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Original contribution

IMP-3 is differentially expressed in normal and neoplastic lymphoid tissue☆,☆☆

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Summary IMP-3 is a member of the insulin-like growth factor II mRNA binding protein (IMP) family of proteins that play a role in RNA trafficking and stabilization and cell growth and migration during embryogenesis but which are down-regulated in adult tissue. However, IMP-3 has recently been shown to be overexpressed in several epithelial malignancies, with increased expression correlating with aggressive behavior. To our knowledge, there is no published literature evaluating IMP-3 in lymphoid tissue. Accordingly, we immunohistochemically evaluated IMP-3 expression in normal lymphoid tissue and 141 lymphoid neoplasms. Physiologically, IMP-3 expression was restricted to germinal center B cells. Among lymphoid neoplasms, Hodgkin lymphoma demonstrated the highest percentage of positive cases (26/26, 100%) often with bright staining. Burkitt lymphoma was positive in 10 (83%) of 12 cases with moderate to bright staining. Although follicular lymphoma was also positive in a high percentage of cases (12/15, 80%), the intensity was exclusively weak to moderate. Although 22 (85%) of 26 of diffuse large B-cell lymphomas were positive for IMP-3, there was wide variability in staining intensity, which did not correlate with classification into activated B cell versus germinal center B origin. By contrast, lower proportions (8%-20%) of other non–germinal center B lymphoma subtypes were IMP-3–positive. In conclusion, although IMP-3 expression is seemingly restricted to physiologic germinal center B cells, its expression in lymphomas of germinal center B origin is less robust. However, there does appear to be some association with the latter group of lymphomas, which may prove to have diagnostic or therapeutic relevance as the biologic role of IMP-3 is further elucidated.

1. Introduction

The contemporary evaluation of lymphomas typically requires a multiparametric approach, integrating histomorphologic, immunophenotypic, genetic, and clinical data [1]. Immunophenotypic analysis, performed by flow cytometry and/or immunohistochemistry (IHC), is fundamental to the initial diagnostic process and helps determine a number of key parameters that are central to current diagnosis and

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classification. This includes (1) assignment of lineage (eg, B-cell, T-cell, or NK-cell); (2) stage of maturation (eg, immature/lymphoblastic versus mature/peripheral); and (3) identification of the normal physiologic counterpart (best exemplified in B-cells, eg, mantle cell versus germinal center [GC] cell versus marginal zone cell, among others). This has resulted in a better understanding not only of the pathogenesis of these tumors but also that the immunophenotypic profile can be a particularly useful parameter in predicting clinical behavior and prognosis [1]. In addition, monoclonal antibody therapy has revolutionized the treatment of lymphomas and relies on identification, by immunophenotypic analysis, of specific antigenic targets [2]. Despite these advances and the plethora of diagnostic antibodies at our disposal, there is still much to be learned about the pathogenesis and clinical behavior of lymphomas. Furthermore, it has become increasingly apparent that not all immunophenotypes are specific, especially when assessing single parameters. Accordingly, the search for novel, diagnostically, and prognostically relevant markers and therapeutic targets continues.

IMP-3 is a member of the insulin-like growth factor II (IGF-II) mRNA binding protein (IMP) family that includes IMP-1, IMP-2, and IMP-3 [3]. These proteins have been shown to play a role in mRNA trafficking and stabilization, as well as cell growth and migration during embryogenesis [3,4]. Quantitative reverse transcriptase–polymerase chain reaction studies of IMP-3 mRNA demonstrated the virtual absence of IMP-3 expression in most adult tissues with the exception of testes and ovary [5]. Overexpression of IMP-3 has been identified in a number of epithelial malignancies including tumors of the liver, kidney, bladder, cervix, endometrium, and testes [5-14]. In addition, recent studies have shown that increased IMP-3 expression correlates with aggressive behavior and/or metastasis in melanoma, renal cell carcinoma, and hepatocellular carcinoma, among others [7,8,11,15]. These findings implicate IMP-3 as an oncofetal protein and suggest its role as a biomarker for aggressive malignancies.

In the course of a pilot immunohistochemical study evaluating the normal distribution of IMP-3, we observed that IMP-3 expression in normal lymphoid tissue is restricted to germinal center B (GCB) cells. To the best of our knowledge, there is no published full-length literature directly evaluating expression of IMP-3 in normal or neoplastic lymphoid tissue. Therefore, the aim of our study was to evaluate the expression of IMP-3 in a series of well-characterized lymphomas, specifically to determine its utility in discriminating B-cell lymphomas of GC origin from those of non-GC origin.

2. Materials and methods

2.1. Normal controls

To evaluate IMP-3 expression in normal lymphoid tissue, formalin-fixed, paraffin-embedded tissue blocks from a total of 21 cases consisting of reactive lymph nodes (6), normal spleens (6), tonsil (4), and thymus (5) were selected for evaluation from the archives of the Department of Pathology and Laboratory Medicine at the Hospital of the University of Pennsylvania.

2.2. Lymphoma case selection

A representative series of 143 lymphoma cases, classified according to World Health Organization criteria [1], was retrieved from the archives of the Department of Pathology and Laboratory Medicine at the Hospital of the University of Pennsylvania. The cases included diffuse large B-cell lymphoma (DLBCL) lymphoma (35, including 9 cases of primary mediastinal large B-cell lymphoma [PMLBCL]), Hodgkin lymphoma (HL) [28], follicular lymphoma [15], marginal zone lymphoma (12, 10 extranodal and 2 nodal subtypes), Burkitt lymphoma [12], small lymphocytic

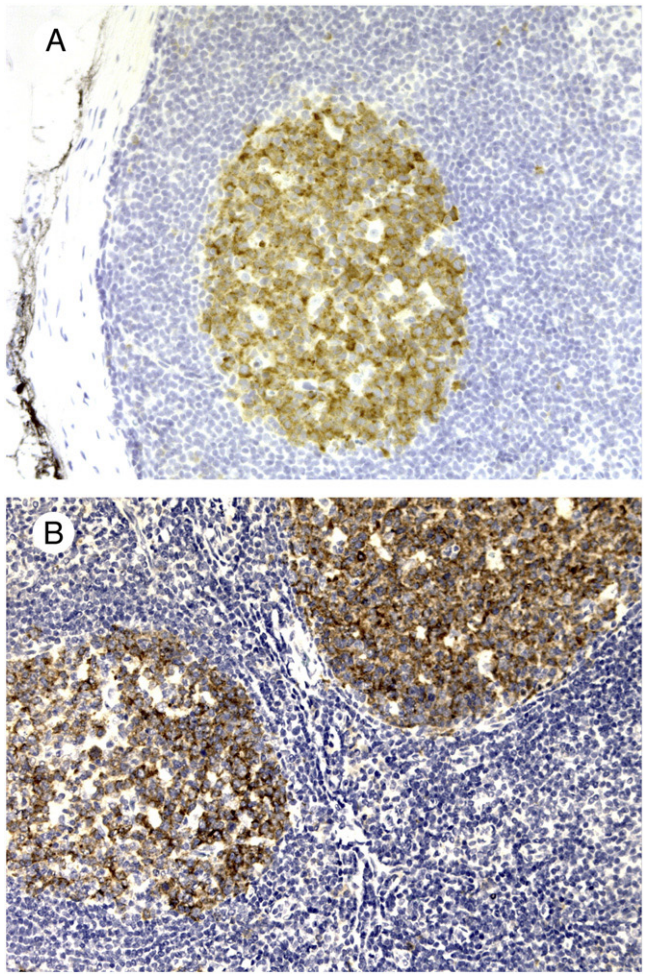

Fig. 1 IMP-3 IHC in normal lymphoid tissue. Reactive lymph node with weak to moderate staining (A) and normal tonsil with moderate to strong staining (B) (original magnification ×200). Note that IMP-3 expression is restricted to GCs only.