Acute Transmural Myocardial Infarction by Coronary Embolism in a Patient with *JAK2* V617F-Positive Essential Thrombocythemia

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Essential thrombocythemia (ET) is an acquired myeloproliferative disorder which results from malignant transformation of a multipotent hematopoietic progenitor cell. The disease is characterized by platelet count elevation (> 450 000 /µl) and augmented platelet reactivity causing thrombotic events and haemorrhages. The etiology of bleeding in ET is multifactorial and includes among others an acquired von Willebrand syndrome especially in the presence of extreme thrombocytosis (> 1 000 000 /µl). Thromboses can occur in arterial and venous vessels and are far more frequent than bleeding. Thrombotic complications are the major cause of morbidity and mortality in ET patients and do not correlate with platelet count.[1]

Herein, we report the case of a 53-year old man with low cardiovascular risk profile and untreated ET presenting with a transmural myocardial infarction (STEMI) in the territory of the left anterior descending and the right coronary artery most likely due to multiple coronary embolisation.

Case Report

A 53-year old man presented to the coronary care unit with a first episode of severe retrosternal chest pain beginning 3 hours earlier during a sauna visit. The patient reported no fever, cough, dyspnea, lower extremity edema, immobility, or trauma. He had hypercholesterolemia as a traditional risk factor for atherosclerosis. His family history was unremarkable for premature coronary artery disease. He did not use tobacco, alcohol or illicit drugs. Essential thrombocythemia had been diagnosed 5 years ago and was based on chronic non-reactive thrombocytosis and detection of Janus kinase (*JAK*)*2* V617F mutation in the peripheral blood. A bone marrow biopsy was not performed. Without previous thrombotic or bleeding events an antiplatelet or cytoreductive therapy was not recommended by a hematologist.

On physical examination, he was afebrile and his vital signs were stable. The blood pressure was 156/103 mmHg (approximately the same in both arms), heart rate 93 /min and the oxygen saturation 98 %. Cardiac examination revealed a regular heart rhythm without extra heart sounds. Chest palpitation did not produce pain. Examination of lungs and abdomen was unremarkable.

A 12-lead electrocardiogram (ECG) showed a normal sinus rhythm and significant ST-segment elevations in leads II, III, aVF and V2-V4. Clinical presentation and ECG were characteristic of an STEMI in the territory of the left anterior descending and the right coronary artery. The patient was treated with aspirin (400 mg orally) and a 5000 U bolus of intravenous unfractionated heparin.

He was taken urgently to the catheterisation laboratory. Coronary angiography revealed a thrombus in the mid-right coronary artery (RCA, ►**Fig. 1A**) and thrombotic occlusions in the distal left anterior descending artery (LAD) and in the second diagonal branch (RD) (►**Fig. 1B**). The patient received a loading dose of the P2Y12 inhibitor prasugrel (60 mg p.o.) and an intracoronary bolus of GPIIb/IIIa inhibitor abciximab (250 mg) followed by intravenous abciximab infusion (10 µg/min) for 12 hours.

Thrombus aspiration significantly reduced thrombus burden but failed to restore adequate blood flow in the RCA.

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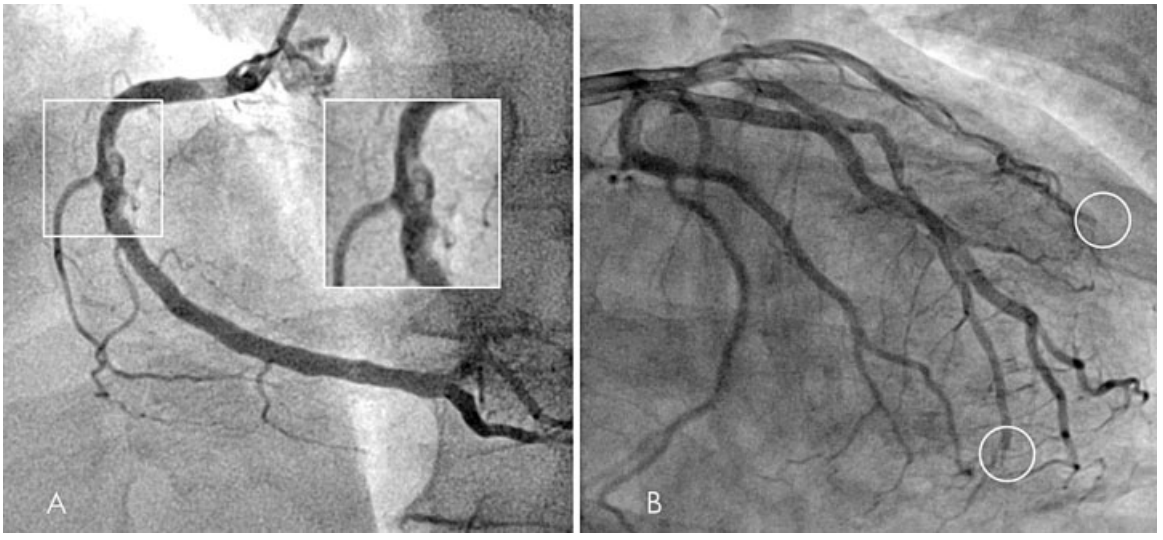

Fig. 1 Coronary angiography of the right coronary artery (left anterior oblique view) reveals a non-occlusive, non-calcified thrombotic filling defect in the mid right coronary artery (A, inset) and distal occlusions in the left descending artery and the diagonal branch (B, circles).

Normal epicardial coronary flow (TIMI grade III) was achieved after drug-eluting stent (3.5 × 22 mm) implantation. A conservative management was opted for the occlusions in LAD and RD (►**Fig. 1B**) because both were located distally and in vessels of small diameters. After percutaneous coronary intervention (PCI) ST-segment elevations in the ECG and chest pain resolved confirming that revascularisation and antithrombotic therapy had been successful.

Cardiac biomarkers were elevated and confirmed myocardial injury. The initial high-sensitive troponin-T level of 0.071 ng/ml peaked at 1.33 ng/ml within 18 hours (normal value, < 0.009 ng/ml). Peak serum creatine kinase (CK) concentration was 1140 U/l 18 hours after admission (normal value, < 180 U/l) with an MB isoenzyme level of 121 U/l (normal value, < 25 U/l). Laboratory data showed a leukocyte count of 18 000 /µl (reference range 4600–10 200 /µl), a platelet count of 482 000 /µl (reference range 150 000–400 000 /µl), and a haematocrit of 41.8 % (reference range 43–49 %). The lipid panel revealed total cholesterol of 268 mg/dl (normal value, < 200 mg/dl), high density lipoprotein (HDL) 40 mg/dl (normal value, > 55 mg/dl), and low density lipoprotein (LDL) 203 mg/dl (normal value, < 130 mg/dl). To reach the LDL cholesterol goal of < 70 mg/dl after STEMI high-intensity statin therapy with atorvastatin 80 mg daily was initiated. The results of other blood chemical and liver-function tests were unremarkable.

After PCI transthoracic echocardiography showed a reduction of the left ventricular ejection fraction (EF) to 40 % with akinesia of the anterior, inferobasal and inferoseptal wall. Given the impaired EF after STEMI treatment with beta blocker bisoprolol 2.5 mg and ACE inhibitor ramipril 2.5 mg daily was started.

Occlusion of multiple coronary vessels can be caused by embolisation. A diagnostic work-up to detect sources of emboli was undertaken. To detect atrial fibrillation, a 24-hour Holter ECG monitoring was performed and showed continuous sinus rhythm without arrhythmias. The transoesopheal echocardiography (TOE) revealed a patent foramen ovale (PFO) allowing rapid and extensive passage of microbubbles from the right to the left atrium even without valsalva manoeuver. In the presence of a PFO paradoxical embolism is a potential mechanism that caused embolic STEMI. However, deep vein thrombosis of lower extremities was excluded by compression ultrasound. Another potential source of coronary embolism are aortic thrombi. A thrombus (1.5 × 1.5 cm) attached to the aortic arch was seen in the TOE and was confirmed by a contrast-enhanced multidetector computed tomography (MDCT) (►**Fig. 2**). Moreover, MDCT of the aorta visualised multiple mural non-occlusive thrombi in the aortic arch and in the abdominal aorta. Infarction areas in spleen and kidneys due to arterial embolisation were ruled out. The patient̀s history was unremarkable for acute lower extremity or abdominal pain due to arterial occlusion.

In regard to the thrombotic risk and the coronary embolism the patient received an antithrombotic triple therapy to prevent recurrent paradoxical embolism or stent thrombosis. According to recent expert recommendations prasugrel was replaced by clopidogrel 75 mg/d. Rivaroxaban 15 mg/d was started in addition to aspirin and clopidogrel. Four days after the STEMI the patient was discharged in a good condition and attended cardiac rehabilitation.

After 4 weeks the PFO was effectively occluded with an Amplatzer® PFO occluder device. The TOE confirmed the complete resolution of the thrombus in the aortic arch. After PFO closure, it was considered safe to discontinue anticoagulation with rivaroxaban. In addition to rivaroxaban clopidogrel was stopped. The patient received acetylsalicylic acid and ticagrelor (90 mg bidaily for 12 months, then 60 mg bidaily on a long-term basis).

After 6 month, coronary angiography revealed complete restoration of coronary blood flow (TIMI III). The TOE confirmed a correct position of the PFO closure device. The leukocyte count was normal (9.270 /µl) and the thrombocyte

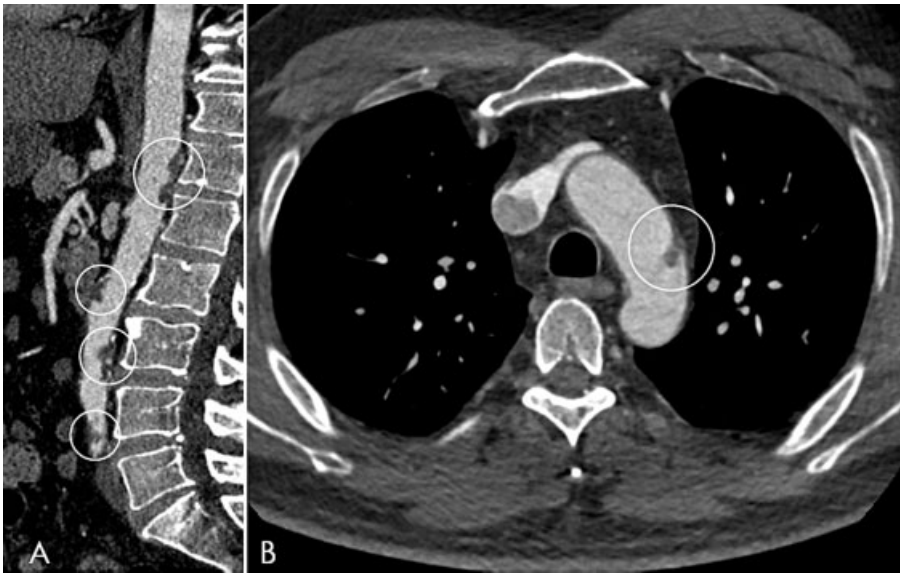

Fig. 2 Multidetector computed tomography (MDCT) revealed several mural thrombi in the abdominal aorta (A, sagittal scan) and in the aortic arch (B, axial scan).

count had increased to 580 000 /µl. Testing of peripheral blood for the *JAK2* V617F mutation was positive again. A new bone marrow biopsy revealed hypercellularity with trilineage hematopoiesis (►**Fig. 3A**, **B**). Megakaryocytes were increased in number and showed large, atypical forms (►**Fig. 3B**). The histological features confirmed a myeloproliferative neoplasm consistent with either myelofibrosis or ET. Results of karyotypic analysis were normal. Treatment with pegylated interferon alpha (pegINFα) was recommended at a dose of 90 mg s. c. weekly.

Discussion

In general, a STEMI occurs after complete occlusion of a coronary artery and is mostly caused by rupture of an unstable atherosclerotic plaque with subsequent occlusive thrombosis.[2] Approximately 50 % of STEMI patients present with significant multi-vessel disease.[3] Most of these patients had several risk factors for coronary artery disease including smoking, arterial hypertension, diabetes mellitus, hyperlipidemia and family history of coronary artery

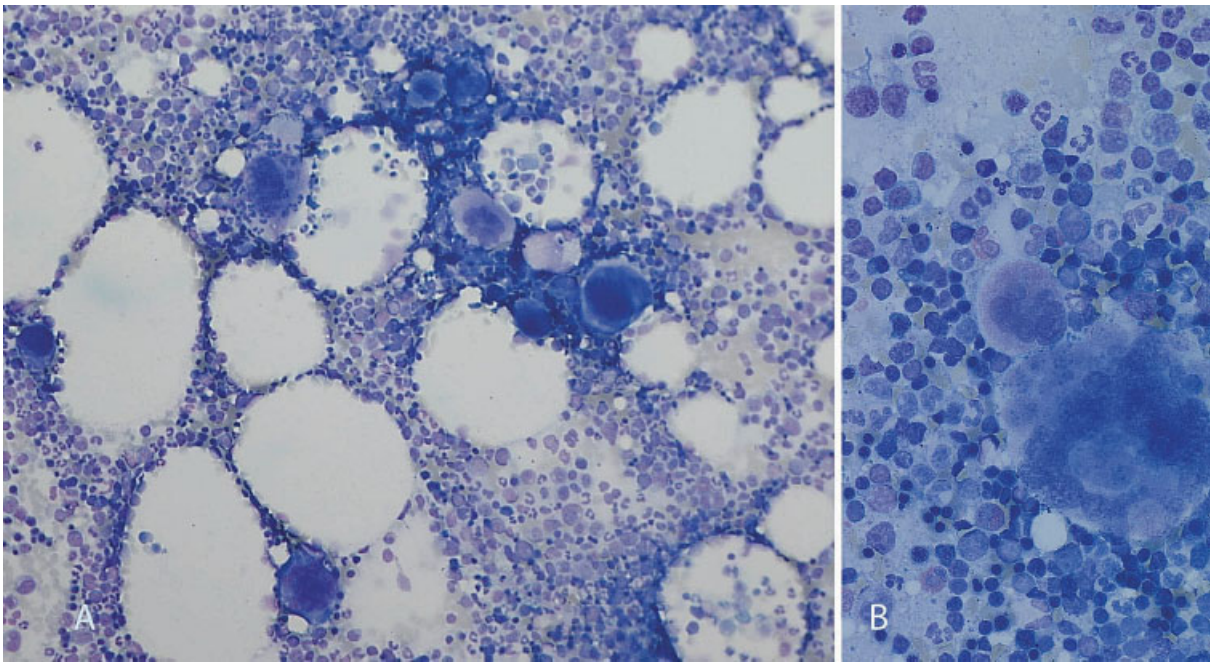

Fig. 3 Bone marrow aspirate smear showing hypercellular bone marrow with proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes (A). Two enlarged megakaryocytes with hyperlobulated nuclei (B).

disease.[4] This STEMI patient had only mild hypercholesterolemia but showed several focal occlusions in otherwise normal-appearing coronary arteries (►Fig. 1).

If multiple occlusions occur in coronary arteries with smooth contours, other causes than simultaneous rupture of atherosclerotic plaques should be considered. Alternative etiologies include

- severe coronary inflammation,
- coronary embolism,
- or vasospasm provoked by cocaine, cigarettes, cannabis or alcohol.[5]

Moreover, coronary thrombus formation may be promoted by coagulation disorders such as heparin-induced thrombocytopenia and antithrombin III deficiency or by other thrombophilic conditions such as essential thrombocythaemia.[4]

In this case, the patient had an untreated essential thrombocythemia (ET) with *JAK2* V617F mutation. Compared with the general population the incidence of thrombosis in ET patients is significantly elevated.[1] In a study of 891 patients with essential thrombocythemia, 13 % of these patients experienced arterial (9 %) or venous (4 %) thrombosis within a median follow-up of 6.2 years.[6] Clinical presentations of arterial thrombosis are stroke, myocardial infarction and peripheral arterial occlusion.[1] Predictors of arterial thrombosis include

- age > 60 years,
- history of thrombotic events,
- leukocytosis,
- presence of cardiovascular risk factors,
- and the *JAK2* V617F mutation.[1]

An acquired gain-of-function mutation (V617F) in the *JAK2* gene can be found in approximately 55 % of the ET patients.[1] The presence of *JAK2* V617F mutation increases the risk for thrombotic events through alterations in platelet and mega–karyocyte biology by increasing expression of P-selectin and tissue factor on platelets and exhibiting hypersensitive signaling through the thrombopoietin receptor in mega–karyocytes.[7–9] Other mechanisms of thrombosis in ET comprise platelet activation by neutrophils through the release of proteolytic enzymes (elastase and cathepsin G) and reactive oxygen species or endothelial dysfunction with upregulation of adhesion receptors.[10]

Drug therapy is based on effective platelet inhibition and cytoreduction. Low-dose aspirin is recommended for all low-risk ET patients with a *JAK2* V617F mutation.[1] Since ET is associated with abnormal megakaryopoiesis, increased platelet turnover and faster renewal of platelet cyclooxygenase (COX)-1 low-dose acetylsalicylic acid dosing once daily may not be adequate. A crossover study showed efficient platelet inhibition in ET patients with a twice-daily regimen of low-dose aspirin.[11]

Cytoreductive therapy requires risk stratification into a low risk (age < 40 years, no history of thrombosis), intermediate (age 40–60 years, no history of thrombosis) or high risk group for thrombotic events and is recommended for all high-risk patients (age > 60 years, prior thrombosis, history of hemorrhage, platelet count > 1500 × 10^9/l).[12] Hydroxycarbamid is the first line therapy for the majority of ET patients and has proven efficacy in the prevention of thrombosis.[1,12] Since results of preclinical and clinical studies are still conflicting regarding the leukemogenic potential of hydroxycarbamid,[13] treatment with interferon alpha (IFNα) may be preferable in younger patients (i.e. in those < 40 years of age).[14–17] In addition, IFNα reduces the allele burden in *JAK2* V617F-positive patients and may induce a response that persists even after discontinuation of treatment. However, the toxicity associated with IFNα treatment should always be considered. In this regard pegylated IFNα has been shown to be better tolerated.[18]

To date approximately 30 cases of patients with ET and acute myocardial infarction due to coronary occlusion have been published. Only 4 cases report multi-vessel thrombosis and acute myocardial infarction in ET patients.[19–22] Treatment strategies of ET patients with STEMI are mostly derived from case reports. In general, reperfusion should be performed as early as possible.[3] In a systematic review comprising 56 patients the management of coronary thrombosis was evaluated. 14 % received aspiration thrombectomy and stent implantation was performed in 91 %.[4] If coronary flow is unsatisfactory after thrombus aspiration implantation of drug-eluting stents represents the method of choice. Ultimately, the individual risk of haemorrhagic and thrombotic complications must be weighed up.

In the absence of obstructive atherosclerosis myocardial infarction, especially in younger patients with no or low cardiovascular risk factors, STEMI may be caused by coronary embolization.[23] After exclusion of cardio-embolic sources we detected multiple mural aortic thrombi in this patient (►Fig. 2). In general, embolisation of aortic thrombi into the coronary artery is an uncommon finding and occurs more often in women without a preference concerning RCA or LAD.[24–26] An association between ET and aortic thrombi has been previously described.[27–35] However, this is the first case report of an ET patient with myocardial infarction and simultaneous detection of aortic thrombi. Options to treat aortic thrombi include medical treatment with antithrombotic therapy or surgical treatment with aortic thrombectomy or endovascular repair.[32,33,36,37]

In the presence of a PFO the possibility that myocardial infarction results from paradoxical embolism should also be considered. Paradoxical coronary embolism is a rare cause of myocardial infarction and is reported to account for 10–15 % of all paradoxical emboli.[38] The association of ET with the suspicion of paradoxical embolism is very uncommon.[39] Therapeutic approaches include administration of anticoagulants or closure of the PFO.[40] Trials assessing whether these patients benefit from medical or interventional treatments are lacking.

However, an individualised approach to PFO closure may be recommended and after careful consideration interventional PFO occlusion maybe justified as a valuable therapeutic option.

In regard to the increased thrombotic risk of this patient with ET and *JAK2* V617F mutation the PFO was occluded. Subsequently, it was considered safe to stop anticoagulation with rivaroxaban and dual antiplatelet therapy with

acetylsalicylic acid and ticagrelor (90 mg bidaily) was continued.[41] After 12 month ticagrelor dose reduction to 60 mg bidaily was recommended. Long term addition of ticagrelor to low-dose acetylsalicylic acid not only reduces the risk of cardiovascular death, myocardial infarction, or stroke in patients with prior myocardial infarction, but also increases the risk of TIMI major bleeding.[42] This has to be taken into consideration especially in ET patients with extreme thrombocytosis. In this case efficacious cytoreductive therapy, as described above, is necessary to prevent bleeding complications when antithrombotics are administered.

Conclusion

When coronary occlusions are unexplained and occur in patients with low cardiovascular risk and normal appearing coronary arteries, screening for alternative etiologies may be considered. In this patient with untreated ET, myocardial infarction resulted most likely from thrombi that embolised to the coronary arteries. Sources of emboli were detected in the aorta, but in the presence of a patent foramen ovale myocardial infarction due to paradoxical embolism should also be considered.

In the absence of evidence-based clinical practice guidelines an individualized and risk-adapted approach to interventional, cytoreductive and antithrombotic therapy is recommended in ET patients with myocardial infarction due to coronary embolism.

Conflicts of interest

CB has received speaker's fees from Merck, AstraZeneca, Sanofi und Bayer; MM has received speaker's fees from Bayer Vital GmbH, AstraZeneca GmbH, Daiichi Sankyo Deutschland GmbH, Pfizer/Bristol-Myers Squibb, Berlin Chemie AG, Lilly Deutschland GmbH, Boehringer Ingelheim Pharma GmbH & Co. and KG Sanofi-Aventis Deutschland GmbH; JRDL, JR, TK and TH declare that there are no conflicts of interest.

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