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Occult Adenocarcinoma Presenting as Presumed Periorbital Cellulitis

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Occult Adenocarcinoma Presenting as Presumed Periorbital Cellulitis

Abstract

Background: Orbital tumors are uncommon entities seen by optometrists. They may initially present as common, benign conditions, but if not appropriately diagnosed can lead to devastating results.

Case Report: This case report demonstrates an atypical presentation of adenocarcinoma that was initially diagnosed as preseptal cellulitis. The patient in this case was ultimately referred for imaging and biopsy to reveal the correct diagnosis. Despite treatment, this patient died about 1 year after his clinical presentation.

Conclusion: The detection of orbital tumors and the subsequent management of patients with orbital tumors can be challenging. When considering orbital tumors as a possible diagnosis, careful examination is necessary to identify key clinical characteristics and to assist with ordering the appropriate imaging studies. Identifying these critical findings will allow an eye care provider to make a timely and appropriate referral for continued management of the patient.

Keywords

Adenocarcinoma of unknown primary, orbital tumors

BACKGROUND

Orbital tumors are uncommon entities seen by optometrists. They may initially present as common, benign conditions, but if not appropriately diagnosed can lead to devastating results.

CASE REPORT

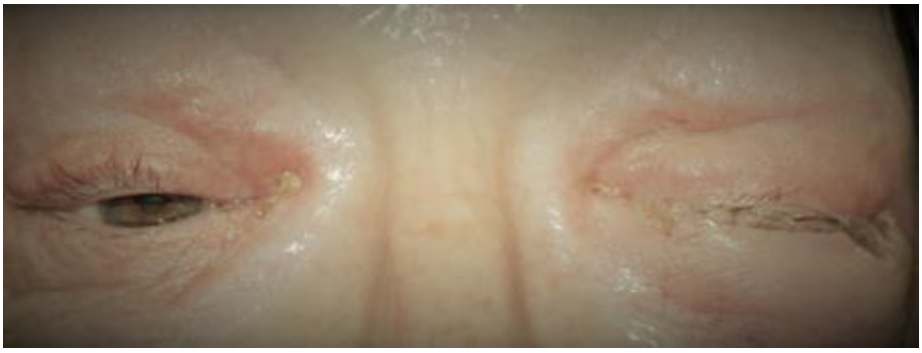
A 67-year-old Caucasian male presented to the eye clinic for follow-up regarding left eyelid redness and swelling. His initial exam findings one month prior, included visual acuities of 20/25 right eye (OD) and 20/25 left eye (OS), with pupils and extraocular motilities being described as unremarkable. Past medical history was significant for hypertension for which he was taking lisinopril 20 mg daily, and environmental allergies for which he was taking loratadine 10 mg daily. Initially, he was diagnosed with preseptal cellulitis and was started on amoxicillin/clavulanic acid 500 mgby mouth, three times daily for ten days.

At his follow up visit his entering corrected distance visual acuities were 20/30 OD and 20/80 OS, without any improvement with pinhole. Pupils were equal, round, reactive to light (4□2mm OD and OS) without relative afferent pupillary defect. Ocular alignment appeared grossly orthophoric in primary gaze, while ocular motility was restricted, left eye greater than right (Figure 1).

EOMS:

OD			OS		
-2	-2	-2	-3	-3	-3
0		-1	0		-1
0	0	0	-2	-2	-2

Figure 1: Extraocular motility findings at presentation. The right eye shows moderate EOM



restriction in supraduction and mild restriction in adduction. The left eye shows moderate-severe restriction in supraduction, mild restriction in abduction and moderate restriction in infraduction.

Figure 2: External photograph demonstrating periorbital swelling and erythema, left eye greater than right. The patient also displays significant matting of the eyelashes mostly with the left eye.

External examination of the patient was significant for periorbital swelling and erythema, left eye greaterthan right, both upper and lower lids, with the left eye shut (Figure 2). There was crusting along the eyelashes, left eye greater than right, as well. Palpation of the eyelids revealed firm, nodular masses of the upper and lower lids, worse in the left eye, and without pain or discomfort. Significant pressure was needed to open the eye (even the slightest) to evaluate EOM and pupil function. Margin to reflex distance (MRD1) was 0 in the right eye and roughly -5mm left eye. Further ancillary testing, including exophthalmometry, proved to be difficult because of significant eyelid involvement. Anterior segment showed significant tear film debris, left eye more than right, but the conjunctiva and anterior chamber appeared quiet, and the cornea and irides were of normal appearance. Intraocular pressures were 15 mm Hg in the right eye and 17 mm Hg in the left eye with a tonopen. Upon dilation, the patient's crystalline lens showed very mild nuclear sclerosis in both eyes, not likely contributing to the patients reduced vision. A dilated examination of the posterior pole was normal in both eyes, although the left eye was extremely difficult to assess. Given the unremarkable pupils and a grossly normal posterior pole, it was postulated that the patient's reduced vision in the left eye was due to possible tear film abnormalities and/or corneal distortion due to lid infiltration causing compression of the cornea.

An oculoplastic specialist was also consulted on the same day for evaluation, and a computed tomography (CT) of head and orbits, with and without contrast, was completed within 48 hours. The radiology report showed bilateral homogenously enhancing pre- and post-septal orbital masses involving the medial canthus and lacrimal glands, the largest lesion measuring 2 cm x 4 cm. Abnormal enhancement of the superior, medial, and inferior rectus was present bilaterally. Figures 3 and 4 show some of the extent of infiltration into periorbital tissue. Optic nerves appeared within normal limits. Enlarged lymph nodes measuring 1.5 cm in size were also noted on the left side. The impression given by the radiologist was consistent with a neoplastic process involving the orbits, glands, and cervical lymph nodes.

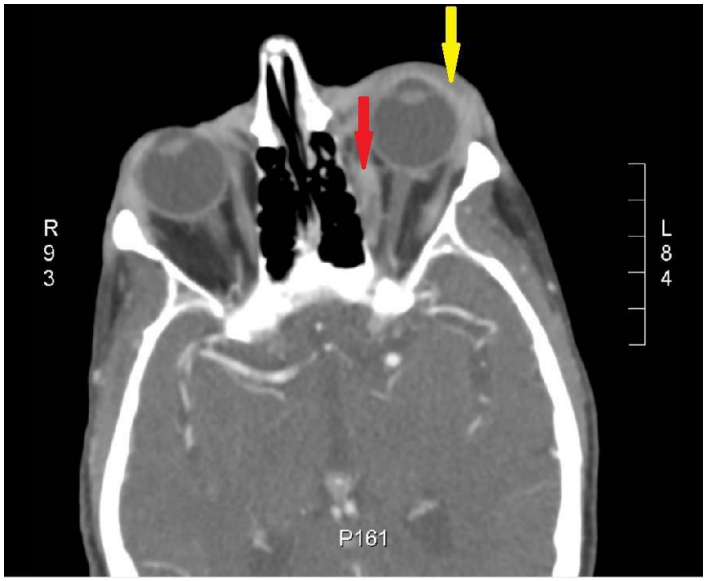


Figure 3: CT scan showing left sided medial rectus infiltration (red arrow), along with periorbital softtissue thickening (yellow arrow). This scan also shows mild proptosis of the left eye, although overaccentuated due to head rotation and lid tissue thickening.

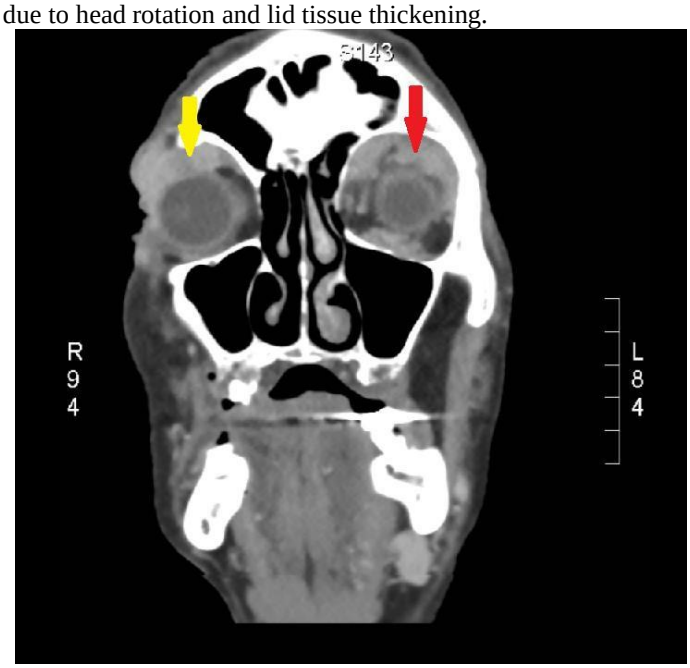


Figure 4: CT scan showing periorbital soft tissue involvement left eye (red arrow) more than right (yellow arrow).

The radiology report concluded that the findings from the CT were most concerning for a neoplastic condition such as lymphoma, but they could not rule out a granulomatous condition.

One week later, the patient underwent an incisional biopsy of the left orbital mass as well as a left lateral canthotomy and inferior cantholysis. The pathology analysis was most consistent with adenocarcinoma. Further evaluation with immunohistochemical staining (IHC) ruled out evidence of a pulmonary or gastrointestinal primary tumor, therefore it was determined to be an adenocarcinoma of unknown etiology, most likely originating from the lacrimal gland.

An oncologist was consulted for further testing and management. The patient was scheduled for magnetic resonance imaging (MRI) of the brain, orbits, and neck, with and without contrast, as well as a positron emission tomography (PET) scan. The MRI displayed bilateral orbital masses with extension, surrounding the left optic nerve (Figure 5). Figure 6 displays the significant degree of EOM involvement in the left eye, while Figure 7 shows a possible affected lymph node. The cavernous sinus appeared intact and unremarkable. PET scan showed multiple small, enhancing foci present in the brain as well as lesions within the spine (Figure 8) and left sided lymph node (Figure 9) which was concerning for metastases. (Both figures 8 and 9 are PET only MIP (maximum intensity projection) 3D images that are relatively low-resolution images but are highly sensitive to activity. Higher resolution is possible but wouldn't capture the extent of activity displayed on the 3D image. While PET images are great for visualizing activity, their resolution is never as high as CT or MRI images.)

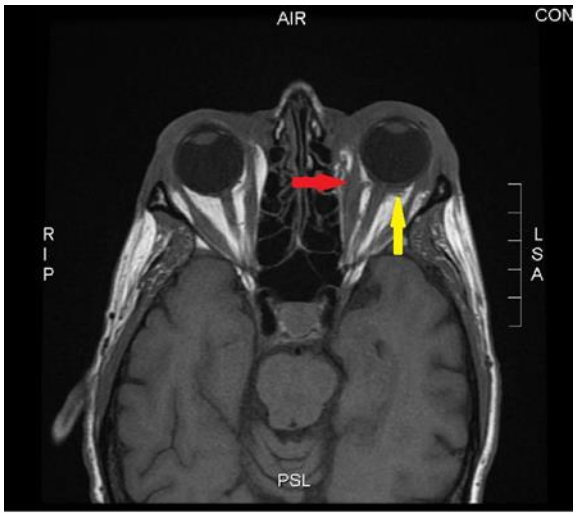


Figure 5: MRI showing significant medial rectus thickening (red arrow) compared to the other extraocular muscles. Also displayed is the tumor extension in the retrobulbar space, surrounding the optic nerve of the left eye (yellow arrow).

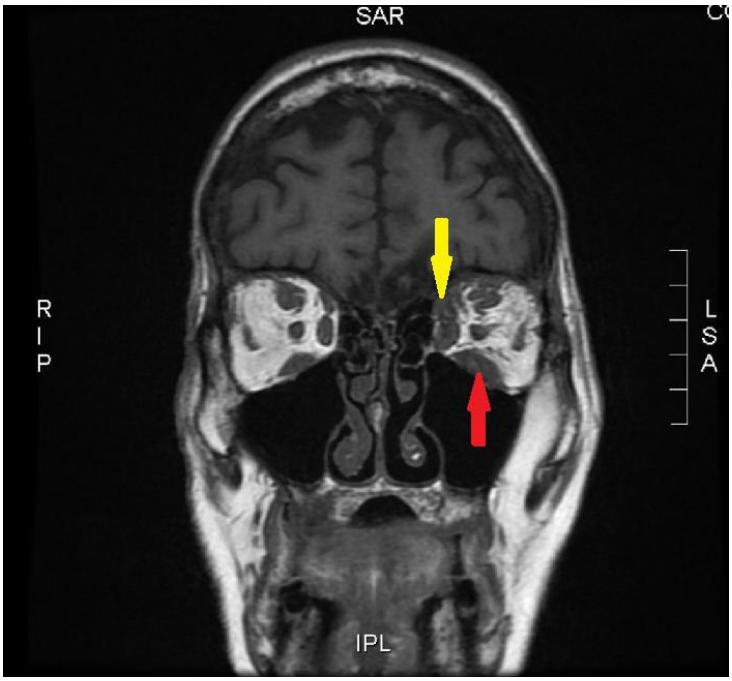


Figure 6: MRI displaying significant asymmetry of EOM involvement. Inferior (red arrow) and medialrectus (yellow arrow) of the left eye were thickened compared to the right eye.

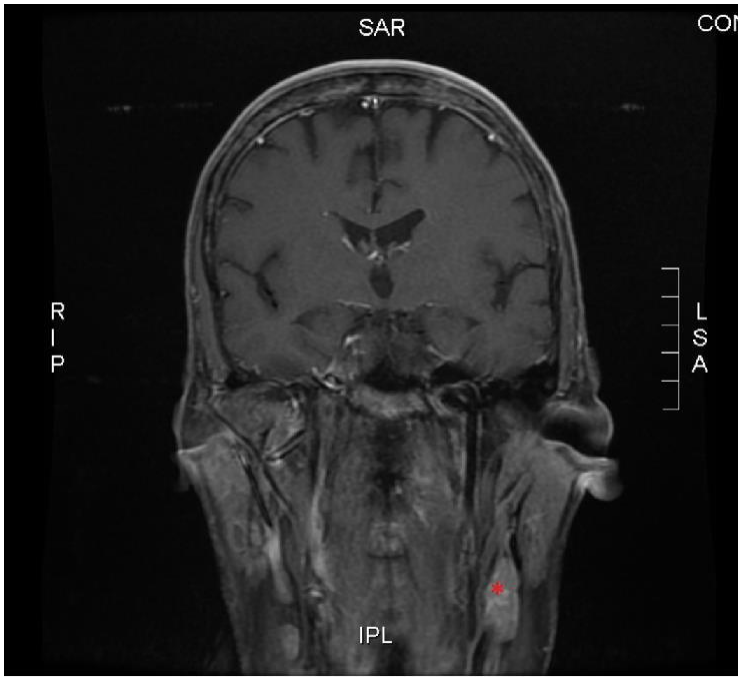


Figure 7: MRI displaying left sided enlarged enhancing jugular lymph node (red star).

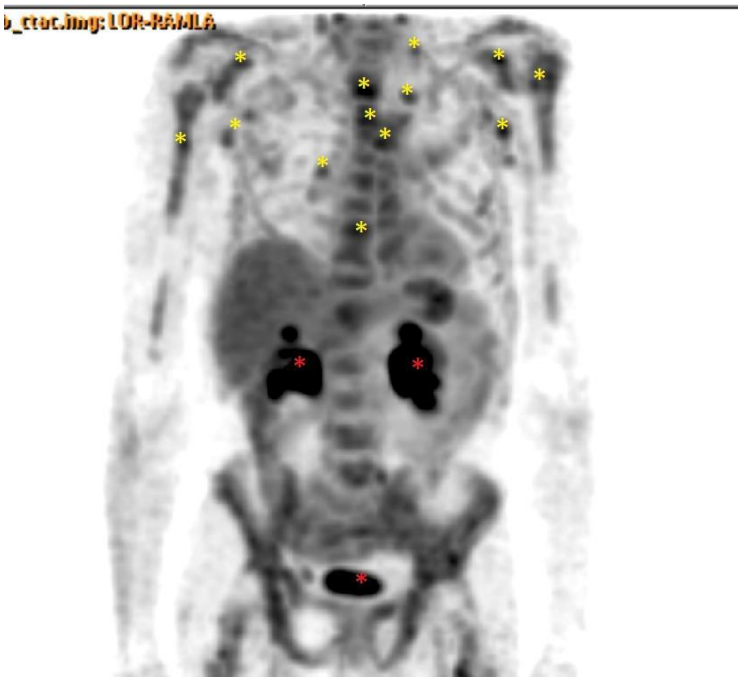


Figure 8: PET scan showing normal uptake within the kidneys and bladder (red stars). Also noted aremultiple areas (yellow stars) of activity within the vertebrae, sternum, and other boney structures, displaying significant metastases.

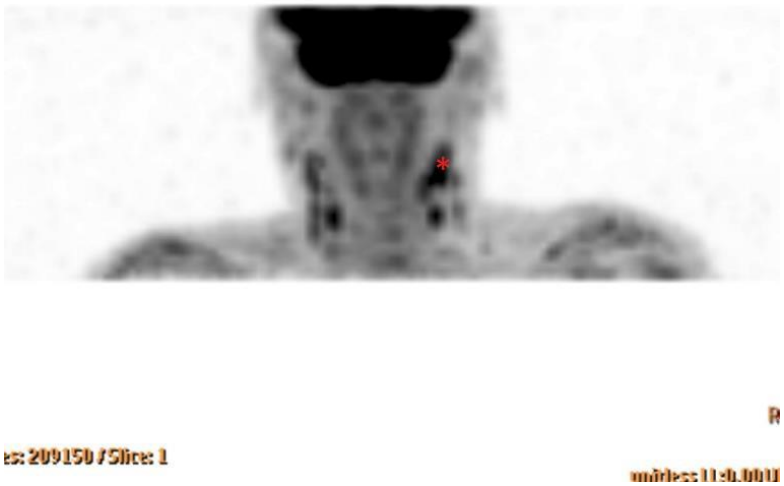


Figure 9: PET scan showing activity within the left side lymph node (red star), demonstrating metastases that corresponds to enlarged lymph node on MRI.

Since there was metastasis to the brain, bone, cervical, and possibly axillary lymph adenopathy, palliative chemotherapy was the mode of treatment. The goal was to alleviate the deterioration of vision, pain, and central nervous system (CNS) progression. Even though it would have been beneficial to re- evaluate the patient after management from oncology and ophthalmology, the patient was placed in hospice and declined any further follow up eye care. The patient subsequently passed away about a year after the initial eye visit.

DISCUSSION

There are several conditions to consider when a patient presents with swollen eyelids. Clinical evaluation and testing should guide the practitioner to an appropriate differential diagnosis. In this case, the patient initially presented with unilateral eyelid edema and erythema. A diagnosis of preseptal cellulitis was given and the patient was started on oral antibiotics. The patient returned to clinic after he failedantibiotic therapy, with additional involvement bilaterally.

When a patient presents with orbital involvement, manifest by motility restriction in both eyes, as with our patient, a physical examination should be thorough to help direct additional testing necessary for proper and timely diagnosis. Examination should include visual acuity, color vision testing, pupillary function testing, exophthalmometry, ocular motility testing, visual field testing, intraocular pressures, and a dilated fundus exam. Additionally, palpation for resistance to retropulsion can be beneficial when suspicious for an orbital mass. Finally, neuroimaging of the orbits is critical to determine the presence, extent, and cause of orbital involvement.

When considering cellulitis as a diagnosis, it is important to distinguish between preseptal cellulitis and orbital cellulitis for adequate and prompt treatment. Orbital cellulitis, an emergent condition, should be ruled out when a patient presents with a red swollen eye, orbital pain, and double vision. Some signs might include ocular motility restriction, proptosis, chemosis, or reduced vision with optic nerve involvement. A careful case history should include questions regarding recent history of an upper respiratory infection, sinus infection, fever and malaise. Although more likely unilateral, orbital cellulitis should be considered on the list of differential diagnoses for bilateral orbital swelling, along with inflammatory causes (i.e., thyroid eye disease and idiopathic orbital inflammatory syndrome) and infiltrative causes (i.e., lymphoma, sarcoidosis, and other metastatic disease). Since imaging studies will usually display concomitant sinus disease, ENT experts need to be consulted as well for possible surgical intervention. If not sent for immediate evaluation and management, orbital cellulitis can lead to further complications like

cavernous sinus thrombosis, meningitis, or cerebral abscess. Patients with a number of oncologic conditions are prone to cellulitis, for example patients with leukemia. Certain types of patients, usually those with diabetes mellitus or who are immunocompromised, may develop a cellulitis with mucormycosis, a fungus which is an inexorably progressive condition that needs rapid diagnosis to prevent death. Aspergillosis is another serious cause of fungal orbital cellulitis in predisposed cases.

Thyroid eye disease (TED) is an autoimmune condition where orbital involvement may present with all or some of the following: pain with or without eye movement, lid swelling and erythema, conjunctival redness and, chemosis, and caruncle/semilunar fold swelling and erythema, eye lid retraction, diplopia, and proptosis. In severe cases, progressive swelling can even lead to vision loss due to compression on the optic nerve, which is a medical emergency. Thyroid function testing, including thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) are helpful when ruling out thyroid eye disease (TED), but thyroid-stimulating immunoglobulin (TSI) is one of the better tests to prove the diagnosis is likely thyroid eye disease. CT imaging in patients with TED displays the characteristic finding of enlargement of the extraocular muscle bellies with sparing of the tendons.[1] A referral of patients to an oculoplastic specialist is important as there is now a new drug (teprotumumab), a monoclonal antibody, that is effective in the treatment of this condition when in the active state.[2]

Idiopathic orbital inflammatory syndrome (IOIS), or orbital pseudotumor, should also be considered when a patient presents with a rapid onset of orbital pain and swelling. Restriction of extraocular movements and chemosis are also some likely exhibited signs. Orbital imaging studies, like CT, may show inflammation of the lacrimal gland, extraocular muscles and tendons, orbital fat, and sclera. IOIS, which is also usually unilateral, is a diagnosis of exclusion when infection, systemic inflammatory disease and neoplasms are ruled out. The condition may be associated with rheumatic conditions.[3] Also, IgG4 is another systemic condition that is associated with orbital inflammation, but it is a syndrome of its own that has CNS as well as systemic signs. Therefore, these types of patients should be referred to orbital experts (because sometimes biopsies are necessary) and rheumatologists.

Sarcoidosis is a systemic granulomatosis process that commonly occurs in the second to fourth decade of life. It may present as palpable periocular lesions and can affect the lacrimal gland and orbit as well as most ocular structures, like in the presented case. It is important to look for intra-ocular inflammation since uveitis is the most common ocular manifestation of sarcoidosis.[4] Careful evaluation of the anterior chamber for cell and flare, as well as a dilated fundus examination to rule

out posterior uveitis is necessary. A chest x-ray and serum ACE testing should be considered in cases of suspected sarcoidosis.

Orbital lymphoma is the most prevalent orbital neoplasm that can affect the orbit, lacrimal gland, and eyelids with a similar presentation as in this patient. CT and MRI imaging of a lymphoma will display a well-defined orbital mass that molds to adjacent orbital structures without bony destruction.[5] In cases of a suspected lymphoma or other orbital tumors, a biopsy is necessary for further identification. Other oncologic conditions that may metastasize to the orbit include, but are not limited to, breast and melanoma.

When considering an orbital tumor as a differential diagnosis, it is important to look for common signs and symptoms that would increase suspicion. In one retrospective review of 200 patients age 60 years or older with orbital tumors, the main clinical features were palpable or visualized masses (26%), proptosis (18%) and pain (15%). Visual acuity in these patients may range from not being affected to no light perception (NLP) with around 76% presenting with visual acuity better than 20/50.[6] An additional review of 100 patients with orbital metastasis found the most frequent clinical findings to be limited ocular motility (54%), proptosis (50%) and palpable mass (43%).[7]

Orbital tumors can be benign or malignant in nature. Malignant tumors are further classified into primary, secondary, and metastatic tumors. Primary tumors originate from the orbital tissue itself. A secondary tumor of the orbit arises from adjacent tissue, such as the eyelid or uveal track. Finally, a metastatic tumor is a lesion which arises from a remote location, such as the liver. Current literature indicates that the most common primary malignant tumor is lymphoma, and the most common secondary malignant tumor was of conjunctival and intraocular orgin.[6,8] The most common benign primary tumor was a cavernous hemangioma and the most common metastatic orbital tumors were from breast and prostate cancers.[6,8] The types and frequencies of orbital tumors varies highly in the literature based on the source of information. In a report from Hakan et. al, the orbital tumor was malignant in 63% and benign in 27% of lesions surveyed.[6] Of the 1264 patients reviewed by Shields et al, 64% of the lesions were benign while 36% were malignant.[8] The Shields paper included patients of varying ages, while Hakan included patients older than age 60. There is limited information in the literature about the spectrum of orbital tumors in the senior adult population aged 60 years or older.[6]

Adenocarcinoma is a type of cancer associated with mucus secreting glands located throughout the body. The most common sites of origin are the hepatobiliary tree (comprised of the gallbladder, liver, and bile ducts), the lung, and the

pancreas.[9,10] The initial diagnosis and tumor subtype should be made with light microscopy, but further labs, imaging and tissue studies are usually needed to fully assess the lesion and the possibility of metastasis. As with this patient, if there is no known primary tumor site determined it is considered a cancer of unknown primary (CUP), which makes up for about 3-5% of all cancers.[11,12] About 70% of CUPs are adenocarcinomas and the prognosis for these patients is poor due to extensive metastases, most commonly extending to the liver, lungs, lymph nodes, and bones.[9] Interestingly, lymph node involvement can be an indicator of survival time. A twelve-month survival rate was 17% for those displaying extranodal characteristics compared to 41% whose adenocarcinoma was limited to the lymph nodes. The mean survival times were 3 and 8 months respectively.[13]

Different imaging modalities can be very useful when trying to identify possible orbital pathology. These modalities include ultrasonography, color Doppler imaging, computed tomography (CT) and magnetic resonance imaging (MRI).[14] Ultrasound imaging is non-invasive, safe, fast and can help to detect lesions before deciding on further imaging with CT or MRI. Ultrasound imaging is, however, limited to more anterior located lesions. Color Doppler imaging is beneficial for differentiating between normal orbital vasculature and tumor vascularization. The two most important modalities in orbital imaging are CT and MRI. CT imaging is widely available, relatively inexpensive, and images can be acquired quickly. CT images are often ordered in emergent situations, such as acute hemorrhage, orbital or ocular trauma, and when an MRI is unavailable or contraindicated. CT gives excellent visualization of the orbital bones, lacrimal drainage system and possible calcified lesions. When ordering CT scans, it is recommended that contrast be ordered, unless the patient has iodine contrast allergy or renal failure. The use of contrast improves the sensitivity and specificity of the CT scan interpretation.[15] In contrast, MRI is more expensive, has longer acquisition time, and is not as widely available compared to CT imaging. However, when available, MRI is generally the imaging modality of choice when imaging the orbits. An MRI is able to image soft tissue of the orbit, the optic nerves and the orbital apex well. MR images can either be T1 weighted, which better identifies normal structures, or T2 weighted, which better identifies pathology. Generally, the provider ordering the MRI does not need to specify T1 and T2 as they are both done routinely with an MRI of the orbits or brain. Fat suppression should be included in a provider's imaging order for MRI, as it allows for better interpretation of pathology while suppressing the bright signal of normal fat tissue.[15] Potential contraindications for MRI would include the presence of medical implants, such as a cardiac pacemaker or extreme claustrophobia.

Improved understanding of these lesions due to utilization of immunohistochemical (IHC) staining and molecular cancer classifying assays

(MCCAs) has led to more targeted and effective therapies. IHC analysis, used in our patient, is a technique that uses stains on biopsied tissue to look for target proteins that can help determine a tumor's site of origin. It can be difficult when deciding which specific markers to test for due to the limited amount of excised tumor tissue and time constraints to make a diagnosis. In certain situations, specific markers can lead a clinician toward a primary site diagnosis allowing them to create a more precise site-specific therapy and lessen the toxicity for the patient. Unfortunately, IHC correctly identifies less than 30% of CUPs, making management more difficult for these patients.[12] A small percentage of patients with cancer of unknown primary may benefit from resection or more targeted therapy, but unfortunately the majority rely on empiric chemotherapy. Historically, average life expectancy for someone with adenocarcinoma of unknown primary is around 4-6 months, but withimproved methods of classification and more precise treatment modalities, that number is expected to be greater.[9]

When examining patients, it is important to carefully consider the findings and the patient's symptoms to make sure they correspond to an appropriate diagnosis. Lid erythema and swelling can be a manifestation of various conditions such as hordeolum, preseptal and orbital cellulitis, contact dermatitis, inflammation, or tumors. While this patient did display some signs of preseptal cellulitis, the bilateral nature, absence of inflammatory signs, restriction of the extraocular muscles, and poor response to oral antibiotics suggested an alternative diagnoses for consideration. This case is unusual as it presented as a preseptal cellulitis, with evolution into a bilateral infiltrative orbitopathy with massive lid, lacrimal, and orbital muscle tumor invasion. This was likely metastatic from the lacrimal gland, but this was not definite and could therefore be classified as an unknown primary adenocarcinoma metastatic to both orbits, lymph nodes and bones. As clinicians, determining when to order imaging studies can be complicated due to a cost burden on both the patient and the health care system. Careful but prompt examination can help determine when imaging may be the necessary next step. Unfortunately, even after multiple exams, labs, and imaging, the patient may still be left with a poor prognosis with ineffective treatment options.

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