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Orbital Pathology Update

An update on mesenchymal tumours of the orbit with an emphasis on the value of molecular/cytogenetic testing

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Abstract

Mesenchymal tumours of the orbit are uncommon. Beyond childhood primary sarcomas are extremely rare and the literature is limited to case reports and short case series. However there is a diverse assortment of benign and malignant soft tissue tumours that may involve the orbit. Techniques to identify tumour specific cytogenetic or molecular genetic abnormalities often resulting in over- expressed proteins are becoming an increasingly important ancillary technique for these tumours. This review focuses on 3 specific areas: 1. Orbital mesenchymal tumours where cytogenetics are important to reach the correct diagnosis. The majority of these are chromosomal translocations that often result in a fusion gene and protein product; 2. Orbital mesenchymal tumours where cytogenetics are important to identify patients who will do well versus those with a poorer prognosis. This is turn helps with therapeutic options. In some tumours e.g. synovial sarcoma the chromosomal translocations can occur with 2 different regions resulting in different fusion products that carry a different prognosis. Alternatively whilst the majority of alveolar rhadomyosarcomas are fusion positive a minority are fusion negative with a better prognosis; 3. Orbital mesenchymal tumours where the identification of specific cytogenetic abnormalities has resulted in overexpression of specfic proteins which are diagnostically useful biomarkers for immunohistochemistry.

Keywords: Cytogenetics, Molecular genetics, Mesenchymal tumour, Soft tissue tumour, Orbit

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Introduction

There is a predominance of mesenchymal tissues in the orbit however despite this primary mesenchymal tumours are relatively rare. In adults the most common mesenchymal tumour (excluding cavernous haemangioma) is solitary fibrous tumour. In children embryonal rhabdomyosarcoma is the most common mesenchymal tumour (excluding capillary haemangioma). Beyond childhood primary sarcomas are rare with only individual reports and small case series in the literature.

Cytogenetic and molecular genetic assays are used routinely for diagnostic purposes in soft tissue pathology and represent a powerful adjunct to complement conventional microscopy. Many soft-tissue tumours are characterised by recurrent chromosomal rearrangements commonly translocations that produce specific gene fusions which allow precise classification of tumours.[1] This has been particularly useful for separating small round blue cell tumours of childhood. Furthermore overexpressed genes in mesenchymal tumours may result in overexpression of protein products that have provided novel and specific immunohistochemical markers.[2] In addition the identification of morphologically similar

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tumour groups with different behaviour and different cytogenetic findings has allowed better prognostication of some mesenchymal tumours.[3]

Molecular techniques have transformed the diagnosis of mesenchymal tumours in soft tissue. The diagnosis of orbital mesenchymal tumours should follow the same algorithm as soft tissue diagnosis elsewhere and include morphological, immunohistochemical and where appropriate molecular diagnostic techniques. The aim of this review is to consider the appropriate uses of these molecular techniques as applied to mesenchymal tumours occurring in the orbit (see Table 1).

Orbital mesenchymal tumours where cytogenetics is useful for diagnosis

Small round blue cell tumours

A number of small round blue cell tumours can rarely present within the orbit. Those encountered include Ewing's sarcoma, poorly differentiated synovial sarcoma, alveolar rhabdomyosarcoma and mesenchymal chondrosarcoma.

Ewing's sarcoma

Ewing's sarcoma is a high grade malignant tumour which typically presents in the long bones of children and young adults. It is only rarely seen in the head and neck and then generally involves the jaw bones. Most cases are metastatic from distant sites and primary orbital Ewing's sarcoma is extremely rare.[4,5] Histologically the tumour is composed of sheets of small round blue undifferentiated cells. They have a very small amount of cytoplasm. Nucleoli are usually not discerned. Immunohistochemical staining reveals strong membranous CD99 positivity. FLI1 shows nuclear staining. It is important to ensure that lymphoma is excluded by immunohistochemistry. Molecular studies are extremely helpful in the diagnosis of Ewing's sarcoma and should be carried out on all cases. A translocation involving chromosomes 11 and 22 is the commonest abnormality seen and is present in 85% of cases.[6] A rearrangement fuses the *EWSR1* gene with part of the *FLI1* gene forming the *EWSR1/FLI1* fusion gene in the vast majority of cases. This abnormality can be detected on fluorescent in situ hybridisation (FISH) analysis and by Reverse transcriptase polymerase chain reaction (RTPCR). There are alternative fusion partners for EWSR1 in a smaller number of cases. These include the *ERG* gene

Table 1. Summary of the key role of molecular genetics in the more common mesenchymal tumours of the orbit.

Mesenchymal origin	Chromosomal abnormality	Gene involved or fusion gene	Prevalence	Role of cytogenetics	References
Small blue cell tumours					
Ewing Sarcoma	t(11;22)(q24;q12) t(21;22)(q21′p12)	*EWSR1-FLI1* *EWSR1-ERG*	85% 5–10%	Diagnostic	Chen et al. 7
Synovial Sarcoma	t(X;18)(p11;q11)	*SS18-SSX1/SSX2 or SSX4*	66% SS18-SSX1 33% SS18-SSX2 Few SS18-SSX4	Diagnostic and Prognostic (SSX1 less favourable)	Stagner et al. 9
Mesenchymal Chondrosarcoma	t(8;8)(q21.1:q13.3)	*HEY1-NCO2*	Most	Diagnostic	Moriya et al. 14
Rhadomyosarcoma					
Embryonal RMS	Multiple events – no specific gene	–	–	–	Parham et al. 16
Alveolar RMS	t(2;13)(q35;q14)	*PAX3-FOXO1*	60%	Diagnostic & Prognostic (Less favourable for those without translocation)	Parham et al. 16
	t(1;13)(p36:q14)	*PAX7-FOXO1*	20%		Kubo et al. 57
Liposarcoma					
Well differentiated LS/ ALT	Amplication of 12q14-15	Overexpression of *MDM2*	100%	Diagnostic	Jakobiec et al. 18
Myxoid LS	t(12;16)(q13;p11)	*FUS-DDIT3* *EWSR1-DDIT3*	95% 5%	Diagnostic	Rao et al. 27
Spindle cell proliferations					
Low grade Fibromyxoid Sarcoma	t(7;16)(q33;p11)	*FUS-CREBL2*	76–96%	Diagnostic	Mohamed et al. 30
	Ring chromosome t(11;16)(p11;p11)	*FUS-CREBL1*	4–6%		
	3q29	Over expression *MUC4*	100%	Biomarker – MUC4 IHC	Doyle et al. 55
Nodular Fasciitis	t(17;22)(p13;q13)	*USP6-MYH9*	100%	Diagnostic	Compton et al. 31
Solitary Fibrous Tumour	Inv(12)(q13;q13)	*NAB2-STAT6*	100%	Diagnostic Biomarker – STAT6 IHC	Thway et al. 45
Miscellaneous mesenchymal tumours					
Alveolar Soft Part Sarcoma	t(X;17)(p11;q25)	*ASPOL-TFE3*	NK – majority	Diagnostic Biomarker – TFE3 IHC	Folpe et al. 47
Chordoma	6p27	Brachyury	NK – majority	Biomarker – Brachyury	Miettinen et al. 58

LS-Liposarcoma; ALT – atypical lipomatous tumour; t – translocation; NK – not known; IHC – immunohistochemistry.

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