with non-valvular atrial fibrillation.[2] Nevertheless, the data about the role of new oral anticoagulants in the management of LV thrombus is deficient.

Case report

A 68 years old male patient with history of dyslipidemia and smoking was admitted to our emergency department with complaint of dyspnea. The ECG was in sinus rhythm and there were precordial T wave negativity. In his initial evaluation, the consecutive two troponin levels were greater than the upper reference limit. After then he was transferred to the coronary care unit with the pre-diagnosis of acute coronary syndrome. In his transthoracic echocardiography, we detected anterior, anterior septal and apical wall akinesia with an LV ejection fraction (EF) of 25%, moderate mitral regurgitation and 13 × 6 mm sized thrombus in the LV (Fig. 1). The thrombus was detected to be mobile and attached to the distal portion of the anterior septum. The D-dimer level was greater than the upper reference level. In coronary angiography, left anterior descending artery was found to be totally occluded in its ostium. In positron emission tomography, the anterior wall was detected to be non-viable. As a result, the patient was decided to be managed medically. Aspirine 100 mg po qd, clopidogrel 75 mg po qd and warfarin 5 mg po qd were prescribed and then he was discharged. The patient did not come for early outpatient visit for measurement of international normalized ratio (INR). After 30 days of discharge, he was admitted to our outpatient clinic with gastrointestinal (GI) bleeding. In his laboratory examination, he was found to have an INR of 10. Then, he was hospitalized and the warfarin was stopped. Both upper and lower GI endoscopy were performed by gastroenterology clinic and there was not any active bleeding points in the gut. The bleeding was considered to be due to warfarin overdose. During follow up, the patient was hemodynamically stable. In the control transthoracic echocardiograpy, the thrombus was found to be persisted with its previously measured dimensions. His body weight and creatinine level were in suitable range for apixaban treatment (weight:72 kg and creatinine:0,9 mg/dl). Since the patient was non-compliant and could not tolerate warfarin therapy, apixaban 5 mg po bid was started. In the second month transthoracic echocardiograpy, the thrombus in LV was found to be disappeared (Fig. 2).

Discussion

In this report we present a patient whose LV thrombus was successfully treated after myocardial infarction by apixaban. LV thrombus after MI is related to worse prognosis and increased thromboembolic risk.[3]

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Fig. 1. Two dimensional echocardiogram shows left ventricular apical thrombus (13 × 6 mm).

Anticoagulation with dual antiplatelet therapy (triple antithrombotic therapy) increases bleeding risk substantially.[4] As a result, time of initiation and duration of triple antithrombotic therapy should be adjusted according to the atherothrombotic, cardioembolic and bleeding risk of the patients. Our patient had triple therapy for one month because of high bleeding risk (HAS-BLED score greater than 2).[4] After one month, clopidogrel has stopped and we have continued with aspirin and apixaban. LV thrombus resolution with warfarin therapy was demonstrated in some previous observational studies and meta-analyses.[3,5] The role of new oral anticoagulants in reducing thrombo-embolic risk in patients with LV mural thrombus is needed to be clarified. The slow onset of action, need for dose adjustments and regular monitoring to provide adherence to the narrow therapeutic range, dietary restrictions, and multiple drug interactions limit the use of vitamin K antagonists.[6] NOACs do not have these kind of limitations and may also reduce the risk of hemorrhagic stroke.[6] In the ARISTOTLE trial, apixaban was shown to have superior efficacy in reducing stroke, systemic embolism, and all cause mortality compared to warfarin.[7] In 2014 American Heart Association stroke guidelines, NOACs are recommended for three months in patients with LV mural thrombus intolerant to warfarin with a new class 2b recommendation and a level of evidence C.[8] We stopped warfarin and started apixaban in our patient because of highly increased supratherapeutic INR and gastrointestinal bleeding. In the second month of therapy, LV thrombus was found to be completely resolved.

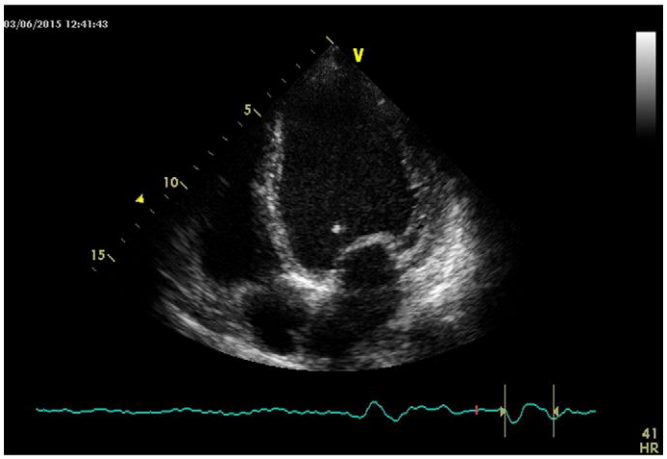


Fig. 2. Apical mural thrombus resolved completely after 8 weeks treatment with apixaban.

There are several limitations of the use of NOACs. The careful use in elderly and patients with renal impairment is recommended.[9] The data is scant regarding the use of NOACs in pregnant women, pediatric patients and the patients with valvular disease.[9] Except dabigatran, the absence of approved antidotes in the case of life-threatening hemorrhage or surgery is another limitation for their use.[9]

In conclusion; our case showed that LV thrombus can be successfully treated by apixaban. However, randomized clinical trials are needed in order to elucidate and confirm the use of NOACs as an alternative to warfarin.

Conflict of interest

The authors declare that they have no conflicts of interest related to the publication of this manuscript.

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Case report

A giant hematoma in the left atrial wall; A rare complication of percutaneous coronary intervention☆

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ABSTRACT

Left atrial intramural hematoma (LAIH) is a rare complication of the percutaneous coronary interventions (PCI) which can cause severe hemodynamic instability. In this report a patient with a giant LAIH presenting with an acute cerebrovascular accident (CVA) is summarized.

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Introduction

LAIH is a very rare clinical entity that has been reported to occur either spontaneously or as a rare complication of cardiac intervention. We report a case of acute LAIH which had developed after PCI to the chronic total occlusion of right coronary artery (RCA). To the best of our knowledge, there is no analogous case of LAIH presenting with a CVA which has been reported previously.

Case report

A 66-year-old man who had undergone PCI for the left anterior decending (LAD) and circumflex artery (CX) three weeks ago was admitted for the management of his recurrent angina. His latest coronary angiogram showed the chronic total occlusion of RCA. He was managed medically; however, he continued to experience severe stable angina. On this hospital admission, he underwent a successful and challenging PCI for the chronic total occlusion of RCA. At the end of the procedure, there was a small rupture at the distal segment of the posterolateral artery presenting with a small amount of opaque extravasation to the pericardial cavity. (Fig. 1) The patient was totally asymptomatic with no sign of hemodynamic instability. Intraprocedural echocardiography showed no significant pericardial effusion.

After the procedure, he experienced aphasia. Cranial CT was normal, however, diffusion magnetic resonance imaging (MRI) demonstrated a segment with a restricted diffusion in front of the central sulcus at the left lobe. Antiplatelet and anticoagulant treatment (unfractionated heparin, aspirin and clopidogrel) was applied to the patient immediately. There wasn't any sensorimotor deficit except for aphasia during the follow-up.

Echocardiogram was performed and showed a mass echogenicity arising from the lateral wall of the left atrium. The left atrium was almost totally filled with the mass causing a moderate restriction of the inflow through the mitral valve. (Fig. 2A,B) As the patient was hemodynamically stable, there was no need of an urgent operation, and patient was followed conservatively.

The patient underwent cardiac MRI to investigate the nature of the mass. MRI images showed, the mass as originating from the left atrial wall and protruding to the atrial cavity. The findings were concordant with a left atrial intramural hematoma. (Fig. 2C,D,E) Meanwhile carotis and vertebral artery Doppler ultrasound were totally normal.

24 h later patient's aphasia was completely resolved. Serial follow-up echocardiography revealed a significant reduction in the size of LAIH. Patient was discharged from the hospital at the fourth day of hospitalization with a totally normal clinical situation. A control echocardiography was performed ten days later which showed complete resolution of the hematoma. (Fig. 3).

Discussion

Intralayer dissection of the LA wall following coronary artery perforation during coronary angioplasty is extremely rare.

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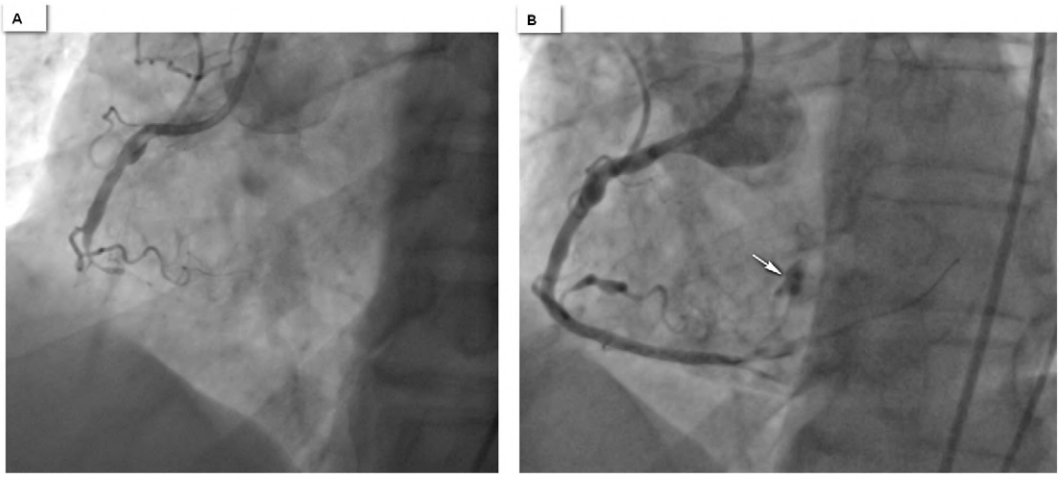


Fig. 1. Coronary angiography of the RCA before PCI (A), after PCI (B). Arrow indicating the extravasation of opaque.

Only a few similar, but not identical, cases have been described previously. We thought that the damage to the LA wall was caused during the positioning of the guide wire, which probably had penetrated the distal vasculature and caused the bleeding. Once there is an intramural bleeding, the low pressure within the left atrium allows the hematoma to enlarge into the atrial cavity. This is a potentially life-threatening complication necessitating clinical awareness, rapid diagnosis, and prompt treatment. Our case is the first case of LAIH presented with cerebrovascular symptoms. We speculate that cerebrovascular event is probably caused by concomitant partial endocardial layer dissection

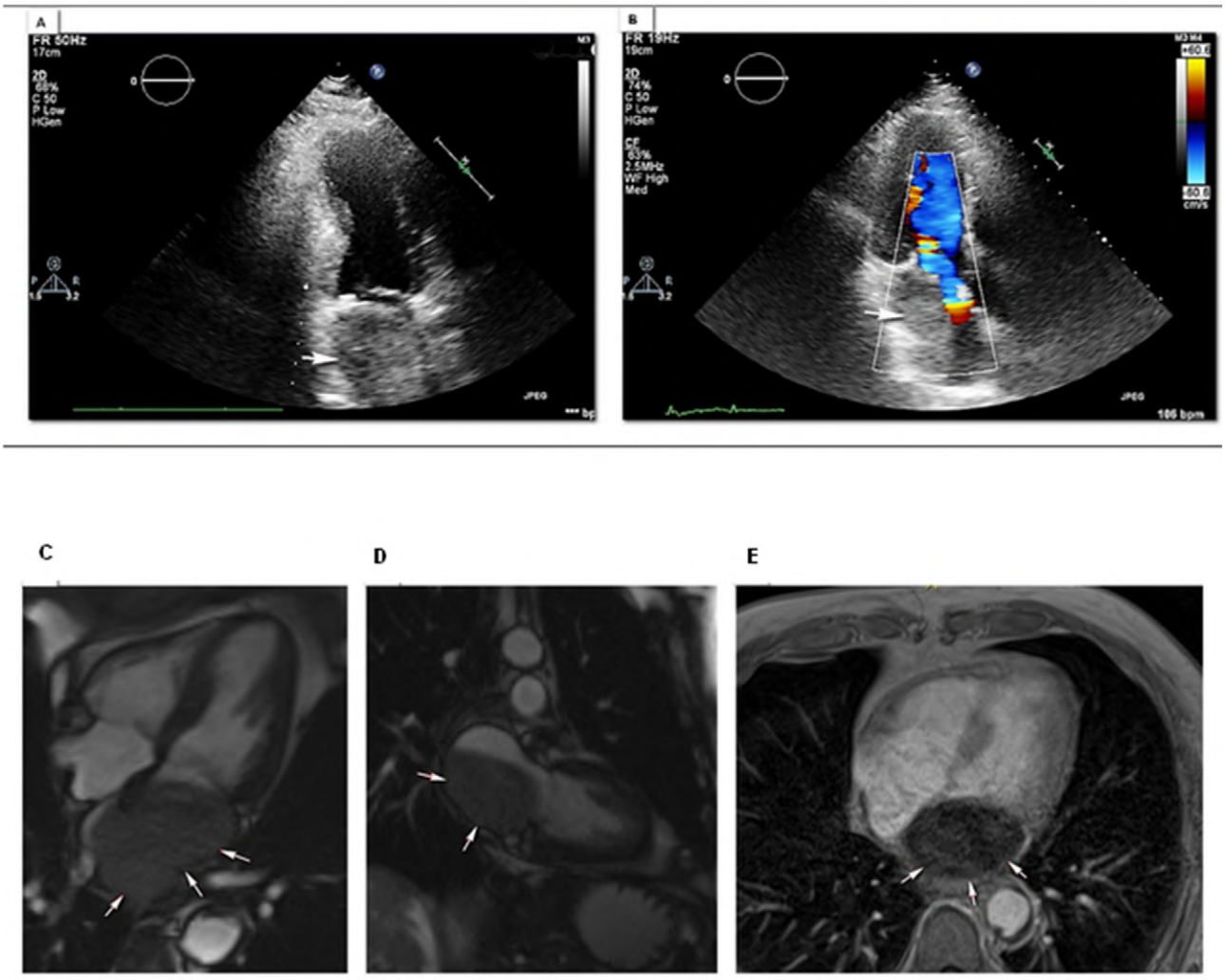


Fig. 2. Echocardiography showed a mass echogenicity arising from the lateral wall of the left atrium (A,B). MRI showed a giant left atrial intramural hematoma (C,D,E).

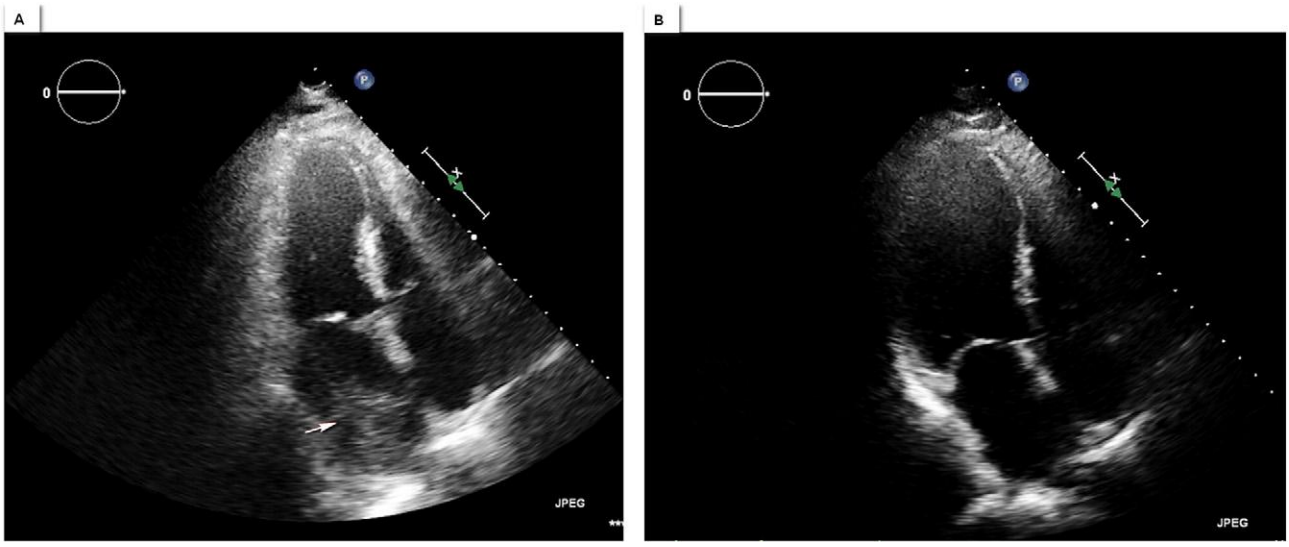


Fig. 3. Partial (A) and complete (B) resolution of hematoma.

letting the content of hematoma to pass to the systemic circulation. Endocardial layer dissection was demonstrated during the surgery of one previous case in the literature.[1] There are a few cases of LAIH associated with coronary interventions and they were managed conservatively.[2–4] Also some cases were treated surgically.[1,5]

Conclusion

LAIH is a rare complication of the PCI which can cause severe hemodynamic instability. Our case is the first in literature presenting with a CVA rather than a hemodynamic compromise. The literature data consist of individual case reports that no definite therapy can be described. Patients can be managed conservatively or surgically depending on the hemodynamic status. Awareness of this entity and its potential life threatening consequences is very important.

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Case report

Cholesterol embolization syndrome after primary percutaneous coronary intervention in patient with acute anterior myocardial infarction☆

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ABSTRACT

Background: Cholesterol embolization syndrome is a rare and under-diagnosed clinical entity. Vascular procedures such as angiography of vascular surgery have been identified as triggering factor.
Case report: A 71-year-old man presented with acute ST segment elevated anterior myocardial infarction and coronary stenting was performed. At the clinic follow-up, coloured skin lesions were observed at both hands and feet. During follow-up, progressive deterioration in renal functions also developed gradually. Supportive therapy was provided in addition to standard treatment for myocardial infarction.
Conclusion: In conclusion cholesterol embolization syndrome should be considered in any patient presenting with cutaneous features and renal failure after invasive vascular procedure.
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Introduction

Cholesterol embolization syndrome (CES) is caused by distal embolisation of cholesterol crystals from aortic atheromatous plaques, which then result in end-organ damage.[1] Herein, a case of probable CES with cutaneous manifestation on all extremities and renal failure after performing primary percutaneous coronary intervention in patient with acute anterior myocardial infarction was presented.

Case report

A 71-year-old man presented with chest pain radiating to both arms accompanied by nausea and sweating came to emergency department. He had a history of hypertension and diabetes mellitus. He was a non-smoker and had no other remarkable history of medical condition. At the admission, his blood pressure was 100/60 mmHg and heart rate was 88 beats/min. Electrocardiogram was in sinus rhythm and revealed ST segment elevation over leads V1–V6 in accordance with acute ST segment elevated anterior myocardial infarction. Echocardiography showed hypokinesia of the anterior wall, anterior septum and left ventricular apex with left ventricular ejection fraction of 48%. Left ventricle end-diastolic diameter and left atrial diameter were 52 mm and 36 mm, respectively. However, left ventricular thrombi were not detected. In laboratory findings glucose level was 188 mg/dl, HbA1c was 7.2 and total cholesterol level was184 mg/dl. Aspirin and clopidogrel were given and heparin was used for anticoagulation. He transferred to coronary angiography laboratory. Emergent coronary angiography revealed totally occluded left anterior descending (LAD) coronary artery. Circumflex and right coronary artery angiography showed non-significant stenosis. LAD lesion was crossed with guidewire and drug-eluting stent was implanted. Thrombolysis in myocardial infarction III (TIMI III) flow was observed. After the procedure the patient was transferred to coronary care unit and two days later transferred to cardiology clinic. At the clinic follow-up, painful, blue-coloured, macule lesions were observed at both hands and feet (Figs. 1, 2). These lesions became larger over the ensuing days. His blood pressure was 115/70 mmHg with a pulse of 75 beats per minute, his respiration was 16 per minute and the body temperature was 36.8 °C. His oxygen saturation was 96% on air and all peripheral pulses were present. During follow-up, progressive deterioration in renal functions developed gradually and his initial serum creatinine level aroused from 1.12 mg/dL to 3.02 mg/dL over the next days. Laboratory investigation showed hypereosinophilia (10%), increased erythrocyte sedimentation rate (68 mm/h) and normal platelet count. Serum levels of antinuclear antibody and antineutrophil cytoplasmic antibody tests were in normal range. Close chronological association with coronary intervention, the signs and the laboratory results suggested the diagnosis of probable CES. Anti-inflammatory therapy or corticosteroid therapy was not started due to the acute myocardial infarction. Antiplatelet therapy was maintained. High dose statin therapy with rosuvastatin 40 mg/day was continued. Supportive therapy was provided by effective hydration and wound care. At

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Fig. 1. Clinical image of purple coloured skin manifestation on both of the hands.

outpatient follow-up, skin lesion healed over two months. The serum creatinine level of the patient decreased to 1.9 mg/dL three weeks after. Six month after the admission, the patient remains asymptomatic with a creatinine level of 1.33 mg/dL and a serum urea level of 64 mg/dL. To date, there has been no adverse event with the patient.

Discussion

We hereby described a case of CES with renal and cutaneous involvement affecting extremities after performing coronary intervention in patient with acute myocardial infarction. This case was unique in that cutaneous lesions were observed both on lower extremities and also upper extremities.

CES is a systemic disorder that can spread to multiple organs resulting renal failure, heart failure, gastrointestinal ischemia and skin necrosis. Most affected organs related to CES are the brain, the kidney, the gastrointestinal tract and the skin. Central nervous system involvement may lead to confusion or memory loss.[1] In our patient, there was no symptom or sign of brain injury. The retinal artery occlusion may present with Hollenhorst plaques on retina examination. Embolization to the kidneys has usually patchy distribution. Elevation of serum creatinine and proteinuria are the main laboratory findings.[2] In the present case, serum creatinine level increased progressively but with supportive care not reached to end-stage renal disease. Cutaneous manifestations of CES include livedo reticularis, gangrene, cyanosis, nodules, macule, ulceration and purpura. Purple or blue discoloration of the foot lead to call ' blue toe syndrome ' synonymous with CES. Cutaneous manifestations almost always located to the lower extremities and rarely extended to upper extremities.[3] In our case bluish lesions were observed not only on the feet but also on the hands. Risk factors for CES are male gender, smoking, advanced age, hypertension and aortic aneurysm. Development of clinical event is triggered by invasive procedures of aorta, anticoagulation and thrombolysis.[4] Mainly, a plaque located at proximal, large-calibre artery is ruptured by iatrogenic trauma such as catheter manipulation or spontaneously. Embolization of plaque debris to small or medium sized arteries leads to mechanical occlusion and foreign body inflammatory response which result in end-organ damage. Common source of atheroembolism is the abdominal aorta thus embolism to upper extremities is unusual. CES during coronary angioplasty is uncommon with the incidence of 0.6%.[5]



Fig. 2. Clinical image of painful macules on the feet.

In the diagnosis of CES, constitutional symptoms and signs are frequent in addition to specific end-organ damage presentation. Leukocytosis with hypereosinophilia, arise in erythrocyte sedimentation rate and C-reactive protein and a decrease in serum complement level may be seen in laboratory tests. Biopsy for any target organ such as kidney or skin could also be obtained for histopathological confirmation. However, none of the test is specific for CES so clinical suspicion is very crucial in the diagnosis of CES. Skin biopsy was not performed in this case. Although pathological findings may be seen in cases, cholesterol cleft identification is limited. Furthermore, in delayed biopsies necrotizing vasculitis may also be seen.[6] In differential diagnosis, sepsis, disseminated intravascular coagulation (DIC) and heparin-induced thrombocytopenia (HIT) should also keep in mind. While the prolonged activated partial thromboplastin time and prothrombin time and also low levels of protein-C and antithrombin are associated with DIC, coagulation tests is usually normal in HIT with increase in platelet count after cessation of heparin. Positive blood culture and positive sepsis criteria are main determinants in sepsis without DIC. As CES is a clinical entity, in this case diagnosis of CES is confirmed by using symptoms, signs, laboratory findings and close chronological association with coronary intervention.

There is no widely acceptable treatment for CES. Supportive therapy is aimed at end-organ damage. Risk factor modification for

atherosclerosis should always be considered such as smoking, hypertension, diabetes mellitus and hyperlipidemia. Corticosteroid use may control the inflammation. Statins are considered as key therapy for stabilising atherosclerotic plaque. Antiplatelet agents, renin-angiotensin system blockers should be considered for therapy. Surgical repair of the diseased aorta should also be used for therapy.[7] In our patient, antiplatelet therapy maintained due to acute myocardial infarction and coronary stenting. Oral rosuvastatin was administered at a dose of 40 mg/day. The skin lesions improved gradually in two month follow-up. Serum creatinine level was also decreased to 1.9 mg/dL.

High clinical suspicion is critical for the diagnosis of this clinical entity. CES should be considered when the patient has acute renal failure and specific skin lesions in the extremities after an invasive vascular procedure.

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Case report

Large coronary aneurysm may indicate concomitant asymptomatic huge thoracic aortic aneurysm

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ABSTRACT

Simultaneous aneurysms of coronary vessels and aorta were rarely reported with an involvement of abdominal aorta. Co-incidence of isolated thoracic aortic aneurysm (TAA) and coronary aneurysm is not known. Herein, we presented a silent TAA presented with aortic dissection. Previously performed coronary angiography via right radial route revealed large coronary aneurysm with a diameter of 12 mm. Ascending aorta was evaluated as normal size with echocardiography. "Clinical intuition" might be the only way to seek and detect asymptomatic TAA. Diffuse atherosclerotic coronary heart disease with coronary aneurysm should be an impulse to screen asymptomatic aortic aneurysms.

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Introduction

Simultaneous aneurysms of coronary vessels and aorta were rarely reported with an involvement of abdominal aorta. Co-incidence of isolated thoracic aortic aneurysm (TAA) and coronary aneurysm is not known. Herein, we presented a silent TAA presented with aortic dissection which also possesses large coronary artery aneurysm. We think that, extensive coronary artery atherosclerosis and large coronary aneurysm may strongly indicate silent isolated TAA.

Case report

A 67 year-old male patient admitted emergency department with a complaint of severe claudication in the right leg. Previously performed coronary angiography via right radial route revealed large coronary aneurysm with a diameter of 12 mm (Fig. 1). Ascending aorta was evaluated as normal size with echocardiography in last presentation. Computed tomography performed in the final presentation showed a large dissected 6.6 cm TAA beginning from the osteum of left common carotid artery and extending beyond the left subclavian artery (Fig. 2). Dissection flap was began within the aneurysm and extend to right iliac arteries. Patient had been followed with a diagnosis of CAD for 7 years and coronary angiography performed 7 years ago also revealed coronary aneurysm. Aortic pathology was progressed silently until dissection formation occurred. Hybrid therapy consisting of debranching operation and endovascular repair was scheduled for the patients.

Discussion

Coronary aneurysms are not uncommon with a frequency of 1–4% in routine autopsies or coronary angiographies.[1–2] Hovewer, giant coronary aneurysms are rarely reported in the medical literature. In adults, atherosclerosis is a main factor for progression of coronary aneurysms and clinical presentation can variate.[1–2] Diffuse and advanced atherosclerotic involvement of coronary vessels are associated with other vascular pathology including aortic diseases.[3–4] Aortic aneurysms usually observed in the elderly men with predominantly abdominal involvement. Advanced atherosclerotic process and weakening of medial layer are proposed major pathophysiologic mechanism for aortic aneurysm. Abdominal aortic aneurysms (AAA) are frequently associated with various forms of coronary artery disease. Approximately 80% of patients with AAA will have angiographic evidence of atherosclerosis in at least one coronary vessel and nearly 20% percent of all AAA patients will have surgically treatable coronary artery disease. Whereas, the incidence of aortic aneurysms among patients with coronary artery disease (CAD) is 4.4% to 7%.[3] Furthermore, significant aortoiliac artery aneurysm was associated with CAD in 90% of patients, while it's prevalence was directly correlated with the severity of CAD being depicted in 40.2% of patients with three-vessel disease or more. Multivessel CAD (three-vessel disease or more), age older than 60 years, and three or more risk factors were revealed as independent predictors of abdominal vessel stenosis or aneurysm.

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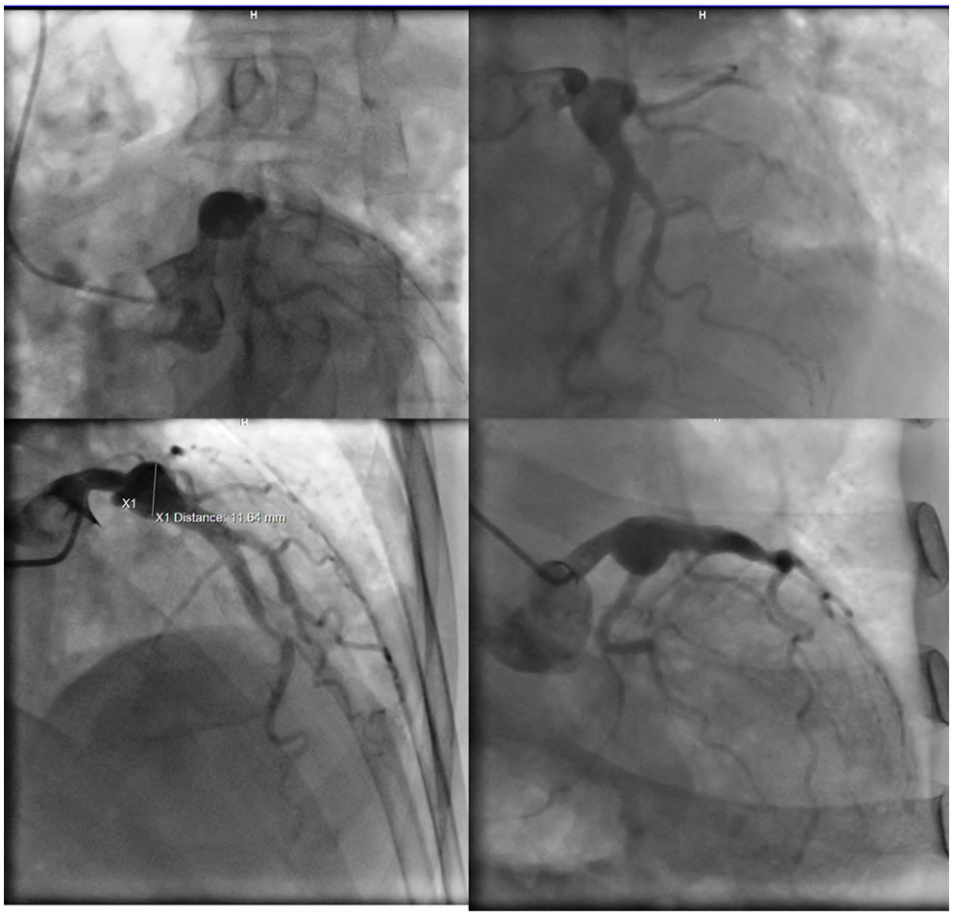


Fig. 1. Large coronary aneurysm extending between distal left main coronary artery and proximal left anterior descending artery.

Isolated thoracic aortic aneurysm (TAA) is rare situation and majority diagnosed either incidentally or catastrophic clinical presentation with dissection or rupture. Association of CAD and coronary aneurysm with TAA was not well-defined.[5] In addition, simultaneous aneurysms of coronary vessels and aorta were rarely reported with an involvement of abdominal aorta. Co-incidence of isolated TAA and coronary aneurysm is not known. We thought that, extensive coronary artery atherosclerosis and large coronary aneurysm may strongly indicate silent isolated TAA. Further epidemiologic studies may clarify our speculation.

Conclusion

Thoracic aortic aneurysm usually progress without symptom which make difficult to earlier definite diagnosis. “Clinical intuition” might be the only way to seek and detect asymptomatic TAA. Large coronary aneurysms are usually associated with diffuse and accelerated atherosclerotic process which may indicate concomitant silent TAA. Routine screening of such patient facilitate earlier diagnosis of TAA and prevent mortal complication including dissection and rupture.

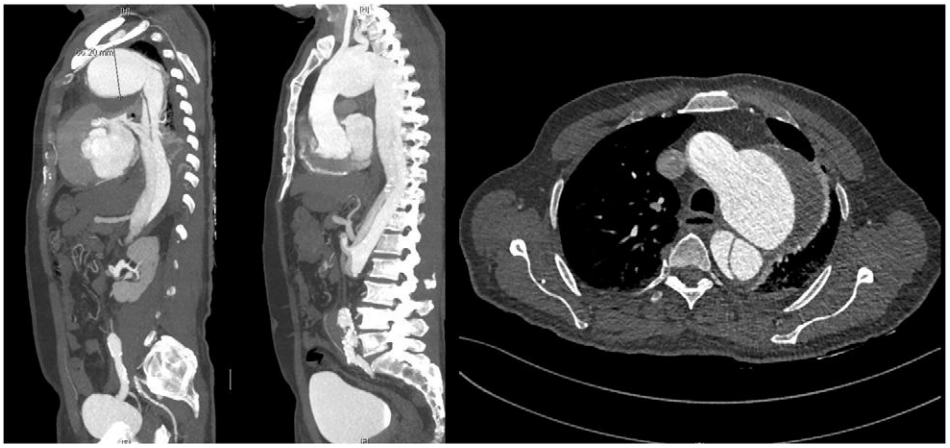


Fig. 2. Computed tomographic aortography showing huge dissected thoracic aortic aneurysm.

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Short communication

Coronary injection ventriculography: Multiple coronary-cameral fistulas as a rare cause of stable angina pectoris

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ABSTRACT

Coronary-cameral fistula is a rare, abnormal fistulous communication between a coronary artery and a cardiac chamber or large vessel. Being mostly asymptomatic, corona-cameral fistulas can seldom cause myocardial ischemia, congestive heart failure, arrhythmias and infective endocarditis. We represent you a case of stable angina pectoris found to have multiple corona-cameral fistulas between left coronary arteries and left ventricle in conventional coronary angiography.

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Introduction

Coronary-cameral fistula (CCF) is an abnormal fistulous communication between a coronary artery and a cardiac chamber or large vessel. CCF is rare and mostly diagnosed incidentally. In diagnostic coronary angiography (CAG) the incidence is reported as 0.1%.[1] Being mostly asymptomatic CCF can seldom cause myocardial ischemia, congestive heart failure, arrhythmias and infective endocarditis.[2] We represent you a case of stable angina pectoris found to have multiple microfistulas between left coronary arteries and left ventricle in conventional CAG.

Case

A 65-year-old male patient referred to our outpatient clinic with chest pain and exertional dyspnea. The patient was suffering from retrosternal exertional chest pain for 6 months which relieved with rest. Previous medical history revealed hypertension and diabetes mellitus. Physical examination was normal while the electrocardiogram showed inferolateral T wave inversion and left ventricular hypertrophy according to Sokolow-Lyon index (Fig. A). In echocardiography, LV wall thickness were normal, left ventricle mass index was normal (LVMI: 102 g/m^2) and LVEF was found 65%. Coronary angiography was performed with an early diagnosis of coronary artery disease. There was not any significant coronary stenosis, however in late phase of contrast injection to the left coronary arteries, left ventricle filling and opacification was seen through extensive multiple microfistulas (Figs. B, C, Video 1-2-3). Due to multiple microfistulas between left coronary arteries and left ventricle, this condition was defined as "coronary injection ventriculography". Because of extensive spreading of microfistulas through left ventricle myocardium, the patient was not an appropriate candidate for surgical or transcatheter repair and regular follow up with medical therapy was planned. Symptomatic relief was provided by medical therapy with acetylsalicylic acid, ramipril, amlodipin, metoprolol and atorvastatin.

Discussion

CCFs are rare and defined as anomalous connections between coronary arteries and cardiac chambers.[1] The frequency of CCF is reported as 0.1% in diagnostic CAG.[1,3] Various series from Turkey showed a similar incidence of CCF as 0.08–0.11%.[3,4] Being mostly asymptomatic, CCF is usually suspected by hearing a murmur in physical examination and diagnosed in further evaluation or incidentally in diagnostic CAG. Hemodynamically significant fistulas can cause symptoms like angina or dyspnea. The angina is usually associated with coronary steal phenomenon. In this phenomenon, coronary blood flow is shifted to the territory of the fistula because of the low blood pressure in diastole. As a consequence, enough blood supply cannot be provided and ischemia

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Fig. A. The twelve-lead electrocardiogram showed left ventricular hypertrophy and inferolateral T wave inversion.

occurs in the distal territory of the fistula bearing artery.[5] Koh et al. showed exertional myocardial ischemia in CCF patients.[6] Kiuchi et al. reported that CCFs may cause myocardial infarction due to coronary steal phenomenon.[7] Complications associated with coronary artery fistulas (CAF) are myocardial ischemia, heart failure, arrhythmias, infective endocarditis, coronary thrombosis, aneurysm or rupture.[8] Aging increases the risk of dilatation and/or aneurysm formation of the fistula therefore increasing the risk of complication.[9] Incidence of symptoms or complications under the age of 20 is 19%, which increases to 55% above the age 20 years.[10] Asymptomatic and small diameter CAFs are emphasized to be followed medically. Main indications for surgical or interventional treatment of CAFs are hemodynamically important fistulas, symptomatic patient, development of myocardial infarction, heart failure, arrhythmias or infective endocarditis.[11] Main purpose of treatment is the closure of fistula without damaging coronary blood flow. Surgical therapy or transcatheter coil embolization method which is currently wider in use, can be preferred. Transcatheter coil embolization method is similar to surgical therapy according to morbidity and mortality rates.[12] However this method is superior to surgical therapy according to patient comfort and duration of hospitalization. Surgery is applied in patients who cannot undergo transcatheter coil embolization. In our case, due to multiple small caliber CCFs, neither surgical nor transcatheter

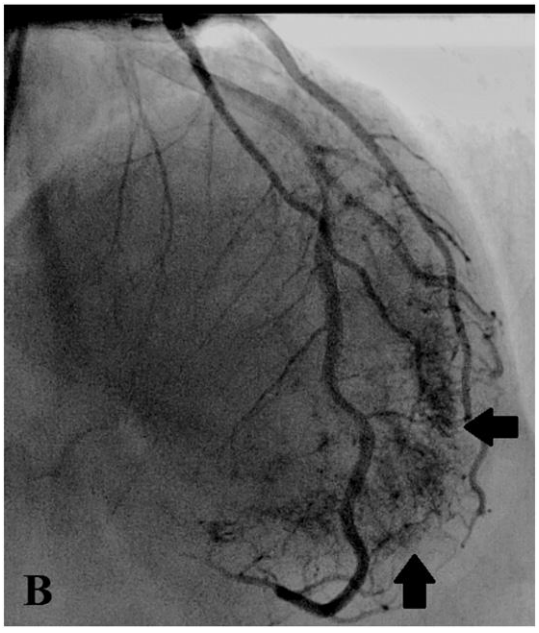


Fig. B. In late phase of contrast injection to the left coronary arteries, left ventricle opacification was seen through extensive multiple corono-cameral microfistulas (arrows).

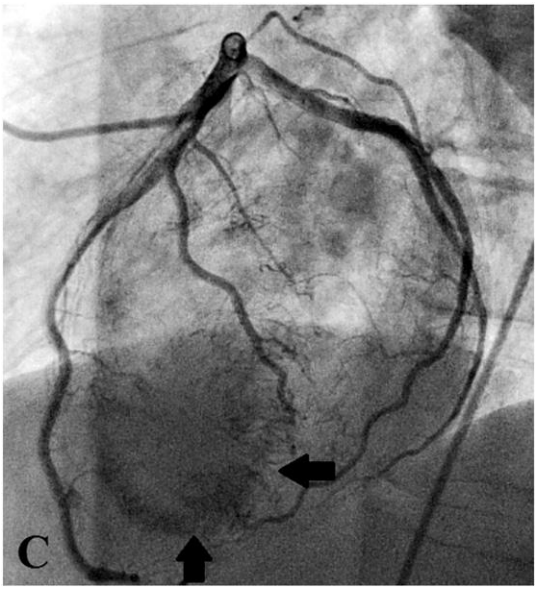


Fig. C. In late phase of contrast injection to the left coronary arteries, left ventricle opacification was seen through extensive multiple corono-cameral microfistulas (arrows).

therapy were found appropriate and follow-up with medical therapy was planned for the patient.

Conflict of interest

There is no conflict-of-interest.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcac.2016.03.001.

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Short communication

Coronary thrombus in 34-year-old female patient with 4G/4G polymorphism in the PAI-1 gene

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ABSTRACT

Genetic factors and hypofibrinolytic state may contribute to the likelihood of developing in myocardial infarction (MI) in young women rather than traditional risk factors. High plasminogen-activator inhibitor-1 (*PAI-1*) level and *PAI-1* gene polymorphism have been shown to be associated with thrombotic events such as myocardial infarction, deep venous thrombosis, and stroke. We determined *4G/4G* polymorphism in a 34-year-old female patient with subacute anterior myocardial infarction and coronary thrombus in left anterior descending artery on coronary angiogram.

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Introduction

The pathogenesis of myocardial infarction (MI) is complex and multifactorial, including multiple interacting environmental and genetic factors. Traditional risk factors such as hypertension, diabetes mellitus, and hypercholesterolemia are less pronounced in the younger patients in development of the myocardial infarction. Therefore, additional factors such as genetic factors and hypofibrinolytic state may contribute to the likelihood of developing in the myocardial infarction and may be required to determine in young participants.[1] Plasminogen-activator inhibitor-1 (*PAI-1*) is a member of serpin superfamily of protease inhibitors and a key regulatory protein of fibrinolysis cascade by inhibiting plasminogen activators which are tissue plasminogen activator (t-PA) and urokinase (u-PA).[2] High plasma *PAI-1* levels have been shown to be associated with atherosclerosis, restenosis, and in the pathogenesis of disorders associated with thrombotic events such as myocardial infarction and deep venous thrombosis.[2–4] It was reported that *PAI-1* gene polymorphism such as *4G/5G* and *4G/4G* genotypes has been associated with the higher gene expression and higher *PAI-1* levels in the circulation resulting in an increased risk for thrombotic events such as MI and stroke.[5–10]

Case report

A 34-year-old female patient had been admitted for chest pain of about 5 days, which accelerates with exertion and resolves with rest. She has no any history of smoking, alcohol, drug abuse, systemic disease, or family history of cardiovascular disease. Blood pressure was 115/70 mm Hg and heart rate was 88 BPM. Cardiac auscultation was normal heart sounds with no murmur. Other physical examination findings were normal. ECG revealed loss of R progression on V2–3, ST segment elevation on V2–5, and new developed deep inverted T waves on V1–V6 (Fig. 1). Two weeks before symptoms, ECG was normal with positive T waves. Echocardiography was normal with absence of any wall motion abnormalities. Blood tests were troponin 0.419 mcg/L, CK-MB <21 ng/mL. Coronary angiogram revealed long intracoronary thin thrombus adjusted to endothelium at LAD artery (Fig. 2). Because of lack of response to repeated dosages of intracoronary nitroglycerin, and typical thin trombus appearance, vasospastic angina was excluded. Patient has received tirofiban infusion for 24 hours. Repeat coronary angiogram has shown partial resolution of coronary thrombus (Fig. 3). During hospital care, chest pain diminished with enoxaparine 6000 IU twice daily, clopidogrel 75 mg, acetyl salicylic acid 300 mg, metoprolol 50 mg, and nitrate therapy. Statin therapy was not initiated because of absent conventional risk factors. ECG follow-up showed that resolution of ST segment elevation, but negative T waves were persisted. Warfarin was started and acetyl salicylic acid dose was adjusted as 100 mg per day. Patient has been discharged with prescribing same medical treatment. Genetic analysis showed that negative for protrombin gene mutation (*G20210A*), Factor V Leiden

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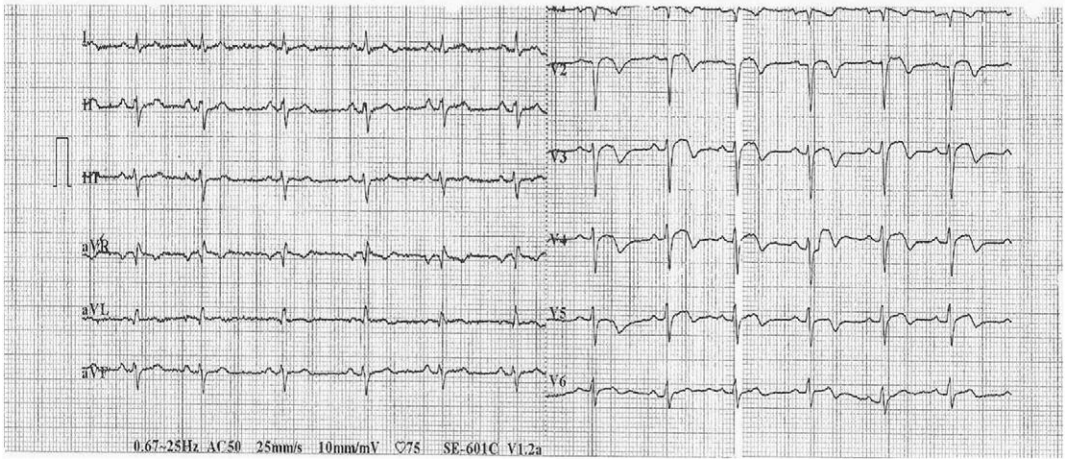


Fig. 1. ECG on admission.

(*G1691A*), Factor XIII *V34L*, *MTHFR* (*C677T*), Protein C and Protein S mutation, antithrombin III, antiphospholipid antibody.

Lupus anticoagulant had a weak positive result of 1.35, thought as clinically irrelevant (cut-off value: negative: <1.2; weak positive: 1.2–1.5, positive: >1.5, markedly positive: >2.0). Heterozygot *MTHFR* (*A1298C*) mutation has been revealed as positive, but homosistein levels were normal, and there was weak evidence of developing thrombus with this mutation in current literature. Protrombine Activator Inhibitor 1 (*PAI-1*) serpine 4G/4G mutation has been revealed by genetic analysis. This mutation has been known to be a high risk for thrombotic events. So we thought it was responsible for this event. During follow-up, the patient has complained of intermittent chest pain with short duration as couple of minutes and resolves spontaneously. After 2 months, ECG findings were similar with negative T waves on V1–V6, and there was short duration of angina attacks. At 4 months, ECG revealed that negative T wave was only at V2–V3 leads, and at 5 months, ECG was normal with positive T waves and clinically asymptomatic.

Discussion

An increased capacity to form blood clots or decreased fibrinolytic capacity due to high plasma *PAI-1* levels has been shown to play an important role in the pathogenesis of disorders associated with thrombotic events such as MI and ischaemic stroke.[1,8,11,12] It was also found that increased levels of *PAI-1* were associated with coronary endothelial dysfunction, plaque progression, and vulnerability leading to unstable angina pectoris and acute myocardial infarction.[2,13–15] It has been also reported that several genetic variations in coagulation and fibrinolytic proteins were associated with the development of the risk of MI.[7] The *PAI-1* gene known as *SERPIN 1* gene in humans is located on chromosome 7q22.[4] Two genetic variations, which were guanosine insertion/deletion, −675 *4G/5G*, and −844 G/A promoter polymorphisms in the *PAI-1* gene, have been associated with increased *PAI-1* levels and linked to various vascular diseases such as MI and deep vein thrombosis.[5,7,13,16,17] Homozygosity for the deletion genotype (*4G/4G*) has been associated with higher gene expression than those associated with the insertion genotype (5G/5G) resulting in higher *PAI-1* levels in the circulation and an increased risk for venous thrombosis, pulmonary thromboembolism, and MI through impairment of fibrinolytic function by elevated *PAI-1* activity.[5,7,8,16,18] Plasma levels of *PAI-1* have a wide and peak in the morning, whereas concentrations of t-PA exhibit less prominent circadian variation, and a relative hypofibrinolytic state may occur in the morning with increased platelet reactivity. That condition may contribute to the increased risk of MI seen during this period. In a study, it has been also reported that morning increase in *PAI-1*

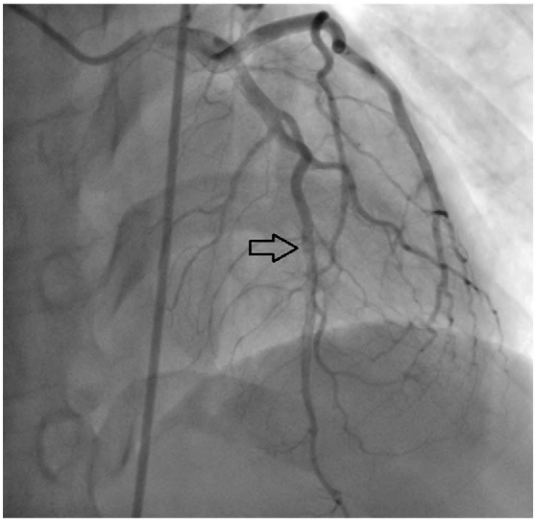


Fig. 2. Coronary thrombus on left anterior descending artery.

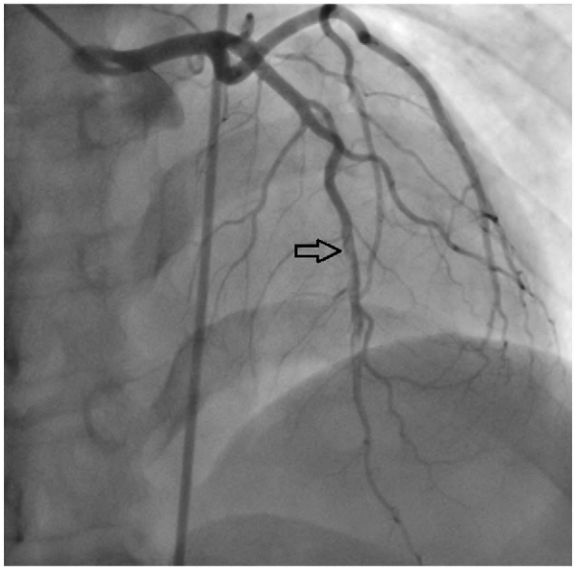


Fig. 3. After tirofiban infusion, thrombus with partial resolution persisted on the left anterior descending artery.

activity may be determined in *4G/4G* genotype subjects.[13] Boekholdt et al. showed that homozygosity for the *PAI-1 4G* allele was significantly associated with increased risk of myocardial infarction.[7] In a large Japanese study, the *PAI 4G/5G* polymorphisms appeared to be a risk factor for myocardial infarction in women.[19] In a recent study, Ismail et al. found that *PAI-1* genotype was higher in Egyptian patients with myocardial infarction. There was about twofold increased risk of MI associated with *4G4G + 4G5G* compared with *5G5G*. However, in that study, the *PAI-1* polymorphism (*4G*) was not found associated with MI, whereas modest risk could not be excluded.[13] While the mentioned data suggested positive association between the development of MI and *PAI-1* gene polymorphism, Atherosclerosis, Thrombosis, and Vascular Biology Italian Study Group (2003), did not find any association between *PAI-1* gene polymorphisms and the development of acute MI at a young age (under the age of 45 years).[20] Ding et al. also found that *PAI-1* gene polymorphisms were associated with high plasma *PAI-1* levels, whereas they were not associated with MI or stroke.[21]

There are some studies in the literature that reported that *PAI-1* antigen levels are positively correlated with cholesterol, LDL-cholesterol, VLDL, and triglyceride levels and negatively with HDL cholesterol.[4,18,22] In addition, it was suggested that the 4G/4G genotype has been reported to be associated with high cholesterol levels.[22] It was also claimed that the increase in *PAI-1* levels resulting from the activation of the renin–angiotensin system and hypertension in subjects with the *4G/4G* genotype.[4] It was also found that smoking by patients carrying the 4G allele may have an important impact on the frequency of MI.[13] Consequently, data about the relation of *PAI-1* with myocardial infarction are still inconclusive and contradictory.

The etiology of cardiovascular disease is multifactorial and strongly involves genetic and environmental factors. The interaction of genetic and traditional risk factors such as smoking, hypertension, hypercholesterolaemia may have a role in the development of MI. So that, identifying them for primary prevention early in life, especially in the presence of genetic predisposition, is important. Despite aforementioned data, the clinical use of fibrinolytic markers to determine coronary risk offers only marginal value and no data available suggest analysis of fibrinolytic function in addition to traditional risk scores. We propose that the determination of well-described polymorphisms in the *PAI-1* promoter and other components of the fibrinolytic system as a novel risk factor in addition to traditional risk factors is important.

Conclusion

Certain genetic disorders have tendency to myocardial infarction. Genetic testing should be considered for patients with young age, atypical presentation, and who have specific angiographic findings.

Conflict of interest

No conflict of interest.

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Short communication

Intolerable wide and narrow QRS complex tachycardia in the same patient: What is your diagnosis?☆

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ABSTRACT

A 54-year-old female with recurrent syncope was referred to our institution for electrophysiological study. The patient had two documented intolerable tachycardia; one of them was a wide QRS, and the other one was a narrow QRS. As a clinical puzzle format, we aimed to present our basic electrophysiological approach of an intolerable and rare clinical tachycardia.
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Introduction

Common type atrioventricular nodal re-entrant tachycardia (AVNRT) and atrioventricular re-entrant tachycardia (AVRT) via an accessory pathway are the most common causes of sustained regular narrow complex tachycardia, the electrocardiographic presentation of the tachycardia may be rarely with wide QRS.[1] Distinguishing between these arrhythmias can often be challenging during electrophysiology study (EPS). The detection of a wide QRS tachycardia switching to a narrow QRS tachycardia is an uncommon clinical presentation.[2,3]

Case question

A 54-year-old female with recurrent syncope and palpitation attack was referred to our institution for EPS. The patient had two documented tachycardia; one of them is a wide QRS left bundle branch block and the other one is a narrow QRS regular tachycardia (Fig. 1). Both tachycardias terminated with administration of intravenous diltiazem. First, a sustained tachycardia with wide QRS was induced by programmed atrial stimulation (PAS) (Fig. 2A and B). Due to hemodynamic deterioration, we were forced to terminate tachycardia in a short time. Surprisingly, the tachycardia could be terminated by atrial burst pacing. We tried to induce the tachycardia again for differential diagnosis. The tachycardia was not induced by programmed by ventricular pacing. However, PAS with same protocol induced two distinct narrow QRS tachycardia (Fig. 2C and D). Dual atrioventricular (AV) node physiology and a single AV nodal echo beat were demonstrated. Ventricular pacing during sinus rhythm showed ventriculoatrial (VA) conduction that was concentric and detrimental. The induction of the tachycardia by atrial extrastimulus testing and the response to a single premature atrial extrastimulus introduced during His refractoriness were repeatedly observed. Due to significant hemodynamic effects of the tachycardia, all pacing maneuvers could not be performed during the tachycardia. On the base of the present findings, what are the mechanisms of the tachycardia?

Case answer

The presence of 1:1 VA relationship during wide QRS tachycardia (Fig. 2A) and the termination of the tachycardia by atrial stimulation are unlikely for ventricular tachycardia. Due to short VA interval, the most likely mechanisms for the wide QRS tachycardia likely are an antidromic atriofascicular bypass tract tachycardia, typical AVNRT, or atrial tachycardia with aberrant conduction. However, the transition of a narrow QRS tachycardia to a wide (Fig. 2B) without a change in cycle length and in VA interval excludes the presence of an atriofascicular bypass tract or antidromic AV reentrant tachycardia. Also, constant HV intervals at the transition from narrow QRS to wide QRS tachycardia and typical LBBB pattern during the wide QRS tachycardia indicate that the mechanism of the wide QRS tachycardia is a supraventricular tachycardia with aberrant conduction. The concentric atrial activation pattern and short septal VA interval in the wide QRS tachycardia and one of the narrow QRS tachycardia favor typical AVNRT. The tachycardia with 1:1 AV relationship shown in Fig. 2B was terminated with AV block, indicating that the tachycardia was dependent on the AV node, also favors AVNRT.

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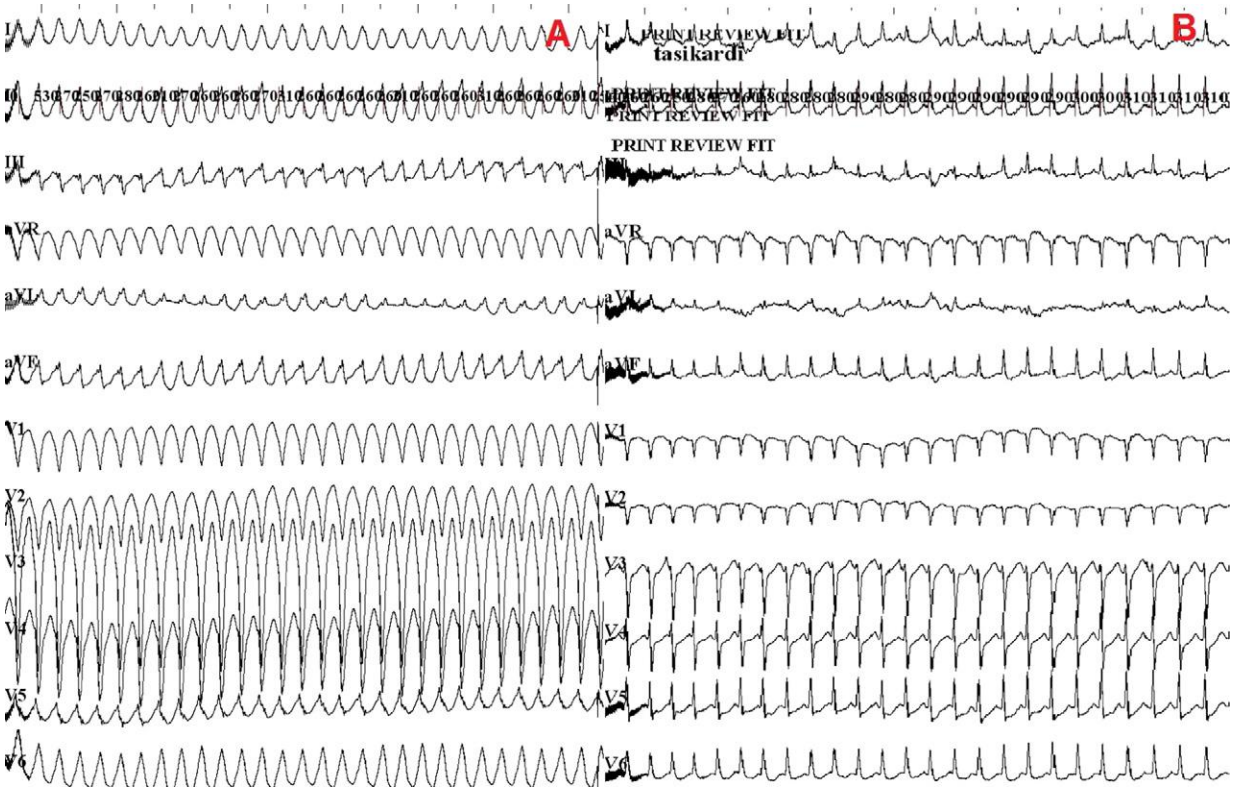


Fig. 1. (A) Twelve-lead electrocardiogram of the clinical wide QRS tachycardia. (B) Twelve-lead electrocardiogram of the clinical narrow QRS tachycardia.

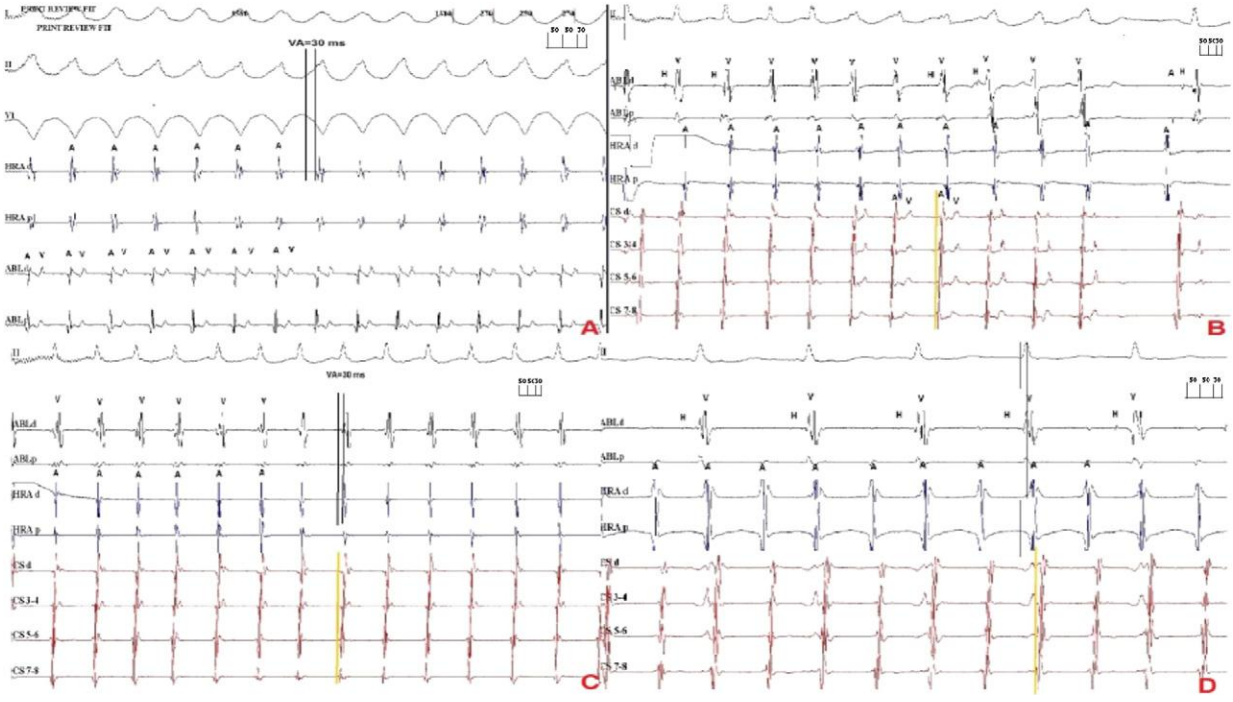


Fig. 2. (A) Wide QRS tachycardia induced by atrial programmed stimulation at a cycle length of 270 ms. (B) Intracardiac recording shows transition and termination of a wide QRS tachycardia to a narrow QRS tachycardia without a change in cycle length and in VA intervals. (C) Narrow QRS tachycardia by atrial programmed stimulation at a cycle length of 270 ms. (D) Narrow QRS tachycardia with 2:1 AV block induced by atrial programmed stimulation at a cycle length of 450 ms. Fig. 2 Legend A. Shown are leads I, II, and V 1, and intracardiac electrograms from the high right atrium (HRA), proximal coronary sinus (ABLp), and distal coronary sinus (ABLd). VA interval is 30 ms. Please pay attention to the 1:1 VA relationship. B. Shown are lead II and intracardiac electrograms from HRA, distal His bundle (ABLd), proximal His bundle (ABLp), proximal coronary sinus (CS 7–8), and distal coronary sinus (CSd). VA interval is 30 ms. Concentric atrial activation pattern is seen on CS electrograms. Please pay attention to the 1:1 VA relationship and the termination of tachycardia with an A. C. Shown are lead II and intracardiac electrograms from HRA, distal His bundle (ABLd), proximal His bundle (ABLp), proximal coronary sinus (CS 7–8), and distal coronary sinus (CSd). VA interval is 30 ms. Concentric atrial activation pattern is seen on CS electrograms. Please pay attention to the 1:1 VA relationship. D. Shown are lead II and intracardiac electrograms from HRA, distal His bundle (ABLd), proximal His bundle (ABLp), proximal coronary sinus (CS 7–8), and distal coronary sinus (CSd). VA interval is 30 ms. Concentric atrial activation pattern is seen on CS electrograms.

The presence of constant VA and AV interval rules atrial tachycardia with aberrant conduction out. Also, the termination of the tachycardia with an A makes atrial tachycardia unlikely. For the second tachycardia, which is a narrow QRS tachycardia (Fig. 2C) with 1:1 AV relationship, the differential diagnosis mainly includes septal atrial tachycardia, typical AVNRT, and automatic junctional tachycardia (JT) due to short VA interval and concentric atrial activation pattern. The presence of constant VA and AV interval are unlikely for atrial tachycardia. Also, dual AV node physiology and very short VA interval favor but are not confirmatory of typical AVNRT. The reproducible induction of the tachycardia with premature stimulation is unusual in automatic JT. The delay of the subsequent tachycardia beat after his refractory atrial extrastimulus rules JT out. For the last tachycardia with 2:1 AV block (Fig. 2D), the differential diagnosis mainly includes atrial tachycardia and typical AVNRT due to concentric atrial activation pattern. In this tachycardia, a different atrial activation pattern with the early atrial activation at the HRA and His bundle region was detected. Although the proximal to distal CS activation seems as concentric, the early activation at the HRA and his bundle should suggest the tachycardia may be atrial tachycardia with an eccentric atrial activation and AV block. The VA interval of 30 ms is too short for an atrial tachycardia. Although the constant VA relation could not exclude atrial tachycardia in every time, we accepted typical AVNRT as the responsible mechanism of all seen tachycardia. Thus, we decided to ablate slow pathway. Any tachycardia could not be further induced after modification of the slow pathway.

Discussion

AVNRT is a relatively common supraventricular arrhythmia, and an accurate diagnosis is essential before proceeding with ablative therapy. Along with specific electrocardiographic clues, specific electrophysiological techniques enable accurate diagnosis of AVNRT. Para-Hisian pacing, “His” refractory extrasystole and entrainment techniques are crucial to differentiate AVNRT from other supraventricular tachycardias, especially orthodromic reciprocal tachycardia with a concealed septal accessory pathway.[4] In this case presentation, we could not perform these discrimination techniques due to hemodynamic effects of the tachycardia. However, we tried to explain that the discrimination of AVNRT can be done with basic electrophysiological properties without pacing maneuvers. Also, to the best of our knowledge, we firstly presented all tachycardia forms of typical AVNRT in a same patient.

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Short communication

Autologous bone marrow concentrate enriched in progenitor cells — An adjuvant in the treatment of acute myocardial infarction

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ABSTRACT

Despite advances in revascularization techniques, acute myocardial infarction (AMI) still carries significant morbidity and mortality. Over the past decade, the use of regenerative medicine methodologies, and specifically bone marrow derived progenitor cell therapy has been tested in more than 35 Phase I and Phase II clinical studies demonstrating overall safety and measurable clinical benefit, 12–61 months post-treatment as evaluated by improvement in the Left Ventricular Ejection Fraction (LVEF) and changes in infarct size post AMI. Recent meta-analysis on the subject highlighted several important parameters that include timing of the cell therapy post AMI, the cell dose, and the baseline LVEF on enrollment. We further postulate that the mythologies and timing for cell handling and delivery including the specific devices are essential for clinical efficacy. Addressing this we have developed a rapid 60 to 90 minute process and integrated system which is carried out in the heart catheter lab, using a combination product (U.S. Food and Drug broadly defined as the combination of co-labeled optimized "cell friendly" devices, effective cell/biological formulation and dose) for harvesting, processing, verifying, and delivering an autologous dose of bone marrow progenitor/stem cells via the intracoronary artery proximal to the infarct myocardial region. The methodology has been demonstrated to be safe and feasible for autologous in vivo use and presented by our groups' earlier studies[1–3] and most recently used in a Phase Ib critical limb ischemia trial of 17 subjects (NCT01472289) (manuscript under preparation). This is the first case study prior to beginning the AMIRST trial [**A**cute **M**yocardial **I**nfarction **R**apid **S**tem cell **T**herapy], specific to our proprietary combination product kit for acute myocardial infarction, and was completed under the Independent Ethics Committee and Institutional Committee for Stem Cell Research and Therapy approval (TIEC/2011/32/02) for process and safety endpoints post-treatment.

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Introduction and background

Cell therapy is being widely explored in the management of various unmet medical need, and our own group has demonstrated safety and efficacy of autologous bone marrow derived stem cells in treating various clinical indications.[1–3] Cardiovascular disease (CVD) is the number one cause of morbidity and mortality worldwide. An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths.[4] Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke.[5] More remarkably, low- and middle-income countries are disproportionally affected, driving the need for regenerative therapies in lieu of chronic drug treatment regimens. Regenerative therapies must be offered in formats eliminating the need for high cost GMP laboratory infrastructure or extensive multi-hour usage of vascular catheter labs. Over 80% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women.[4] In the progression of CVDs, plaque lesions develop in arteries that result in the narrowing of vessels, and in severe

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cases they break open and create a blockage of blood flow (ischemia) to vital parts of the heart. Such ischemia may be reversed if treated within a short period of time by reperfusion therapy, and further prevention of devastating remodeling is hypothesized by the infusion of adult tissue-derived stem/progenitor cells. Despite significant advances in medical therapy and revascularization strategies, the prognosis of certain patients with acute myocardial infarction (AMI) remains dismal without the introduction of early biological repair intervention.

Along with reperfusion, adjuvant progenitor cell therapy has been shown to be potentially efficacious in the repair and regeneration of damaged heart tissue. These potent progenitor cells can be isolated from different sources within the adult human body. Specifically, the current cardiac regenerative field is experiencing diverse adult stem/progenitor cell clinical trials at different stages of clinical development including bone marrow derived mononuclear cells (BMMNCs),[6–8] mesenchymal stem cells (MSCs),[9] adipose tissue-derived stem cells,[10] and cardiac-derived expanded stem cells.[11] Of the above mentioned cellular populations, bone marrow derived mononuclear cells have received greater scientific and translational attention. MSCs, although easily expanded in a laboratory setting and creating the ideal off-the-shelf cellular product, can generate local immune responses and disturb homeostasis within a tissue environment by releasing inflammatory mediators.[12] Autologous bone marrow derived stem cell (aBMMNCs) therapy has emerged as a novel approach to treat patients with residual left ventricular dysfunction following AMI despite successful revascularization.[7,38] Autologous sources are preferable because immunologic rejection is avoided by default.[39] The first clinical trial evaluating the effects of stem cell therapy on ischemic heart failure was reported in 2002. In 2006, three large randomized clinical trials (ASTAMI, REPAIR-AMI, and TOPCARE-CHD) were published.[40–42] Although results on the beneficial effects of stem cells on myocardial function from these first trials were somewhat conflicting, further clinical trials (BOOST, STAR-HEART, SCIPIO, CADUCEUS, REGENT, FocusHF, and others) suggest the beneficial effects of stem cells on the function and remodeling of ischemic myocardium.[43–47] Autologous BMMNCs not only circumvent the ethical and legal issues related to embryonic stem cells, but also overcome the risk of transmitting diseases and immune rejection. In last 12 years, autologous BMMNCs has been extensively studied for cardiac repair and regeneration in a number of randomized-controlled trials (RCTs). More than 1800 subjects have been investigated in these studies, and there is a clear evidence for safety of this therapy, however, its efficacy is still debated because of inconsistent results reported in the literature.[27] Here we are presenting a case report utilizing our integrated treatment platform (combination product) that is specific for Acute Myocardial Infarction and has appropriately considered the essential devices, diagnostics, cell formulations, and instructions for use ensuring the treatment meets the objectives of providing a safe, effective, rapid, bedside therapy for treating low ejection fraction primary acute myocardial infarction.

Case report

Case presentation

A 43 year old male, non-diabetic, normotensive, non-obese, smoker presented with a history of two hours of chest pain and symptomatic of an AMI into the emergency department. On admission, the patient presented with a 2 mm ST segment elevation in V1 and V2 anterior leads with on-going chest pains, and AMI was further confirmed with biochemical blood tests. The patient's Left Ventricular Ejection Fraction (LVEF), was estimated to be around 35% by bedside 2D ECHO. Diagnostic coronary angiography showed 95% occlusion in the LAD in the proximal segment, and no collaterals were noted. RCA, and circumflex arteries were patent. Primary percutaneous coronary intervention (PCI) was performed within 24 h of onset of chest pains using a routine technique, and a single drug-eluting stent was deployed in the proximal LAD with TIMI-3 grade flow results. Post-PCI, the patient's LVEF remained <40% at the 120 h time-point as measured by multigated acquisition (MuGA) and ECHO, which met our inclusion criteria and is predictive of a higher than acceptable one year mortality rate. Also, the ECG showed T-wave inversion in anterior leads and resolution of J-point elevation post-PCI.

The patient was advised that he met the inclusion criteria for the AMIRST clinical trial program using his own (autologous) bone marrow progenitor cells. The clinical trial is registered with clinicaltrials.gov (NCT01536106) and is approved by the Institutional Ethics Committee (IEC) (IEC Approval #TIEC/2011/32/02) and Institutional Committee for Stem Cell Research (ICSCRT). The Patient, Primary Investigator and Clinical Investigator concurred, and consent was obtained. On the sixth day post PTCA/stent implant, the patient was transferred to the heart catheterization laboratory, and the AMIRST (Acute Myocardial Infarction Rapid Stem cell Therapy) protocol was completed. The entire procedure was completed within 90 min, in the catheterization laboratory using our point-of-care technology. As a preliminary safety study prior to full subject enrollment, the patient was followed up for 24-months, and evaluated with standard diagnostic metrics. No major adverse cardiac events (MACE) including re-hospitalization were reported during the 24 month follow-up period, demonstrating the preliminary safety of the device output, that is, autologous bone marrow cell concentrate enriched progenitor cells and the corresponding adjuvant treatment. The patients' LVEF improved from 35% (Day 0) at the time of the AMIRST treatment to 60.3% following 24 months post-AMIRST intervention. It is noted that although the authors believe cardiac MRI is now the gold standard for measuring LVEF; in this study we used MuGA as the enrollment measurement technique. Caution should be taken in comparing MuGA and MRI LVEF results; however the enrollment LVEF was confirmed via a secondary method i.e. ECHO and the 3-month and 24-months LVEF results were confirmed by the same radiology team.

Method: BMCePC adjuvant therapy

Upon written informed consent, and within our maximum window of 10 days post MI, the patient was taken to the heart catheterization laboratory (operating room suite) on Day 6 post-PCI; mildly to moderately sedated using 0.2 mcg/kg of Fentanyl, and 120 mL of bone marrow was aspirated from the patient's iliac crest using an 11-gauge Jamshidi needle optimized for cell harvest. Careful bone marrow aspiration technique was employed to reduce peripheral blood contamination in the aspirate. Following the aspiration, the bone marrow was processed employing our proprietary point-of-care technology platform to produce bone marrow concentrate enriched in progenitor cells (BMCePC). Our point-of-care technology processes autologous bone marrow to a pre-determined multi-phasic concentrate effectively and safely in minimal time ex-vivo within 90 min (from aspiration to delivery) in the operating room. The technology employs a linked two phase stratification process using optical sensors to detect the different cell strata and additional sensors to detect the mass and volume. The point-of-care device automatically separates the different cellular fractions into their designated compartments. Our point-of-care technology is a completely closed sterile system with minimal manipulation of the cells, that is, no addition of xenogeneic or chemical substance at any step from harvest to delivery (except anticoagulant) achieving at least 85% of cell yield. Rapid point-of-care quality testing instruments have been optimized and are used to ensure a safe and consistent cell dose. The cellular product obtained after processing the bone marrow using our device contained a total of 3.54×10^8 BMMNCs. A guide-wire was introduced into the femoral artery followed by a double lumen ultra-low profile PTA intracoronary catheter, and the patient had four separate induced ischemia/progenitor cell infusions using the “stop-flow” technique before the entire optimal dose of nucleated cells was distally delivered to the stent in the LAD. The complete process was accomplished in 90 min at patient's bedside. The patient's hematological and

Table 1
Clinical laboratory values pre- and post-BMCePC therapy.

	Pre-BMCePC infusion	Post-BMCePC infusion
	Day −2	Day 0
Hemoglobin (g/dL)	13.5	13.8
RBC count ($\times 10^6$/μL)	4.84	4.92
Platelet count ($\times 10^3$/mL)	110	120
Creatinine, serum (mg/dL)	0.8	0.9
Urea nitrogen (mg/dL)	13	12
Creatine kinase, serum	106	188
N-terminal pro-B type natriuretic peptide (pg/mL)	731.3	—

biochemical parameters are listed in Table 1. There were no adverse events (AE) or serious adverse events (SAE) reported during the procedure. The patient remained hospitalized for telemetry an additional 24 hours post cell transplant, and released with standard cardiac therapeutics as listed in Table 2.

Patient follow-up

The patient was scheduled for follow-up on 1, 2, 3, 6, 12 and 24 months to assess the primary endpoints of safety and the secondary endpoints of efficacy that include LVEF, MACE, cardiac remodeling and quality of life assessments. The 12-month follow-up could not be completed due to non-availability of patient, but all other follow-up points were completed. No Major Adverse Cardiac Events (MACE) or re-hospitalization events were reported. The patient continued to follow a normal life, after 2 weeks post the AMIRST procedure. At the 1-month follow-up, HOLTER monitoring was performed for 23 h and 6 min. No ventricular ectopic were observed, and the heart variability was normal. The slowest episode of bradycardia (HR 53 bpm, 1 min 13 s) was observed at midnight and the fastest episode of tachycardia (HR 141 bpm, 1 min 2 s) was observed in the afternoon. Cardiac imaging was performed at each follow-up. The cardiac chambers appeared normal with no signs of pericardial effusion.

Overall, the study demonstrated preliminary safety of our bone marrow aspiration, processing and infusion methodology in an acute low LVEF infarct patient post PTCA. Fig. 1 shows cardiac MR images obtained 3 and 24-months post-BMC infusion. At the 24-month follow-up, the cardiac MR findings were summarized as "Basal and mid-cavity anterior and anteroseptal and apical anterior and septal and apex myocardial post contrast sub-endocardial <25% to 50% with a focal spec of 75% transmural hyper enhancement, consistent with ischemic infarction."

The pre-BMC infusion cardiac MR imaging was performed on a different instrument than the 3- and 24-months post-BMC infusion. Therefore, an absolute quantitative equivalency measurement of LVEF between the pre-treatment and 3-months post-treatment was evaluated cautiously. Also, the MuGA and ECHO scan results have a level of user-dependency, and each result was cautiously interpreted.[13,14] Nevertheless, a considerable improvement in the LVEF has been noted over the study period and between 3-months and 24-months follow-up, post-BMC infusion, the LVEF further improved from 55.4% to 60.3% as shown in Table 3. This degree of improvement is considered atypical for a patient having suffered an ST elevated myocardial infarction with an ejection fraction below 40% post reperfusion (stenting). The cardiac output (volumetric) also showed an improvement from 2.7 L/min to 3.4 L/min over the same period, and is a secondary endpoint. No reduction in scar size was observed with a heart mass of 115.5 g and a scar mass of 11.5 g (approximately 11%).

Table 2
Medications prescribed on discharge post-BMCePC therapy.

Drug	Dose	Frequency	Drug class
Aspirin	150 mg	Oral, once daily	Anti-platelet
Copidogrel	75 mg	Oral, twice daily	Anti-platelet
Rosuvastatin	20 mg	Oral, once daily	Statin
Pantoprazole	40 mg	Oral, once daily	Dyspepsia/Antacid

Discussion

The AMIRST trial has been designed to determine the safety and preliminary effectiveness of our patented point-of-care technology (combination product) for aspiration, processing and intracoronary administration of BMCePCs for treatment of acute ST segment elevation MI with low ejection fraction. Here we are presenting the preliminary safety and effectiveness data from a single case prior to starting an elaborate, randomized-controlled AMIRST trial on a larger patient population. The results from this case study demonstrate that our combination product which is the first of its kind point-of-care technology that includes all the devices necessary for aspiration, processing and delivery of BMCePCs and also, checks the quality and quantity of the cells prior to administration using our optimized point-of-care diagnostic devices is efficacious for cardiac disorders in terms of safety and feasibility. We observed no significant major adverse effects in terms of MACE or pro-arrhythmia following administration of BMCePCs, and there was significant improvement in myocardial perfusion following administration of BMCePCs as determined by cardiac MRI, MuGA and 2D ECHO. Compared to baseline, there was a significant improvement in LVEF at 3 and 24 months in the treated patient. However, there was no significant improvement in scar size after administration of BMCePCs. Nevertheless, this case study was designed to demonstrate the preliminary safety and effectiveness data for our rapid bedside point-of-care technology (combination product) in the treatment of low ejection fraction AMI.

The adult human body possesses the potential to repair damaged cardiac tissue, and in the last decade considerable attempts have been made to harness this intrinsic regenerative capability. Adult human bone marrow represents the richest source of multi-potency progenitor cells. These progenitor cells can be harvested, processed/expanded and applied to regenerative applications. Despite obtaining excellent results in lab animal studies, human clinical results have remained underwhelming in the prior studies. The review of current and past literature, recent meta-analysis and reviews, all revealed critical stepwise procedural, instrumentation, and chemical/biological variables that should have been controlled and measured in order to ensure proper cardiac repair and regeneration in everyday interventional cardiology settings. Simply assuming specific cell types demonstrated in a lab model are ready for clinical trial, and expectations that such biology alone is predictable and reproducible equates to the pharmaceutical industry completely skipping the quality demands and parameters of statistical process control in manufacturing.

The main finding of the present study was that intracoronary cell therapy after AMI was potentially safe and resulted in a modest yet significant increase in LVEF. LVEF is one of the key indications of mortality rates post MI with a reduced LVEF being a risk factor for both sudden and non-sudden death, with the odds ratio for 1-year mortality after MI at 9.48 for patients with LVEF ≤30% compared with patients with LVEF >50%, 2.94 for patients with LVEF 30–40%, whereas the risk was not significantly increased in patients with LVEF 40–50%. Intracoronary cell therapy helps improve myocardial functions, however the exact mechanism of action is still debatable. Several hypothesis have been proposed and a recent well-conducted study suggested that bone marrow derived progenitor cells do not transdifferentiate into cardiomyocytes, instead they adopt mature hematopoietic characteristics.[29,30] However, adult CD34+ cells can differentiate into cardiomyocytes, mature endothelial cells and smooth muscle cells in vivo.[31] Another proposed mechanism is that, following cell therapy angiogenesis increases, thus, improving blood supply to the ischemic regions, which can potentially aide in revascularization of hibernating myocardium[32] and inhibit cardiomyocyte apoptosis.[33] The alternate possible reasons for LV recovery

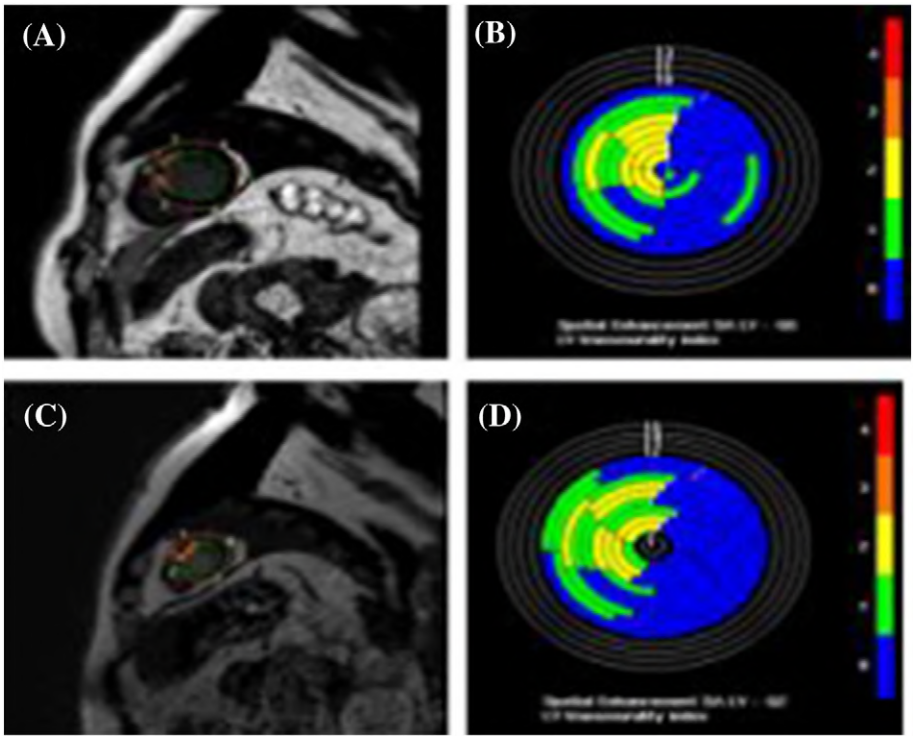


Fig. 1. Images (A) and (C) show one section of the cardiac MR stacking used to calculate the myocardial volume at the 3- and 24-months exam post-BMCePC infusion, respectively. Images (B) and (D) represent the LV transmurality index at 3- and 24-months post-BMCePC infusion, respectively.

could be due to absence of co-morbidities, normal after load and early presentation of the patient.[34]

The regenerative potential of bone marrow derived cellular products is highly influenced by the handling, aspiration, processing, and re-delivery techniques as well as the chemistry, biology and timing of the cellular product intervention. It has been extensively reported and is well understood that the chemokine receptor-4 (CXCR4)/stromal cell-derived factor-1 (SDF-1) axis plays a crucial role in homing to and engraftment of progenitor cells to the heart after myocardial infarction (MI).[15,16] Within minutes following a myocardial infarction, the cardiac tissue turns hypoxic leading to cardiac myocytes apoptosis and upregulation of several important factors, especially the stromal cell-derived factor-1 (SDF-1) chemokine. The increased levels of SDF-1 lead to homing of endogenous and bone marrow derived progenitor cells including endothelial progenitor cells (EPCs) that play a pivotal role in angiogenesis (formation of blood vessels). The progenitor cells that express CXCR4 respond swiftly to an increased SDF-1 gradient. Although, progenitor cells present in the bone marrow do express CXCR4 receptors, they need to mobilize or egress into the blood stream to efficiently perform the cardiac repair. It has been suggested in prior publications that bone marrow pro-genitor cells become more responsive to SDF-1 over 4 to 7 days post MI, however, the local (heart organ) cardiac SDF-1 levels decline quickly within 4 to 7 days from the cardiac injury (MI) leading to ineffective prolonged homing of progenitor cells to the injured tissue.[17] Therefore, harvesting these potentially SDF-1 responsive, CXCR4 expressing bone marrow stem/progenitor cells, and infusing them locally (proximally) to the stunted or scarred cardiac tissue represents a logical and viable approach for cardiac regenerative therapy. Fig. 2 represents an overview of the approach.

Table 3
Time endpoints: left ventricular ejection fraction (LVEF) values and safety.

Measurement time	Method	Value	MACE
Time 0 days	2D echo	35%	N/A
Time 6 days	MuGA	<40%	N/A
Time 7 days	IC angiogram	<40%	None
Time 3 months F/U	cMRI	55.30%	None
Time 24 months F/U	cMRI	60.30%	None

The importance of the CXCR4/SDF-1 axis is unambiguous in the arena of regenerative medicine, and chemicals that interfere with this mechanism definitely impact the over-all efficacy of the infused cellular product. Anticoagulants, a chemical added to bone marrow aspirate to prevent the formation of microthrombae, plays a crucial role in the overall efficacy of regenerative cell therapy. It is understood that the addition of any chemical entity in the presence of proteins or cells may have an effect on their structure or function or both. Heparins are the most commonly employed anticoagulants for bone marrow aspiration, and are reported to disrupt the pivotal CXCR4/SDF-1 axis[18] and immunomodulation.[19] Heparins have a high affinity for SDF-1 (Kd 22.7 nM), and bind to SDF-1 by electrostatic interactions that can inhibit its receptor (CXCR4) interactions.[16] The heparin-treated bone marrow cells become unresponsive due to inhibition of the CXCR4 receptor internalization that further blocks CXCR4 downstream signaling.

It has also been reported that circulating VEGF levels, a potent proangiogenic factor, decrease by 93.2 + 5% within 30 min of unfractionated heparin (UFH) therapy.[22] The decrease in circulating VEGF levels could be due to sequestration of VEGF into the extracellular matrix. Moreover, heparins are associated with high rates of pre-procedural bleeding, which may be related to their inability to bind to clot-bound thrombin. Heparins can bind to platelet factor-4 in vivo that may lead to formation of antibodies against the heparin/PF-4 complex and can cause heparin induced thrombocytopenia (HIT).[20]

Williams et al. demonstrated that the presence of antibodies to the platelet factor-4/heparin complex serves as an independent predictor of myocardial infarction at 30 days in patients presenting with acute coronary ischemic syndromes.[21] Therefore, our first variable control that we have devised and utilized in the AMIRST procedure and combination product kit is a novel anticoagulation methodology utilizing a U.S. FDA approved short synthetic peptide that can keep the aspirated bone marrow in a non-coagulated state, during processing and infusion, without affecting the biological efficacy of cellular product.

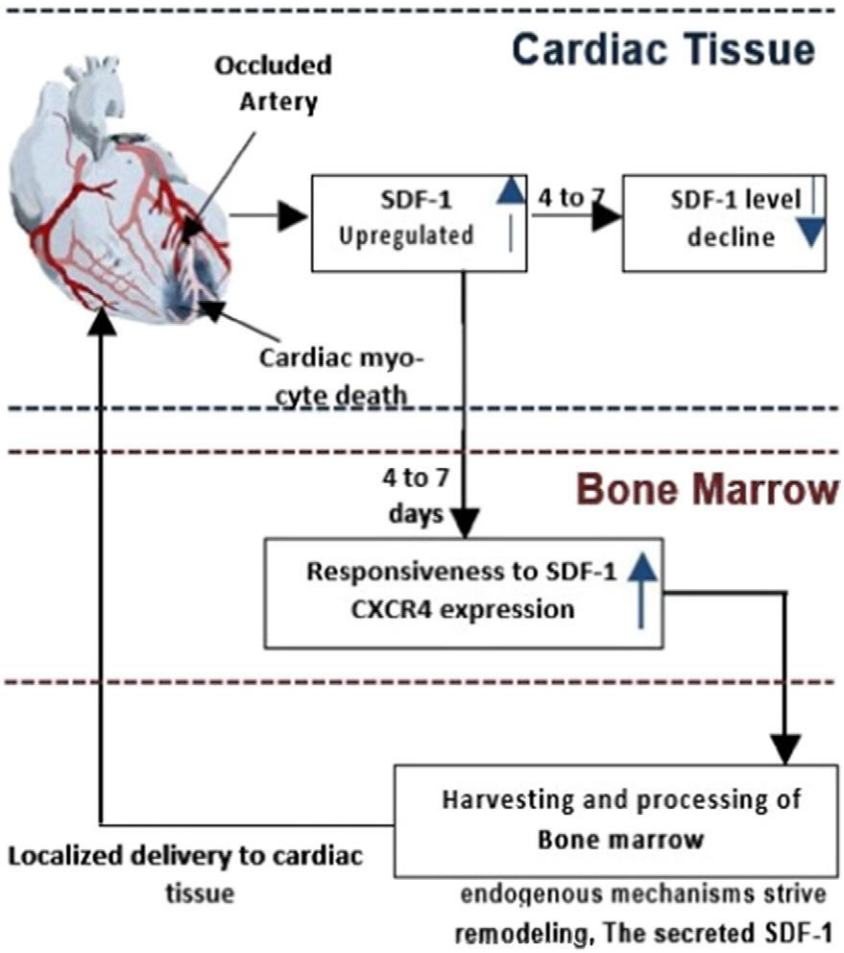


Fig. 2. Increase the responsiveness of CXCR4-positive bone marrow progenitor cells, however, due to limited mobilization the effective repair does not take place. Harvesting, enriching and infusing potential progenitor cells are our approach for cardiac repair and regeneration.

Another major factor that influences the potency of bone marrow derived cellular product is the processing technology employed to harvest the desired cellular fraction(s). Some scientists and clinicians suggest that different processing techniques utilized in bone marrow processing, at least to some extent, are a plausible reason for conflicting and unpredictable results in clinical trials.[22] It has been reported in the literature that efficacy and functionality of bone marrow derived cellular product is significantly influenced by various factors such as red blood cell contamination,[23] content of apoptotic cells, washing steps, and inclusion of neutrophils. Till date, most clinical and pre-clinical studies have used the Ficoll-paque density gradient method to extract the cell fraction enriched with mononuclear cells, and most recently the TIME randomized trial[24] used such a combination of automation and Ficoll-paque and reported consistently low total nucleated cell recoveries. Manual cell preparation studies have reported that ficoll-paque methods result in a mere 15 to 30% recovery rates of bone marrow mononuclear cells following a multi-hour laboratory processing requirement.[25] The lower recovery rates of ficoll-paque may among others be a consequence of density-medium related cytotoxicity. Moreover, the manual ficoll-paque method is highly user-dependent but should have been addressed in the automated approach used in the TIME study. This is likely another plausible reason for inconsistent results in clinical trials thus far.[28] We have thus focused on critical variable number two by developing an automated chemical free "intelligent" cell-processing technology with Thermogenesis Corporation (USA) that yields reproducible cellular product and is independent of the user, assuming basic training. The method produces autologous BMCePC, without the addition of density grade medium, at the patient's bedside in under 30 min. Additionally, a clinical team using the AMIRST approach is able to verify that the harvesting and processing steps have yielded the desired minimum cellular dose by employing our rapid bedside diagnostics.

Handling time is a critical parameter in cellular therapy and the time interval between bone marrow aspiration and delivery of cellular product must be reduced. It has been suggested that bone marrow derived autologous cellular products prevent adverse cardiac remodeling by a synergy of mechanisms as described in Fig. 3. One of the crucial factors essential for a remodeling minimization effect is the mobility of progenitor cells. Prerequisite for the success of cell therapy is the homing and, thus, engraftment of transplanted cells into the target area. The migratory capacity of the infused cells is a major determinant of infarct remodeling, disclosing a causal effect of progenitor cell therapy on regeneration enhancement. Britten et al. first time demonstrated that the migratory capacity of transplanted progenitor cells is an independent predictor of infarct remodeling as measured by MRI-determined LE volume.[35] Similarly Poole et al. showed that product potency (in terms of improvement in perfusion and LVEF) was related to the mobility of CD34+ cells in an SDF-1 gradient.[26] Furthermore, they showed that cell mobility towards the chemokine gradient declined over time following bone marrow harvest, with a median 57% decrease between 24 and 48 hours post-harvest and a further 11% decline by 72 h. Thus, administration of cells without delay after harvest may reduce the quantity of cells required for the therapeutic effect, increase the migratory capacity of the cells and enhance the therapeutic effect of cell therapy.[36,37] Thus, the numbers of CD34+

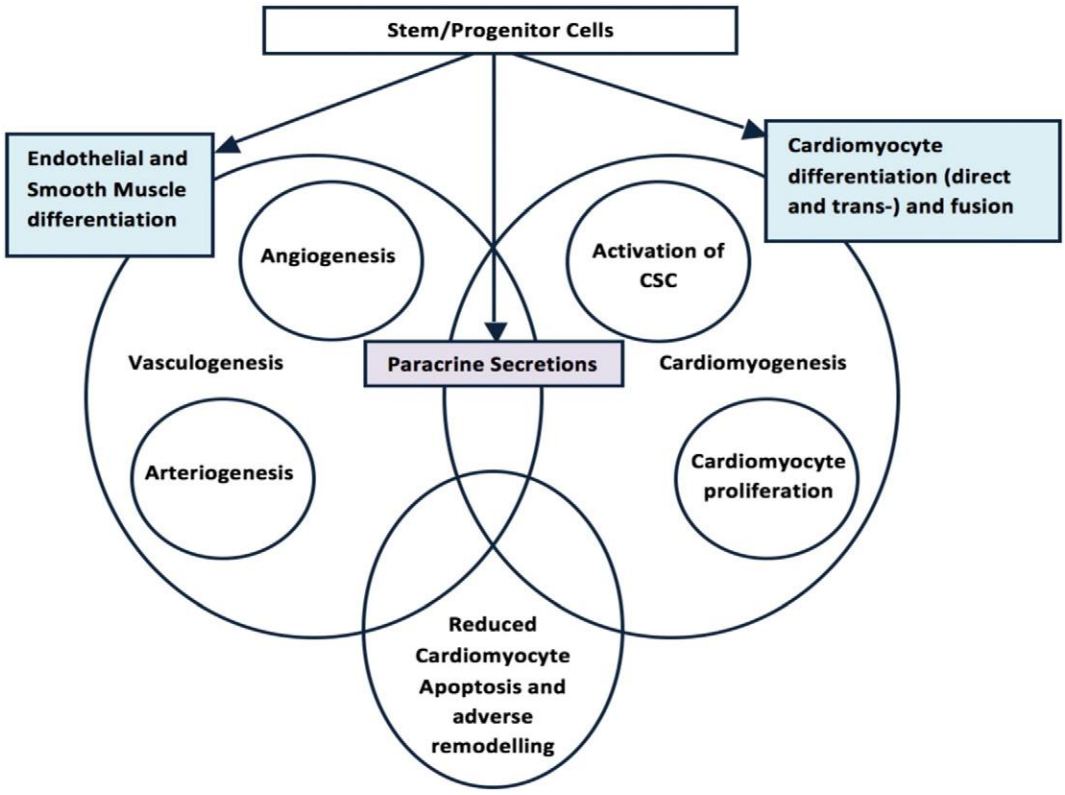


Fig. 3. Schematic representation of proposed mechanisms that stem/progenitor cells recruit for cardiac repair and regeneration following myocardial infarction (MI). Intra-coronary (IC) delivery of stem/progenitor cells, upregulation of CXCR4 and egress of progenitor cells from the bone marrow into the vascular bed to sustain repair and modulate inflammation.

cells, their SDF-1 mobility, and the time from harvest to infusion are all factors that appear to determine potency of the cell therapy product. Delivering the cellular product with a minimum interval lag time presents an ideal technology to the enthusiastic clinicians. Our point-of-care technology can accomplish the complete procedure, from bone marrow harvest to infusion, in 60–90 min, thus minimizing any impact of time and environmental effects on the therapeutic cells.

The final critical variable controlled in our treatment method is the utilization of an inherently cell friendly and endothelium safe intracoronary catheter designed to measure and control the impact of pressure, shear, and surface chemistry within the delivery lumen on the therapeutic cells. Most studies analyze the cellular viability, and fewer analyze the cellular potency of the cells pre- and post-traversing the catheter. The lack of attention given in previous cardiac therapies to the impact of such physical conditions has on the infuscate, again opened the possibilities for highly unpredictable results. Our procedure utilizes a proprietary controlled process and device which minimizes and measures these critical variables.

Conclusion and future directions

In brief, we have developed a rapid bedside (point-of-care) method and technology for the aspiration, processing and infusion of BMCePC, as an adjuvant treatment in cardiovascular disorders – specifically primary acute myocardial infarction. The methodology employs a heparin-free bone marrow aspiration along with a user independent automated processing system to extract BMCePC rapidly in a point-of-care controlled environment. The technique helps overcomes few of the current problems encountered in the field of cardiac regenerative medicine and provides the first combination product (both device and therapeutic cells) for a rapid point-of-care technology of aspirating, isolating, and delivering of bone marrow derived progenitor cells and factors from the patient's own body. Many experimental studies and clinical trials have proven the feasibility, safety, and efficacy of cell-based therapy, including our case study, however, the mechanisms underlying the regeneration of damaged cardiac tissues by progenitor cells are not fully understood. There are many issues related to the use of cell therapy, including the eligibility of patients, optimal timing of cell transfer, dosage, the best way to prepare the cells, method of cell administration, and selection of the correct type of cells, that remain to be solved. Thus, large scale randomized-controlled trials are warranted to assess the clinical effects of the BMCePC administration in patients with acute myocardial infarction with an optimal delivery systems.

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Short communication

Myocardial infarction in the early postoperative period of renal transplantation: Case report and review of literature

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ABSTRACT

Coronary artery disease (CAD) is the leading cause of mortality in the end-stage renal disease. Although risk of myocardial infarction (MI) decreases after renal transplantation compared to hemodialysis period, CAD remain the major cause of mortality after transplantation also. Risk of MI is maximal during the perioperative period and it's incidence decreases gradually after transplantation. Pre-operative cardiac evaluation is essential prior to renal transplantion. Herein, we prensented a case of acute anterior myocardial infarction observed in the early post-operative period of renal transplantation and review the current literature. We discussed the demographic and clinical predictors of the perioperative cardiac events.

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Introduction

Coronary artery disease (CAD) is the leading cause of mortality in end-stage renal disease (ESRD), hence ESRD is accepted as the equivalent of CAD. Although risk of myocardial infarction (MI) decreases after renal transplantation compared to the hemodialysis period, CAD remains the major clinical issue regarding mortality.[1] Risk of MI is at peak during the perioperative period and its incidence decreases gradually after transplantation.[1] Effective preoperative cardiac evaluation prior to renal transplantation may prevent the possible cardiac complication in the perioperative period. Herein, we presented a case of acute anterior MI observed in the early postoperative transplantation period and discussed the perioperative risk assessment and management.

Case report

A 57-year-old male patient was admitted to hospital for renal transplantation. On medical background, he had been followed up with a diagnosis of polycystic kidney disease and he was taking hemodialysis therapy for 10 years. Coronary bare metal stent (3.0 × 20 mm) was implanted to the proximal left anterior descending artery (LAD) a year ago and he was free from anginal symptoms for a year. He was a current smoker and also under medication for hypertension. Physical examination did not show specific pathology and functional capacity was more than 7 METS. He also did not define typical anginal chest pain on exertion. Laboratory data showed dyslipidemia with LDL cholesterol 150 mg/dl. Aspirin therapy was discontinued for a week and the patient did not take any additional antiagregant therapy. Live donor transplantation was performed without any complication. In the postoperative period, the patient defined atypical chest pain which was not thought as an acute cardiac event. But, there was not any ischemic finding in the ECG. The patient was discharged from the hospital on the seventh postoperative day. However, the patient was readmitted to hospital on the same day with a complaint of typical chest pain, palpitation, and shortness of breath. ECG showed anterior ST elevation and the patient was transferred to a catheter laboratory for primary coronary interventions. Coronary angiography revealed thrombotic critical lesions in the mid and distal LAD (Fig. 1A). Angioplasty and stent deployment was performed to LAD lesion (Fig. 1B). Bare metal stent was preferred by the operator to shorten the dual antiplatelet therapy. Heparin 60 unit/kg was given prior to angioplasty and was not continued after procedure. The patient was discharged without any complication including bleeding and additional renal pathology. Dual antiplatelet therapy consists of acetylsalicylic acid 100 mg and clopidogrel 75 mg daily was prescribed for a month. One-year follow-up of the patient was uneventful with functional renal graft.

Discussion

Kidney transplantation is associated with 17% risk reduction for myocardial infarction (MI) compared to patients in the waiting list.[1] However, MI remains a leading cause of death in patients with functioning renal transplantation. The risk of MI is highest in the early postoperative period and mortality rates after hospitalization for MI is approximately 50% at 5 years, which affects allograft longevity also.[1] Perioperative cardiac events might occur as a result of demand-mediated ischemia and/or plaque rupture. A detailed preoperative cardiac assessment should be performed to cover both clinical issues.[2]

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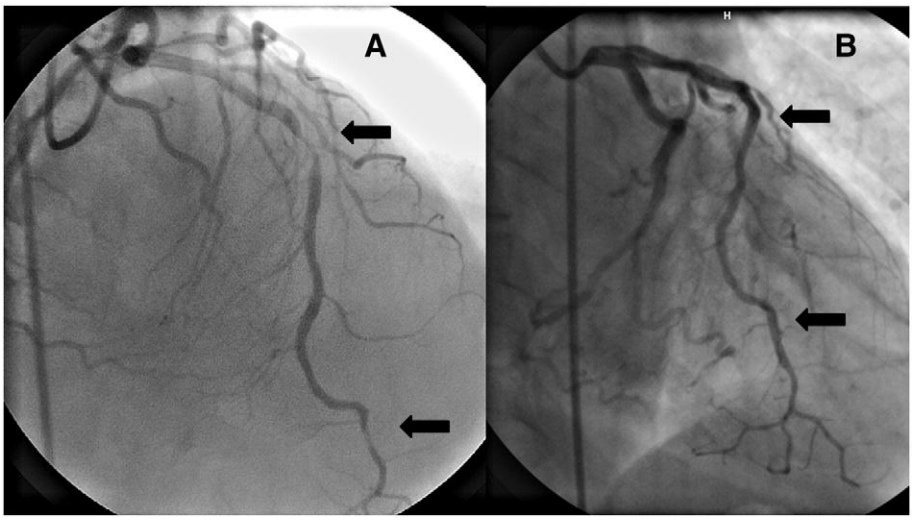


Fig. 1. A. Left anterior oblique projection showing thrombotic subtotal lesion in mid left anterior descending artery and thrombotic 70% lesion in the distal segment. B. Left anterior oblique projection showing successful percutaneous coronary interventions.

The risk and predictors of post-renal transplantation MI are not well described. Nonetheless, renal allograft recipients have higher prevalence of traditional atherosclerotic risk factors. The risk factors for posttransplantation period might be defined as age > 60,obesity, smoking, left ventricular hypertrophy, diabetes, hypertension, and dyslipidemia.[2–3] Besides traditional risk factors, male gender, time on dialysis before transplantation (>a year), donor history of hypertension, transplantation from older donor, immunosuppressive regimen, quality of allograft function, and posttransplantation diabetes also are proposed as predictors of cardiovascular risk in this population.[3–4] Both Framingham risk score and European Society of Cardiology Score chart can be used to determine risk for cardiovascular disease especially in low-risk patients. Framingham risk score may underestimate cardiovascular risk in the high-risk patients.[5] CT coronary angiography has a high negative predictive value in screening of CAD and it would be an ideal screening test in low- to intermediate-risk patients. However, coronary calcification is usually widespread in the ESRD, which may interfere with the sensitivity and specificity of the study.[2] Myocardial perfusion scintigraphy or dobutamine stress echocardiography is the primarily recommended noninvasive tests for asymptomatic high-risk patients. Despite, both studies may give useful information in the assessment of coronary ischemia mediated by demand-blood supply discrepancy, they would not predict cardiac events secondary to plaque rupture.[2] Thus, modification of risk factors and effective medical therapy prior to surgery may diminish the acute thrombotic ischemic events. In addition, preoperative coronary angiography might be a logical approach for assessing cardiovascular risk in symptomatic high-risk patients. Our case was already diagnosed CAD and also possess traditional risk factors including hypertension, dyslipidemia, and smoking. Relatively longer dialysis time and immunosuppressive therapy are the other risk factors for cardiac complications. Preoperative coronary angiography would be logical to show patency of stent regarding our case. On contrary, preoperative angiography would not predict the acute coronary events for our patients. Because LAD stent was already patent and preoperative angiography would not change the transplantation schedule, efficacy of preoperative cardiac revascularization was also not clear. Lifestyle modification including cessation of smoking and regular exercise and also regulation of medical antiischemic agents would be the most important prognostic factors to prevent perioperative coronary events for our patient. On the other hand, postoperative routine screening of troponin I levels may also be beneficial for diagnosing cardiac complication. Although abnormal troponin level is highly prevalent following renal transplantation, normal troponin levels had a high negative predictive value in excluding patients likely to develop postoperative MI.[6] Troponin level was not checked in our patients despite atypical chest pain definition.

Early postoperative percutaneous coronary intervention is associated with bleeding complication because of dual antiplatelet therapy plus heparin. It was reported that thrombus aspiration and lone balloon angioplasty may be logical in the selected cases.[7] However, our case characteristic was not suitable for both strategy because of tight thrombotic subtotal lesion in the mid LAD. The operator preferred bare metal stent to shorten dual antiplatelet therapy. Bare metal stents are the classical choice in the intervention before the transplantation surgery for shorter dual antiplatelet therapy. A small case series show that, kidney transplant surgery may performed under antiplatelet therapy with lower bleeding complication contrary to general consensus of discontinuation of antiplatelet therapy for 5 days.[2,8] Drug eluting stents (DES) are superior to BMS in terms of restenosis and acute coronary events also in the patients with ESRD. Compared to older DES, new-generation DES showed less stent thrombosis with shorter dual antiplatelet therapy.[9] Palmerini T et al demonstrated that major adverse cardiac events were similar with the 3-month and 12-month antiplatelet therapy in the new-generation DES era.[10] We think that dual antiplatelet therapy is not a limitation for renal transplantation recipients and DES should replace traditional BMS implantation in ESRD patients regardless of the time of transplantation.

Conclusion

Acute myocardial infarction is a major cause of mortality in the perioperative period of renal transplantation. A detailed preoperative assessment of cardiac status, effective preoperative anti-ischemic therapy including lifestyle management and preoperative coronary angiography in the symptomatic high-risk patients, will prevent mortality and provide allograft longevity.

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Short communication

Coronary artery rupture during high-pressure post-dilatation of coronary stent in a heavily calcified lesion of an ectatic right coronary artery

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ABSTRACT

Coronary artery perforation (CAP) is a rare but feared complication of percutaneous coronary intervention. With the use of novel instruments, including hydrophilic and ultrarigid guidewires, rotablator devices, and cutting balloons, the success rate of intervention for coronary artery chronic total occlusion (CTOs) and calcified lesions has increased. Along with these changes, the risk of CAP has also increased. In this case report, we present a tip III CAP due to high-pressure postdilatation of coronary stent in a heavily calcified lesion of an ectatic right coronary artery.

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Introduction

Coronary artery perforation (CAP) is a rare and serious complication of percutaneous coronary intervention (PCI).[1] The reported incidence of CAP ranges from 0.1% to 3%, with a mortality ranging from 7% to 17%.[2,3] With the use of novel instruments, including hydrophilic and ultrarigid guidewires, rotablator devices, and cutting balloons, the success rate of intervention for coronary artery chronic total occlusion (CTOs) and calcified lesions have increased. Along with these changes, the risk of CAP has also increased. The treatment of these patients can involve prolonged balloon inflation with perfusion balloons, coil embolization,[4] and implantation of polytetrafluoroethylene (PTFE)-covered stents.[5]

In this case report, we present a tip III CAP due to high-pressure post-dilatation of implanted coronary stent in a heavily calcified lesion of an ectatic mid right coronary artery (RCA).

Case report

A 75-year-old man was referred to our clinic complaining of chest pain, dyspnea, and pneumonia during the last week, with the past medical history of chronic obstructive pulmonary disease (COPD), hypertension, and diabetes mellitus without any history of coronary artery disease. He was admitted due to the high levels of troponin and dynamical electrocardiographic changes. Transthoracic echocardiography showed a dilated left ventricle with depressed systolic function and regional wall motion abnormality (ejection fraction was 40%), with mild mitral and tricuspid regurgitation. The estimated pulmonary artery systolic pressure was significantly elevated at 60 mmHg. High dose antibiotherapy was started and he transferred to the catheter laboratory on the second day of admission due to high risk nature of NSTEMI (increasing troponin levels) and persistent heart failure symptoms despite of medical therapy. Coronary angiography revealed a severe lesion (80% stenosis) in the proximal left anterior descending artery (LAD) and a bifurcation lesion involving a large first diagonal branch and severe calcified lesion (99% stenosis) at the mid region of the right coronary artery (Fig. 1). Due to the high risk nature of the procedure he refused coronary artery bypass grafting surgery. Because of his clinical instability, we decided to perform percutaneous coronary intervention of the ectatic right coronary artery and elective PCI for LAD and first diagonal branch true bifurcation lesion. First, the right coronary artery lesion which considered as the culprit lesion was crossed softly with a 0.014-inch floopy guidewire, and predilatation was performed using a 3.0 × 12 mm compliant coronary balloon catheter (Simpass ® Plus PTCA Balloon Dilatation Catheter). After predilatation, a 5.0 × 16 mm bare metal stent (Liberte® Bare-Metal Coronary Stents) was deployed at the nominal (10 atm) pressure recommended by the manufacturer. A subsequent coronary angiography revealed a 40% residual stenosis in the mid segment of implanted stent (Fig. 2). Thus, we performed a post dilatation with a 5.0 × 12 mm (Apollo® Brosmed Balloon Dilatation Catheter) non-compliant coronary balloon catheter. After the postdilatation, patient's clinical condition worsened with accompanied chest pain, severe hypotension, bradycardia, and dyspnea. Control coronary angiography images demonstrated a massive and pulsatile

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Fig. 1. Severe calcified lesion in mid portion of right coronary artery with right anterior oblique view.

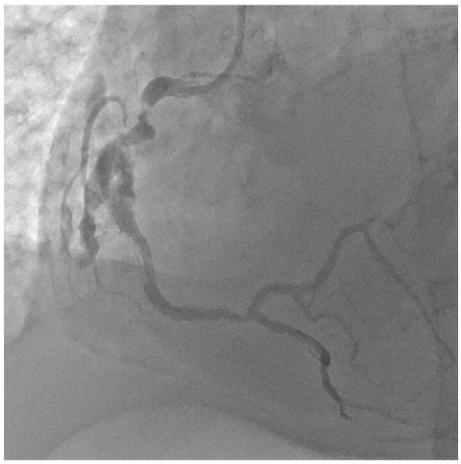


Fig. 3. Radiocontrast agent extravasation from the implanted stent portion of right coronary artery into the pericardial space.

radiocontrast agent extravasation from the implanted stent portion of right coronary artery into the pericardial space (Fig. 3). Immediately, we inflated a 5.0 × 10 mm (Simpass ® Plus PTCA Balloon Dilatation Catheter) compliant coronary balloon within the implanted stent to block blood extravasation to the pericardial sac. At the same time, echocardiogram also confirmed the presence of the small amounts of pericardial effusion without signs of pericardial tamponade. Blood pressure was increased with intravenous serum physiologic and dopamin infusion. After the hemodynamic stabilization of the patient, control coronary angiography showed continued extravasation. Because of the clinical instability, we attempted to stop the leakage by using a PTFE covered stent. Thus, we implanted a 4.0 × 16 mm PTFE covered stent (Graftmaster® RX Coronary Stent Graft System, Abbott Vascular) (Fig. 4). Due to the continued extravasaton, a 3.5 × 16 mm PTFE-covered stent was implanted distally in an overlap manner. A smaller diameter graft stent was used because a second large diameter one was not available at the moment. The result was satisfactory with no pericardial opacification anymore (Fig. 5). The patient was transferred to the coronary intensive care unit with a normal blood pressure. Control echocardiography revealed a small amount of pericardial effusion. There was no any increase in the pericardial effusion amount observed in the 12 and 24 h after the procedure. A week later, follow-up echocardiography showed complete disappearance of effusion. The patient did not suffer from repeated chest pain, and there was no electrocardiographical change or high levels of troponin and the patient was discharged at the seventh postoperative day.

Discussion

Coronary artery perforation is a rare but feared complication of PCI. Several factors can be associated with these conditions: (1) clinical variables: advanced age, female sex, renal dysfunction, and non-ST-segment elevation myocardial infarction; (2) angiographic factors: chronic total occlusion, coronary artery calcification, tortuous vessels, target lesions in the circumflex and right coronary arteries, diffuse target lesions (above 20 mm), and eccentric lesions; (3) technique-associated factors: use of hydrophilic/extrastiff wires, atherectomy devices, increased balloon to artery ratio, intravascular ultrasound guided PCI, optimization and high-pressure stent postdilatation, percutaneous excimer laser coronary angioplasty, and cutting balloons.[6–8]

Ellis and colleagues classified coronary perforation into three types: Type I, extraluminal crater without extravasation; Type II, pericardial or myocardial blush without contrast jet extravasation; Type III, perforation ≥ 1-mm diameter with contrast streaming; and cavity spilling (CS).[9] Type I and II perforations are predominately caused by hydrophilic and stiff wires, and their course is usually mildly symptomatic and does not require pericardial drainage or surgical intervention.[10] Type III perforations are more often associated with stent placement by over dilatation or oversized stent placement as might be the cause in our case or during aggressive usage of athero-ablative devices. Major adverse clinical outcomes including cardiac tamponade occur more frequently in patients with Type III perforations.



Fig. 2. Right coronary artery after the stent implantation with a residual 40% lesion in right anterior oblique view.



Fig. 4. Right coronary artery and minimal radiocontrast agent extravasation after the first covered stent implantation in right anterior oblique view.



Fig. 5. Right coronary artery after the procedure and second covered stent with no radiocontrast agent extravasation.

The therapeutic alternatives for CAP include prolonged inflation with either the angioplasty balloon or a perfusion catheter as soon as the perforation is recognized to prevent further blood extravasation. Perfusion balloons having a perfusion lumen communicating with the blood vessel lumen will occlude the hole, while attempting to seal the defect, permit distal vessel perfusion and reduce the ischemia during the prolonged inflation. Stent grafts for emergency implantation in case of CAP must be an obligatory inventory of catheterization laboratories. The PTFE-coated stent is a safe and effective alternative that can be used for sealing a major CAP and obviating cardiac surgery. The utilization of synthetic graft stent is less invasive, faster, and more effective when compared to surgical interventions and is generally considered to be the gold standard in the management of CAP.[5] Other alternatives include emergency bypass surgery for drainage and artery repair in situations where hemostasis cannot be achieved by prolonged balloon inflation, and in patients with hemodynamic compromise who do not respond to pericardiocentesis.[8] Rare cases, especially those with CAP of distal part of vessels, may require microcoil embolization.[4] Additively, recent studies showed that the double guide catheter technique is a new approach for coronary perforation, which is helpful to reduce the duration of uncontrolled hemorrhage through the perforation and deliver the graft stent to the target site.[11,12]

In the presented case, we implanted the stent in a calcified lesion of the ectatic RCA at a high pressure that was lower than the burst pressure of the stent recommended by the manufacturer, and it seemed that the mid part of stent did not expand enough due to heavily calcification. Hence, in consequence of performed high-pressure stent postdilatation, oversizing of stent, calcified, and possibly ectatic nature of the vessel were the main reasons to CAP as the index vessel diameter was probably about 4.5 mm. We performed immediately prolonged balloon inflation and then covered stenting with two PTFE stents to close the perforation, which eventually proved to be successful in the management of CAP in our case.

In conclusion, type III CAP is a dramatic, feared, and lethal complication of PCI, but it can be managed successfully by immediate diagnosis and prompt treatment, which involves sealing of the perforation or rupture by prolonged balloon inflation and covered stents. Our case is unique in that it occurred in a highly calcified lesion within an ectatic vessel.

Conflict of interest

None.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcac.2016.04.003.

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Short communication

Primary PCI in a patient with congenitally corrected transposition of the great arteries

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ABSTRACT

Congenitally corrected transposition of the great arteries (CCTGA) is a rare disease in which there is both ventriculoarterial and atrioventricular discordance. The systemic ventricle is of right morphology and patients are at high risk of developing systemic ventricular dysfunction. We report on a 41 year old male patient with primary PCI and congenitally corrected transposition of the great arteries.

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Introduction

Congenitally corrected transposition of the great arteries (CCTGA), first described by Karl von Rokitansky in 1875. CCTGA is a rare disease in which there is both ventriculoarterial and atrioventricular discordance.[1] The atrioventricular discordance implies that the morphological left atrium into the morphological right ventricle (RV), and the morphological right atrium drains into the morphological left ventricle (LV). Thus, the RV supports the systemic circulation, and the LV supplies the pulmonary circulation. The systemic ventricle is of right morphology and patients are at high risk of developing systemic ventricular dysfunction.[2] The clinical course is complicated by associated intracardiac defects such as ventricular septal defect, left atrioventricular valve regurgitation, subvalvar and valvar pulmonary stenosis, and atrioventricular conduction disturbances. Their life expectancy is limited by the onset of systemic (morphologically right) ventricular failure in their 40s or 50s.[3]

We report here the interesting case of primary PCI (Percutaneous Coronary Intervention) with congenitally corrected transposition of the great arteries.

Case report

A 41 year old male presented to the emergency department complaining of chest pain with no history of previous episodes in the 5 March 2011. His chest pain began at the rest and lasted several hours. The pain was substernal, with radiation to his back and left arm. He had several risk factors including smoking and dyslipidemia. On admission, he was diaphoretic and restless. His pulse was regular at 85 beats/min and his blood pressure was 110/70 mm-Hg. Physical examination showed no remarkable findings. His initial electrocardiogram (ECG) demonstrated sinus rhythm, 2 mm ST elevation and peaked T wave in leads V1–V3 and negative T wave in leads D1,aVL,V4–V6, incomplete LBBB (Fig. 1). We administered 100 IU/kg unfractionated heparin i.v., 300 mg aspirin per os (chewed), 600 mg clopidogrel per os. It was decided to perform emergency coronary angiography with primary PCI.

The left coronary angiogram was performed. Left main was normal. LAD had got 40% stenosis after first diagonal (D1). D1 was small and had got proximal 60% stenoses. Coronary angiography showed two Cx arteries arising from the left main and right coronary arteries. Coronary angiography revealed that the left Cx (LCx) originating from the left main coronary artery was normal. There was another Cx (RCx) arising from the proximal part of the right coronary artery (RCA) with a significant stenosis in the mid segment. The right coronary angiogram was performed and it was shown that the RCA had got plaque (Fig. 2a–b) Primary percutaneous coronary intervention including balloon angioplasty and stenting was successfully performed for the RCx lesion (Fig. 3).

Cardiac biomarkers on admission were; CK: 83 U/L, CKMB:24 IU/L, Troponin I: 0.35 μg/L. Cardiac biomarkers after 6 h on admission were; CK: 487 U/L, CKMB:78 IU/L, Troponin I: 3.66 μg/L. Cardiac biomarkers after 2 days on admission were CK: 857 U/L, CKMB:67 IU/L, Troponin I: 8.5 μg/L.

Echocardiography showed that the aorta to arise from the morphological RV, which was identified by the three leaflet tricuspid valve that inserted more proximally than the mitral valve (Fig. 4a–b). The pulmonary trunk, identified by its bifurcation, arose from the morphological LV. The systemic ventricle (RV) was normal, the walls measured 11 mm, and the systolic RV function was normal. There was mild

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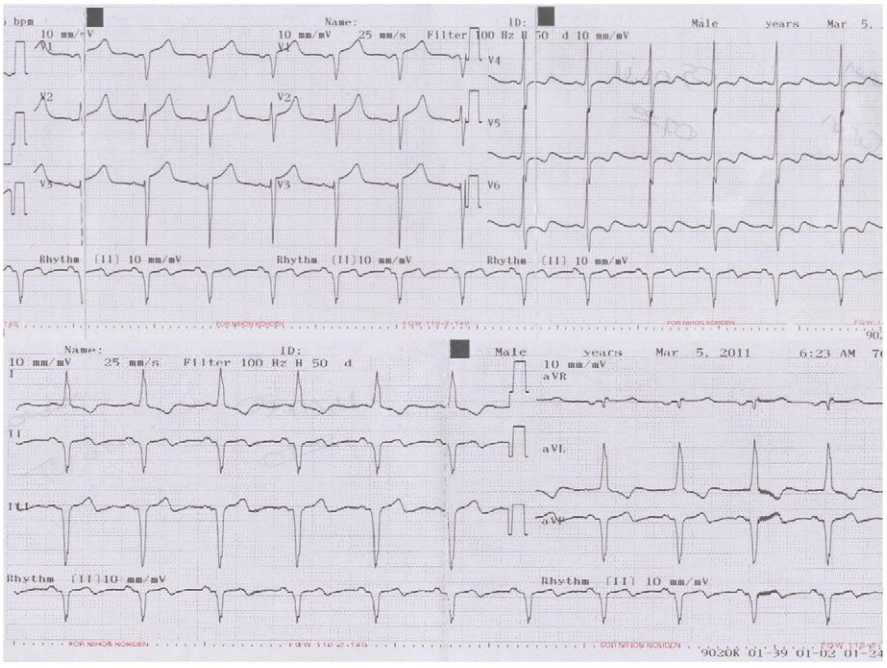


Fig. 1. Electrocardiogram of patient at admission to coronary care unit.

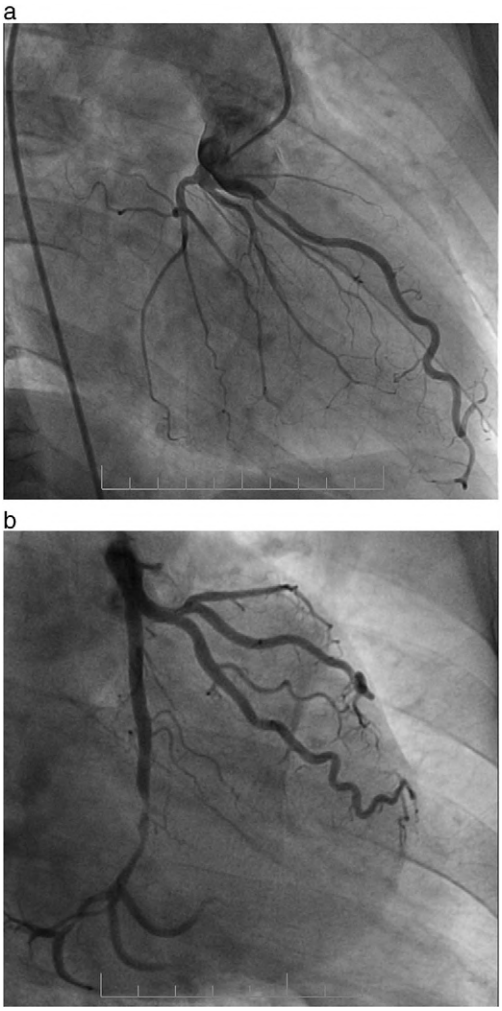


Fig. 2. a: Coronary angiograms of a patient with congenitally corrected transposition of the great arteries pre PCI. b: Coronary angiograms of a patient with congenitally corrected transposition of the great arteries pre PCI.

atrioventricular (tricuspid) valve regurgitation. The pulmonic ventricle (LV) function was mildly reduced (ejection fraction 55%). Echocardiography showed that mild hypokinesis in basal septum. There was a mild atrioventricular (mitral) valve regurgitation. There was a moderate aortic regurgitation but no pulmonary valvar stenosis. No intracardiac shunts were found. The systolic pulmonary pressure was 42 mmHg. Informed consent was obtained from the patient.

Discussion

The usual coronary arrangement in patients with congenitally corrected TGA being coronary inversion; therefore, although the morphologic right ventricle is on the left side of the heart, it is supplied by a morphologic right coronary artery system. This system may provide inadequate flow in the presence of considerable myocardial hyperplasia and hypertrophy seen when the right ventricle functions at systemic pressures for long periods. Examination of the right ventricle subjected

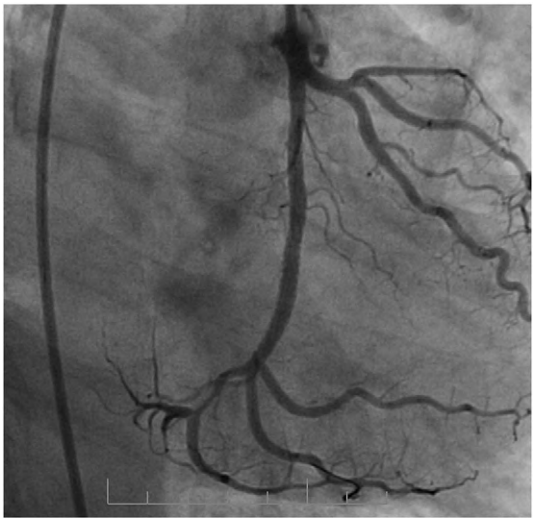


Fig. 3. Coronary angiograms of a patient with congenitally corrected transposition of the great arteries after PCI.

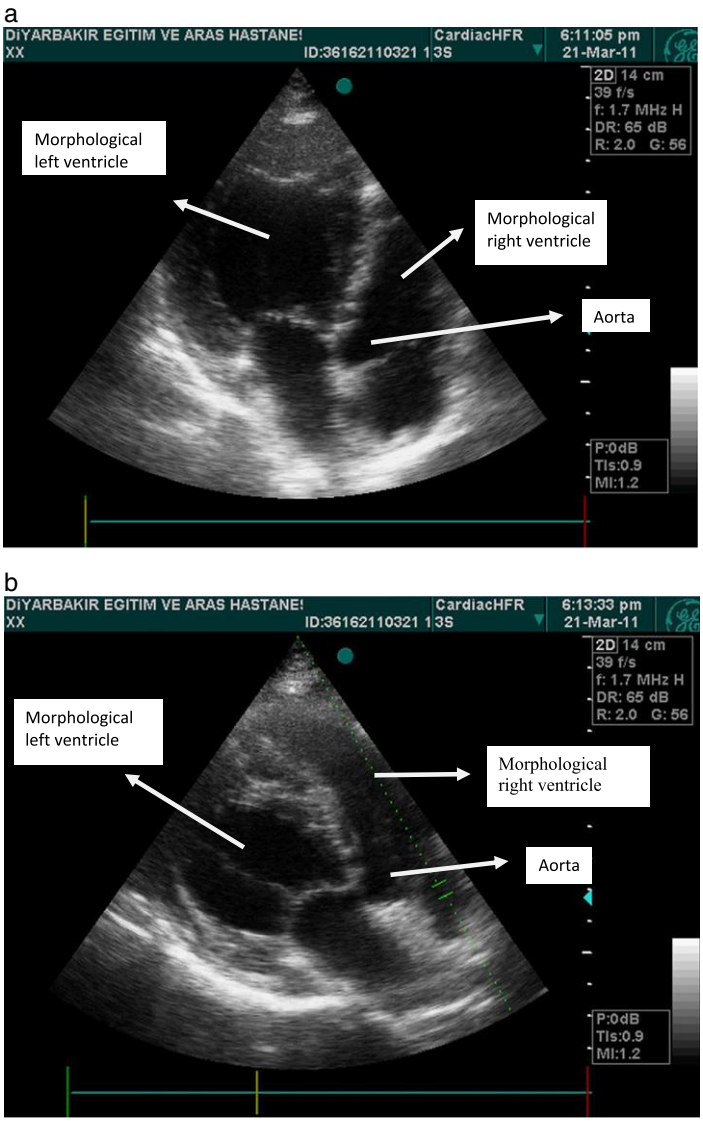


Fig. 4. a: Echocardiography of a patient with congenitally corrected transposition of the great arteries. b: Echocardiography of a patient with congenitally corrected transposition of the great arteries.

to systemic pressure shows gross hypertrophy compared with the thin wall of the right ventricle subjected to normal pressure, the discrepancy being especially conspicuous towards the apex. Hypertrophy places substantial extra demand on the right coronary arterial supply, which is less extensive than from a left coronary system. Progressive ischaemia will probably develop in this condition. Coronary artery anomalies in congenitally corrected transposition of the great arteries have seldom been reported in the medical literature due to the rarity of this disorder and the relatively small number of patients in each reported series.[3]

Patients with CCTGA rarely survive to old age. Our patient is noteworthy for several reasons. CCTGA without associated intracardiac defects is very rare. Our patient had got congenital coronary artery anomalies. In addition this case presents rarely described in the medical literature, namely, the primary PCI in patients with a CCTGA.

Much controversy exists regarding the ability of the morphological RV to support the systemic circulation. In patients with CCTGA, who present as a naturally occurring model of this adaptation, systemic ventricular failure is the cause of death in more than 50%.[4] A progressive deterioration of the systolic function of the systemic ventricle has also been described in patients without associated cardiac defects. Complete heart block and increasing left (tricuspid) atrioventricular valve regurgitation are known contributing factors.[1,4] However, our patient presented with a protected systemic ventricular systolic function. Causes of protected systemic ventricular function of our patient are no evidence for severe concomitant heart disease, advanced age and, hypertension.

Conclusion

This case is an example of a typical presentation of acute coronary syndrome and primary PCI in a patient with a congenitally corrected transposition of the great arteries.

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Short communication

Wegener's granulomatosis with cardiac involvement☆

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ABSTRACT

Wegener's granulomatosis (granulomatosis with polyangiitis) is a form of vasculitis of small-to-medium-sized vessels and associated with diffuse anti-neutrophil cytoplasmic antibodies (cANCA). Cardiac involvement is not uncommon with 6–25% of unselected patients and up to 44% of patients with severe renal involvement. We report a 23-year-old man with Wegener's cardiomyopathy with 25% ejection fraction. The overall mortality rate of Wegener's granulomatosis with cardiac involvement has been reported to be between 15 and 45%. So it is important to keep in mind that cardiac examination is a must to detect if cardiac involvement is present.
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Introduction

Wegener's granulomatosis (granulomatosis with polyangiitis) is a form of vasculitis of small-to-medium-sized vessels and associated with diffuse anti-neutrophil cytoplasmic antibodies (cANCA). It typically affects the upper and lower airways, lungs, and kidneys. Cardiac involvement is not uncommon with 6–25% of unselected patients and up to 44% of patients with severe renal involvement. It usually presents as pericarditis, myocarditis, and aortitis, although conduction disturbances and myocardial infarction are also recognised (1). Cardiac manifestations are often not clinically apparent, but are associated with increased morbidity and mortality (2). We report a case of Wegener's cardiomyopathy with renal involvement.

Case presentation

A 23-year-old man presented with 1 month history of paroxysmal nocturnal dsypnoea, fatigue, fevers, and joint pains. On examination, he was tachypnoeic with a respiratory rate of 26/min and had a tachycardia of 116/min. He was normotensive. Auscultation of his heart revealed a gallop rhythm and crackles were heard throughout both lung fields. The initial diagnostic workup involved a complete blood count, urine analysis, electrocardiogram (ECG), and chest x-ray. Abnormal laboratory findings were as follows: creatinine level was 2.7 mg/dl, potassium level was 5.9 mmol/L, serum sodium level was 129 mmol/L. He had hematuria and proteinuria, ECG revealed sinus tachycardia with 118 beats per minute. Chest x-ray revealed extensive bilateral interstitial pulmonary infiltrates, small bilateral pleural effusions, and cardiomegaly. Due to elevated serum creatinine levels and hematuria, patient evaluated by nephrologist. After a detailed examination, with his physical findings, blood counts (levels of ESR, CRP, cANCA) were high, initial diagnosis was vasculitis, especially Wegener's granulomatosis. Renal biopsy was performed and the result was compatible with Wegener's granulomatosis (Fig. 1). Transthorasic echocardiography was performed and revealed severely reduced left ventricular ejection fraction (EF) estimated around 25%. Haemodialysis was performed. To determine if conduction pathway involvement was present or not, Holter ECG was recorded, and no rhythm problem was established.

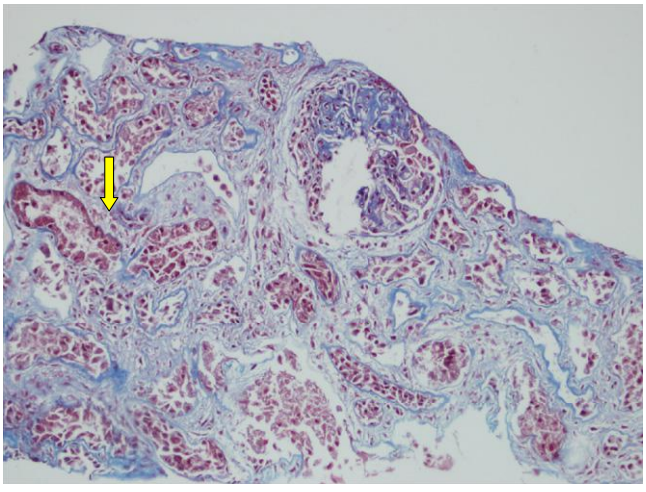


Fig 1.

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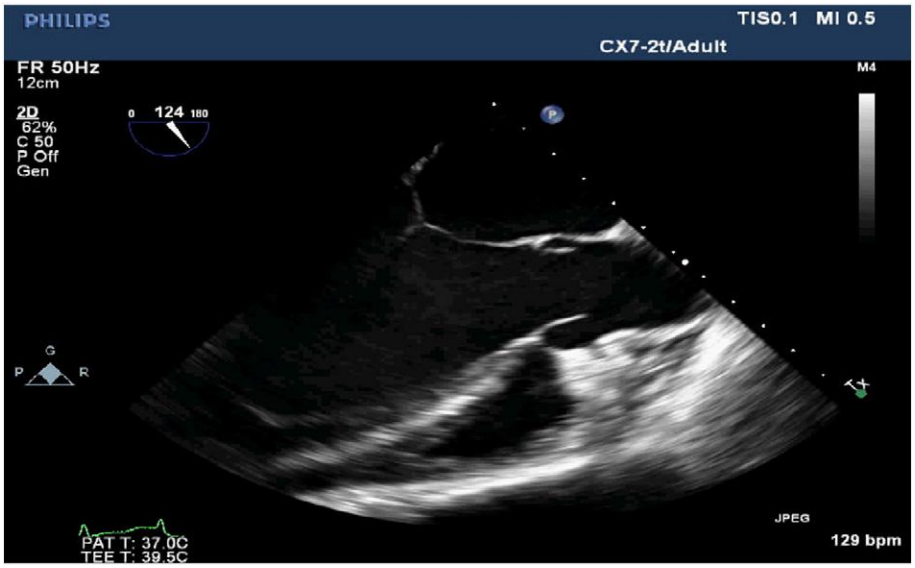


Fig. 2. Transesophageal echocardiography of the patient.

Transeosephagial echocardiography showed no aortic involvement accept trivial aortic regurgitation (Figs. 2,3).

Cardiac MRI that was performed for myocarditis revealed dilated ventricules; late gadolinium enhancement (LGE) lesions involving LV myocardium and LGE lesions were found in subepicardial, midwall, and subendocardial LV myocardial layers, LVEF %24.

We recommend coronary angiography but he refused it.

He was treated with furosemid, cyclophosphamide, and prostacyclin. He admitted to routine haemodialysis programme. After 1 month of follow-up, transthoracic echocardiography was performed again but no cardiac remission obtained. Medication continued for 3 months and then for the depressed systolic functions of left ventricle echocardiography repeated but no changes revealed. At the end of 6 months of follow-up period, his LVEF is the same as diagnosis period.

Discussion

Cardiac involvement of Wegeners's granulomatosis was first reported by Wegener in 1936 (3). Classical or generalised WG is characterised by necrotising granulomatous vasculitis of the upper and lower respiratory tract together with glomerulonephritis. Widespread disseminated vasculitis involving both small arteries and veins occurs to a greater or lesser degree as the disease progresses. A localised form of WG limited primarily to the upper and lower respiratory tracts has been described (4,5). Despite histopathological diagnosis of WG, with autoantibodies against to circulatory neutrophilic cytoplasmic antigens, we can diagnose WG easily and early. WG must be kept in mind as the differential diagnosis of dilated cardiomyopathy, especially in the existence of pulmonary and renal pathologies. The clinical presentation of WG can be so diverse that the list of differential diagnoses is vast, ranging from infections (fungal, bacterial, and mycobacterial) to other vasculitides, including Henoch–Schönlein purpura, sarcoidosis, Behcet syndrome, and malignancies(6). Table 1 shows signs and symptoms and systemic involvement of WG (6,7). Despite that involving the heart is well described, significant cardiac complications occurring during the course of the disease are rare (7). Pericarditis is the most common cardiac manifestation accounting for about 50% of cardiac diseases in Wegener's granulomatosis, which is asymptomatic in most of the cases, or may be manifested by chest pain and dyspnoea (8,9). The overall mortality rate of Wegener's granulomatosis with cardiac

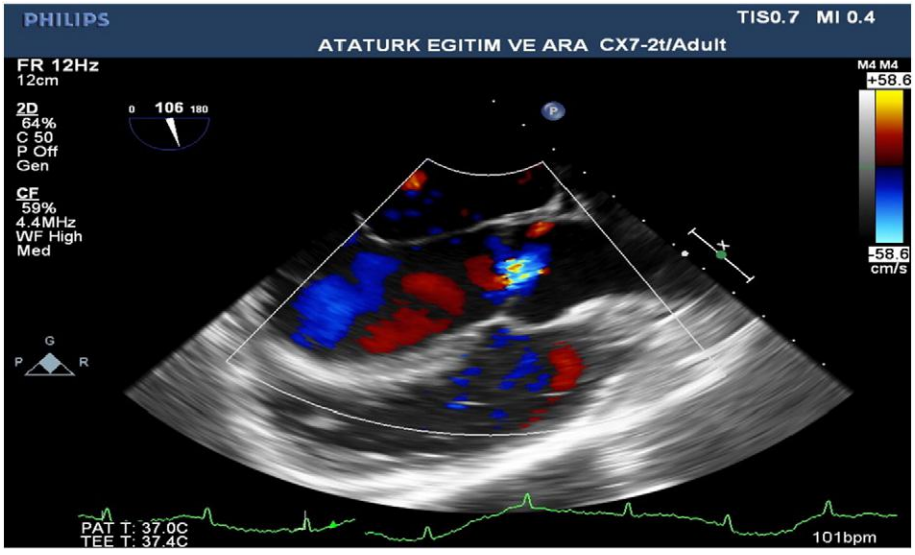


Fig. 3. Transesophageal echocardiography of the patient.

Table 1
Signs and symptoms and systemic involvement of WG.

Signs and symptoms	%		Systemic involvement
Rhinorrhea and sinus pain	94	100	Respiratory tract
Fever	78	83	Renal
Anorexia and weight loss	78	56	Joints
Cough	61	44	Skin or muscle
Chest pain	56	39	Eye
Arthralgia	56	39	Middle ear
Skin lesions	44	28	Heart or pericardium
Otitis media	39	22	Nervous system
Eye symptoms	39		
Hemoptysis	22		
Arthritis	22		
Neurological symptoms	22		

involvement has been reported to be between 15 and 45% (10). Cardiac manifestations are presented in Table 2 (11,12).

In summary, Wegener's granulomatosis not infrequently affects the heart, particularly in more advanced cases of the disease, and may cause clinically important complications. Pathologically, pericarditis, and coronary arteritis are the commonest manifestations. Clinically, evidence of pericarditis and its complications as well as supraventricular arrhythmias and varying degrees of heart block are the most common features. The advent of cANCA monitoring and the benefits of modem therapeutic approaches have resulted in many long-term survivors with previously severe Wegener's granulomatosis. Such patients not infrequently relapse with atypical presentations and cardiac involvement may therefore be seen more often in the future.

Table 2
Cardiac manifestations in Wegener's granulomatosis.

-Pericarditis	-Conduction abnormalities
-Coronary arteritis	-Myocarditis
-Myocardial ischemia	-Noninfectious endocarditis
-Valvular regurgitation–stenosis	-Heart failure

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Short communication

Warfarin treatment in stent thrombosis☆,☆☆

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ABSTRACT

A 62 year-old male patient was admitted to the hospital due to anterior ST segment elevated myocardial infarction. Thrombotic complication developed three times during the hospitalization after primary percutaneous coronary intervention (PCI). Instent thrombus was identified despite the optimal medical therapy, new antiplatelet agents and intravascular ultrasound guided PCI. Therefore, symptoms were controlled with warfarin + clopidogrel treatment. At the third month of warfarin + clopidogrel treatment, the patient was asymptomatic and no active electrocardiographic changes were observed. Stent thrombosis developing under new antiplatelet agents constitutes a great problem and there are no clear data for the solution. We described an interesting case in which we achieved symptomatic control by warfarin + clopidogrel in the stent thrombosis developing during the treatment with dual antiplatelet therapy.

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Introduction

Current guidelines recommend timely applied primary percutaneous coronary intervention (PCI) for all patients with ST segment elevation myocardial infarction (STEMI).[1] Despite the developments in medical treatment and intervention methods, stent thrombosis (ST) has still been a great challenge. There are limited data, in particular, about what to do after ST developed under the treatment with new antiplatelet agents. We have identified an interesting case without complications under warfarin + clopidogrel treatment that did not have hereditary thrombophilia and had recurring thrombotic complications despite the use of prasugrel, ticagrelor and intravascular ultrasound (IVUS) guided PCI.

Case report

A 62 year old male patient without any additional risk factor except hypertension was admitted to the hospital due to acute anterior ST segment elevated myocardial infarction (STEMI). In the coronary angiography (CAG), LAD was found to be occluded in the proximal segment and there were no any significant lesions in RCA and LCX. A 3.5 × 9 mm bare metal stent (BMS) was implanted to proximal LAD and a 3,5 × 28 mm BMS was implanted to mid-region. Post-dilatation was applied to both stents with 3,5 × 15 mm noncompliant balloon of Simpass (NCB) at nominal pressure. 180 mg ticagrelor, 300 mg acetyl salicylate and intravenous abciximab were administered during the procedure. The patient was taken to post-MI follow-up and anginal complaints developed again two days after PCI. In the patient's electrocardiography (ECG), there were 2 mm ST segment elevation in the anterior leads, and CAG was applied to the patient again. It has been found that proximal stent was occluded with thrombosis. The lesion was reached with floppy guidewire (FGW) and it was dilated with 4 × 18 mm NCB. Trofiban was started as intracoronary and systemic, ticagrelor discontinued and 60 mg prasugrel was administered. After the patient was delivered to the intense care unit in a stable condition, tirofiban infusion was interrupted one day later. Because of chest pain and 1 mm ST segment elevation in anterior leads, the patient was referred to CAG again one day later. It was found that the proximal stent was occluded with thrombus and the lesion was dilated with 4 × 18 mm NCB at 18 atm pressure, following 1.5 × 15 mm balloon and 3.5 × 20 mm BMS at nominal pressure was implanted. The examinations were sent in terms of thrombosis tendency. No disease or condition leading to thrombosis was identified. IVUS was planned for the patient. The expansion of stent to lumen was evaluated with IVUS. It was observed that proximal stent expanded insufficiently (Fig. 1). It was dilated again with 4.5 × 15 mm NCB. It was checked with IVUS and seen that the stent apposition was optimal. Due to presence of thrombus during the IVUS (Fig. 2), thrombectomy was performed by thrombus aspiration catheter. Intravenous tirofiban infusion was initiated and the patient was referred to the intense care unit. However, angina and ECG changes

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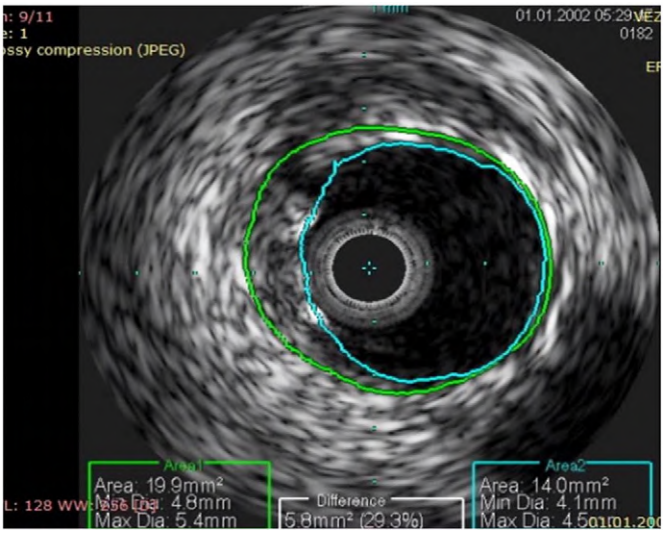


Fig. 1. IVUS image demonstrated that proximal stent expanded insufficiently.

were developed again 8–10 h later following the discontinuation of tirofiban. After readministration of intravenous tirofiban infusion the patient's chest pain was regressed. ST was observed in LAD during control CAG. Because of presence of TIMI 3 flow, we decided to start warfarin plus clopidogrel 75 mg daily and prasugrel was discontinued. No angina developed and no ECG changes were found during the monthly follow-up visits. We aimed the target INR value between 2.0 and 3.0 and the last two INR values of patients were 2.3 and 2.5. The patient was discharged after three days without symptoms. At the third month of the follow-up, the patient was asymptomatic, and there were no changes in the ECG compared to the ECG examination during discharge.

Discussion

PCI in the treatment of acute coronary syndromes is the most significant and efficient treatment option for morbidity and mortality.

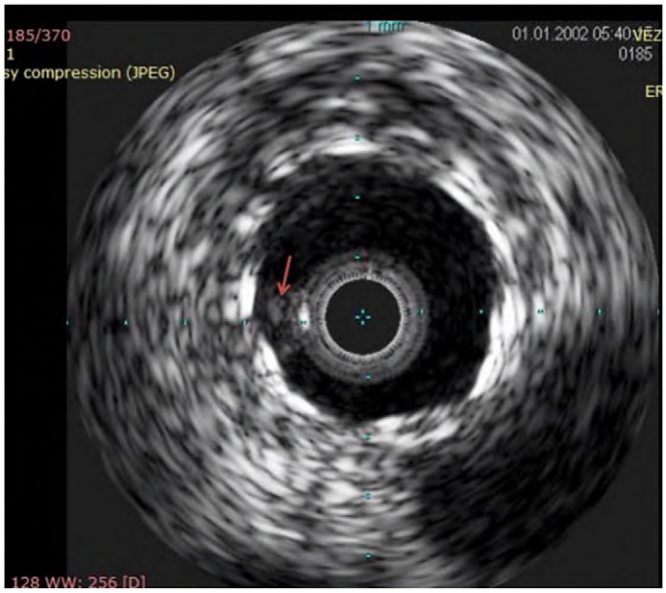


Fig. 2. IVUS image reveals optimal appositiona and thrombus formation (red arrow).

However, ST is still a significant problem in terms of mortality. We described an interesting case having thrombotic complications three times during the hospitalization that referred to the hospital due to anterior MI. ST is a rare but usually catastrophic event that complicates the stent implantation and it is associated with considerable mortality and adverse outcomes due to abrupt vessel closure.[2] It was defined as the occlusion originating in the peri-stent region or presence of a thrombus originating in the peri-stent region in the presence of acute onset ischemic symptoms, or the presence of new ECG changes indicating acute ischemia or the presence of typical rise and fall in cardiac biomarkers.[3] ST etiology is multifactorial and it is associated with the procedural factors, lesion and patient charecteristics.[4] Although a significant decrease was reached in ST with the use of DES, ST has still been a significant mortality and morbidity problem. In our case, the stents implanted were BMS. However, due to a large stent diameter, it may not be an appropriate approach to associate ST to the stent type used.[5]

During the first stent implantation, dual antiplatelet therapy with ticagrelor was used, and the treatment was replaced with prasugrel after stent thrombosis. However, ST developed again, considering that hereditary thrombophilia was not found in our case. ST development for 3 times makes the case quite complicated. It is known that IVUS guided PCI decreases ST prominently. IVUS enables us to get information about ST and to evaluate the stent underexpansion, arterial remodeling, neointimal structure and distribution.[6] In our case, we applied IVUS after second ST. After IVUS examination, we observed that the proximal stent was underexpanded. Then, the stent diameter, which was 3,5 mm, was dilated with 4,5 mm NCB. It was observed that the stent expanded to the lumen completely. However, intraluminal thrombus was still found (Fig. 2). Thrombectomy was applied and TIMI III flow was provided. Upon the detection of intrastent thrombus in the control angiography performed two days later, warfarin + clopidogrel treatment was initiated as the maintenance therapy. No anginal complaint occurred during this treatment, and no active ECG changes were observed. After the discharge from hospital, it was seen that the symptom and ECG did not change at 1st and 3rd months of follow-up.

The thrombotic process of patients continued although treatment with IVUS guided PCI, glycoprotein 2b/3a antagonists and new antiplatelet agents. No chest pain and active ECG change were observed under warfarin + clopidogrel treatment. There has been no clear data in the guides yet about the treatment method in case that ST develops during treatment with new antiplatelet agents. As in our case, warfarin usage may provide solution in such cases.

Conflict of interest

The authors have no commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest.

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Short communication

Prognostic value of anatomical SYNTAX score in patients with acute ST elevation myocardial infarction undergoing percutaneous coronary intervention for unprotected left main coronary artery

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ABSTRACT

Objective: Acute ST-elevation myocardial infarcion (STEMI) due to left main coronary artery (LMCA) disease has high mortality rate. Advancements in stent technology have shown promising results in patients with unprotected left main coronary artery (ULMCA) disease. SYNTAX score (SxS) is recommended to determine appropriate patients for revavascularization with PCI. However, predictive value of SxS in patients with STEMI who underwent primary PCI due to ULMCA disease has not fully been evaluated.

Methods and Results: 53 patients with STEMI who underwent emergent PCI to a culprit LMCA lesion were enrolled in this study. Patients were divided into three groups on the basis of their SxS; low (≤22; n = 14), intermediate (23–32; n = 14) and high (≥33; n = 25). During a follow-up of 3 years, SxS exhibited 62.2% sensitivity and 62.5% specificity for predictiing development of MACE at a cut off value 28.25 (AUC: 0.731, P = 0.008), 70% sensitivity and 66.7% specificity for predicting mortality at a cut off value 31.25 (AUC:0.675, P = 0.034). At 3-year follow-up, the incidences of mortality, major adverse cardiac events (MACE) and targel vessel revascularization (TVR) were significantly higher in patients with high SxS group than in the intermediate and low SxS groups. In Kaplan–Meier survival analysis, survival rates of the low, intermediate, and high SxS groups were 91.7%, 78.6%, and 64.7%, respectively.

Conclusions: Patients with acute STEMI who were treated with emergency PCI to a culprit ULMCA lesion, SxS is an important aid to deciding the appropriate revascularization strategy, can be derived quickly and repeatable.

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Introduction

Unprotected left main coronary artery (ULMCA) disease occurs in 5% of patients undergoing coronary angiograpy and is a class I indication for coronary artery bypass graft (CABG) surgery. Acute myocardial infarction (AMI) due to LMCA occlusion has significantly higher rates of mortality than non-culprit LMCA lesion (16.0% vs. 8.9%).[1] In long-term follow-up, patients with LMCA disease have higher rates of cardiogenic shock, target lesion revascularization (TLR) and mortality.[2] Recent studies have demonstrated that percutaneous coronary intervention (PCI) of the LMCA disease has acceptable in-hospital and long-term mortality rates. The SYNTAX score (SxS) is an angiographic scoring tool for grading the complexity of the coronary lesion. It can be used to help select optimal revascularization strategy in patients with coronary artery disease.[3,4] SxS is an independent predictor of mortality and TVR after PCI.[5,6] Few studies have evaluated the role of SxS in patients with acute STEMI undergoing primary PCI due to ULMCA disease. The aim of this study was to assess the prognostic value of SxS in predicting in-hospital and long term clinical outcomes among patients who underwent primary PCI for ULMCA lesion.

Methods

Our single-center, retrospective study included 53 patients with AMI treated with emergency PCI to a culprit ULMCA lesion in our catheterization laboratory between May 2009 and March 2013. Clinical, biochemical, radiological and social data were extracted from the national health data system, telephone contact and outpatient examinations. Patients with protected LMCA disease, renal dysfunction, chronic anemia, instent thrombosis and who underwent emergency CABG surgery were excluded from the study.

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SxS was calculated by summing the total points assigned to each individual lesion identified in the coronary artery with >50% luminal obstruction in vessels >1.5 mm in diameter.[5] For the calculation, the soft ware at web site (http://www.syntaxscore.com) was used. On the basis of their SxS, patients were divided into three groups; low (SxS ≤22; n = 14), intermediate (SxS 23–32; n = 14) and high (SxS ≥33; n = 25).

Angiographic data of the patients were analyzed by 2 interventional cardiologists blinded to the clinical characteristics. In the case of disagreement, a third observer was consulted and a final decision was reached by consensus. Patients received 300 mg of aspirin and a loading dose of (300 to 600 mg) clopidogrel and intravenous (IV) standard heparin 100 U/kg (maximal dose 10.000 U, 60 U/kg in patients who were treated with glycoprotein IIb/IIIa inhibitors) before the procedure. All primary PCI procedures were performed by femoral approach. The decision on direct or conventional stenting was made by the operator. The LMCA lesion was considered unprotected if there was no patent bypass graft to the left anterior descending (LAD) coronary artery or left circumflex coronary artery (LCX). Acute myocardial infarction (MI) was defined as the presence of typical ongoing ischemic chest pain lasting for more than 30 min and ST-segment elevation ≥1 mm in 2 contiguous leads or a new left bundle branch block on the initial electrocardiogram. Reinfarction was defined as a recurrent typical chest pain with new electrocardiogram changes and a further increase in enzyme levels (twice the upper limit of normal reference range or any rise by 50% of the lowest recovery enzyme level). Target Lesion Revascularization (TLR) was defined to be any repeat revascularization with PCI or CABG within the stent, or within the 5-mm borders proximal or distal to the stent. Revascularization was considered as successful treatment of a new lesion in the epicardial vessel. All deaths, including cardiac deaths, were assessed and ascertained by national databases. Major adverse cardiovascular events (MACE) were defined as all-cause mortality, new myocardial infarction and repeat revascularization.

Statistical analysis

Continuous variables were expressed as the mean + standard deviation and categorical variables were expressed as number (percentage). Group means for continuous variables were compared through 1-way analysis of variance. Likewise, categorical variables were compared by using chi-square test. The Cox proportional hazard model was applied to relate the SX score and long term mortality, reinfarction, revascularization, and overall major adverse cardiac event (MACE). Multivariate analysis was applied separately for all outcomes and overall MACE. The relationship between the SX score and the incidence of MACE was evaluated. Event free survival curves were generated by the Kaplan–Meier method and differences in survival were compared by using log rank test. The receiver-operating characteristic (ROC) curve was utilized to determine the cut-off value of SX score in order to predict 3 year clinical outcomes. A p value less than 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS 22 for Windows (SPSS Inc., Chicago, Illinois).

Results

Fifty three acute STEMI patients who underwent primary PCI for ULMCA disease were enrolled in the study. Baseline characteristics of the patients are shown in Table 1. Mean follow-up period was 28.1 ± 15.5 months (range, 0.17–61.5) and average age of the patients was 66.5 ± 11.8 (range, 34–87) years. Among the 53 patients 43 (81.1%) of them were male and the remaining (18.9%) were female. Increasing age was associated with higher SxS values, but this difference was not statistically significant. There was no difference between groups with respect to smoking status and family history of cardiovascular disease. Frequency of diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure and cardiogenic shock was significantly higher in the high SxS group compared to low/intermediate SxS groups. Patients with high SxS were treated more often with diuretics, inotropic agents and glycoprotein IIb/IIIa inhibitors, intra-aortic balloon pump support during hospitalization. Three patients required temporary pacing due to third degree atrioventricular block. Patients in SxS high group had higher length of hospital stay.

Angiographic findings of patients are shown in Table 2. Patients were treated with BMS only, DES only and hybrid stenting (DES + BMS). Stent type and diameter, balloon length and diameter, distal, ostial/body LMCA disease and pre-dilatation and post-dilatation rates were not significantly different between the three groups. Multivessel

Table 1
Patients' clinical characteristics and medications.

	Low SxS	Intermediate SxS	High SxS	p
Male gender, n (%)	10 (23.3)	14 (32.6)	19 (44.1)	0.52
Mean age (years)	62.86 ± 16.3	65.86 ± 8.2	69.04 ± 10.3	0.29
LVEF (%)	56.2 ± 9.8	55.1 ± 7.3	41.8 ± 7.6	<0.001
Current smoker, n (%)	7 (50)	8 (57.1)	15 (60)	0.83
Family history of CAD, n (%)	5 (35.7)	4 (28.6)	10 (40)	0.77
DM, n (%)	4 (28.6)	5 (31.3)	18 (78.3)	0.002
HT, n (%)	10 (71.4)	10 (62.5)	22 (95.7)	0.03
HL, n (%)	10 (71.4)	7 (48.7)	20 (87)	0.015
In-hospital medical treatment, n (%)				
ACE-I/ARB	10 (71.4)	9 (64.2)	14 (56)	0.62
BB	11(78.5)	12 (85.7)	15 (60)	0.19
Glycoprotein IIb/IIIa inhibitors	3 (21.4)	4 (28.5)	15 (60)	0.03
Statins	8 (57.1)	7 (50)	13 (52)	0.92
Calcium channel blocker	4 (28.5)	5 (35.7)	4(16)	0.36
IV diuretic	3 (21.4)	4 (28.5)	16 (64)	0.02
Inotropic drugs	3 (21.4)	2 (14.2)	13 (52)	0.03
Clinic				0.002
Killip class ≥2	3 (21.4)	3 (21.4)	14 (56)	0.035
Cardiogenic shock	1 (7.1)	0 (0.0)	8 (32)	0.02
Length of hospital stay, (day)	4.29 ± 1.13	4.36 ± 1.08	6.08 ± 2.9	0.03
Follow-up period, (day)	923.1 ± 325.3	810.2 ± 305.7	886.5 ± 606.1	0.65
IABP	2 (14.3)	0 (0.0)	8 (32)	0.04
Temporary pacemaker	2 (14.3)	0 (0.0)	1 (0.4)	0.24
SxS	18.42 ± 3.2	26.6 ± 2.3	36.38 ± 4.1	<0.001

ACE-I; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, BB; beta blocker, CAD; coronary artery disease, IABP; intraaortic balloon pump, LVEF; left ventricular ejection fraction, and SxS; SYNTAX score.

Table 2
Angiographic findings of the patients.

	Low SxS	Intermediate SxS	High SxS	p
Lesion location, n (%)				0.73
Ostium	4 (28.6)	4 (25)	9 (39.1)	
Shaft	4 (28.6)	3 (18.8)	2 (8.7)	
Distal	6 (42.9)	9 (56.3)	12 (52.2)	
Number of diseased vessel, n (%)				0.02
LMCA isolated	4 (28.6)	1 (7.1)	4 (16)	
LMCA + 1 vessel	10 (71.4)	9 (64.3)	12 (48)	
LMCA + 2 vessel	0 (0.0)	2(14.3)	9 (36)	
LMCA + 3 vessel	0 (0.0)	0 (0.0)	3 (12)	
Predilatation	9 (64.3)	11 (68.8)	10 (43.5)	0.23
Postdilatation	4 (28.6)	5 (33.3)	8 (34.8)	0.92
Types of stent				0.49
BMS	5 (35.7)	6 (37.5)	9 (39.1)	
DES	7 (50)	4 (25)	5 (21.7)	
Hybrid	1 (7.1)	5 (31.3)	8 (34.8)	
Stent length (mm)	20.6 ± 5.9	23.3 ± 7.5	18.1 ± 6.0	0.07
Stent diameter (mm)	3.01 ± 0.48	3.38 ± 0.71	3.02 ± 0.49	0.13
Number of stent used	2.14 ± 1.0	2.71 ± 1.4	2.17 ± 1.1	0.33
Balloon length (mm)	16.25 ± 2.3	14.8 ± 3.1	15.46 ± 3.3	0.61
Balloon diameter (mm)	3.17 ± 0.9	3.02 ± 0.9	3.12 ± 0.8	0.92

BMS; bare metal stent, DES; drug eluting stent, and LMCA; left main coronary artery.

coronary artery diseases were found to be significantly higher in the SxS group than those of in the low/intermediate SxS groups. An average of 2.3 ± 1.1 (min: 1; max: 6) stents were implanted per patient.

There was no difference in in-hospital reinfarction, TLR, and MACE rates in three groups, while patients with high SxS showed higher rates of mortality as compared to low/intermediate SxS patients.

During long term follow-up, 51.2% of patients with documented myocardial ischemia underwent diagnostic coronary angiograpy, of these 48.7% underwent PCI. There was no difference in MI rate between the three groups while ischemia-driven TLR was required more often in patients with high SX scores. Total mortality and total MACE rates were significantly higher in the SX high group compared with the aggregate Sx low and Sx intermediate group. In-hospital mortality and 3-year mortality rates of aggregate Sx low and Sx intermediate group and SX-x high group were 7.1% and 21.4% vs 40% and 56% respectively. In-hospital complications and 3-year follow-up results are shown in Table 3.

Figs. 1 and 2 show the cutoff value of SxS to predict the development of MACE and mortality. ROC curve analysis showed that the SxS exhibited 62.2% sensitivity and 62.5% specificity for predicting the development of MACE within 3-years after PCI at a cutoff value of 28.25. (AUC: 0.731 p = .008). SxS predicted mortality with a sensitivity of 70% and a specificity of 76% at a cutoff value of 31.25 (AUC: 0.675, p = 0.034). Kaplan–Meier estimated long-term survival rates were similar in the three groups (see Fig. 3). Three-year survival rates were 91.7%, 78.6% and 64.7% for SYNTAX low, intermediate, and high groups, respectively.

Table 3
In-hospital complications and 3-year follow-up results of the patients.

	Low SxS	Intermediate SxS	High SxS	p
In-hospital				
Death, n (%)	2 (14.3)	0 (0.0)	10 (40)	0.01
MI, n (%)	1 (7.1)	2 (14.3)	3 (12)	0.83
TLR, n (%)	1 (7.1)	2 (14.3)	3 (12)	0.83
PTCA	1 (7.1)	2 (14.3)	3 (12)	
MACE	4 (26.8)	2 (14.3)	10 (40)	0.24
Long-term outcomes				
Cardiac deaths, n (%)	1(7.1)	3 (21.4)	4 (16)	0.01
Myocardial infarction, n (%)	2 (14.3)	4 (28.6)	5 (20)	0.73
TLR, n (%)	4 (28.6)	5 (35.7)	11 (44)	0.02
PTCA	2 (14.2)	2 (14.2)	10 (40)	
CABG	2 (14.3)	3 (21.4)	1 (4)	
MACE, n (%)	6 (42.9)	9 (64.3)	11 (44)	<0.001
Total death, n (%)	3 (21.4)	3 (21.4)	14 (56)	0.03
Total TLR, n (%)	4 (28.6)	7 (50)	14 (56)	0.25
Total MACE, n (%)	6 (42.9)	10 (71.4)	21 (84)	0.04

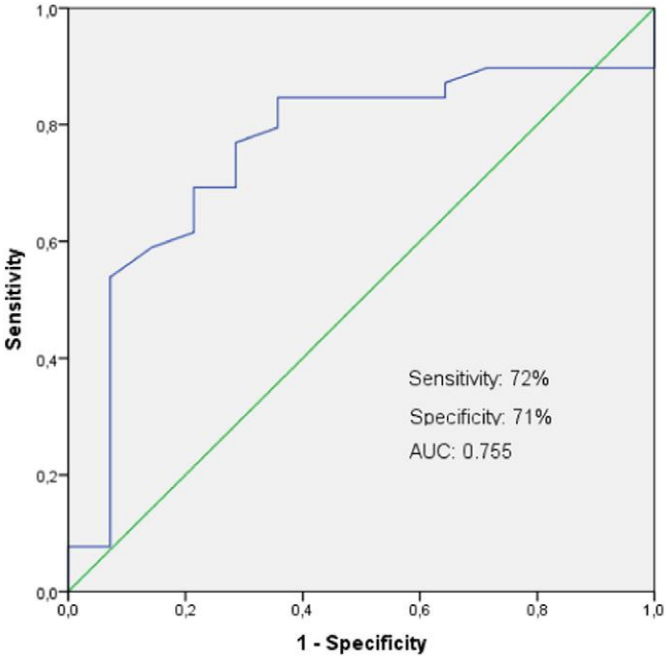


Fig. 1. Cutoff value of SxS for predicting the development of MACE.

Discussion

Our results showed that SxS was a useful tool for prediction of in-hospital and long-term outcomes in STEMI patients who were treated with emergency PCI to a culprit ULMCA lesion. The optimal cutoff values for 3-year mortality and MACE were 31.25 and 28.25, respectively. Our results support the hypothesis that high SxS indicates more complex coronary artery disease, worse clinical outcomes (worse Killip class, cardiogenic shock, hemodynamically unstable arrhythmias) and

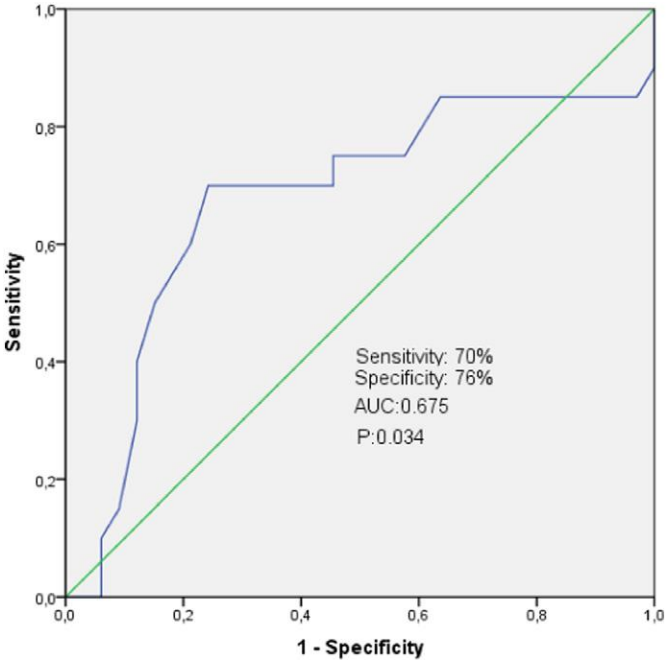


Fig. 2. Cutoff value of SxS for predicting the development of mortality.

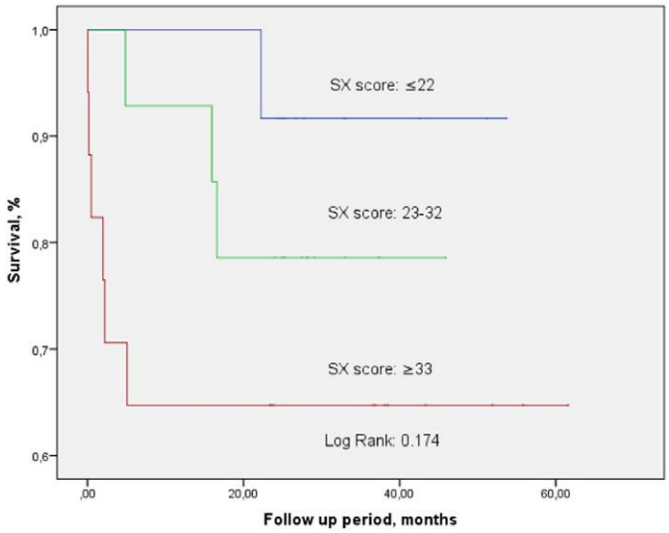


Fig. 3. Kaplan–Meier estimated long-term survival rates in the three groups.

multiple risk factors (diabetes mellitus, hypertension, hyperlipidemia, advanced age). Length of hospital stay, use of intravenous diuretics and positive inotropes, in-hospital MACE and mortality increase in parallel with the SxS. In our previous study,[6] we showed that the SxS was an independent predictor of both in-hospital and long-term mortality in patients with acute STEMI who underwent primary PCI. Nozue et al. reported that score 26 was the optimal cutoff value for predicting one-year MACE in patients who underwent elective PCI for ULMCA disease.[7] Another study showed that a score of 28 was the optimal cutoff value to distinguish patients at low and high risk of one-year MACE.[8] Our results are in agreement with previous studies. SxS is an easily applicable angiographic scoring tool for grading the complexity of coronary artery disease. It assists in patient selection for interventional or surgical revascularization.

Acute MI associated with ULMCA occlusion is a clinically catastrophic event. These critically ill patients frequently present with cardiogenic shock or cardiac arrest. Patients undergoing primary PCI because of ULMCA culprit lesion and presenting with cardiogenic shock have high in-hospital mortality.[9] The average estimated 30-day all-cause mortality was 15% and 55% in patients presenting without and with cardiogenic shock, respectively.[10] Complication rates are twice to four times higher in patients who undergo primary PCI in acute MI than elective PCI.[11–14] LVEF, previous MI, door-to-balloon time, anemia, chronic renal failure and diabetes mellitus are independent predictors of mortality. TIMI and GRACE risk scores are used for risk stratification and prognostic evaluation.

In addition to several clinical risk scores, angiographic characteristics are used to predict both in-hospital and long-term prognosis. SxS has been developed aiming to grade the coronary lesions with respect to their functional impact, location, and complexity.

Consensus treatment guidelines continue to recommend CABG as the “gold standard” for revascularization of ULMCA lesions but note that PCI is feasible and may be a promising strategy in selected patients.[15–17] Patients with ostial and trunk LMCA lesions treated with PCI have better outcomes than patients with distal lesions.[16,17]

Our in-hospital and 3-year follow-up results suggest that PCI is an acceptable alternative revascularization method to CABG when treating patients with low or intermediate SX scores. Our results are consistent with recent studies. Recently published EXEL-trial compared the efficacy and safety of PCI with CABG surgery in patients with ULMCA disease and low-intermediate anatomical SxS. In this study, although PCI patients had worse baseline characteristics (older age, male gender, COPD), 4-year mortality rate was significantly lower than that of CABG patients. The 4-year predicted mortality for PCI patients was 8.5% and 10.5% for CABG patients.[18]

High SxS is associated with increasing cardiac mortality, MACE and TVR at 3 years. Patients with high SxS have significantly higher 3 year mortality, MACE and TVR rates. Despite improvement in stent technology and operator experience, LMCA disease is still associated with high in-hospital and long term mortality rates and there is a need of development of new agents and clinical techniques to improve outcomes further.

Limitations

This was a single-center retrospective study, but the patients were prospectively followed up. In order to prevent bias, in-hospital and follow-up data were collected by different clinical investigators. Only 51.2% of patients underwent coronary angiography and clinical SYNTAX score of the patients was not calculated.

Another limitation was that the development of post-PCI contrast nephropathy was not evaluated.

Conclusion

The SxS has prognostic value in patients with acute STEMI undergoing primary PCI due to ULMCA disease. It may be useful in selecting the patients for the most appropriate revascularization strategy.

Conflicts of interest

None declared.

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Short communication

A rare case of Kounis syndrome provoked by mad honey poisoning

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ABSTRACT

Kounis syndrome, resulting in acute coronary syndromes, as a result of allergic or hypersensitivity reaction is triggered by several factors. Vasospasm which is mediated by mediators released after mast cell activation, is the responsible mechanism for comprising of type 2-myocardial infarction. Mad honey containing grayanotoxin is previously shown to be associated with gastrointestinal, neurological and cardiac disorders. In this case report, we presented a Kounis syndrome that has occurred after the mad honey intake and treated successfully, previously not mentioned in the literature.

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Introduction

Kounis syndrome which is described as the occurrence of acute coronary syndromes with allergic or hypersensitivity reactions, was first defined in 1991 by Kounis and Zavras.[1] Later in 1998 Braunwald reported that vasospastic angina might be induced by allergic mediators such as histamine or leukotrienes.[2] Several factors including drug use, foods, sedative and anesthetic agents are associated with Kounis syndrome.

Mad honey poisoning can occur after ingestion of honey, made of the nectar from flowers of the Rhododendron family.[3] Clinically, grayanotoxin can cause gastrointestinal, neurological, and cardiac signs and symptoms as a result of toxic cellular effect on the sodium channels.[4]

Herein, we report a case of patient who presented with acute myocardial infarction after consuming mad honey for reasons of gastrointestinal disorder.

Case presentation

A 58-year-old male patient was admitted to our Emergency Service with nausea and chest pain lasting for 1 h. His medical history was unremarkable except for smoking history. On his physical examination, arterial blood pressure was 90/70 mmHg and pulse rate was 45/min. Unexplained abnormal skin findings were noted during general examination. Electrocardiography (ECG) of the patient that was performed in the Emergency Service revealed 47/min sinus bradycardia and 2 mm ST elevation on the leads D1, aVL and V7–9 accompanied by reciprocal ST depression on the leads D2–3, aVF and V4R–6R (Fig. 1A–C).

The patient was transferred to the catheter laboratory with the diagnosis of acute posterolateral myocardial infarction. He received 300 mg acetylsalicylic acid (ASA) and 600 mg clopidogrel load via oral route and 8000 IU heparin via intravenous route. We performed right and left selective coronary angiography which revealed no significant stenosis (Fig. 2A–D). Later, the patient was transferred to intensive care unit for routine follow up. His control electrocardiograms showed no improvement in ST elevation and his echocardiographic evaluation did not demonstrate apical ballooning pattern that support Takotsubo Cardiomyopathy. On his biochemistry analyses, leukocyte count was 6.762/mm^3, hematocrit was 44%, neutrophil was 61%, lymphocyte was 18.5%, eosinophil was 18.8%, troponin T level was 474.7 pg/mL (reference: 0.03–14 pg/mL), creatinine kinase-MB was 7.82 ng/mL (reference: 0.00–4,9 ng/mL), postprandial blood glucose was 115 mg/dL, low-density lipoprotein level was 115 mg/dL, and creatinine level was 0.95 mg/dL.

Because of severe hypotension and bradycardia, iv atropine and saline infusion treatment was provided. When his medical history was reevaluated, it was learned that he had received honey from eastern black sea region of Turkey in order to heal his digestive disorder. Moreover, his unexplained skin findings were confirmed as allergic rash by dermatology. After much deliberation the patient was considered to have Kounis syndrome as a result of mad honey poisoning. Following administration of intravenous antihistamines (pheniramine maleate 22.75 mg, administrated intravenously) his chest pain was improved and the ST segments normalised (Fig. 1D). In addition, plasma histamine, beta-tryptase, C4 and IgE levels were investigated in order to confirm our diagnosis. Results of blood biochemistry analyses revealed that plasma beta-tryptase, C4 and IgE levels were over the upper limit of

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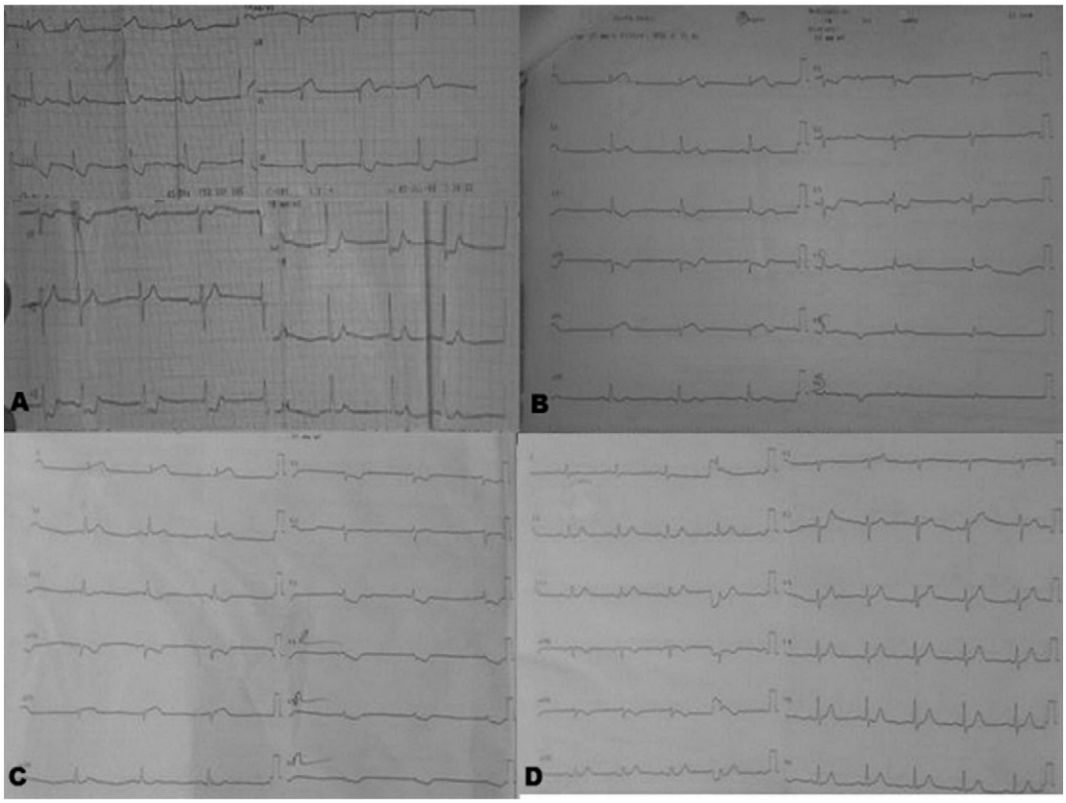


Fig. 1. A–D: 1A: Electrocardiogram (ECG) at admission to emergency service, 1B: ECG of posterior derivations, 1C: ECG of right derivations, and 1D: ECG after administration of intravenous antihistamines.

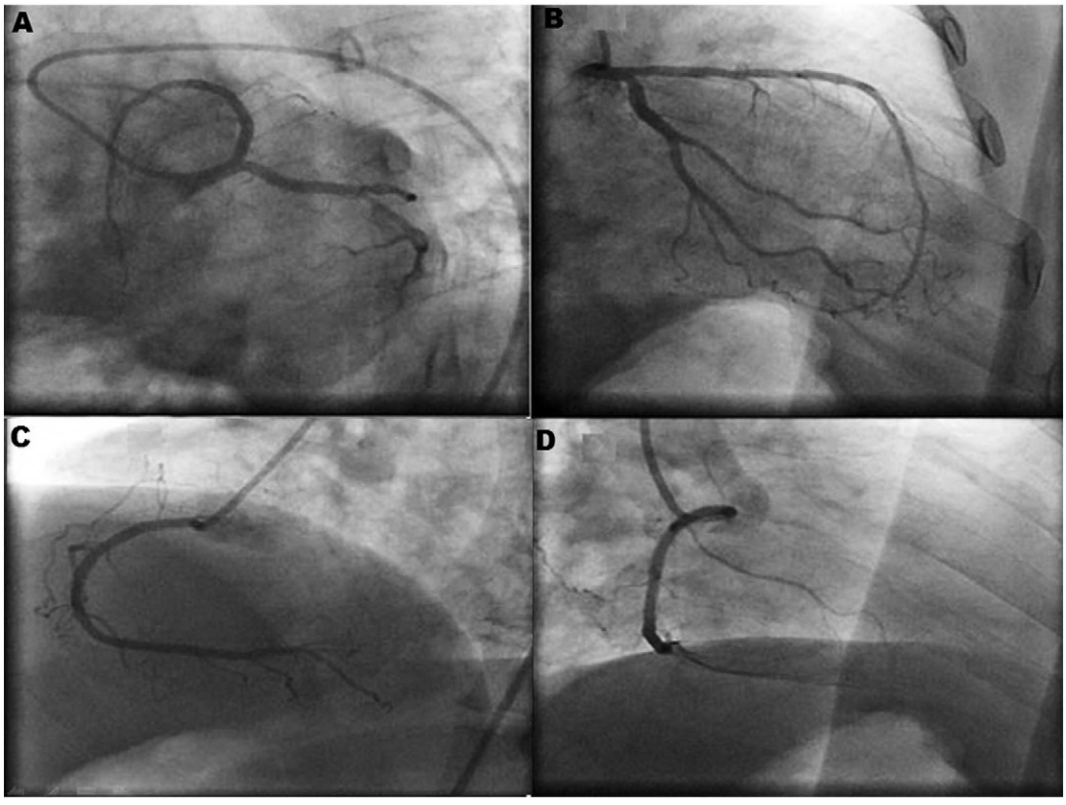


Fig. 2. A–D: Images of coronary angiography 2A: Left anterior oblique (LAO) caudal view of left coronary system, 2B: Right anterior oblique (RAO) caudal view of left coronary system, 2C: RAO cranial view of right coronary artery (RCA), and 2D: LAO view of RCA.

normal serum value. On his control transthoracic echocardiographic examination, left ventricular ejection fraction was measured to be 65%. No regional wall motion impairment or any other pathology was observed. During routine follow up his physical examination revealed no complaint or sign of allergic reaction. His cardiac enzymes decreased and the patient was discharged on the 4th day of hospital admission.

Discussion

Kounis syndrome is described as the occurrence of acute coronary syndrome as a result of mast cell activation provoked by the release of inflammatory mediators. Histamine and leukotrienes are major culprit mediators which cause coronary events via vasoconstriction. Moreover, serum proteases trigger coronary events not only via metalloprotein activation but inducing atheromatous plaque erosion.[5,6] According to current classification three types of Kounis syndrome are identified. Type I is observed in patients with the absence of cardiovascular risk factors. The underlying mechanism is allergic mediators that provoke endothelial dysfunction or microvascular angina. Type II is observed in patients with history of coronary artery disease in whom allergic mediators induce coronary vasospasm or erosion/rupture of the atheromatous plaque, resulting in acute myocardial infarction. Type III is observed in patients presented with drug-eluting stent thrombosis in whom aspirated thrombus material obtained from the culprit coronaries stain positive for mast cells and eosinophils.[7,8] Variety of factors have been identified in the literature that cause Kounis syndrome such as environmental toxins, antibiotics, contrast media, intravenous anesthetics, analgesics, skin disinfectants, steroids, thrombolytics, anti-inflammatories and antineoplastics.[9]

Mad-honey intoxication may be observed after ingestion of Grayanotoxin, also known as andromedotoxin, acetylandromedol, or rhodotoxin,[10] is found in the nectar of *Rhododendron ponticum*, a plant that is endemic to the Black Sea region of Turkey, Nepal, Japan, Brazil, and some regions of North America.[11] In endemic regions these plants can be used as alternative remedy for infections and gastrointestinal disorders even for sexual disorders. There are several reports in literature which demonstrate the association between mad honey poisoning and conduction disorders such as ST elevation, sinus bradycardia, sinoatrial block, QT prolongation, nodal rhythm, and asystole.[11–13]

It is well known that the mismatched oxygen supply and demand due to impaired myocardial perfusion lead to evolvement of type 2 myocardial infarction. In our patient, we observed acute posterolateral MI, 4 h after ingestion of honey. In addition his vital signs improved after iv saline infusion and supportive medical therapy. Due to patient's symptoms that did not associate with stress and no apical ballooning was seen on echocardiographic evaluation, we ruled out stress-induced cardiomyopathy. Moreover, coronary vasospasm considered as a differential diagnosis. In our patient, coronary vasospasm due to allergic reaction and development of a thrombus formation which dissolved spontaneously might be a result of other conditions. Although intravascular ultrasonography (IVUS) or OCT (optical coherence tomography) might be useful to distinguish this situations, but we did not use these instruments because of patient's worsening clinical status during procedure.[14] In addition, hypercoagulability syndromes such as antiphospholipid antibody syndrome, activated protein C resistance, antithrombin III and protein C or S deficiency should bear in mind as differential diagnosis. Consequently, the most possible diagnosis was type I Kounis Syndrome. Allergic skin reactions, normal coronary arteries and rapid recovery after supportive therapy also support this decision.

To our knowledge, no case of Kounis Syndrome as a result of mad honey poisoning has been reported in the literature. Typically, patients with mad honey poisoning presented with excessive hypotension and bradycardia which usually responds to atropine and saline infusion treatment. However intravenous antihistamine and in some cases more aggressive therapy with steroids are not common under these circumstances. Although we provided supportive medical care, clinical improvement was observed following administration of iv antihistamine therapy.

In conclusion, physicians should keep in their minds that patient with mad honey poisoning may present with acute myocardial infarction. In addition, those patients may develop Kounis Syndrome which requires alternative therapies.

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Short communication

Successful closure of atrial septal defect by retrograde transarterial approach after unsuccessful transfemoral venous approach☆

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ABSTRACT

Although many of the ostium secundum atrial septal defects can be successfully closed by percutaneous transvenous approach, surgical method as well is preferred in some cases due to vascular reasons or due to the anatomical characteristics of the defect. Detecting ostium secundum atrial septal defect in a 26-year-old female patient, who presented with shortness of breath, percutaneous closure procedure was planned. During percutaneous closure, it was observed that guidewire and catheter persistently went towards patent foramen ovale because of quite flaccid structure of interatrial septum. For this reason, occluder could not be placed in the defect area. Before using the option of surgery for the patient, guidewire and simmons 1 diagnostic catheter were pushed forward towards to the left ventricle and then left atrium by transarterial approach through the femoral artery. Guidewire and the catheter were easily passed through atrial septal defect without passing through patent foramen ovale benefiting from the left atrial pressure. Occluder was retrogradely carried via transarterial route and successfully implanted in the defect area. Transarterial approach may be an alternative before surgery in selected cases in which percutaneous closure of atrial septal defect has failed.

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Introduction

Atrial septal defect is one of the most prevalent congenital heart diseases in adulthood.[1] The most common type of atrial septal defect is the ostium secundum atrial septal defect, which accounts for 75% of overall atrial septal defect cases.[2] Today, secundum atrial septal defect is widely treated by a closure device implanted via percutaneous transvenous route.[3] Although closure device implantation is an effective and reliable procedure, there may be some procedure-related difficulties. One of the most important difficulties is the flaccid septal tissue encountered in case of co-existence of atrial septal defect and patent foramen ovale. In such cases, the catheter heads towards the loose tissue instead of the defect area during procedure and makes the implantation difficult.

Herein, we present an adult atrial septal defect case, which had undergone successful device implantation by transarterial approach after unsuccessful attempts via transvenous approach due to presence of patent foramen ovale and loose septal tissue.

Case

A 26-year-old female patient presented with effort dyspnea. Her personal medical history revealed no documented known cardiac disease. Her blood pressure was 115/70 mm Hg, pulse rate was 75 bpm and rhythmic. Cardiac examination revealed a grade of 2/6 systolic murmurs on pulmonary area. Electrocardiography was in sinus rhythm with incomplete right bundle branch block. Her laboratory parameters were within the normal limits. Transthoracic echocardiography showed dilated right ventricle, with mild tricuspid regurgitation and estimated systolic pulmonary pressure measured from Bernoulli equation was 35 mm Hg. Atrial shunt was detected with color Doppler from apical four-chamber view. Transesophageal echocardiography revealed a 19 mm defect in interatrial septum, compatible with ostium secundum atrial septal defect. Patent foramen ovale, which was 4 mm in diameter and 10 mm in length, was detected 11 mm distant from the atrial septal defect. Despite flaccid interatrial septum, rims of the defect were considered to be appropriate for percutaneous closure.

The procedure was performed under general anesthesia with transesophageal echocardiography. A 7-F sheath was placed through the right femoral vein. Afterwards, an attempt was made to pass into the left atrium with a 7-French multipurpose catheter over a 0.35 j-tipped wire. Despite many attempts, however the catheter persistently headed

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towards to patent foramen ovale instead of atrial septal defect because of flaccid interatrial septal tissue and entered into the left atrium through patent foramen ovale. Upon this, it was planned to pass the catheter through atrial septal defect from the opposite side, through the left atrium benefiting from the direction of shunt flow in the interatrial septum to prevent the wire passing through patent foramen ovale. For this purpose, a 7-French sheath was placed into the right femoral artery at first. Thereafter, Simmons 1 diagnostic catheter was passed through the aortic valve over 0.35 j-tipped long guidewire, and pushed into the left ventricle. Accordingly, the catheter was pushed forward over the wire and passed into the left atrium through the left ventricle. By further pushing forward the wire, right atrium was reached through the left side. The wire was passed through the right ventricle and the main pulmonary artery. The wire in the right pulmonary artery was caught with a snare, which was sent through the right femoral vein, and pulled out of the right femoral vein sheath. Thus, an arteriovenous loop had been created. The size of the defect was measured to be 19.4 mm by sizing balloon (Fig. 1). A 22 mm Cardio-O-Fix (Starway Medical Technology, Beijing, China) closure device was loaded in the delivery system and pushed forward into the left ventricle via aortic route and then passed through the left atrium to the right atrium. The left atrial disk of the device was opened in the right atrium, slightly pulled back, and then leant on the interatrial septum. Afterwards, the right atrial disk was allowed to open in the left atrium. Transesophageal echocardiography demonstrated that shunt flow had stopped. Lock system of the device was opened and the device was left in the interatrial septum. Before finalizing the procedure, mitral valve function and caval and pulmonary flows were checked for procedure-related complications. Control transthoracic echocardiography was performed one day after procedure and the device was visualized in place , with no residual shunt flow (Fig. 2), and the patient was discharged from the hospital.

Discussion

To our knowledge, the present case is the first case, which had undergone atrial septal defect closure by retrograde approach, reported in the literature. Cases that had undergone atrial septal defect closure by non-femoral venous approach have been reported previously. In these cases, the main reason for preferring non-femoral venous approach is anatomical and mechanical inconvenience of the vascular system, through which the device would be pushed forward. The most striking reasons have been the presence of thrombus, interruption and total occlusion of the inferior vena cava.[4–8] Most frequently, jugular vein had been preferred in those cases; but the device had been rarely implanted using transhepatic approach as well. In the present case, the basic difference was the absence of anatomical vascular problem. The main reason for not preferring jugular vein in the present case was the absence of anatomical problem in the inferior vena cava, which was the main reason also in the other cases, as well as the fact

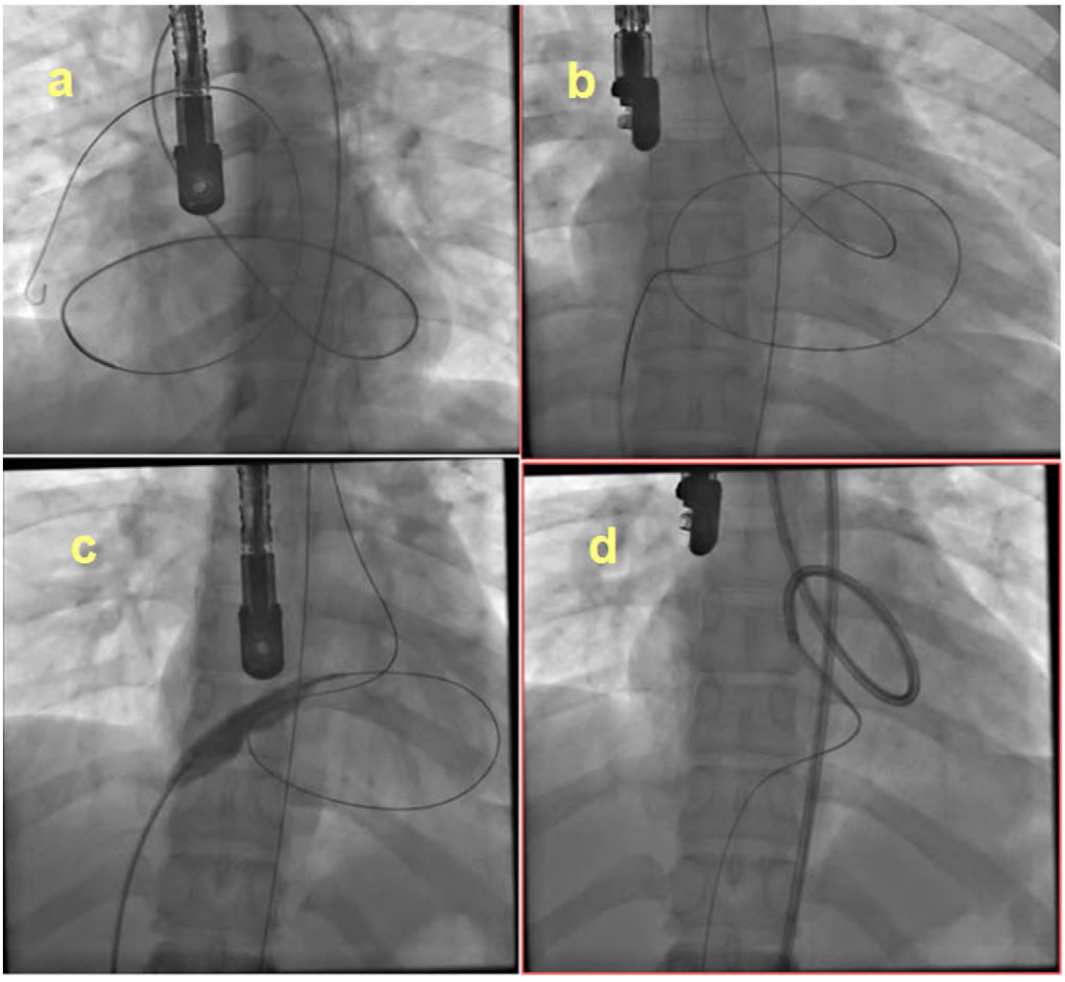


Fig. 1. a. The guidewire, which was sent through the femoral artery, passed through the aortic valve and reached into the left ventricle and subsequently into the left atrium over the mitral valve. The guidewire was further pushed forward and accessed into the right atrium passing through the ASD in the opposite direction. The guide wire pushed forward from there and reached to the right ventricle first over the tricuspid valve and finally was left in the right pulmonary artery. b. The tip of the wire in the pulmonary artery was caught with the snare, which was sent through the right femoral vein, and pulled out of the right femoral vein .c. Sizing balloon procedure. d. Transportation of carrier system to the left atrium via arterial route and passage into the right atrium through ASD.

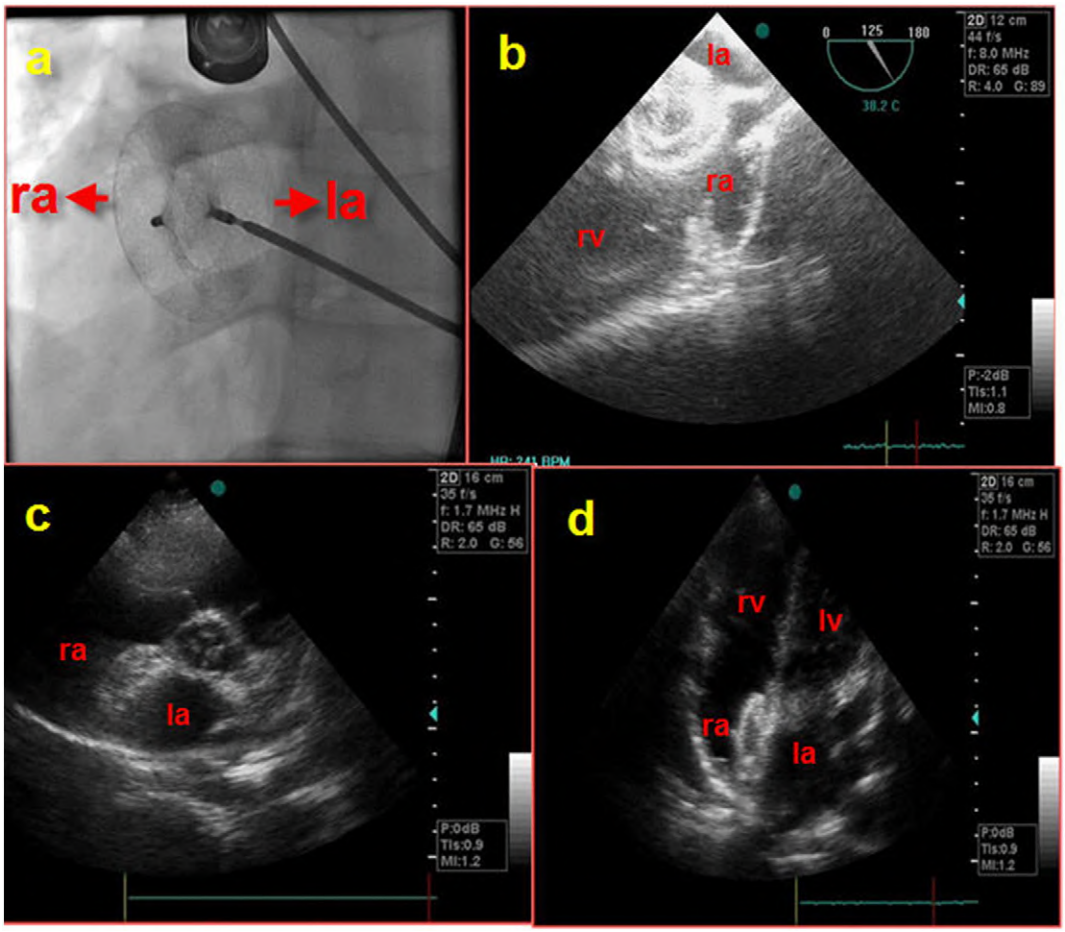


Fig. 2. a. Fluoroscopic image of the open left atrial disk of the device in the right atrium and open right atrial disk in the left atrium. b. Transesophageal echocardiography view of ASD occluder. View of the device by short axis examination on post-procedure Day 1. d. View of the device by apical four-chamber examination on post-procedure Day 1.

that passing the defect directly through atrial septal defect instead of patent foramen ovale and implantation of device so as to completely cover the interatrial septum would be more difficult via jugular venous route.

How to manage the cases with co-existing atrial septal defect and patent foramen ovale and with flaccid interatrial septum is unclear. According to the expert opinion, closure with a single patent foramen ovale device is one of the recommendations in the event the distance between atrial septal defect and patent foramen ovale is close.

The other recommendation is the closure of patent foramen ovale with a patent foramen ovale device and closure of atrial septal defect with another device in the same session.[9] We didn't prefer this method for several reasons. First In the present case, it was thought that, a single patent foramen ovale device wouldn't be wide enough to close the atrial septal defect, as for there was distance in between patent foramen ovale and atrial septal defect. The second reason, it was difficult to pass separately through ASD closure device in case patent foramen ovale is closed with the patent foramen ovale closure device which could cause the probability of unsuccessfulness. And also implantation of two devices might cause the probability of increased risk of complications.

As known, the patent foramen ovale opens into the left atrium from the right atrium because of its anatomical configuration. The patent foramen ovale remains closed, no blood flows into the right atrium from the left due to higher left atrial pressure. Atrial septal defect instead of patent foramen ovale was easily passed by retrograde approach benefiting from the direction of shunt flow as well as from physiological and anatomical properties of patent foramen ovale, and the defect was successfully closed with a single device.

Conclusion

Although transfemoral atrial septal defect closure is currently the preferred choice of procedure, retrograde closure by transarterial approach can be preferred in selected cases, in which interatrial septum anatomy is not suitable for closure by transfemoral venous approach.

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