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Immune-mediated Vasculitis as an Initial Presentation of Leukemia: A Diagnostic Challenge

Bennett Agard*

Department of Hematology & Diagnostic Pathology, University of Toronto, Princess Margaret Cancer Centre, Toronto, Canada

Introduction

The intersection of autoimmunity and malignancy is an increasingly recognized phenomenon in clinical medicine andone of the most compelling examples is the emergence of immune-mediated vasculitis as an initial presentation of leukemia. While vasculitis typically arises from primary autoimmune processes such as ANCA-associated vasculitis or connective tissue disease-related vasculitides, secondary vasculitis induced by underlying malignancy presents a unique diagnostic and therapeutic challenge. Leukemia, especially in its early or indolent stages, may manifest subtly and without overt hematologic abnormalities, leading to diagnostic ambiguity when patients present primarily with signs of systemic vasculitis. The convergence of inflammatory and neoplastic processes can obscure the underlying malignancy, delaying diagnosis and treatment. This clinical overlap necessitates heightened awareness among physicians and a rigorous, multidisciplinary approach to evaluation. One prominent mechanism involves the production of autoantibodies by leukemic cells or dysregulated B-cell clones. These autoantibodies may target neutrophil cytoplasmic antigens (e.g., myeloperoxidase or proteinase 3), leading to ANCA-associated small-vessel vasculitis. Alternatively, immune complexes composed of leukemia-related antigens and host antibodies may deposit in vessel walls, activating complement and triggering neutrophilic infiltration and destruction of vascular tissue. This is particularly common in leukemias with B-cell lineage, where clonal B cells may exhibit autoimmune behavior akin to those seen in autoimmune diseases [1].

Description

Cytokine dysregulation represents another critical pathogenic link. Leukemic blasts and the leukemic microenvironment often overproduce proinflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), interleukin-6 (IL-6) andinterferon-gamma (IFN-γ), creating a systemic inflammatory milieu that can provoke endothelial activation and immune cell infiltration into the vessel wall. Additionally, impaired regulatory T-cell function and unchecked T-helper cell activation in leukemia may further propagate autoimmunity, enhancing susceptibility to vasculitic processes. Clinically, patients with leukemia-associated vasculitis may present with a classic leukocytoclastic vasculitis (LCV), characterized by palpable purpura, predominantly on the lower extremities. However, systemic features such as fever, night sweats, fatigue andweight loss—often attributed to primary vasculitis may in fact represent constitutional symptoms of leukemia. Multi-organ involvement may mimic classic vasculitic syndromes like polyarteritis nodosa (PAN) or microscopic polyangiitis (MPA), further complicating the diagnostic picture. Neurological manifestations such as mononeuritis multiplex or central nervous system vasculitis can occur and may be mistaken for primary autoimmune vasculitis [2].

Diagnosis is especially difficult when routine blood counts are within normal limits or show only subtle abnormalities. Peripheral blood smears may appear unremarkable in early-stage leukemia or may reveal only mild cytopenias. Inflammatory markers such as ESR and CRP are typically elevated but nonspecific. The presence of circulating ANCAs may mislead clinicians toward a primary autoimmune vasculitis diagnosis, especially when found in isolation. However, such findings should prompt further scrutiny when accompanied by atypical clinical features, resistance to standard immunosuppressive therapy, or unexplained organ dysfunction. A thorough and systematic evaluation is critical. Skin biopsy of purpuric lesions often shows leukocytoclastic vasculitis, but this finding is not specific to malignancy. Renal biopsy in cases with glomerular involvement may reveal a pauci-immune crescentic glomerulonephritis, similar to that seen in ANCA-associated vasculitis, or immune complex-mediated glomerulonephritis. Bone marrow biopsy and aspiration remain indispensable for confirming leukemia and should be pursued when clinical suspicion is high, even in the absence of overt hematologic abnormalities. Flow cytometry, cytogenetics andmolecular studies can provide further insights into clonality and genetic alterations characteristic of leukemia [3].

Imaging studies such as CT or PET scans may incidentally reveal lymphadenopathy or organomegaly, raising suspicion for an underlying hematologic malignancy. Serum protein electrophoresis, immunoglobulin quantification andautoantibody panels may aid in identifying monoclonal proteins or autoimmune mimics. In cases with pulmonary involvement, bronchoalveolar lavage and high-resolution CT may help differentiate vasculitic alveolar hemorrhage from infectious or leukemic infiltrates. Treatment poses significant challenges. Standard immunosuppressive regimens for vasculitis—including high-dose corticosteroids and cytotoxic agents such as cyclophosphamide—may produce transient clinical improvement but can be detrimental if the underlying leukemia remains untreated. In fact, corticosteroids may mask or delay the recognition of leukemia by suppressing blast proliferation temporarily. Therefore, early identification of the hematologic malignancy is essential to guide appropriate treatment. Once leukemia is diagnosed, disease-specific therapy, including chemotherapy, targeted agents, or bone marrow transplantation, often leads to resolution of the vasculitic manifestations [4].

In CLL-associated vasculitis, for example, targeted therapies such as ibrutinib (a BTK inhibitor) or venetoclax (a BCL-2 inhibitor) may control both the malignancy and the associated immune dysregulation. Similarly, in acute leukemias, induction chemotherapy directed at blast eradication often results in improvement or resolution of vasculitis. Rituximab, an anti-CD20 monoclonal antibody, has shown benefit in cases of B-cell leukemia with vasculitic manifestations, especially when autoimmune features predominate. Plasmapheresis may be considered in cases with severe immune complex-mediated vasculitis or ANCA-associated glomerulonephritis, though its role remains controversial and should be individualized. Prognosis in leukemia-associated vasculitis varies based on the leukemia subtype, disease burden andtiming of diagnosis. Patients in whom vasculitis precedes the hematologic diagnosis may experience delays in initiating appropriate therapy, potentially resulting in irreversible organ damage. Conversely, prompt recognition and

***Address for Correspondence:** Bennett Agard, Department of Hematology & Diagnostic Pathology, University of Toronto, Princess Margaret Cancer Centre, Toronto, Canada, E-mail: agard.bennett@pmcc.ca*

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treatment of the underlying leukemia often lead to remission of vasculitic symptoms and improved outcomes. However, the presence of vasculitis may also reflect a more aggressive or immunologically active leukemia, potentially portending a worse prognosis [5].

Conclusion

In conclusion, immune-mediated vasculitis as an initial presentation of leukemia represents a complex and often underrecognized diagnostic entity. It exemplifies the intricate relationship between malignancy and autoimmunity and underscores the need for heightened clinical vigilance when evaluating patients with atypical or treatment-resistant vasculitis. Timely and accurate diagnosis hinges on a multidisciplinary approach involving dermatologists, nephrologists, rheumatologists, hematologists andpathologists. Recognition of the underlying leukemic process is crucial for effective treatment and improved prognosis, as standard immunosuppressive therapy alone is insufficient and potentially harmful if the root malignancy is not addressed. As our understanding of the immune-oncologic interface deepens, future strategies may better integrate immunologic and oncologic therapies to address both components of this challenging clinical syndrome.

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Conflict of Interest

None.

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