Evolution of a primary lymphoma of the orbit

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SUMMARY A patient with a histologically benign lymphoid pseudotumour of the orbit developed a recurrent mass which proved to be a well differentiated lymphocytic lymphoma. Immunohistological studies showed that a majority of cells in the pseudotumour bore the same immunological markers as the subsequent lymphoma. There were no clinical or radiographic features of the initial lesion which indicated its eventual malignant course.

Inflammatory ‘pseudotumours’ of the orbit frequently present as mass lesions suggestive of a primary lymphoma. Several studies have shown that there are no clinical or radiographic features by which benign and malignant lymphoproliferative processes can with certainty be distinguished.1-3 This diagnostic dilemma often makes open biopsy of orbital lesions a necessity for proper patient management, yet even after tissue is obtained uncertainty may persist. The pathological evaluation of lymphoid proliferations in extranodal sites such as the orbit is fraught with difficulty. An exuberant chronic inflammatory process may be virtually indistinguishable from a well differentiated lymphocytic lymphoma by conventional histological and cytological criteria. So much effort has gone into the study of these lesions that the range of identifiable subtypes of pseudotumours is beginning to approach the breadth of the classifications of lymphoma.4 Many authors have attempted to define criteria for deciding which processes are unequivocally benign and which malignant; which benign proliferations will respond to medical therapy; which benign lesions herald the onset of lymphoma; and which subtypes of lymphoma will rapidly disseminate.

Like many other investigators we have found that immunological techniques can help to answer the above questions to some degree.5,6 The case we present below provides an example of the usefulness of these methods. Biopsy specimens were taken from our patient because of a recurrent orbital mass; the first specimen showed a benign pseudotumour, the second a malignant lymphoma. Immunohistological studies retrospectively disclosed within the patient’s initial lesion the seeds of her subsequent lymphoma.

Case report

A 67-year-old white woman was referred for examination with a 10-month history of pain and proptosis of the right eye. Her symptoms had been relieved by steroid therapy, but recurred on withdrawal of medication. Examination showed the right globe to be displaced upwards by a mass in the floor of the orbit (Fig. 1). The eye was painful to palpation and movement. Visual acuity was 20/40 bilaterally. Hertel exophthalmometry showed the right eye 22 mm, the left eye 20.5 mm, at an interorbital distance of 95 mm. Ultrasonography revealed an anechoic area in Tenon’s space, contiguous with the optic nerve shadow, and mottling of the retrobulbar fat (Fig. 2). A CT scan showed a poorly defined mass within the retrobulbar muscle cone, with thickening of the lateral sclerouveal rim (Fig. 3). These findings...
were felt to be consistent with an inflammatory pseudotumour.

Laboratory studies, including thyroid function tests and serum immunoglobulin levels, were normal. Steroid therapy was continued but was complicated by the development of upper gastrointestinal bleeding. It was decided to obtain a tissue diagnosis and then institute radiation therapy.

Kronlein orbitotomy was performed 2 years after the first onset of symptoms. At surgery an ectopic lacrimal gland was found in the inferotemporal portion of the outer surgical space, with an adjacent mass of inflammatory tissue infiltrating Tenon's space and expanding within the muscle cone. Microscopical examination showed chronic dacryoadenitis with extensive lymphoid infiltrates, consistent with benign pseudotumour (Fig. 4). A more detailed pathological description is given below. After the operation the patient received 1000 rads of radiation therapy to the right orbit, with resolution of all symptoms, except for some dryness of the eye.

Four years later the mass recurred, and at this time an area of swelling in the soft palate was also noted. The right eye was once more displaced upwards, and a mass was palpable in the right lower lid anterior to the orbital septum. Hertel exophthalmometry was 17 mm bilaterally; slit-lamp examination and ophthalmoscopy were unremarkable. CT scanning revealed a poorly marginated mass fixed to the posterolateral sclera between the inferior and lateral rectus muscles, extending along the optic nerve (Fig. 5), with oedema of the optic nerve sheath (Fig. 5, arrow).

Orbital exploration was once again performed. What appeared to be a single continuous mass was found arising within the muscle cone, extending anteriorly and inferiorly in front of the inferior rectus muscle into the extrasurgical space, and protruding anteriorly through the orbital septum into the lower lid. The entire mass was excised. Pathological examination revealed well differentiated lymphocytic lymphoma. A biopsy of the soft palate also showed lymphoma. Immunohistological studies were per-
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Table 1  Patient's serum immunoglobulin levels (normal values for our laboratory: IgG 564–1765 mg/dl, IgA 85–385 mg/dl, IgM 53–375 mg/dl)

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SI conversion: mg/dl×0.01 = g/l.

formed on these specimens and on paraffin embedded tissue from the original biopsy (see below).

Laboratory studies at this time demonstrated the presence of an IgM lambda monoclonal paraprotein in the patient's serum. The total IgM was in the high normal range, while the IgG and IgA levels were decreased (Table 1). No coagulopathy or other complications of macroglobulinaemia were observed. Bone marrow examination, liver-spleen scan, and other studies were normal.

The patient received 3400 rads of radiation therapy to the right orbit and palate, with resolution of symptoms, and 20 months later there is no evidence by x-ray or physical examination of recurrent tumour. However, the paraprotein has persisted in her serum, and during the past year and a half it has shown a steady rise, consistent with systemic dissemination of her disease.

Materials and methods

Frozen sections of tissues from the recurrent orbital mass were air-dried in the cold, fixed in chilled acetone, rinsed in phosphate-buffered saline (PBS), pH 7.4, then covered with solutions of fluorescein-conjugated rabbit antisera to human IgG, IgA, IgM, and to kappa and lambda light chains (Kallestad, Inc., Chaska, MN, USA). The slides were incubated for 30 minutes, then immersed in 2 changes of PBS for one hour, cover-slipped, and examined by fluorescence microscopy. A negative control section received PBS only; positive control sections of tonsil were run concurrently.

Immunoperoxidase staining was performed on deparaffined sections from all 3 biopsies. The sections were incubated for 20 minutes in 3% H2O2, then covered with normal sheep serum. Subsequent incubations with rabbit antisera to human heavy and light chains, with sheep antirabbit serum and with rabbit peroxidase-antiperoxidase complexes (Immulok Corp., Carpentaria, CA, USA) followed the Sternberger PAP method. Stains were developed in a diaminobenzidine-H2O2 solution. Positive and negative controls were run as for immunofluorescence. The specificity of antisera was tested by staining bone marrow biopsies from patients with myeloma.

Pathologic Examination

Sections of the original biopsy showed lacrimal gland elements, surrounded and focally infiltrated by large numbers of mature lymphocytes, plasmacytoid and plasma cells, and occasional histiocytes and acute inflammatory cells. No eosinophils were seen. Scattered germinal centres were present. The tissue excised from within the muscle cone, adjacent to the optic nerve, was composed of masses of mature lymphocytes with occasional plasma cells. No cyto-

![Fig. 5](http://bjo.bmj.com/68/4/255.png)  Direct coronal CT scan of the recurrent lesion demonstrating a poorly marginated mass in the right orbit between the inferior and lateral rectus muscles, with oedema of the optic nerve sheath (arrow).
logical features of malignancy were seen. In retrospect the process was still entirely consistent with a benign lymphoid pseudotumour associated with an ectopic lacrimal gland.

The recurrent mass showed typical microscopical features of a diffuse, well differentiated lymphocytic lymphoma with plasmacytoid characteristics. It consisted of a diffuse infiltrate of somewhat pleomorphic small lymphocytes, plasmacytoid cells, and plasma cells, with occasional lymphoblasts. The nuclear membranes were often slightly irregular. Many nuclei contained prominent nucleoli; most showed peripheral chromatin clumping. Occasional mitotic figures were observed (Figs. 6, 7). Many blood vessels showed thickened, hyalinised walls, but special stains for amyloid were negative.
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Immunoperoxidase staining of the first biopsy specimen revealed a predominance of cells positive for IgM and for lambda light chain. Smaller numbers of lymphoid cells positive for kappa chain were seen singly or in clusters in all areas. The total number of cells which failed to stain for lambda light chain was roughly equal to the number positive for kappa. No areas of pure monoclonal staining were observed. The polyclonal pattern was present throughout the biopsy, including the totally benign-appearing foci of chronic dacryoadenitis, where most of the mature plasma cells were positive for IgM and for lambda.

Immunofluorescence and immunoperoxidase staining of the recurrent orbital mass showed a monoclonal IgM lambda staining pattern (Figs. 8, 9). The biopsy of the soft palate showed the same histological and immunohistological features (not shown).

Discussion

We have attempted without success to recognise any clinical, radiographic, or conventional pathological feature of this patient’s presenting lesion which might have forewarned us of its impending malignant transformation. The clinical signs and symptoms were typical for benign pseudotumour. The fact that the process failed to resolve despite prolonged steroid therapy does not imply that it was neoplastic from the start, since pseudotumours are frequently steroid resistant. In the series of patients with benign lesions described by Garner and Chavis, for example, 50% responded only transiently, or did not respond at all, to corticosteroids.

There was also nothing in the appearance of the original ultrasonogram to suggest that the process was other than inflammatory. This image shows the familiar features, first described by Purnell and Coleman, of mottling of retrobulbar fat and a well defined echolucency of Tenon’s space and the optic nerve sheath, forming a partial T-sign, which are associated with orbital inflammation. The absence of any discrete, recognisable mass agrees with Restori’s observation that usually only small portions of a pseudotumour are included in B-scan sections, so that the diagnosis must be based largely on the inflammatory changes. The only unusual feature of her initial imaging, from our point of view, was that the existence of the ectopic lacrimal gland went unrecognised prior to surgery.

The appearance of the primary lesion by CT scanning was also typical of lymphoid pseudotumour. As with ultrasound, the diagnostic CT features are principally those of an inflammatory process: oedema of soft tissue structures, the suggestion of a mass of uneven density in Tenon’s space, which accentuates with contrast medium, and thickening of the sclero-
lymphoma of the orbit, both of whom died with widespread lymphoma. One of these patients had a monoclonal IgA lambda paraprotein, the other an IgM. There was no description in these reports of coexisting orbital inflammation. We have speculated that in our patient’s case the chronic inflammatory stimulus provided by an ectopic lacrimal gland may have led to the development of a well differentiated lymphoma as a type of defective inflammatory response. Further immunohistological studies of the lymphoid infiltrates associated with ectopic lacrimal glands in other patients may help to clarify the role of these lesions as possible tumorigenic stimuli.

This case provided us with a unique opportunity to follow the evolution of an orbital lymphoma. The lesion appeared benign on initial biopsy, yet immunological studies revealed that many cells in the inflammatory infiltrate were members of a clone which subsequently transformed into a malignancy. Our results substantiate the value of immunological studies in the complete evaluation of lymphoproliferative processes in the orbit.

The ultrasonogram was performed by Lt-Col Kenyon Kramer MC, USA, at Walter Reed Army Hospital. The initial biopsy was reviewed by Dr Lorenz Zimmerman, chief of ophthalmic pathology, Armed Forces Institute of Pathology, Washington DC. Immunohistologic procedures were performed by Mr Wilfred Shelton.

This research was performed in the clinical laboratory of the Department of Pathology, Washington Hospital Center. No outside funding was involved.

References