

Cutaneous polyarteritis nodosa presenting as a paraneoplastic phenomenon in chronic myelogenous leukemia



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INTRODUCTION

There is a well-established relationship between vasculitides and malignancy. The most common type of cutaneous vasculitis associated with both hematologic and solid organ malignancy is leukocytoclastic vasculitis, a small-vessel vasculitis.¹⁻⁴ Other systemic vasculitides with cutaneous manifestations seen in association with malignancy include systemic polyarteritis nodosa (PAN) and the antineutrophil cytoplasmic antibody-associated vasculitides, including microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis.³

Cutaneous polyarteritis nodosa (cPAN), a rare variant of systemic PAN, is a skin-limited small-to-medium vessel vasculitis affecting patients of all ages.⁵ Clinically, cPAN and systemic PAN present similarly with initial cutaneous findings of livedo reticularis and tender subcutaneous nodules, which are most commonly found on the lower extremities.⁵ Cutaneous ulceration and retiform purpura may also be seen in both conditions. Cutaneous PAN is not commonly associated with malignancy. We present a case of cPAN developing in the context of underlying chronic myelogenous leukemia (CML) and resolving with treatment for CML, supportive of a paraneoplastic presentation of cPAN.

CASE REPORT

A 78-year-old Caucasian woman with a history of erosive osteoarthritis, hypertension, and chronic rhinosinusitis presented with asymptomatic lesions

Abbreviations used:

c-ANCA:	cytoplasmic antineutrophil antibodies
CML:	chronic myelogenous leukemia
cPAN:	cutaneous polyarteritis nodosa
PAN:	polyarteritis nodosa

on the lower parts of her legs persisting for 2 years. Initial physical examination found multiple scattered erythematous-to-violaceous non-tender macules, thin papules, and mobile nodules isolated to the anterior and posterior aspects of the lower extremities (Fig 1, A). Over the course of 4 weeks, lesions spread to the patient's arms, chest, and abdomen. Three punch biopsies were performed; 1 at the initial presentation on the posterior aspect of the right calf, and 2 after dissemination of lesions on the upper portion of her left arm and left forearm.

Histopathologic examination of the right calf biopsy revealed a small-to-medium-sized deep dermal vessel distended by fibrinous material with surrounding mixed inflammation, including lymphocytes, histiocytes, and sporadic eosinophils. No microorganisms were detected by Periodic acid-Schiff, Grocott methamine silver, and Kinyoun stains. Follow-up biopsies of the left arm revealed a deep dermal medium vessel vasculitis characterized by a more marked fibrin and neutrophilic accumulation in the vessel wall with surrounding lymphocytes, histiocytes, and rare eosinophils (Fig 2). In all cases, the overlying epidermis was largely unremarkable. No evidence of palisading extravascular granulomas,

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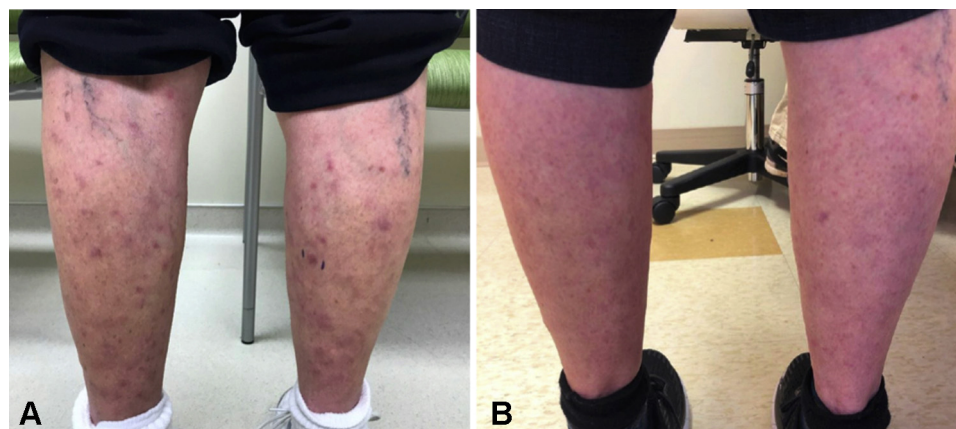


Fig 1. Cutaneous polyarteritis nodosa. **A**, Posterior aspects of the legs showing scattered erythematous-to-violaceous non-tender macules, thin papules, and subcutaneous nodules on both lower extremities. **B**, Posterior aspects of the legs showing near-complete resolution of vasculitic lesions, with only a few violaceous macules remaining after 3 months of treatment with imatinib.

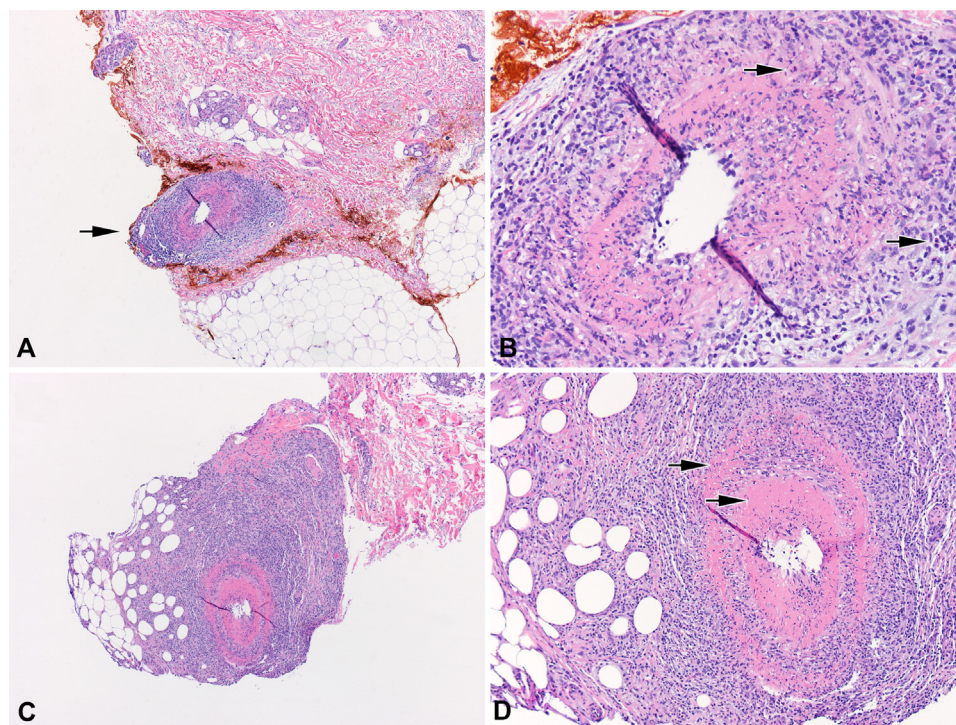


Fig 2. Hematoxylin-eosin–stained sections of a medium vessel vasculitis in the left forearm (**A**, **B**) and left upper arm (**C**, **D**). **A** and **C**, Medium-sized vessel at the junction of the deep dermis and subcutaneous tissue. (*black arrow*) (Original magnification, $\times 40$). **B**, Prominent neutrophilic inflammation (*black arrows*) present within the vessel wall and surrounding tissue. (Original magnification, $\times 200$). **D**, Marked fibrin deposition (*black arrows*) in the vessel wall. (Original magnification, $\times 100$).

multinucleated giant cells, or necrotizing granulomas were identified in either case.

Upon further history, the patient denied fever, weight loss, new-onset muscular weakness or

arthralgias, neuropathy, or gastrointestinal symptoms. Laboratory workup revealed chronic leukocytosis with a rising white blood cell count of $24.3 \times 10^9/L$ (normal range, $4.0\text{--}11.1 \times 10^9/L$), an

absolute neutrophil count of $15.1 \times 10^9/L$ (normal range, $1.8-6.6 \times 10^9/L$), thrombocytosis with a platelet count of $494 \times 10^9/L$ (normal range, $150-400 \times 10^9/L$), and a normal red blood cell count. Liver and kidney function, urinalysis, and complements C3 and C4 were normal. Serum cryoglobulins, rheumatoid factor, and hepatitis B and hepatitis C antibodies were negative. Cyclic citrullinated peptide was >200 units (reference value, <20 units). The patient had a positive C-antineutrophil cytoplasmic antibody (c-ANCA) with a titer of 1:320 (reference value, negative), while serine proteinase 3, myeloperoxidase, and p-neutrophil cytoplasmic antibody tests were negative.

Given the positive c-ANCA serology and medium vessel vasculitis found on skin biopsy, a subsequent workup for granulomatosis with polyangiitis was pursued. Evaluation by otolaryngology and chest and sinus computed tomography (CT) failed to provide evidence of granulomatous disease.

Her rising leukocytosis and thrombocytosis prompted referral to hematology where she was subsequently diagnosed with CML with a BCR/ABL mutation. Treatment for CML was initiated with imatinib 400 mg daily.

After 3 months of treatment with imatinib, the patient reported significant improvement in her skin lesions. Her upper extremities, chest, and abdomen were completely clear with only a few resolving violaceous macules present on her lower legs (Fig 1, B). There has been no recurrence of her skin lesions for the 27 months she has been receiving imatinib.

DISCUSSION

Given the resolution of cutaneous lesions with the imatinib treatment, we believe this case to be an interesting presentation of paraneoplastic cPAN. A relationship between vasculitides and malignancy is well established in the literature^{1,4,6-8}; however, there is a paucity of information available on cPAN presenting as a paraneoplastic phenomenon.

Although paraneoplastic cPAN is not readily reported in the literature, there have been reports of paraneoplastic systemic PAN in association with hematologic malignancies. Of note, there appears to be a relationship between systemic PAN and hairy cell leukemia as well as chronic myelomonocytic leukemia.^{4,6,8} In spite of this, given our patient's lack of systemic symptoms and negative systemic workup, her presentation was consistent with cPAN.

Our patient's history of chronic rhinosinusitis, c-ANCA positivity, and perivascular granulomatous inflammation were initially concerning for granulomatosis with polyangiitis and required further investigation. Although her c-ANCA was positive at a titer

of 1:320, she tested negative for both proteinase-3 and myeloperoxidase antibodies. Additionally, the CT scans of her chest and sinuses were both negative for granulomatous disease. These findings lead us to believe that there is insufficient evidence to support a diagnosis of granulomatosis with polyangiitis despite the positive c-ANCA titer.

Interestingly, there is a report in the literature of a patient with systemic PAN in the context of chronic myelomonocytic leukemia with c-ANCA positivity, but proteinase-3 and myeloperoxidase antibody negativity.⁶ Unfortunately, this report does not comment on the relevance of c-ANCA in relation to systemic PAN.⁶ Our patient was being seen by rheumatology for suspected rheumatoid arthritis, so it is possible that her c-ANCA level was falsely elevated, as evidence of false positive c-ANCA values in rheumatoid arthritis has been reported.⁹

Depending on the severity, cPAN can be treated topically or systemically with agents such as corticosteroids, colchicine, dapsone, and azathioprine. Imatinib is Food and Drug Administration-approved for the treatment of CML. We would not have expected a case of cPAN to resolve with imatinib therapy alone. To date, we could find only one case report of eosinophilic granulomatosis with polyangiitis unexpectedly responding to imatinib.¹⁰ This argues for an indirect relationship between imatinib therapy and the resolution of this patient's cPAN.

While this patient's case was complex, we strongly believe that the cutaneous vasculitis of her initial presentation was a manifestation of her underlying CML. While data are scarce with regard to paraneoplastic cPAN, we encourage clinicians to be diligent in terms of investigating cases of cPAN for more insidious, underlying disease.

Conflicts of interest

None declared.

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