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A Case of Critical Essential Thrombocythemia Complicated by Severe Lower-Extremity Arterial Disease

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 66-year-old
Final Diagnosis: Essential thrombocythemia with CML • peripheral artery disease
Symptoms: Fever • infection • necrosis • pain
Medication: —
Clinical Procedure: —
Specialty: Cardiology • Dermatology • Diagnostics, Laboratory • Hematology

Objective: Unusual clinical course
Background: Atherosclerosis and malignancies are leading causes of morbidity and mortality worldwide. In lower-extremity arterial disease (LEAD), progressing or ruptured atherosclerotic plaques are the main culprit for limb ischemia and may cause claudication, chronic wounds, or necrotic lesions. In those cases, standard of care includes revascularization in addition to best medical therapy. Other sources for acute or chronic limb ischemia different from atherosclerosis are often overlooked, especially once atherosclerotic plaques have been detected.

Case Report: We report the rare case of a patient presenting with painful necrotic ulcerations of the lower extremity due to critical essential thrombocythemia that was complicated by an atherosclerotic disease. Based on the clinical presentation, 4 major differential diagnoses were initially considered: Martorell's ulcer, pyoderma gangrenosum, LEAD, and recurrent thromboembolic occlusions due to a malignant disease. Following a thorough, holistic diagnostic work-up, we identified the first diagnosis of critical essential thrombocythemia, which was aggravated by LEAD.

Conclusions: This case report highlights the importance of taking malignancies into consideration as a differential diagnosis in patients with repetitive arterial occlusions. With a broad variety of differential diagnoses to be considered for the presented ulcerations, this case report highlights the crucial importance of a rapid interdisciplinary approach to treat and relieve symptoms and prevent further arterial thrombotic events. The learning objective is to give a clear diagnostic work-up to navigate through the most important differential diagnoses of non-atherosclerotic conditions aggravating LEAD.


Keywords: Atherosclerosis • Catheterization, Peripheral • Hematologic Neoplasms • Peripheral Arterial Disease • Thrombocythemia, Essential • Wounds and Injuries

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Background

Atherosclerosis and malignancies are leading causes of morbidity and mortality worldwide. In most cases, atherosclerosis is the underlying pathomechanism of lower-extremity arterial disease (LEAD) and causes claudication and necrotic ulcerations in advanced stages of the disease [1-3]. LEAD is a major manifestation of atherosclerosis, with a high risk of morbidity and mortality. The prevalence of LEAD is as high as 13% in people older than 50 years [4]. Whereas early stages are asymptomatic or characterized by claudication, complications may be ischemic resting pain or necrosis.

For gangrenous ulcerations, the 5-year risk of amputation is 1-3.3%, with an overall 5-year mortality rate of 20%, and dramatically increases in case of chronic wounds [5]. A more patient-tailored estimation of risk for amputation is the WIFL-score, which has been presented in the ESC guidelines [5]. Standard of care at late stages of LEAD includes revascularization of narrowed or occluded arteries in addition to best medical therapy [6,7]. Less frequently, however, aggravated necrotic ulcerations of the lower extremities are caused by non-atherosclerotic conditions, like Martorell's ulcer, pyoderma gangrenosum, or recurrent thromboembolic occlusions due to a malignant disease [8-10]. In such cases, interventional revascularization should not be the first choice of treatment [8-10].

Malignant diseases like essential thrombocythemia are associated with a high incidence of thrombosis in the venous and arterial system, especially in the presence of LEAD [10-13]. Due to a mutation in Janus Kinase 2 (JAK2), which is usually present in essential thrombocythemia, arterial clots develop more frequently, mainly due to hyperlobulated megakaryocytes. Hyperactive JAK2 signaling leads to a denser fibrin configuration, making clots more resistant to lysis. A positive correlation was shown between mutations in JAK2, a procoagulant up-regulation of heparanase, and arterial thrombosis [12,14,15]. Interestingly, patients with essential thrombocythemia have higher incidences of prothrombotic events when presenting conditions of chronic inflammation like LEAD [16].

In this case report we highlight the importance of a holistic diagnostic work-up to navigate through the most important differential diagnoses of non-atherosclerotic conditions aggravated by LEAD.

Case Report

History of Presentation

We report the case of a 66-year-old man who was admitted to our Emergency Department with aggravated, severely painful necrotic ulcerations of both lower extremities, with the right side predominantly affected. The ulcerations had evolved over a period of 6 months. Upon examination, we found circular wounds of the lower legs, with a well-defined line of demarcation on the inner and ventral side, with signs of bacterial infection. The popliteal and foot pulses were weakly palpable on the left side and not palpable on the right side. Examination of the abdomen revealed hepatosplenomegaly. We found no further abnormalities during the physical examination.

Blood tests upon admission showed elevated white blood count (WBC 17.7/nl), platelet count (PC 936/nl), C-reactive protein (CRP 14.7 mg/dl), and normochromic, normocytic anemia (9.7 g/dl) (Table 1).

Past Medical History

The patient had a long-standing history of lower-extremity arterial disease (LEAD), starting in 2013. A thromboendarterectomy (TEA) of the left common femoral artery and left-sided femoropopliteal bypass surgery with a PTFE graft was followed by percutaneous transluminal angioplasty (PTA) of the right popliteal artery.

Due to recurrent thrombotic occlusions, the left-sided PTFE graft was surgically revised in May and June 2018. In February 2019, PTA and stent implantation of the left-peroneal artery was performed.

Table 1. Patient's blood tests over the course of the hospital stay (days 0-24).

Day	0	2	3	5	8	10	11	12	13	16	18	24
WBC [/nl]	17.7	16.9	11.6	10.1	16.6	14.7	12.5	11.7	11.2	10.1	7.2	6.3
CRP [mg/dl]	14.7	19.1	17.5	10.2	1.9				3.9	4.4	4.3	4.3
PC [/nl]	936	889	714	751	800	712	639	593	602	522	459	429
RBC [/pl]	5.0	3.6			3.4	3.1	3.0	3.0	3.2		3.5	3.4
Hb [g/dl]	14.1	10.9			9.9	9.7	8.9	9.3	9.6		10.4	9.7

WBC – white blood count; CRP – C-reactive protein; PC – platelet count; RBC – red blood count; Hb – hemoglobin; development from admission until discharge.

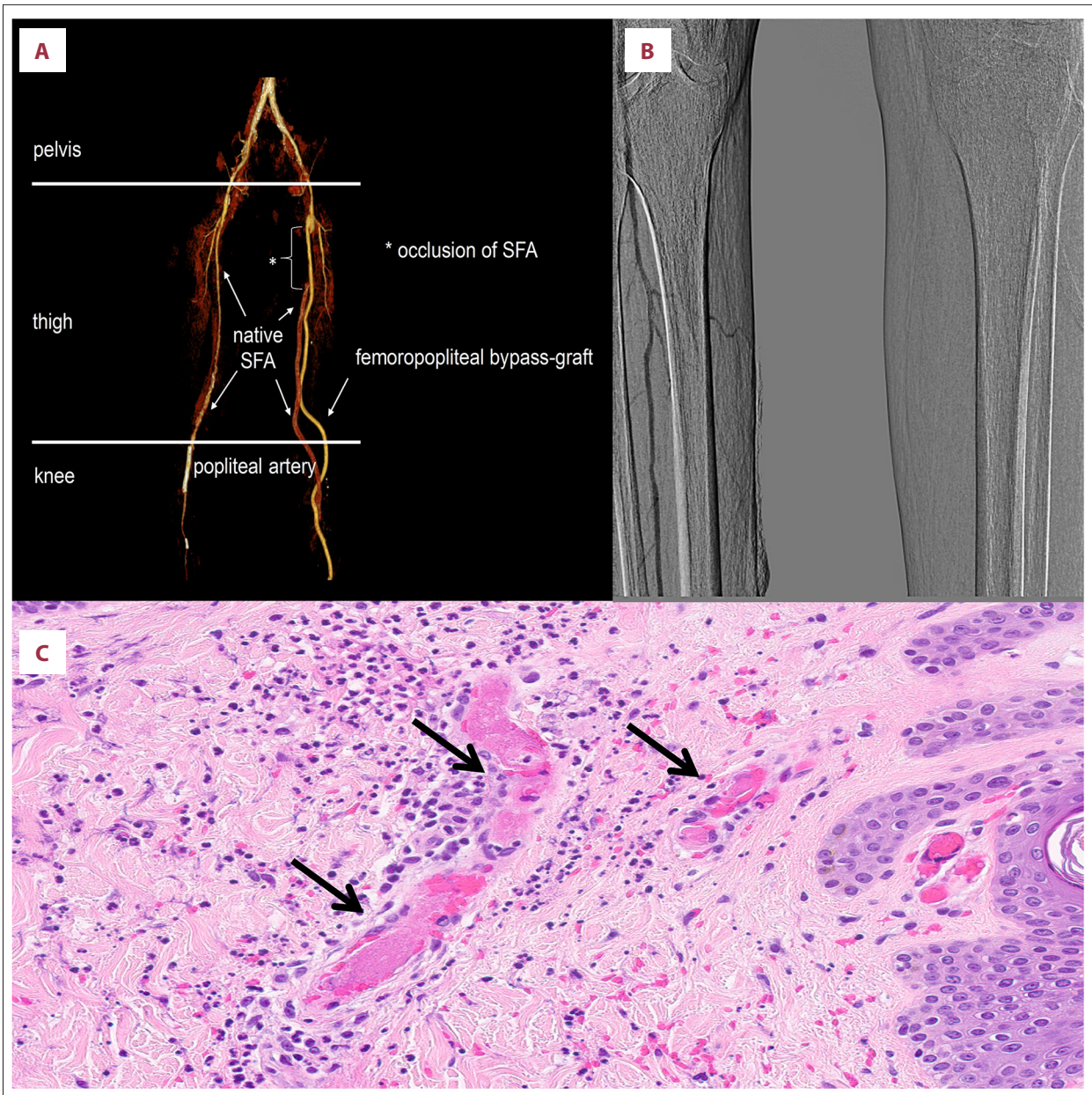


Figure 1. CT-Scan and angiography of lower extremities and HE-staining of affected lesions. CT-scan shows serial stenoses of the right femoral, popliteal, anterior, and posterior tibial artery. The left-sided femoropopliteal bypass graft was occluded (A). Angiography shows reduced perfusion of the left-sided distal lower leg (B). HE-staining (40×) shows interstitial inflammation of the corium with neutrophilic inflammation and occlusion of the vasculature (arrows) (C).

Cardiovascular risk factors were arterial hypertension, hypercholesterolemia, and inhalative smoking (30 pack years). The patient had chronic obstructive pulmonary disease (COPD) stage GOLD II.

Differential Diagnosis

Based on the clinical presentation, 4 major differential diagnoses were considered: Martorell's ulcer, pyoderma gangrenosum,

LEAD, and recurrent thromboembolic occlusions due to a malignant disease.

Martorell's ulcer (hypertensive ischemic leg ulcer) usually affects patients with a long-standing history of poorly treated arterial hypertension. Histologically, an obliteration of the arterioles by arteriosclerosis is characteristic of this condition and is typically located near the Achilles tendon in patients over 70 years of age [17].

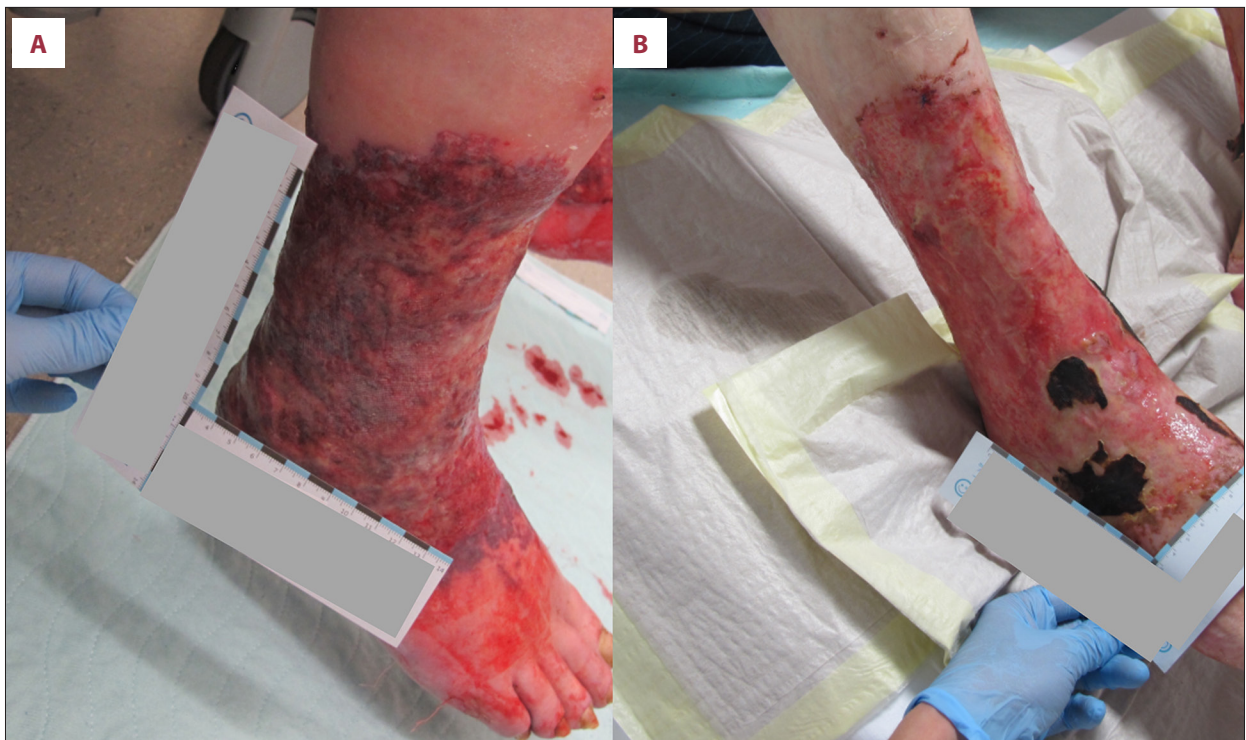


Figure 2. Photographs of the ulcerations upon initial presentation and before discharge. Ulcerations of the right leg upon initial presentation (A) and before discharge after therapy induction (B).

Pyoderma gangrenosum is a rare cutaneous inflammation that is a type of neutrophilic dermatosis. The PARACELSUS score is the first validated score for diagnostics and was used to exclude this differential diagnosis in our patient [18].

Finally, hematological malignancies are a further important differential diagnosis, based on findings linking recurrent thromboembolic occlusions with malignancies [19].

Investigations

Non-invasive vascular diagnostics were performed. Transcutaneous oxygen pressure was 2 mmHg in the right and 30 mmHg in the left lower leg. Computed tomography angiography was performed upon arrival in the Emergency Department and showed several atherosclerotic lesions in the right superficial femoral artery, popliteal artery, and blunted perfusion distal to the popliteal arteries (Figure 1A). Next, we performed an angiography with the aim of intervention of the severe LEAD, but did not find proper target lesions suitable for intervention (Figure 1B).

A histological specimen from the lesion site showed interstitial inflammation of the corium with neutrophilic inflammation, not typical for a pyoderma gangrenosum (Figure 1C).

Molecular diagnostics detected a JAK-2-V617F mutation, characteristic for most myeloproliferative diseases. In combination with complete blood counts, essential thrombocythemia was diagnosed. Thrombotic occlusions and hepatosplenomegaly further corroborated the diagnosis. We sought to perform a bone marrow biopsy to verify the diagnosis, which was unfortunately refused by the patient at the time.

Management

Based on the initial assumption of pyoderma gangrenosum, corticosteroids were applied at the start of treatment (prednisolone, 100 mg q.d.). Due to the peripheral wounds and systemically elevated parameters of inflammation, we initiated an empiric antimicrobial therapy (clindamycin, 600 mg b.i.d.), and inflammation parameters subsequently decreased (Table 1).

Based on platelet count, histopathological findings, and the detection of a JAK-2-V617F mutation, the initial diagnosis of pyoderma gangrenosum was dismissed. Instead, we hypothesized that the essential thrombocythemia may have aggravated LEAD. According to current guideline recommendations, we started chemotherapy with the cytostatic agent anagrelide (0.5 mg b.i.d.) and systemic corticosteroids [20,21]. Subsequently, platelet count decreased rapidly in peripheral circulation (Table 1), accompanied by a substantial clinical improvement of the ulcerations (Figure 2) and pain relief.

Discussion

We present a rare condition of a patient with first diagnosis of critical essential thrombocythemia complicated by severe LEAD. This is in line with other findings linking a worsening of LEAD with hematological malignancies [22-24]. Other studies showed that 1 of 5 patients presenting with acute limb ischemia has a history of cancer and about 3.4% will develop cancer in the 12 months following initial presentation [25]. This further highlights the importance of taking cancer into consideration when evaluating a rapid progressive chronic LEAD. Atherosclerotic vascular disease and malignancies share a set of established risk factors like reactive oxygen species, and sex hormones, and lifestyle factors like nicotine use and a fat- and carbohydrate-rich diet [26].

Myeloproliferative disorders are associated with higher incidences of peripheral artery disease [19]. On a molecular level, the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) has been reported to play a key role in the relationship between progression of atherosclerosis and malignancies [27]. CYP450 polymorphism and homocysteine metabolism also seem to be a link between cancer entities and atherosclerosis [19].

Essential thrombocythemia is one of the myeloproliferative disorders. It is characterized by a megakaryocytic hyperplasia, resulting in thrombocythemia, with an increased risk of thrombosis [28]. The most common mutation is the JAK-2 mutation [29]. In the present case, a bone marrow biopsy would have been necessary to further validate the diagnosis of essential thrombocythemia, which was not performed due to the patient's refusing consent.

Importantly, unlike usual standard of care of ischemic ulcerations due to peripheral artery disease, revascularization via percutaneous transluminal angioplasty should not be the primary goal in this specific case. Angiography showed multiple stenoses of the arteries of the lower limb, without identifying

a target lesion vessel suitable for intervention. Timely start of chemotherapy and steroid treatment to reduce platelet count as the driving force behind the worsening of the patient's LEAD was crucial in this case and led to significant improvement of the patient's symptoms. It also prevents further arterial thrombotic events with possible detrimental consequences like stroke or myocardial infarction [21].

Conclusions

This case report highlights the importance of taking malignancies into consideration as a differential diagnosis in patients with repetitive arterial occlusions and rapid progressing ulcerations, especially in patients with a history of peripheral artery disease.

A rapid interdisciplinary approach is vital in daily clinic routine for a timely diagnosis. Diagnostic work-up should involve a thorough clinical examination of ulcerations, blood-work with special focus on complete blood count, biopsy of recurrent ulcerations, along with standard of care diagnostics like ankle-brachial index, ultrasound, and angiography. The main differential diagnoses are Martorell's ulcer, pyoderma gangrenosum, and malignant disease.

In the present case, diagnostic work-up showed the first diagnosis of essential thrombocythemia acutely complicated by severe LEAD due to a hypercoagulable state. While revascularization strategies via percutaneous transluminal angioplasty should not be the primary goal here, it is vital to decrease the platelet count by establishing a rapid therapeutic approach with chemotherapy and steroid treatment upon diagnosis.

Conflicts of Interest

None.

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