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Editorial

Changing patterns in orbital pathology

The last four decades have witnessed a number of changes in the pathologist's approach to space-occupying lesions of the orbit. The increasing recognition of the morphological and behavioural nuances between lesions of similar appearance or origin, which has been a feature of surgical pathology in general, has been accompanied by technical and conceptual advances. Electron microscopy has been largely replaced by immunohistochemistry (IHC), which becomes ever more sophisticated. Molecular pathology (cytogenetics and molecular genetics) has refined the categorisation of many morphologically similar tumours, particularly mesenchymal neoplasms. Improved classification of lymphomas has made their diagnosis more consistent and the recognition of IgG4-related disease involving the orbital soft tissue and/or lacrimal gland has opened a new perspective on inflammatory pseudotumour/idiopathic orbital inflammation.

One of the most intriguing changes in orbital pathology has been the 'disappearance' of fibrous histiocytomas and haemangiopericytomas (HPC) and their replacement by solitary fibrous tumour (SFT). The concept of fibrohistiocytic neoplasms arose in the 1960s and 1970s out of tissue culture and ultrastructural studies, until by 1980 malignant fibrous histiocytoma (MFH) was regarded as the most common sarcoma in adults.[1] In 1982 Font and Hidayat reviewed 150 cases of fibrous histiocytoma of the orbit and concluded that it was the most common primary mesenchymal neoplasm in that site.[2] Nowadays, with the introduction of IHC and molecular testing, MFH is regarded as more of a morphological pattern than a specific neoplasm.[1] A similar fate has befallen the HPC phenotype, which is now viewed as a morphological pattern shared by a number of tumours and particularly SFT. Furusato et al. have proposed that HPC, giant cell angiofibroma and fibrous histiocytoma of the orbit should all be considered SFT.[3]

The review by Roberts in this issue highlights the value of cytogenetics and molecular genetics in the proper diagnosis of mesenchymal tumours.[4] The author divides these mesenchymal neoplasms into three categories:

1. those for which molecular pathology is diagnostically useful (small round blue cell tumours, liposarcomas and spindle cell proliferations);
2. those for which molecular pathology contributes to prognostication (alveolar rhabdomyosarcoma, synovial sarcoma);
3. those in which molecular pathology has identified specific protein biomarkers that are diagnostically helpful (SFT, alveolar soft part sarcoma, low-grade fibromyxoid sarcoma and chordoma).

There will no doubt be many more examples reported in the coming years and the contribution of molecular pathology to the diagnosis and prognosis of orbital neoplasms, is certain to grow. Already, the delineation of genetic abnormalities in a variety of sarcomas has led to the introduction of targeted therapies.[5]

Another conceptual shift in orbital pathology came with the recognition of IgG4-related disease (IgG4-RD) as a cause of inflammatory pseudotumour/idiopathic orbital inflammation. Although it has long been recognized that fibro-inflammatory lesions of the orbit could be accompanied by similar lesions in other organs and sites, prior to the description of IgG4-RD, there was no satisfactory explanation of the association. Some remain sceptical as to whether this is a real disease – it is named after a non-specific biomarker – but it has become generally accepted that pathologists should categorise fibro-inflammatory lesions of the orbit (and other sites) in terms of the IgG4 status. In the orbit, IgG4-RD may involve the soft tissue or the lacrimal gland, in the form of chronic sclerosing dacryoadenitis, but tends to show less storiform fibrosis and more reactive lymphoid hyperplasia, sometimes in an unusual pattern,[6] than in other sites. Obliterative phlebitis is also unusual. The presence of IgG4-positive plasma cells, although a key diagnostic feature, is not necessarily pathognomonic, since these cells may also be seen in the lesions of Wegener's granulomatosis and syphilis affecting the orbit. They may also be seen in periocular xanthogranulomatous inflammation and it has been suggested that, if IgG4-positive plasma cells are abundant, the patient should be evaluated for systemic involvement by IgG4-RD.[7]

Perhaps the area of orbital pathology where practice has changed most over the past forty years has been the diagnosis and classification of malignant lymphomas. Older pathologists will remember the struggle to master the different classification schemes as they were sequentially introduced: Rappaport (1966); Lukes/Collins (1974); Kiel (1974); National Cancer Institute Working Formulation (1982) and REAL classification (1994). Finally, the WHO Classification based on morphological pattern, immunophenotype, molecular and cytogenetic profiles and clinical presentation was implemented in 2001; this has remained in use and has been updated twice in 2008 and 2016. Along the way pathologists were able to largely abandon the unsatisfactory diagnosis of 'atypical lymphoid hyperplasia', when the concept of MALT

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(mucosa-associated lymphoid tissue) lymphoma was introduced by Isaacson and Wright in 1984.[8]

Lymphoma is the most frequent tumour of the ocular adnexa and the incidence is increasing. Over 50per cent of ocular adnexal lymphomas are of MALT type or, as they are better described, extranodal marginal zone lymphomas. These are located primarily in the orbit, may be bilateral (10%) and, although rather indolent in behaviour with a 75per cent 5-year survival, frequently present with disseminated disease (25%).[9] Unlike metastatic carcinoma, involvement of the extraocular muscles is uncommon and Al Sheikh and Alhammad in this issue report a case where marginal zone lymphoma was confined to one of the muscles.[10] Although the precise diagnosis of lymphomas is challenging, it remains important for ophthalmic pathologists to examine material from the ocular adnexa submitted with this clinical diagnosis in order that alternative diagnoses may not be overlooked. A definitive diagnosis of lymphoma should, however, not be rendered without consultation with a haematopathologist.

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