Orbital Pathology Update

Orbital pathology – Iatrogenic findings and artefacts

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Abstract

The relationship between the ophthalmologist and ophthalmic pathologist is particularly important in orbital disease, as diagnosis is heavily dependent on correlation with clinical context. If the patient has previously had treatment to the orbit or an adjacent area, whether for the same or a different condition, tissue changes may occur which affect the histological appearance of any specimen taken. This article is an overview of therapeutic interventions which may cause either orbital pathology or an altered appearance of the tissue, either of which can pose a diagnostic challenge. The problem of artefact is also addressed as another factor which may alter the appearance of a specimen. It is hoped that the information provided in this brief review will help clinicians better evaluate what information may be relevant when submitting a specimen.

Introduction

Orbital surgery is an ophthalmology subspecialty where diagnosis often requires integration of information from other specialties, including radiology and histopathology. In many organisations the ophthalmologists and histopathologists have a close working relationship. In some countries the ophthalmologist may even examine his or her own specimens histopathologically.

Not all organisations or individuals have such a relationship, however, particularly if few specimens are generated or if the laboratory is geographically distant from the ophthalmology department. The histopathologist typically does not know the patient and relies on the surgeon for information. Ignorance of the history can potentially lead to misdiagnosis. At best, time and resources are wasted: at worst, patient care is compromised. It is particularly important where there is limited opportunity for communication that the ophthalmologist and histopathologist do not inadvertently mislead each other.

Histological diagnosis requires not just macroscopic examination (grossing) of the specimen and examination of microscope slides, but interpretation in the clinical context and judgement as to the most likely diagnosis for a specific case. Relevant clinical information could include: age, sex, clinical presentation, time course, site, and knowledge of previous history and interventions. The more comprehensive the information provided, the more easily and quickly the histopathologist can arrive at a diagnosis.

In management of orbital conditions, two major prior interventions that the patient might not even remember in the context of the current problem are radiotherapy and introduction of foreign material that might affect the orbit. The latter may be related to trauma and reconstruction rather than planned therapy, and either intervention may have occurred years or decades previously.

The two interventions mentioned above may give rise to pathologies of their own (such as radiation damage, radiation-induced tumour or foreign body reaction), which may or may not be directly related to the current indication

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for surgery. The prior intervention might cause an unusual pathology, which might not otherwise be considered in the differential diagnosis. Even if not related, changes in the specimen's appearance because of previous treatment can be taken into account. Knowledge of these prior interventions will therefore contribute to the histopathologist's ability to help.

Prior patient interventions are not the only challenges histopathologists face when examining a specimen. On a more general note, specimens are vulnerable to various artefacts which may occur any time from the surgical procedure and sampling to examination of prepared slides in the laboratory. Artefacts are certainly not unique to orbital surgery and pathology, but they will be briefly covered here, to give a flavour of how they may hinder the diagnostic process. There are opportunities for surgeons to help reduce artefact, and some suggestions will be made.

This review is based on a PubMed literature search and personal experience of the author, with an emphasis on issues which may affect provision of an accurate diagnosis. Illustrative cases from the author's own practice are provided as examples.

An overview of artefacts

In the context of histopathology, artefacts can be broadly defined as any changes in tissue between removal at surgery and microscopic examination that are caused by the process rather than reflecting pathology. Their major significance is that they may either be mistaken for genuine pathology, or obscure the diagnosis.

There are many causes of artefact,[1,2] and laboratories strive to minimise the impact of artefacts that may occur after specimen receipt. However, they are limited in what they can do to rectify artefacts that occur before receipt.

Certain artefacts may occur during surgery. Although some are unavoidable (such as diathermy artefact when ensuring haemostasis), the surgeon may be able to ameliorate some of them. Ideally, diathermy and tissue handling (eg crushing with forceps) should be kept to a minimum. Specimen fragmentation may be unavoidable, particularly when debulking a friable tumour, but it makes assessment of margins nearly impossible. If sampling a specimen eg for research, it is advisable to avoid compromising surgical margins.

Although intraoperative artefact may be inevitable, artefacts due to inappropriate fixation can always be avoided. If tissue is left out of fixative (the standard fixative is 10% neutral buffered formalin), preservation is compromised, and it may dry out. If tissue is put into an inappropriate fluid (such as water or saline) fixation will not take place, the tissue may autolyse and/or structural changes may occur. A specimen in formalin does not need to be refrigerated, and it especially should not be frozen. Freezing causes ice crystals to form and disrupt the tissue (Fig. 1). If intraoperative histological diagnosis is being made, using a frozen-section procedure, the appearance is similar to accidental freezing. However, these are anticipated, and the equipment used freezes the tissue rapidly in order to minimise artefact.

Iatrogenic pathology of the orbit

As previously mentioned, interventions may directly give rise to the presenting pathology (such as radiation-induced tumours) or they may modify the appearance of the tissue.
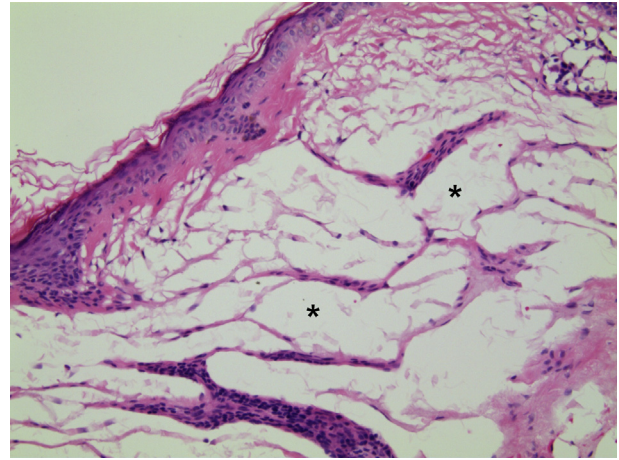

Fig. 1. This probable skin tag was biopsied, placed in a formalin pot and then inadvertently frozen. The dermis has large empty clefts (*) caused by formation of ice crystals, and it is impossible to assess architecture. (Haematoxylin & eosin. Original magnification x200).

This section will cover changes in the orbit that may occur after previous interventions, grouped here as: surgery, foreign material, radiotherapy, and chemotherapy.

Interventions may have occurred a long time ago, including when the patient was a child, and details may not be forthcoming – either because the patient doesn't remember, or because it's not considered relevant to the current problem.

Surgery

Orbital surgery is a form of direct physical trauma, which may have been performed previously for the presenting condition or some other condition. The postoperative healing process includes tissue changes that may obscure the underlying pathology. Such changes include acute and chronic inflammation, tissue necrosis, haemorrhage which may organise (with cholesterol clefts or the impression of a spindle cell proliferation), fat necrosis and scarring.[3] With active scarring there may be an exuberant fibroblastic proliferation that can mimic a spindle cell tumour. In the long term, there may be dense fibrosis with a hyaline or keloidal appearance. If there is associated inflammation, this might suggest a diagnosis of chronic inflammation and fibrosis.

Each time surgery is performed, the healing process is stimulated. Multiple biopsy procedures carried out over time may obliterate the original pathology. Ideally the first biopsy should be of sufficient size to enable a diagnosis.

Other issues arising from previous surgery can include aberrant anatomy and landmarks.

The lacrimal gland can rarely manifest necrotising dacryometaplasia (analogous to the more common necrotising sialometaplasia of the salivary gland) following surgery, trauma or radiation, and possibly related to traumatic ischaemia with or without local anaesthetic injection.[4,5] This condition is a pitfall for the unwary histopathologist as it may mimic carcinoma.

Iatrogenic foreign material

This section will cover foreign material which enters the orbit following an intentional intervention such as surgery

of the orbit or an adjacent site, or other therapeutic intervention. Accidental entry of the orbit following trauma, etc. will not be covered. Although this may cause similar problems,[6] sometimes of pronounced severity[7] the aetiology is accidental rather than iatrogenic and therefore cannot be predicted in clinical practice.

Exogenous foreign material may be introduced into the orbit deliberately (such as with orbital floor fracture repair) or it may have been applied at an adjacent site and migrate into the orbit. Material which may be introduced includes: injected drugs (such as steroids), embolising agents, starch, talc, filler,[3] bone wax and silicone. Discrete items include suture material, reconstructive mesh and tissue grafts such as porcine collagen. Following enucleation, prosthetic implants made of hydroxyapatite or other materials may be placed long term.

Tissue responses are varied and include inflammation, infection, calcification, migration of an implant, allergy and carcinogenesis.[8] The introduced material may not only provoke a tissue response, but it may form a nidus for infection such as Aspergillus or biofilms.[9–11]

Suture material is a common item to find at many body sites following previous surgery. Intensity of tissue reaction, if any, depends partly on the type of material eg whether it is absorbable or not. Fragments of suture may be found at any time after surgery with responses ranging from none to abscess formation. Often there are associated multinucleate foreign body giant cells. Identifying suture material is unlikely to present the pathologist with a problem.

Bone wax is used for haemostasis during orbital bony surgery. Complications, although rare, can include chronic foreign body reaction, reduction of new bone formation, nidus of infection or pseudarthrosis.[12,13] The surgeon as advised to use as little as possible.

Allogenic tissue implants such as dermal collagen xenografts can be used for reconstructive surgery and they may provoke a foreign body response.[14,15] For the histopathologist, it is not always straightforward to identify that the response is to non-patient material (in contrast to obviously foreign non-tissue material).

Synthetic implants such as ocular prostheses may serve as a nidus for infection,[9] and cause inflammation or foreign body response. Cases have been reported of squamous cell carcinoma in anophthalmic sockets after chronic prosthesis wear in the absence of previous neoplasia,[16] suggesting that chronic trauma may be a predisposing factor for cancer. Orbital floor fractures are repaired with various materials, some of which are biodegradable (eg 910/polydioxanone patches, generally for smaller defects) and some of which are not (eg titanium mesh, ceramic plates).[17]

Filler material comes in various types from patient-derived (eg autologous fat) to allogenic bovine or porcine collagen, to hyaluronic acid, calcium hydroxylapatite, silicon or paraffin oil and similar agents.[18] Depending on their composition, they may provoke no or pronounced tissue reaction in the patient. Their histological appearance will depend on the material, with oil and silicon manifesting as rounded spaces and hyaluronic acid potentially as pools of mucoid material.[19]

Fillers may be degradable (at various rates) or non-degradable. The mode of effect may be as a volumiser, where the physical presence of the filler restores volume, or as a stimulator, which relies on host foreign body response

to essentially cause scarring for volume restoration. Tissue responses, as might be expected, tend to include foreign body reaction (Fig. 2) and sometimes more generalised inflammation.[20] There may be fibrous nodules, foreign body response, immune response and indolent or suppurative chronic infection or biofilm.[11]

Embolisation is a technique that may be used in treatment of vascular malformations, attempting to shrink the malformation either prior to debulking surgery or as stand alone treatment. Embolic material includes n-butylcyanoacrylate compound (glue)[21] and ethylene vinyl alcohol (Onyx).[22] The latter compound includes tantalum powder. Histopathology will show vascular channels filled with the material, and there may be associated inflammation (Fig. 3). In some cases the inflammation is intense.

Radiation

In terms of iatrogenic exposure to radiation, the orbit may be intentionally targeted for therapy or imaging procedures, or it may be exposed to radiation when adjacent sites (such as sinus or brain) are targeted. Modern developments within therapeutic radiation including better targeting and dosage calculation reduce the risk of secondary pathology, but patients are still presenting with late effects of historical radiation exposure.[23]

In general, ionizing radiation can cause DNA strand breaks directly, or formation of reactive oxygen species with secondary effects (such as cell death).[24,25] Mitotically active cells are more vulnerable, which is exploited in radiotherapy for tumours, but particularly detrimental to some tissue types (bone marrow, gastrointestinal mucosa) and in some population groups (children). Epithelial and stromal cells may have a bizarre reactive appearance in microscopy (Fig. 4).

The existence of radiation-induced neoplasms is well documented.[26] Historically, radiotherapy was performed not just for cancer, but for benign or non-neoplastic disease such as cavernous haemangioma[26] or acne vulgaris[27] or tinea capitis.[28] Current indications might include thyroid-related orbitopathy.[29] Targeting was less developed and these
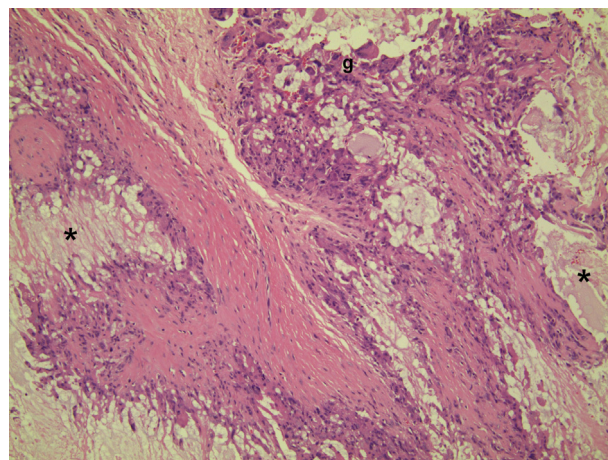

Fig. 2. This orbital biopsy is from a patient with previous filler injection. Within the fibroconnective stroma are pools of acellular pale material (*) and associated foreign body multinucleate giant cells (g). (Haematoxylin & eosin. Original magnification x100).
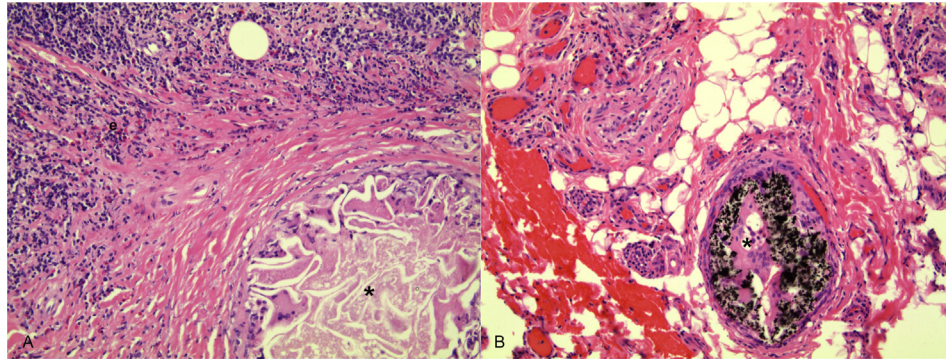
Fig. 3. A. This patient has had embolisation followed by surgery for an orbital vascular malformation. A blood vessel is occluded by glue and foreign body reaction (*). The surrounding tissue shows a brisk inflammatory response including eosinophils (e) (Haematoxylin & eosin. Original magnification x200). B. Another patient has also had embolisation and surgery. There is relatively mild inflammation, but striking black pigment and foreign body reaction within the lumen (*). The black material is probably tantalum powder. (Haematoxylin & eosin. Original magnification x200).
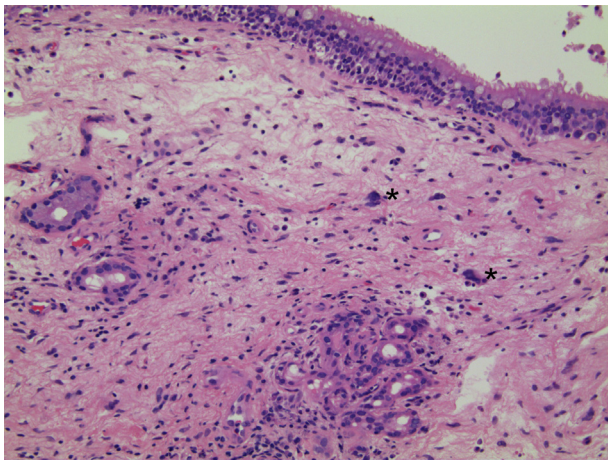

Fig. 4. This specimen of paranasal sinus mucosa shows bizarre multinucleate stromal cells (*) following radiotherapy for transitional cell carcinoma. (Haematoxylin & eosin. Original magnification x200).

historical cases were exposed to more radiation than they would be today.[23]

CT scanning, although typically exposing the patient to a lower dose of radiation than radiotherapy (of any sort), can also cause pathology, particularly if multiple scans are performed over time and/or contrast is used.[30,31]

Children are particularly vulnerable, since radiation (both diagnostic and therapeutic) has a disproportionate effect on rapidly growing tissue. In children with previous childhood cancer treated by radiotherapy (± chemotherapy), the estimated risk of a second malignancy, usually in the radiation field, is 10–20 x that of a first malignancy in age-matched controls.[32] Children under the age of 6 years and during puberty are most vulnerable.[32] Additionally, children in general have a longer expected life span for secondary effects to manifest.[30,31,33] As an additional point for consideration, the indication for diagnostic or therapeutic radiation may also be a factor in subsequent pathology, such as neurofibromatosis 1 or 2.[34]

Examples of non-neoplastic radiation-induced pathologies include: bony hypoplasia, soft tissue atrophy, cosmetic deformities and osteoradionecrosis.[32,35] There may also be lacrimal gland atrophy, which then has secondary effects on ocular surface integrity.[36] Eyelid and ocular surface changes

may occur after orbital radiation, for example for rhabdomyosarcoma.[37] These are less likely to come to the histopathologist, or they present to the histopathologist more indirectly, such as a corneal graft or background tissue when a biopsy is taken for some other indication. As previously mentioned, necrotising dacryometaplasia is a reactive phenomenon which may occur after radiation and histologically mimic malignancy.[4,5] In a study of paediatric anophthalmic sockets that had received radiation and/or chemotherapy, it was noted that there was an increased risk of contracture and exposure,[38] although these are unlikely to come to the attention of the pathologist.

Radiation-induced tumours are commonly osteosarcoma (Fig. 5), particularly in patients with retinoblastoma,[39] or less commonly other soft tissue tumours such as fibrosarcoma or rhabdomyosarcoma.[40] Within the CNS, meningiomas are well recognised to be radiogenic in origin, although they occur less frequently as secondary tumours within the orbit. In comparison to sporadic meningiomas, radiation-induced meningiomas are more likely to present at a younger age, as multiple tumours and with atypical histology.[27,41]

Uncommon radiation-induced tumours include leiomyosarcoma,[42,43] malignant fibrous histiocytoma,[40] pleomorphic adenoma (which is a benign tumour although in this case may be mitotically more active than typical),[44] dedifferentiated chondrosarcoma,[33] and malignant melanoma.[45]

In summary of this section, prior medical radiation, whether for imaging or treatment, may cause significant pathology or modify the histological appearance of background tissue. Knowledge of prior radiation, including its indications, is helpful in formulating a diagnosis, even if (or especially if) the radiation occurred in childhood.

Chemotherapy and other drugs

Patients who have undergone surgery and/or radiotherapy may also have received chemotherapy or other systemic treatments such as immunotherapy. These do not usually have a specific effect on orbital tissue, but on occasion the histological appearance of a specimen may be different after treatment. For example, after chemotherapy for rhabdomyosarcoma, recurrent tumour may manifest a more ''mature'' appearance of rhabdomyoblasts (Fig. 6). The immunotherapy agent rituximab, an anti-CD20 monoclonal
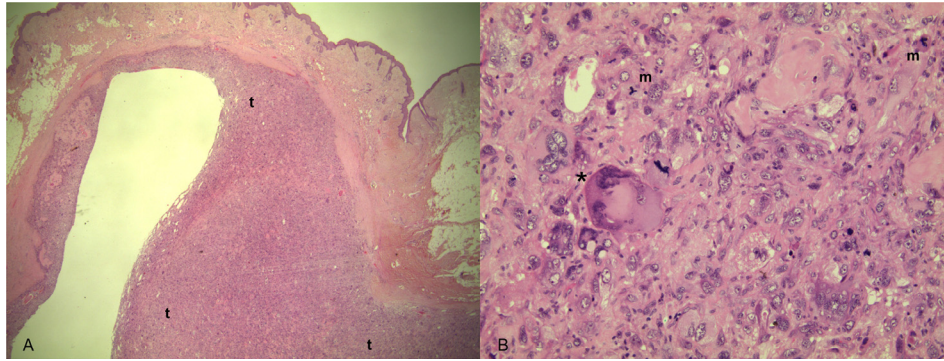
Fig. 5. This orbital biopsy is from an elderly patient who had an enucleation in childhood for retinoblastoma, although is it unclear whether radiotherapy was given. A. The skin overlies fibrofatty tissue which is filled by a malignant tumour (t) (Haematoxylin & eosin. Original magnification x100). B. The higher power shows bone formation, markedly pleomorphic and multinucleate cells (*) and scattered abnormal mitoses (m). (Haematoxylin & eosin. Original magnification x200). This is osteosarcoma.
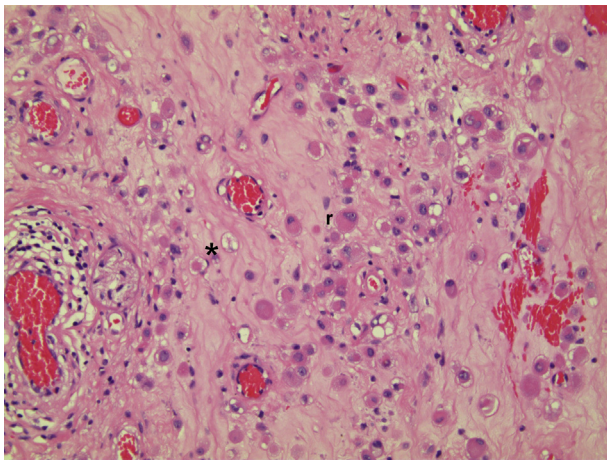

Fig. 6. This orbital biopsy is from a patient who has been treated with chemotherapy for rhabdomyosarcoma. The rounded cells with eosinophilic cytoplasm (r) as well as those with peripheral clearing (''spider cells'') (*) are reminiscent of rhabdomyoblasts, and suggest better differentiation than the original tumour. Rhabdomyoblastic differentiation can be seen following chemotherapy. (Haematoxylin & eosin. Original magnification x200).

antibody, is used in treatment of some lymphomas and autoimmune diseases. Specimens taken following such treatment may demonstrate CD20 negativity of B lymphocytes, which can cause confusion for the pathologist in the absence of information, particularly if immunohistochemistry for CD20 alone is performed to assess presence of B lymphocytes.

Summary

This review has addressed some factors related to previous medical management which may affect the histological appearance of orbital biopsies. Of course such interventions cannot be avoided, but evaluation of specimens is easier when armed with correct knowledge. The clinician managing the patient is advised to inform the pathologist of such relevant history, even if full information is not available or the management was a long time ago. The fuller the information available to the pathologist, the more useful the pathologist's input can be.

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