Small and Medium Vessel Vasculitis in Essential Thrombocythemia during Treatment with Anagrelide

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Abstract

Leukocytoclastic vasculitis has been reported to occur in myleproliferative disorders as well as in the setting of medications. Anagrelide has been increasingly accepted as a non-inferior alternative platelet-lowering agent over hydroxyurea in the management of essential thrombocythemia. From a dermatologic standpoint, anagrelide leads to fewer skin toxicities compared to that of hydroxyurea, though exposure to both has been associated with the development of leg ulcers. Here, we report a case of biopsy-proven small and medium vessel vasculitis in a patient with essential thrombocythemia during treatment with anagrelide.

Keywords: Anagrelide • Vasculitis • Essential thrombocythemia

Introduction

Essential thrombocythemia (ET) is a myeloproliferative disorder that is characterized by extensive thrombocytosis and has also been associated with leukocytoclastic vasculitis [1,2]. Traditional therapies used for the treatment of ET (e.g., hydroxyurea) can commonly cause skin toxicities [3]. Anagrelide is an alternative platelet-lowering agent in the management of ET due to its non-inferiority in efficacy and more selective nature [3-5]. Although the precise mechanism of action is unknown, it is thought to inhibit platelet maturation by suppression of transcription factors necessary for megakaryocytopoiesis [4]. To date, cutaneous toxicity associated with anagrelide has been rarely reported. Here, we report a case of biopsy-proven small and medium vessel vasculitis in a patient with ET during treatment with anagrelide.

Case Report

A 75 year-old male with a 12 year history of ET was treated with hydroxyurea but developed a non-healing ulcer on the left ankle. Hydroxyurea was stopped due to concern for a role in delayed wound healing and he was started on anagrelide. After 4 months, the dose of anagrelide was increased. Two weeks following the dose increase, he developed scattered, painful, purpuric nodules and ulcerated retiform purpura in bilateral lower extremities, for which he presented to the Emergency Department. On presentation, he had normal vital signs, except for a mildly elevated blood pressure. Physical examination was notable for retiform purpura with ulcerations affecting the lower extremities (Figure 1). Initial laboratory findings were notable for white blood cell count of 40,000/microliter and platelets of 1,200,000/microliter. Anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies, complements, rheumatoid factor, antiphospholipid antibodies, cryoglobulin, and infectious hepatitis panel were negative. Two purpuric lesions were biopsied each for histopathology and tissue cultures and revealed epidermal necrosis with small and medium vessel vasculitis (Figure 2). Tissue cultures of both lesions were negative for fungi and mycobacterium but the biopsies grew 1+ and 2+ methicillin-susceptible Staphylococcus aureus (MSSA), respectively. Two days after admission, the patient became febrile and a blood culture grew Klebsiella pneumoniae, which was favored to be due to a chronically infected left lower extremity ulcer. The infections were treated accordingly with antibiotics. Additional studies noted hematuria leading to concern for vasculitis affecting the kidney. A kidney biopsy was deferred due to risks of procedure and because his renal function remained normal throughout his stay. Computed tomography of the chest, abdomen, and pelvis, duplex ultrasound of the lower extremities, and transthoracic echocardiogram did not reveal abnormal findings. Rheumatology was consulted and favored that his vasculitis likely resulted from his underlying myeloproliferative disorder. Given the lack of improvement of vasculitis with antibiotics, rheumatology initiated high dose corticosteroids followed by a steroid taper. The patient's lesions stabilized and he was discharged to a skilled nursing facility with outpatient rheumatology follow-up. He continued to receive corticosteroids with improvement in the purpuric lesions and switched to aspirin for ET treatment.

Discussion

While ET is most frequently associated with thromboses, there are several reports in the literature of ET associated with small vessel vasculitis, specifically urticarial vasculitis and Henoch-Schonlein Purpura [1, 2]. To the best of our knowledge, this is the first case of a small and medium vessel vasculitis associated with ET. Although the patient's tissue cultures grew MSSA, a primary infectious etiology was felt to be less likely by rheumatology and more likely to be a paraneoplastic phenomenon from

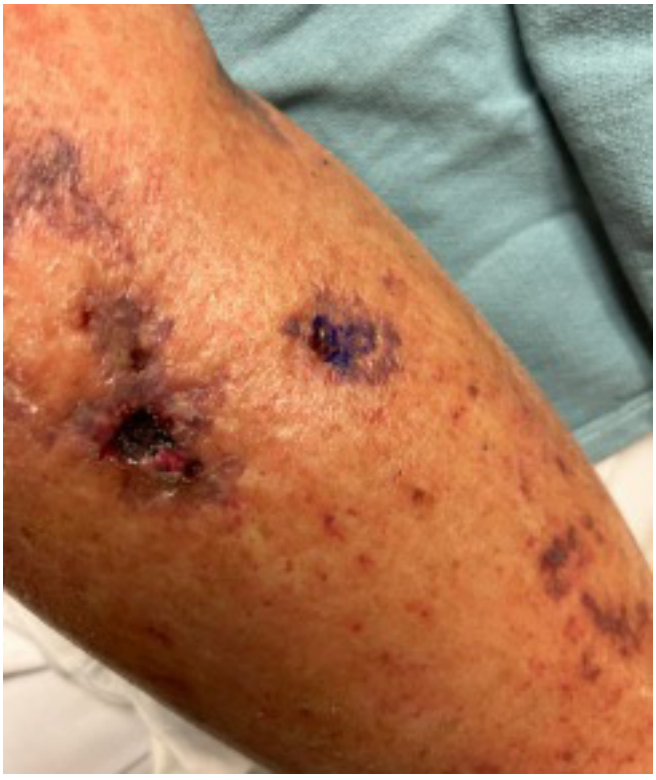

Figure 1. Right lower leg shows retiform purpura.

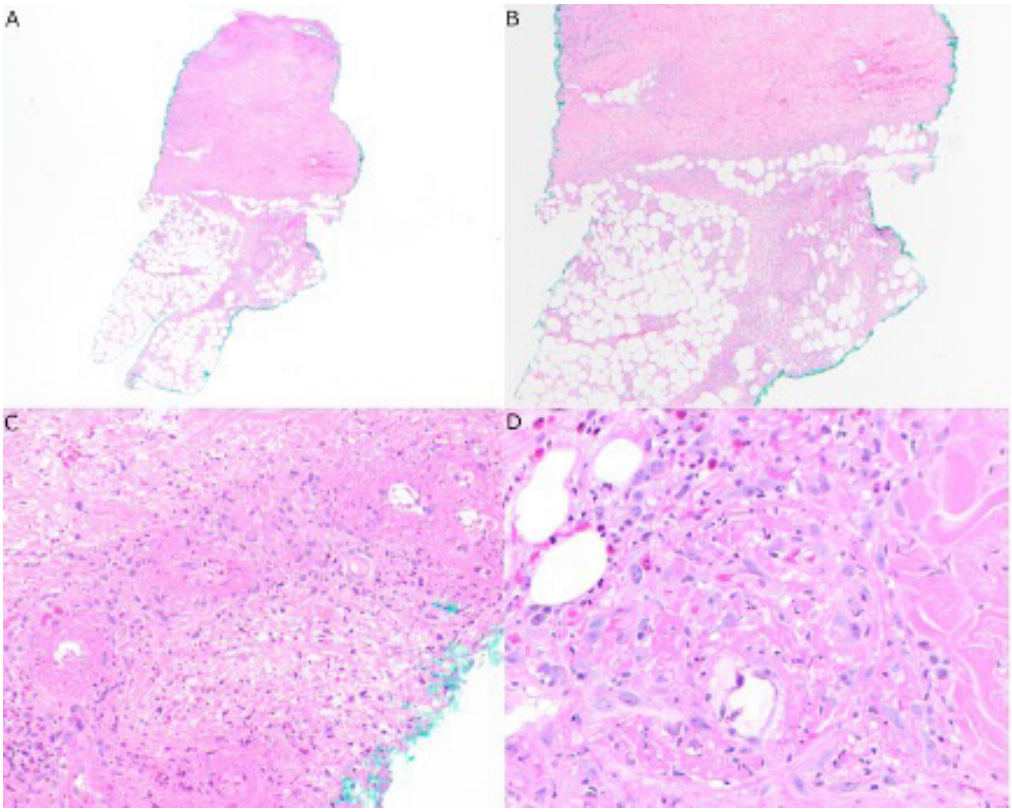

Figure 2. Histopathology from a punch biopsy adjacent to an ulcer on the right lower extremity demonstrates epidermal necrosis with fibrinoid necrosis of superficial and deep dermal vessels, hemorrhage, and abundant perivascular neutrophils and eosinophils (hematoxylin-eosin; A-4x, B-10x, C-20x, D-40x magnification)

his underlying ET. The chronicity of his ET diagnosis and the corresponding dose increase of anagrelide prior to the onset of vasculitis raises a question as to whether anagrelide played a role in development of the vasculitis. Anagrelide and hydroxyurea are cytoreductive agents commonly used to treat ET with similar efficacy and risks of progression to myelofibrosis or acute myeloid leukemia [5]. From a dermatologic standpoint however, fewer reports of cutaneous toxicities are associated with anagrelide [3]. Commonly reported cutaneous side effects of anagrelide include rash, alopecia, skin discoloration, pruritus, and xerosis [3]. To the best of our knowledge, anagrelide-associated vasculitidies have never been reported and only three case reports of leg ulcers associated with anagrelide are noted in the literature [4,6,7]. Drug-induced vasculitis (DIV) is most commonly associated with either immune complex or ANCA positive forms, it has been suggested that not all patients with DIV may test positive for ANCA [8]. The precise pathophysiology of DIV is poorly understood and further studies will be helpful to understand the role of medications in DIV.

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