Marginal-zone B-cell lymphoma, extranodal-malt-type: Report of three cases

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Summary

A high proportion of extranodal lymphoid infiltrates are diffuse small lymphocytic proliferations [1, 2] and therefore pose a particularly challenging diagnostic problem [1-4]. Their benign or malignant nature cannot be determined using clinical and radiologic criteria. The application of traditional morphologic criteria (i.e., cytologic maturity and polymorphism favor benignancy, while cytologic atypia and monomorphism favor malignancy) [5, 6], has probably improved diagnostic accuracy. However, these criteria generally have not been helpful in evaluating the large number of lymphoid infiltrates composed of monomorphic collections of small cytologically-mature appearing lymphoid cells [1-4] and, therefore, have not always accurately predicted clinical behavior.

Extranodal lymphoid proliferations are also of considerable biologic interest since their pathogenesis and natural history have not been fully elucidated.

Localized non-Hodgkin's lymphoma, extranodal-MALT-type, was diagnosed in our Department in three cases: Two arose in the orbit and the third one in the tonsil. The tumors had a typical histologic appearance. The microscopical features and immunohistochemical profile are discussed.

Key words: N H Lymphomas; Orbital lymphoid lesions; Waldeyer's ring lymphoid lesions; CT.

Introduction

While lymphomas of the eye itself are extremely rare, those arising in the ocular adnexa, which include the conjunctiva, eyelids, lacrimal gland and orbit, although infrequent, are less rare and have excited considerable interest among pathologists. Their true incidence is difficult to estimate but in the series of Freeman *et al.* [7] they constituted approximately 8% of extranodal lymphomas. This group of lymphomas, comprised mostly of low-grade B-cell lesions, shares many features with the MALT lymphomas. Like MALT lymphomas, their unusually benign histological appearance and favourable clinical behaviour led to the term 'pseudolymphoma' being applied in many cases; with the advent of more sophisticated methods of assessing clonality this diagnosis is less frequently made and, indeed, it is recommended that the term 'pseudolymphoma' should no longer be used for these lesions. Although there has been considerable recent progress in the understanding of lymphoproliferative lesions of the ocular adnexa, a number of controversies remain.

The function of the tonsils and adenoid is to protect the upper aerodigestive tract from external antigens. The adenoid is lined by ciliated or squamous epithelium and nonciliated flat epithelium composed of cells with multiple microfolds (M cells) [8]. These M cells form compartments (intraepithelial channels) for lymphocytes. This lymphoepithelium probably transplants antigen via the M cells to the lymphoid follicles lying below. In addition to M cells, immunophenotypic examination has shown that the crypt epithelium overlying the lymphoid follicles in the tonsils and adenoid resembles Peyer's patch mucosa, as it contains intraepithelial B lymphocytes, some clusters of CD4-positive T lymphocytes, and some Leu-8-positive cells [9]. Clusters of CD19-, CD20- and CD22-positive B cells are accompanied by fewer CD3- and CD4-positive T lymphocytes, which are often present in small groups. Some intraepithelial lymphocytes are also positive for CD5, CD8, and CD7. There are more α/β T lymphocytes than γ/δ T cells in the crypt epithelium and in the superficial lamina propria. The squamous epithelium contains CD1a-positive Langerhans cells and CD1a-negative dendritic mononuclear cells. The germinal centers within follicles have the expected number of B cells, which are positive for CD19, CD20, CD21, and CD22. Tingible body macrophages and follicle dendritic cells are also conspicuous. The interfollicular zone contains predominantly T lymphocytes with larger numbers of CD4- than CD8-positive T cells.

Most of the progress in distinguishing low-grade lymphomas from non-neoplastic B-cell hyperplasias has depended on the demonstration of B-cell monoclonality

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either indirectly, by showing immunohistochemical evidence of immunoglobulin light-chain restriction, or directly, using molecular methods to show monoclonal immunoglobulin gene rearrangement. Nevertheless, some, including Knowles & Jakobiec [10], argue that demonstration of monoclonality in a lymphoproliferative lesion does not necessarily define that lesion as a lymphoma. While recognizing that monoclonality and malignancy are not necessarily synonymous in all cases, it is our view that, in the great majority of lymphoproliferative lesions, monoclonality is a sign of lymphoma. This is even more so when florid lymphoproliferation, which may be invasive and destructive, is present, as is the case in most of the lesions under discussion here.

Cases and Methods

We report three cases of marginal-zone B-cell lymphoma, extranodal-MALT-type. The first patient was a man, 76 years old, who presented with dacryocystitis. Computed tomography showed a homogeneous soft mass in the anatomical site of the lacrimal gland fossa displacing the ocular structures. After intravenous administration the lesion was enhanced homogenously (Figure 1). The second patient was also a man, 72 years old, who presented with similar symptoms and CT image. The

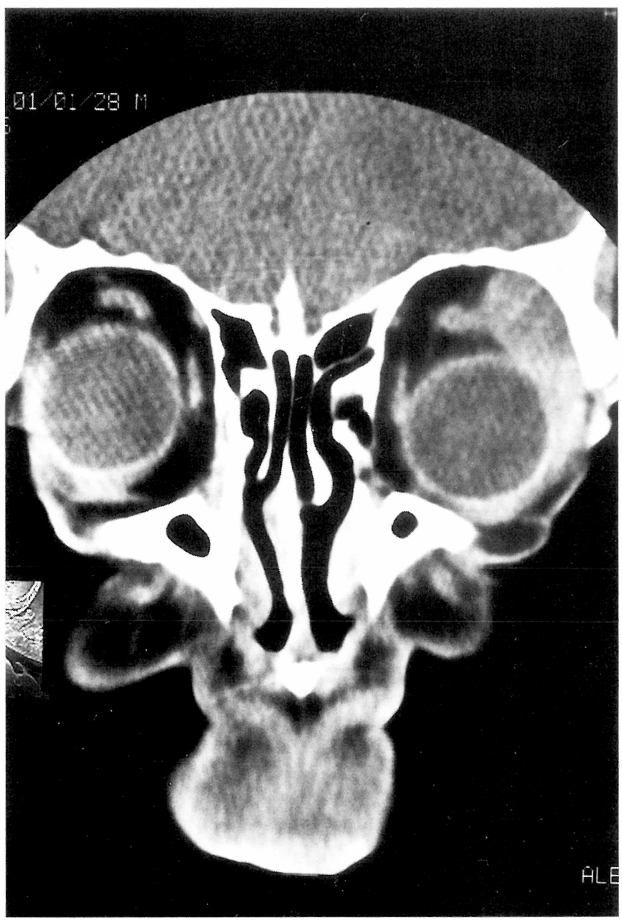

Figure 1. — CT (coronal view). Unilateral homogeneous enhanced soft tissue mass, after i.v. administration.

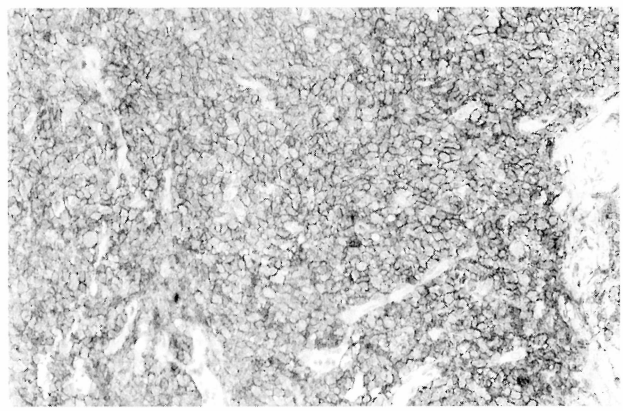

Figure 2. — NLH of the tonsil: Immunohistochemical stain L26x100.

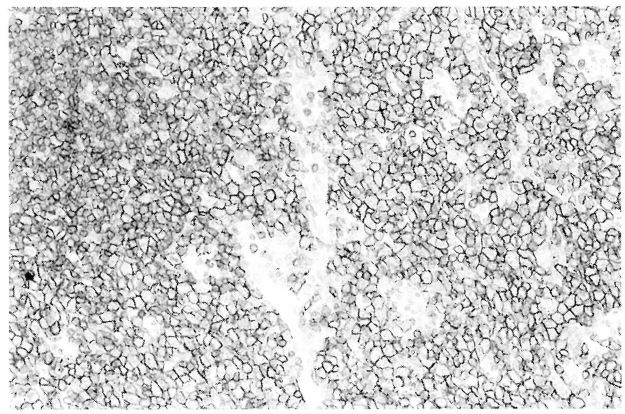

Figure 3. — NLH of the orbit (2nd case): Immunohistochemical stain L26x100.

excised specimen from the right orbit measured about 1.5 cm long. The third patient was a female, aged 71 years and the symptoms included sore throat and dysphagia. On clinical examination a grayish-white lesion arose in her right tonsil. A punch biopsy was performed and the patient was treated by tonsilectomy.

Histologic examination of all three specimens revealed malignant non-Hodgkin's lymphoma of a B-cell lineage, extranodal-MALT-type, according to the REAL classification. Immunohistochemistry confirmed our diagnosis in all three cases.

In the cases arising in the orbit two patterns of growth were recognized: a diffuse pattern with small and medium-sized proliferating cells and a nodular pattern. Nuclei were round with characteristic hyperchromasia there were many centrocyte-like cells, plasma cells and cells with multilobular nuclei. Neoplastic cells extended to the nearest striated muscle fibers at the periphery of the biopsy specimen.

In the case arising in the tonsil there was complete destruction of the architecture of the lymphoid tissue due to diffuse neoplastic cell infiltration. The malignant cells had cytological similarities to monocytes, non-cleaved ones and less to cleaved cells or plasma cells. Mitoses were rare.

In all three cases the immunophenotype was that of a B-cell. CD20 (L26) and CD79α antigens (β-lymphocytes) were strongly positive (Figures 2, 3). CD45Ro (UCHL1), CD4, CD5 and CD8 antigens (T-lymphocytes) showed weak positivity. Control for cyclin and Bcl-2 was negative and λ (lambda) light chain

gene expression was positive in a small population of neoplastic lymphoid cells. Bcl-2 control, in the case of the tonsil, demonstrated complete infiltration of a follicle by lymphoproliferative cells.

Discussion

Orbital lymphoid tumors are soft, friable, tan or salmon-colored masses that lack a connective tissue stroma (11) They are pliable and mold to the globe and other orbital structures. Orbital lymphoid tumors typically occur as an insidius, painless, well-tolerated proptosis in older patients (average age at diagnosis 60 years) [11].

Sometimes an orbital tumor occurs as a conjunctival lymphoid mass. In contrast to small blue round cell epithelial neoplasms of the lacrimal gland, lymphomas involve the superior orbit behind the orbital septum, and more than 40% involve the lacrimal gland, especially the palpebral lobe. Extension to bones is rare except in multiple myeloma. Only a single extraocular muscle is usually affected, and ocular mobility remains normal [11, 12, 20, 21]. Other extranodal sites that have associated lymphoid tissue (e.g., bowel and lung) share many biologic features with conjunctival lymphoid tumors.

Although polyclonal reactive or atypical lymphoid hyperplasias occur, about two-thirds are diffuse low-grade lymphomas composed of well-differentiated monoclonal B-lymphocytes. Some polyclonal reactive B-lymphocyte hyperplasias express immunoglobulin gene rearrangements using molecular genetic analysis [12, 13, 20]. Although monoclonal lymphomatous orbital masses are regarded as neoplastic, many, such as those in the conjunctiva, do not progress to systemic disease. In common with mucosa associated lymphoid tissue (MALT)-derived lymphomas they remain localized for a long time and are often preceded by an apparent reactive inflammatory stage. Extraocular and adnexal lymphomas are diffuse non-Hodgkin's lymphomas. Less than 15% are follicular or nodular lymphomas. T-cell lymphoid hyperplasia is preceded by or followed within 5 years by an extraorbital lymphoma [14, 16, 17].

Histopathologic features of reactive lymphoid hyperplasia include germinal centers, plump hyperplastic vascular endothelial cells, and a polymorphous infiltrate of well-differentiated polyclonal lymphocytes with occasional plasma cells, macrophages, eosinophils, and reactive germinal follicles. These follicles are often irregular in shape and distribution, within a stroma containing loose fibrous tissue, and they often contain tingible body macrophages and significant mitoses [13, 14, 18, 19].

Orbital lymphoid tumors need to be distinguished from the lymphocytic infiltration of Grave's disease. In Grave's disease a focal lymphocytic infiltrate is virtually limited to the extraocular muscles and invades the muscle tendon.

Correct histological diagnosis and careful staging are very important for the treatment outcome of localized low-grade orbital lymphoma. These patients show a very favorable prognosis and radiation therapy alone is very effective in the treatment of this malignancy [15, 17].

Waldeyer's ring consists of the circle of nasophangeal (adenoid), oropharyngeal tonsillar, and base-of-tongue lymphoid tissue. The lymphoid tissues of Waldeyer's ring are not readily included among those of MALT [22], but they do possess some similarities. These include the absence of sinusoids, the introduction of antigens through crypt epithelium, and the presence of marginal zone-related B lymphocytes [23].

Most primary lymphomas of the tonsils are of a B-cell lineage and occur as localized neoplasms. The age range for patients with Waldeyer's ring lymphoma is broad, from the first to the tenth decade. In most studies, the median age ranges from 55 to 64 years, with a 60% predominance in males [24, 26].

Using the Revised European-American Classification of Lymphoid Neoplasms (REAL), 85% of neoplasms would be classified as diffuse lymphomas [25], over half of which are diffuse large cell lymphomas. High-grade lymphomas usually show a destructive pattern of growth, and surface ulceration is often observed. The surface epithelium is often intact in low-grade lymphomas, which may infiltrate crypt epithelium [24]. In a study from the Kiel Lymph Node Registry [26], 12 of 329 cases of low-grade B-cell lymphoma of Waldeyer's ring consisted of low-grade B-cell MALT lymphomas. These neoplasms demonstrated an extrafollicular pattern of growth and a marginal zone-like arrangement of cells with centrocyte-like morphology. Eleven of the 12 cases were located in the palatine tonsil. Two had a high-grade MALT lymphoma showing a tropism for the overlying epithelium, but this finding cannot be considered evidence for the presence of a true lymphoepithelial lesion, which involves glandular epithelium [24].

Treatment for localized lymphoma of Waldeyer's ring consists of radiation therapy. Chemotherapy is used for higher stage lesions. The prognosis for patients depends on tumor histologic grade and stage. Patients with low-grade and low-stage lymphomas have a better prognosis than those with higher grade and stage lesions [24].

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