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The Management of Orbital Tumours

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Orbital tumours are rare, but they have the potential to debilitate vision and become life threatening. Given the serious consequences, all ophthalmologists should be able to recognize and appropriately triage patients with orbital disease. This issue of *Ophthalmology Rounds* reviews some of the more important pediatric and adult orbital tumours, and highlights some of the recent orbital disease literature.

Orbital lesions may represent primary orbital tumours, infiltrations, metastases, secondary lesions, or inflammations. Primary orbital tumours can arise from blood vessels, lacrimal glands, nerves, fibrous connective tissue, or other orbital structures. Infiltrations may be caused by lymphoma, sarcoid, or leukemia. Metastases to the adult orbit include those from the breast, lung, and prostate. Secondary orbital lesions include extensions of intracranial meningioma and sinus carcinomas that invade the orbit. Inflammation resulting from orbital cellulitis, Graves orbitopathy, and orbital inflammatory syndrome are only mentioned briefly in this issue on orbital tumours.

Diagnosis

A medical history and physical examination are important in orbital diagnoses, and some of the classical findings of orbital disease are reviewed in Table 1.

- **Patient age** is an important differentiating factor in orbital diagnosis. In adults, the most common cause of unilateral or bilateral proptosis is Graves (thyroid-associated) orbitopathy that is usually associated with lid retraction.[1] The most common primary orbital malignancy in adults is lymphoma. In children, the most common cause of proptosis is orbital cellulitis, and the most common primary orbital malignancy is rhabdomyosarcoma.
- The rate of **progression** of orbital disease is helpful in diagnosis. Rapid-onset orbital lesions can be seen with infection, hemorrhage, occasional tumours, ruptured dermoid cyst, or following trauma.
- With few exceptions, patients with **lid retraction** and proptosis have Graves orbitopathy[1] rather than an orbital tumour.
- Decreased orbital **retropulsion**, axial **proptosis** (forward protrusion of the globe), and globe **displacement** in the direction opposite the mass ("abaxial" proptosis) are the cardinal signs in orbital disease.
- The **critical ophthalmic signs** that affect the management of orbital-tumour patients include vision loss, dyschromatopsia, field loss, relative afferent pupillary defect, dysmotility, corneal exposure, chorioretinal striae, and disc edema or pallor. The presence of ptosis (alone or with downgaze "hang-up" of the upper lid),[2] and fornix lesion on lid eversion may provide valuable clues.
- **Blood tests** can be helpful in the diagnosis and management of orbital disease. Thyroid-stimulating hormone (TSH), antithyroglobulin antibody, and antimicrosomal antibodies may be helpful in delineating patients with thyroid-associated orbitopathy.[1] A positive staining circulating antineutrophil cytoplasmic antibody (cANCA) is supportive of Wegener granulomatosis. An elevated prostate-specific antigen may be seen in prostate metastasis, and angiotensin-converting enzyme and lysozyme may be elevated in sarcoid. Blood cultures may direct management in orbital cellulitis.
- **Orbital imaging** with ultrasound can be of use, but magnetic-resonance imaging (MRI) and computed tomography (CT) offer superior anatomical detail. MRI of the orbit is useful for apical lesions, for lesions that extend into the brain, and for defining tissue characteristics. CT scans of the orbit with thin cuts provide excellent detail, delineating

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Table 1: Classic findings for orbital disease diagnosis

Orbital finding	Possible orbital process
Lid retraction	Thyroid associated orbitopathy (breast cancer)
Bruit	Carotid cavernous fistula, dural arteriovenous malformation
Proptosis with colds	Lymphangioma
Pulsatile proptosis	Carotid cavernous fistula, sphenoid wing dysplasia
Enophthalmos	Orbital fracture, scirrhous carcinoma, orbital varix
Conjunctival salmon patch	Lymphoma, amyloidosis
S-shaped lid	Neurofibroma, lacrimal gland mass
Eyelid ecchymoses	Neuroblastoma (child), leukemia, amyloidosis
Nasal or palatal eschar	Mucormycosis
Gaze evoked amaurosis	Apical mass or optic nerve sheath meningioma
Temporal fullness	Sphenoid wing meningioma, metastatic neuroblastoma
Optochoroidal collaterals	Optic nerve sheath meningioma, optic nerve glioma
Immotile globe	Metastases, squamous carcinoma, mucormycosis

bony lesions and anatomy for surgical osteotomy approaches.

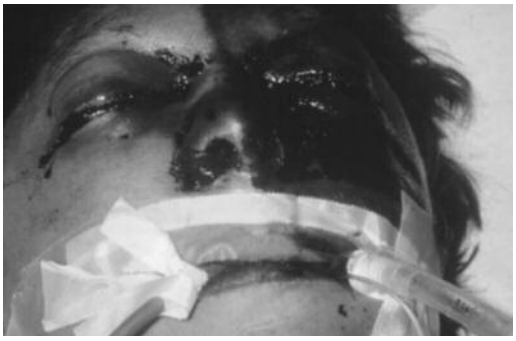
• The **imaging characteristics** of orbital lesions critically guide patient management. If the orbital lesion is well circumscribed (eg, cavernous hemangioma) and the patient is symptomatic, excisional biopsy is performed. If the orbital lesion is infiltrative, the orbit is not markedly inflamed, and lymphoma or metastasis is suspected, incisional biopsy is performed. Infiltrative cystic lesions in a young patient with fluid levels may suggest lymphangioma. In very sick patients or those with suspected metastases, orbital fine-needle aspiration biopsy is an option, requiring a skilled cytopathologist. In patients with small tumours and no pain or vision deficits, or those who refuse biopsy, observation with repeat imaging is an option until the lesion becomes symptomatic. Stereotactic computer-guided imaging may aid in localizing posterior lesions. Positron emission tomography (PET) scans identify the metabolic activity of tumours, and may be useful for staging disease, as well as determining disease activity and the response to therapy.

Adult orbital lesions

Orbital cellulitis

Patients with orbital inflammatory syndrome are usually afebrile, do not have sinus opacification on imaging, and show a dramatic response to systemic steroids. In contrast, patients with orbital cellulitis present with fever, leukocytosis, sinus opacification, and require systemic antibiotics. The aforementioned critical ophthalmic signs may be present. Orbital cellulitis usually arises from the paranasal sinuses, especially the ethmoid sinus, but may represent hematogenous spread or, occasionally, an unrecognized foreign body. Common bacterial organisms include *Staphylococcus* and *Streptococcus* species; blood cultures are required, and intravenous (IV) broad-spectrum antibiotics (eg, vancomycin, ceftriaxone, metronidazole, or levofloxacin) should be started immediately. Consultations with an ear, nose, and throat (ENT) specialist and infectious disease services are recommended. Sinus drainage should be performed if there is sinus opacification with a suggestion of optic-nerve compromise, or if there is no response to IV antibiotics after 1-2 days. Canthotomy-cantholysis may be required if there is a relative afferent pupillary defect or orbital compartment syndrome. Subperiosteal abscess in adults should be drained; superior subperiosteal abscess is worrisome because it may predispose to frontal abscess formation. Cavernous sinus thrombosis is rare, but may manifest with rapid onset proptosis and trigeminal distribution numbness. Aspergillosis and mucormycosis can cause fungal orbital cellulitis in immunocompromised patients; mucormycosis can cause thrombosing arteritis and ischemic necrosis with an orbital apex syndrome (Figure 1). Nasal and palatal eschars occur and possibly require liposomal amphotericin, posaconazole, and surgical débridement.

Figure 1: Mucormycosis in patient with ischemic necrosis of the face



Benign space-occupying lesions

The most common vascular orbital tumour in adults is cavernous hemangioma, which is usually a benign well-circumscribed intraconal process. Small lesions can be observed, but larger or symptomatic lesions can be excised. A lateral orbitotomy approach is usually required for retrobulbar lesions, although a transconjunctival approach to intraconal cavernous hemangioma has been described recently.[3] The differential diagnosis of a well-circumscribed intraconal lesion includes cavernous hemangioma, hemangiopericytoma, schwannoma, neurofibroma, fibrous histiocytoma, solitary fibrous tumour of the orbit and, occasionally, well-circumscribed posterior lymphangioma, lymphoma, or metastasis. Solitary fibrous tumour is a more recently recognized mesenchymal tumour with spindle-shaped cells, strongly positive for cluster of differentiation (CD)34 immunohistochemical studies.[4]

Common cystic lesions in the orbit include mucoceles, dermoid cysts, and hematic cysts. Mucoceles of the frontal sinus or ethmoid sinus are the most common, possibly causing displacement of the globe in

the opposite direction. Treatment is planned in conjunction with an ENT surgeon for possible endoscopic surgery.[5,6] Dermoid cysts in adults are often posterior and usually present later when they accumulate, grow in size, and cause proptosis. A newly described sign in some patients with orbital dermoid cysts is superotemporal subconjunctival fat droplets.[7] Ruptured dermoid cysts may cause extreme inflammation and incompletely removed dermoid cysts can recur. A percutaneous drainage and dual-agent ablation technique with interventional radiology has been described for large, extensive dermoid cysts.[8] Hematic cysts of the orbit (cholesterol granuloma) are associated with orbital trauma; they may have a pathogenesis similar to chronic subdural hematoma. Endothelial cells in the hematic cyst wall oversecrete tissue-plasminogen activator causing hyperfibrinolysis that impaires normal hemostasis, resulting in recurrent hemorrhage and enlargement of the hematic cyst.[9]

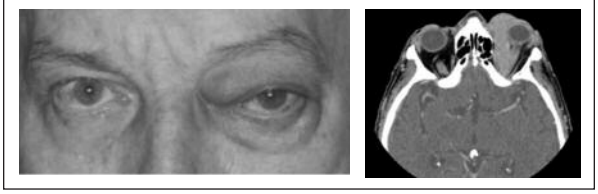
In an adult, the most common optic-nerve tumour is optic nerve sheath meningioma, which may show a slight female preponderance. On neuroimaging, there is usually tram tracking on axial scan and a central "target" sign on coronals. If the patient is experiencing vision loss, stereotactic fractionated radiation treatment can be started and, usually results in stable vision. Surgery can rarely preserve vision in sheath meningioma and is reserved for blind eyes with marked proptosis. Sheath meningiomas are less common than intracranial meningiomas secondarily invading the orbit. Sarcoid may mimic the appearance of optic nerve sheath meningioma or optic nerve glioma.[10] Optic nerve gliomas that present in adulthood are uncommon; they may be malignant with a grave prognosis. Intraorbital malignant optic nerve gliomas may present with a swollen disc and central retinal vein occlusion.

Malignant lesions

Lymphoma is the most common primary ocular adnexal malignancy; it is seen most often in patients >50 years old. The typical presentations are an indolent, painless orbital mass, a salmon-flesh lesion of the conjunctiva, or an eyelid mass. On imaging, orbital lymphoma is typically an infiltrative mass that molds to surrounding orbital structures (Figure 2). The lacrimal gland is frequently involved, but there is usually no bone destruction. Non-Hodgkin monoclonal B-cell lymphoma is the predominant ocular adnexal lymphoma. Orbital lymphoma is distinct from intraocular lymphoma, since the latter is usually a diffuse, large, B-cell lymphoma in association with a central nervous system (CNS) lymphoma.

Incisional biopsy is usually performed and the tissues processed for cell lineage; specimens should be sent fresh to the laboratory to enable flow cytometry. The most common subtypes of orbital lymphoma include mucosal-associated lymphoid tissue (extranodal) lymphoma and follicular lymphoma. Mantle-cell lymphoma and diffuse large B-cell lymphoma are less common, but are more aggressive variants of ocular adnexal lymphoma. In debilitated patients, especially

Figure 2: Patient (62 years old) with a "snow cone" of orbital lymphoma



those with a known lymphoma elsewhere in the body, a fine-needle aspiration biopsy can be considered, but histological information is usually limited.[11]

Orbital lymphoma is traditionally treated with 2000-3000 cGy of radiation. The potential ocular side effects of radiation include dry eye, cataract formation and, in some cases, radiation retinopathy. Systemic involvement occurs in ~40% of patients with orbital lymphoma. All patients should be examined carefully for systemic involvement regardless of the grade given the lymphoproliferative disorder. PET scans may assist in lymphoma staging and for determining a recurrent lymphoma.

Targeted monoclonal antibody therapy is under investigation for the treatment of ocular adnexal lymphoma. Rituximab, for example, attaches to the CD20 molecule on the surface of normal and malignant B cells, and it has less toxicity than traditional chemotherapy. One disadvantage of rituximab monotherapy is distant relapse; as a result, it has been combined with either conventional chemotherapy or radioimmunotherapy (Y-90 ibritumomab tiuxetan), for a more durable response.[12]

Since 2004, the possibility that ocular adnexal lymphoma is an antigen-driven response to infection with *Chlamydia psittaci* has been suggested. However, there may be geographical variations in the patients with ocular adnexal lymphoma and *C psittaci* positivity, as well as a variable response in lymphoma to doxycycline therapy.[13,14]

Lacrimal-gland lesions

Patients with lacrimal-gland tumours often present with ptosis with inferonasal globe displacement. Lacrimal-gland inflammation (eg, orbital inflammatory syndrome), and infiltrations such as sarcoid and lymphoid proliferations of the lacrimal gland are more common than epithelial tumours. In epithelial lacrimal-gland tumours, pleomorphic adenoma (PA; benign mixed tumour) is the most common benign lesion, and adenoid cystic (AC) carcinoma is the most common malignant lesion. Contrasting patients with PA, textbooks suggest that those with AC carcinoma of the lacrimal gland manifest with pain, a more rapid course, and bony erosions. However, the differentiation of PA from AC by clinical features alone is often challenging. Complete excisional biopsy of PA is performed to decrease the 10% per decade risk of transformation to malignant mixed tumour in recurrent disease. Rarely, a malignant tumour may arise within a benign mixed tumour, a phenomenon known as *carcinoma ex pleo-*

morphic adenoma; this adenoma of the lacrimal gland is subclassified into noninvasive carcinoma, with an excellent prognosis after complete excision, and invasive carcinoma for which the prognosis is still guarded despite adjunctive radiotherapy.

If AC carcinoma is suspected, an incisional biopsy with permanent section can be done to confirm the clinical impression. Based on pathological examination, the basaloid form of AC carcinoma has a worse prognosis than the cribriform variant. In the past, exenteration was advocated if the patient had AC; however, recent studies have not found improved survival with exenteration versus complete local excision.[15] Following surgery, radiation (approximately 6500 cGy) and chemotherapy are usually recommended; in addition, adjunctive intracarotid cytoreductive chemotherapy is an option.[16,17]

Orbital metastases and secondary lesions

In adults, choroidal metastases are more common than orbital metastases; the most frequent sites of orbital metastases are the extraocular muscles and orbital bone marrow. In women, breast carcinoma is the most common orbital metastasis and, usually, there is a known history of breast cancer. Any woman presenting with undiagnosed proptosis or orbital disease should undergo a breast examination. Enophthalmos due to scirrhous changes is classic, but a less common presentation of metastatic breast carcinoma. Bilateral breast carcinoma can occur in up to 20% of patients. Fresh tissue can be sent for estrogen-receptor assay to determine responsiveness to hormone therapy. Lung metastases can be seen in men and women, especially smokers. Prostate metastases usually involve the bone first, and may mimic the presentation of orbital inflammatory syndrome. Up to 10% of orbital metastases may be undifferentiated. In patients with orbital metastases, fine-needle aspiration biopsy may spare patients the need for an open biopsy. These patients may receive orbital debulking, palliative radiotherapy and, sometimes, chemotherapy or hormonal therapy, but in general the long-term systemic prognosis is poor.[18]

In the orbit, metastatic lesions and secondary lesions are not synonymous. A secondary lesion of the orbit denotes contiguous spread from an adjacent structure; some of the more common ones are: basal-cell carcinoma from the eyelids, squamous-cell carcinoma from the sinuses, and intracranial meningioma spreading to the orbit. Poor prognostic findings for carcinomas that spread secondarily to the orbit include formication or pain from perineural spread, and dysmotility. It may be extremely difficult to eradicate secondary carcinoma to the orbit despite seemingly negative margins on exenteration. Radiotherapy may be of some benefit in basal- and squamous-cell carcinoma, but chemotherapy is usually ineffective.

Pediatric orbital lesions

Orbital cellulitis

Orbital cellulitis is considered the most common cause of pediatric proptosis. Children <9 years old with medial subperiosteal abscess and without vision compromise may have single-agent infections that usually respond more favourably to IV antibiotics than adults with multiagent infections. Sinus drainage may be required if there is vision loss, relative afferent pupillary defect, or if the disease is unresponsive to medical management (cf. above section on adults).

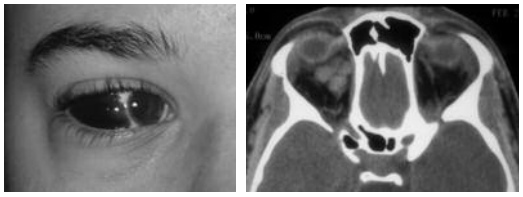
Benign space-occupying lesions

The most common pediatric orbital vascular lesion is capillary hemangioma (CAPH). Superficial CAPH are red, but deep orbital CAPH may appear bluish and may enlarge markedly in patients between 6-12 months of age. Extensive CAPH may result in thrombocytopenia, and glottic hemangioma can compromise the airway. Usually, CAPH will spontaneously resolve by 4-8 years of age, but early intervention is required if they are amblyogenic. Traditionally, intralesional or systemic steroids have been used in the treatment of extensive or amblyogenic CAPH. In patients with orbital CAPH, sub-Tenon capsule steroid infusion may have fewer intraoperative risks compared with direct intralesional injection. Systemic propranolol has recently been used in severe infantile hemangioma and is under investigation at many centres. Some possible mechanisms of action with propranolol include vasoconstriction of the hemangioma, decreased expression of angiogenesis factors and, perhaps, triggered apoptosis of capillary endothelial cells.[19]

Dermoid cysts in children are usually at the frontoethmoidal or frontozygomatic suture lines, unlike the more posterior tumours in adults. If the dermoid cyst is palpable and mobile, usually neuroimaging is not required to exclude a dumbbell tumour.

Lymphangiomas (combined venous lymphatic malformations) are orbital hamartomas that can occur at any age, but usually present in childhood, especially when superficial. The lesions may enlarge with upper respiratory tract infection or with minor trauma, and there may be associated palatal mucosal lesions. When lymphangiomas bleed, there is a characteristically dark subconjunctival or subcutaneous hemorrhage from the outset (Figure 3) and, with pathological examination, "chocolate cysts" are characteristically seen. On imaging there may be cystic grape-like lesions with fluid levels, but if orbital lymphangioma is suspected, brain MRI should be performed with orbital imaging, since there may be noncontiguous intracranial lesions. Lymphangiomas are usually managed conservatively unless there is marked pain, proptosis, or optic-nerve compression. Parents

Figure 3: Lymphangioma in a child reveals dark subconjunctival and subcutaneous blood and loculated lesions on CT

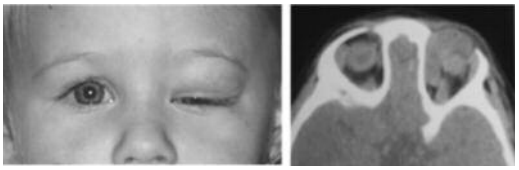


CT = computed tomography

should be counselled that lymphangiomas are infiltrative and usually recur despite repeated attempts at surgery, with or without laser. Some posterior lymphangiomas that appear circumscribed may be more amenable to surgical excision. Systemic steroids have been used to temporize until determining a treatment direction. Some have reported using sclerosing injections with sodium tetradecyl sulphate.

The most common optic-nerve tumour in children is optic-nerve glioma (ONG), which can be associated with neurofibromatosis type 1 (NF1) in 30% of patients. Children with ONG may present with vision loss, strabismus, proptosis, or disc edema; pain is uncommon unless there is a sudden hemorrhage in the tumour. Neuroimaging reveals fusiform enlargement of the nerve on axial view. In patients with NF1 and ONG there may be sagittal kinking of the nerve, and "pseudo-cerebrospinal fluid" from perineural arachnoidal gliomatosis. Dynamic contrast enhanced MRI may be a useful biomarker for clinically aggressive ONG.[20] When the glioma is large, or causes blindness or marked proptosis, surgical excision can be performed; if the tumour is confined to the orbit, observation is an option. The prognosis for childhood gliomas confined to the optic nerve is usually good, but if the chiasm is involved, especially the hypothalamus or third ventricle, prognosis is guarded.[21] Optic-nerve sheath fenestration has been described for progressive vision loss in ONG;[22] however, spontaneous regression of ONG with improvement in vision is also recognized. In younger children with chiasmal, hypothalamic, or intracranial gliomas, chemotherapy (vincristine, actinomycin D, or carboplatin, and possibly imatinib[23]) is considered; radiotherapy may be delayed until progression is seen, or until the child is >10 years old. Radiation may be predisposing for problems such as developmental delay, vasculitis, moyamoya disease,[21] and secondary tumours. Optic-nerve sheath meningioma is uncommon in children, but may occur in association with NF type 2. Although the meningioma may spread in the orbit, to the brain, and intraocularly with subtotal resection, no deaths have been primarily attributed to this tumour.[24]

Figure 4: A 4-year-old patient with rhabdomyosarcoma presenting as progressive ptosis and proptosis after incidental, minor trauma



Malignancies: primary

Rhabdomyosarcoma (RMS) is the most common pediatric orbital malignancy. The tumour does not originate from the extraocular muscles, but from pluripotential cell precursors that normally differentiate into striated muscle. The median age at presentation is 7 years, but it can occur in infancy or adulthood. The most common presentation of RMS is painless proptosis developing over days to weeks. Frequently, there is a history of incidental minor antecedent trauma that often delays the appropriate diagnosis (Figure 4). The differential diagnosis of RMS includes orbital cellulitis, orbital inflammatory syndrome, ruptured dermoid cyst, capillary hemangioma, leukemia, Burkitt lymphoma, allergic sino-orbital aspergillosis, histiocytosis, metastatic neuroblastoma, and lacrimal mucocele.[25] Unlike orbital cellulitis, RMS is usually painless, and there may be associated bone destruction; open incisional biopsy establishes the diagnosis. If the tumour is friable, cupped forceps and suction with a specimen trap may be useful; although complete excision is not usually feasible, patients with RMS localized to the orbit apparently do well irrespective of the initial resection extent. Nevertheless, most surgeons remove as much RMS as possible without damaging vital anatomy, and most orbital RMS are stage 1 (favourable site, orbit)/group III (gross residual disease). The embryonal variant of RMS is common and has a predilection for the superonasal orbit; whereas, the pleomorphic variant of RMS is the least common, but has the best prognosis. The alveolar variant of RMS has a poorer prognosis, and is thought to be more common in the inferior orbit. The usual treatment is chemotherapy (vincristine, actinomycin D, and cyclophosphamide) and radiation (4500-6000 cGy over 6 weeks). Current clinical trials seek to shorten the use of alkylating agents (eg, cyclophosphamide) in low-risk RMS, and decrease radiation sequelae with 3-dimensional conformal radiation therapy and, perhaps, proton therapy. The prognosis for survival is excellent because invasion of the globe or intracranial extensions are uncommon; in addition, regional lymph-node involvement and distant metastases do not occur in most patients. Exenteration is rarely performed for orbital RMS and is only considered for refractory or locally recurrent cases.

Metastases

The most common pediatric orbital metastases are neuroblastoma, Ewing sarcoma, and leukemia. Patients with neuroblastoma metastatic to the orbit usually have previously established disease; it often involves the bone and proptosis may be present. Bilateral periorbital ecchymoses are classic, and may cause initial confusion with child abuse. Subconjunctival hemorrhage may be seen and patients may have a Horner syndrome with cervical neuroblastoma. In ~2% of patients with neuroblastoma, opsoclonus and cerebellar ataxia may be observed. The prognosis for neuroblastoma is better in the following cases: patients are <1 year old; there is no extraorbital spread; increased levels of homovanillic acid are found in the urine; or there are increased levels of vasoactive intestinal peptide. Multiple copies of the neuroblastoma-myelocytomatosis, *N-MYC,* proto-oncogene portend a poorer prognosis in neuroblastoma.

Acute lymphoblastic leukemia is the most common type of leukemia to metastasize to the orbit. A rare variant of myelogenous leukemia, granulocytic sarcoma (chloroma) is a primary leukemic orbital mass that may be the initial presentation of disease. Ewing sarcoma is a round cell tumour usually in the long bones, which can metastasize to the orbit; primary Ewing sarcoma of the orbit can also occur. Hematogenous metastases of rhabdomyosarcoma to the orbit have been described in patients with advanced disease.[26]

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