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Monoclonal Gammopathy and Small-vessel Vasculitis in Indolent B-cell Lymphomas

Cesario Elmquist*

Department of Hematopathology & Clinical Immunology, University of Heidelberg, German Cancer Research Center (DKFZ), Heidelberg, Germany

Introduction

Indolent B-cell lymphomas are a heterogeneous group of hematologic malignancies characterized by slow progression and prolonged survival. These lymphomas, which include entities such as marginal zone lymphoma, lymphoplasmacytic lymphoma (including Waldenström's macroglobulinemia), follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), often follow a relatively stable course. However, despite their slow-growing nature, they are associated with significant immune dysregulation, including the production of monoclonal immunoglobulins (monoclonal gammopathy) and a variety of autoimmune or paraneoplastic phenomena. One such manifestation is small-vessel vasculitis, a rare but potentially severe inflammatory disorder affecting arterioles, capillaries and venules. The co-occurrence of monoclonal gammopathy and vasculitis in the context of indolent B-cell lymphomas represents a unique overlap syndrome with complex pathophysiological mechanisms and challenging diagnostic and therapeutic considerations [1].

Description

Monoclonal gammopathy in indolent B-cell lymphomas arises from clonal proliferation of mature B cells or plasma cells that secrete structurally homogeneous Immunoglobulin (Ig) molecules. These monoclonal proteins, often detected as M-protein on serum electrophoresis, can be complete immunoglobulins or light chains alone (kappa or lambda). While many cases of monoclonal gammopathy are asymptomatic or discovered incidentally as in Monoclonal Gammopathy of Undetermined Significance (MGUS) they may cause organ damage through a variety of mechanisms, especially in the context of malignancy. When present in indolent lymphomas, these monoclonal proteins are not merely bystanders; they often play a direct pathogenic role in complications such as cryoglobulinemia, amyloidosis, glomerulonephritis and systemic vasculitis. Small-vessel vasculitis is characterized histopathologically by Leukocytoclastic Vasculitis (LCV), which involves neutrophilic infiltration and fibrinoid necrosis of the vessel wall. Clinically, it manifests with palpable purpura, arthralgia, peripheral neuropathy, renal involvement, or pulmonary symptoms, depending on the organ systems involved. When associated with monoclonal gammopathy, the underlying pathogenic mechanism is often immune complex-mediated. Monoclonal immunoglobulins may act as autoantibodies or precipitate under certain conditions—such as in cryoglobulinemia—leading to deposition in small vessels and activation of the complement cascade. This triggers recruitment of neutrophils and other inflammatory cells, ultimately causing vascular damage. The complement consumption, particularly of C4 and C3, often noted in such patients, supports the immune complex hypothesis [2,3].

***Address for Correspondence:** Cesario Elmquist, Department: Hematopathology & Clinical Immunology, University of Heidelberg, German Cancer Research Center (DKFZ), Heidelberg, Germany, E-mail: elmquist.cesario@dkfz.gr*

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A key example of this phenomenon is type I cryoglobulinemia, which is commonly associated with indolent B-cell lymphomas that produce monoclonal IgM or, less frequently, IgG. In this condition, monoclonal immunoglobulins precipitate at low temperatures and deposit in small vessels, especially in the skin, kidneys and peripheral nerves. Clinical features include purpura, Raynaud's phenomenon, ulceration, glomerulonephritis and peripheral neuropathy. Renal biopsies often reveal membranoproliferative glomerulonephritis with intraluminal thrombi composed of cryoglobulin deposits. In these cases, vasculitis is a direct result of the physicochemical properties of the monoclonal protein and its proclivity for precipitation and vascular deposition. Diagnosing small-vessel vasculitis in the context of monoclonal gammopathy and indolent lymphoma requires a high index of suspicion and careful evaluation. Clinically, it may be difficult to distinguish between primary vasculitis and secondary vasculitis due to monoclonal gammopathy or lymphoma. Laboratory investigations should include Serum Protein Electrophoresis (SPEP), immunofixation electrophoresis (IFE), serum free light chain assay, cryoglobulin testing, complement levels and autoantibody profiles (including ANCA). Tissue biopsy remains crucial for confirming the diagnosis and identifying the nature of the vascular lesion. Histopathological features such as leukocytoclastic infiltration, immune complex deposition, or direct light chain deposits can help establish the underlying etiology. Bone marrow examination may be necessary to confirm the presence and extent of B-cell lymphoma [4].

Management of patients with this overlap syndrome requires a dual-focused approach: treating the underlying lymphoma and managing the vasculitic process. In many cases, successful treatment of the indolent B-cell lymphoma results in remission of the vasculitic symptoms, supporting a causal relationship between the two. However, corticosteroids do not address the underlying clonal B-cell proliferation and may provide only temporary relief. Therefore, disease-modifying therapy targeting the lymphoma clone is essential for long-term disease control. In refractory cases or when standard treatments are contraindicated, newer targeted therapies such as BTK inhibitors (e.g., ibrutinib) or BCL-2 inhibitors (e.g., venetoclax) may be considered, especially in patients with CLL/SLL or Waldenström's macroglobulinemia. These agents have shown promise in reducing monoclonal protein levels and alleviating associated systemic symptoms. From a pathophysiological standpoint, the co-occurrence of monoclonal gammopathy and small-vessel vasculitis in indolent B-cell lymphomas underscores the complex relationship between neoplastic B-cell proliferation and immune-mediated vascular injury. The monoclonal proteins produced by the malignant clone are not merely markers of disease but active mediators of vascular pathology. They may serve as autoantibodies, form immune complexes, activate complement and directly injure endothelium. The resulting vasculitic manifestations reflect not only the tumor biology but also the host's immune response to this aberrant protein production. Understanding this interplay is crucial for developing more precise diagnostic criteria and targeted therapeutic strategies [5].

Conclusion

In conclusion, monoclonal gammopathy and small-vessel vasculitis in indolent B-cell lymphomas represent a multifaceted overlap syndrome that bridges the domains of hematology, immunology and rheumatology. The monoclonal immunoglobulins produced by malignant B cells are central to the pathogenesis of vasculitis in these patients, primarily through immune complex formation, cryoprecipitation and complement activation. Recognizing this

association is essential for accurate diagnosis, especially in patients with unexplained vasculitic symptoms and evidence of monoclonal proteinemia. A comprehensive diagnostic workup, including serologic testing, tissue biopsy and hematologic evaluation, is required to identify and characterize the underlying disorder. Treatment should be directed at both controlling the inflammatory vasculitis and eliminating the neoplastic B-cell clone. As our understanding of the molecular and immunological mechanisms evolves, it may lead to the development of more effective and less toxic therapies tailored to this unique patient population.

Acknowledgement

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Conflict of Interest

None.

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