MINI REVIEW

Orbital lymphoproliferative disorders

As lymphocytic tumours go, those involving the orbit are rare, accounting for just over 2% of one large series reported from a general oncology unit, and even fewer appear in the orbit as a primary event.¹ The development of lymphoid lesions in this situation is presumed to be due to either neoplasia or reactive hyperplasia. The former is amenable to low-dosage radiotherapy, whereas the latter may sometimes be combated by the administration of corticosteroids on the assumption that it is an inflammatory response, albeit to an unknown antigen. In that case it is of more than academic interest to be able to distinguish between them.

In recent years there has been an attempt, attributable in particular to Jakobiec and his coworkers, to make the distinction on immunological grounds. That the attempt has not been entirely successful has not been through any inadequacy of the methods employed but rather because of a failure, only now beginning to be rectified, to appreciate that the lymphoproliferative disorders may represent a continuous spectrum of disease that is not separable in a conceptual sense. That is to say there are grounds for regarding virtually all pure lymphocytic proliferations in the orbit as either malignant or premalignant processes.

Lymphoid lesions in this situation have something in common with extranodal lymphocytic proliferations in the gut, bronchus, and other sites, the so-called mucosa-associated lymphoid tissues (MALT).² A key property of this type of lymphoid tissue is that, where the lymphocytes accumulate with age, there is a predisposition for lymphomas to emerge after a long phase of localised disease.² The premalignant proliferation may be a polyclonal reaction to repeated antigenic challenge. The case for including orbital lymphoproliferative disease in this bracket is at present speculative, particularly as, other than the lacrimal gland, lymphoid tissue is never a 'normal' component of the orbit. It does help, nevertheless, to regard lymphocytic infiltration in this situation as a potentially progressive spectrum of disease.

LYMPHOID HYPERPLASIA

At one end of the spectrum is a benign proliferation of lymphocytes in which there is an admixture of T and B cells, the latter presenting a polyclonal immunoglobulin profile. The T cell component usually accounts for more than 60% of the lymphocyte population,³⁻⁵ and there is reported to be a preponderance of helper as opposed to suppressor T cells in a ratio of about 5:1, which considerably exceeds the 2:1 ratio usual in normal lymph nodes and the peripheral blood.⁴ Germinal centres may be seen, but, although they have usually been taken to be one of the more reliable histological indicators of a reactive lesion,⁶ they are far from being an infallible guide. Prominence of the interstitial capillaries attributable to endothelial cell hypertrophy is another feature of reactive lesions, and it seems that such cells are a factor in the tendency for MALT in general to remain localised, since they are able to bind lymphocytes equipped with the appropriate surface receptors.⁷

The presence of plasma cells and histiocytes also supports the diagnosis, as does the less frequent finding of eosinophil leucocytes. If eosinophils are a significant feature, it may be that a diagnosis of Kimura's disease (angiolymphoid hyper-

plasia with eosinophilia) should be considered, especially if capillary endothelial hypertrophy is present.⁸ Where, however, there is a conspicuously diverse leucocytic infiltrate including, possibly, polymorphonuclear neutrophils, a diagnosis of idiopathic chronic inflammation is likely to be more accurate than lymphoid hyperplasia, especially if there is an appreciable fibroblastic response. Evidence of polyclonality, as shown by immunohistochemical staining of the tissue for the presence of κ and λ light chains, is a helpful but again not infallible pointer to a reactive process.

There is no radiological distinction between reactive and neoplastic lymphoid proliferations within the orbit⁹ and clinical separation is also largely impossible, though pain sometimes accompanies the inflammatory masses in contradistinction to the essentially painless lymphomas.¹⁰

It might be noted in passing that the term pseudotumour is a totally inadequate way of describing these lesions, especially as it can be variously taken to relate exclusively to hyperplastic lymphoid processes or to encompass the whole gamut of circumscribed orbital inflammatory disorders.¹¹

LYMPHOMA

While it may be supposed that lymphomatous lesions represent the outcome of a mutation affecting a single cell, the progeny are often heterogeneous in terms of subclass expression in that they can synthesise multiple antibody heavy chains and are accompanied by a variable T cell response.¹² In the specific orbital context the T cell component is almost always less than 40%,¹³ but the presence of tumour B cells with anomalous T cell markers can further confuse the picture.¹⁴ MALT-derived lymphomas are, however, relatively homogeneous in respect of light chain expression, and evidence of oligoclonality, if not monoclonality, is a reliable index of neoplastic behaviour. Histological recognition may be possible by virtue of irregularly distributed atypical lymphocytes between the small, mature cells; commonly the former are centrocytes and centroblasts, when the prognosis following radiotherapy is fairly good. Lymphoplasmacytoid forms are also common and of similar low grade malignancy. Higher histological grades of malignancy, usually indicated by increased proportions of lymphoblasts, are less common but carry a worse prognosis.¹⁵

There has been some speculation on why orbital lymphomas tend to be confined to the orbit for long periods before metastasising. One possibility is that they are initially reactive lesions and only subsequently become truly neoplastic,¹⁵ while another is that they share a feature common to several other types of extranodal lymphomas of homing back to their tissue of origin should they enter the general circulation.² The absence of lymphatic drainage channels might also impede dissemination.

INDETERMINATE LYMPHOID PROLIFERATIONS

There are some lymphocytic lesions within the orbit that defy ready categorisation. They may present as masses of mainly small mature lymphocytes with few, if any, of the atypical forms which would point to neoplasia. Or they may lack the mixed leucocyte composition and germinal centre formation

indicative of a reactive process. In those cases where immunohistochemistry serves to demonstrate light chain restriction a diagnosis of lymphoma, usually of low grade malignancy, can be established.¹⁰ The real difficulty arises when there is either absence of immunolabelling by light chain antibodies or, alternatively, a polyclonal pattern.

Failure to respond to immunostaining may be for technical reasons, due to a paucity of reactive groups on the lymphocytes or, conceivably, to the lesion in question being a T cell lymphoma. As yet, however, the only substantiated report of a T cell lymphoma arising within the orbit has concerned a patient in the advanced stages of an HTLV-1 related T cell leukaemia.¹⁶ A polyclonal immunoglobulin profile taken at face value might suggest a reactive process, but clinical experience shows that many patients with this type of lesion later present evidence of dissemination and are seen to be suffering from a true lymphoma.^{14 15 17} That a lymphoma should be masked in this way is understandable if it is allowed that a neoplastic proliferation may supervene in an initially reactive disorder, in which case the two processes would be operating together for a time. Examples of a sequence of this sort have been provided in respect of extranodal lymphomas in other situations, including the bronchus¹⁸ and salivary glands,¹⁹ and there is now good reason to believe that the same is true of the orbit. Indeed, a recent prospective analysis of some 69 patients with orbital lymphoproliferative disease casts serious doubt on the value of making a distinction between neoplastic and putative hyperplastic lesions on the basis that, while 33% of histologically diagnosed lymphomas were associated at some stage with disseminated tumour deposits, as many as 27% of hyperplastic lesions behaved in a similar fashion.¹³ The validity of the histological diagnosis was inferred by an almost identical immunophenotypic analysis.

A study of five orbital lymphoid tumours that appeared to be reactive hyperplasias by light microscopy and which presented a polyclonal immunophenotypic picture showed, by means of molecular gene rearrangement analysis, that three of them were harbouring small clones of monotypic lymphocytes.¹⁵ This is particularly interesting because it provides for an improved understanding of the lymphoproliferative disorders as they affect the orbit as a whole. Moreover, the same study revealed an overall predominance of T lymphocytes with a decided increase in the proportion of helper cells, which could mean that there is an imbalance of immunoregulatory function such that there is an ensuing undue B lymphocyte proliferation. The finding of low serum IgA levels, of slightly reduced numbers of T cells in the peripheral blood, and of circulating autoantibodies in some patients with lymphoproliferative orbital disease also suggests a disturbance of immunoregulation.¹⁰ In these circumstances it would be conceivable that a mutation with neoplastic potential might emerge. An investigation by McCartney (personal communication, 1991) demonstrating the presence of follicle centre cells in proved lymphomas with monotypic light chain restriction adds further support to the concept of origin from a pre-existing reactive lesion.

MANAGEMENT

This is not the place for a detailed discussion of therapeutic strategy, but the information which is now available does call for some comment. Since there would seem to be cause to regard all lymphoid proliferations as potential, if not always actual, neoplastic conditions, it is probably sensible to treat all but the most obviously inflammatory lesions accordingly. The response to low doses of radiotherapy, of the order of 30 gray, has been shown to be an effective way of dissipating the apparently indeterminate lymphoid lesions as well as the undoubted lymphomas²⁰ and is much to be preferred to a trial course of corticosteroids given in the hope that the proliferation will prove to be inflammatory. Even so, a note of caution is appropriate, given that a minority of patients can be expected to have occult extraorbital tumour deposits which will only later become clinically manifest. Consequently, a thorough systemic investigation of every patient with an orbital lymphoproliferative mass would seem advisable.

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