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Original Article

Cognitive biases in orbital mass lesions – Lessons learned

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Abstract

Purpose: A patient's presentation and clinical diagnosis can at times be clouded by their past medical history. Clinicians' anchoring bias towards initial information, such as a history of cancer, may lead them astray when creating a differential diagnosis for a patient who presents with new signs and symptoms of a mass lesion, assuming metastatic disease without seeking tissue confirmation.
Methods: The presentation, workup, diagnosis, and treatment of two patients who presented with orbital masses in the context of a primary prostate cancer are presented in this report.
Results: In both cases, prostate cancer metastasis to the orbit was top on the differential. Ultimately, histopathological examination of biopsies taken from the orbital masses revealed orbital lymphoma in both patients.
Conclusion: With mounting rates of patients who have survived a previous cancer, multiple primary cancers within one patient are becoming increasingly common. While prostate cancer metastasis to the orbit is a relatively rare event, orbital lymphoma is a more common diagnosis in orbital masses. Therefore, when patients present with orbital masses in the context of prostate cancer, the conclusion should not immediately be metastasis and a tissue diagnosis should be sought; especially given that the treatment of these entities is different.

Keywords: Orbital metastasis, Prostate cancer, Orbital lymphoma, Hickam's Dictum, Multiple primary cancers

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Introduction

An increasing source of medical error resulting in unfavorable patient outcomes is cognitive bias in the diagnostic process. A study done by the Institute of Medicine published in 1999 indicated that between 44,000 and 88,000 patients die each year within the United States as a result of medical errors, with 18% of patients being injured during their course in hospital and the cost of preventable adverse events between US$17 and US$19 billion per year.[1]

Cognitive errors and biases refer to context specific prejudices that influence our thought processes. Crosskerry refers to these default processes as ''cognitive disposition to respond''.[2] This is a process that is innate to human cognition and can significantly influence implicit decisions made in medicine. Anchoring bias refers to the human tendency to place too much emphasis on initial data during the diagnostic process.[3] When new crucial information is obtained, there is a failure to reconsider the diagnosis due to this anchoring bias. Occam's Razor is a theory that supports one unifying

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diagnosis to explain all of a patient's signs and symptoms. In modern medicine, this is referred to as diagnostic parsimony, or the desire to attribute multiple symptoms to the fewest possible diagnoses.[4] Hickam's Dictum proposes that there is no limit on the potential number of diagnoses which may explain a patient's presentation. In fact, it is statistically more likely that a patient's symptoms are secondary to several common disease entities as opposed to a single rare disease to explain a myriad of symptoms.[5] The presentation, workup, and diagnosis of two cases of orbital masses in the setting of a primary prostate cancer are presented in this report as an example of anchoring bias and the potential pitfalls in the diagnosis.

Materials and methods

Two cases of orbital lymphoma in patients with suspected metastatic prostate cancer were collected by one pathologist in Ontario, Canada. Their files were reviewed looking at their clinical presentation, laboratory workup, diagnostic imaging, pathology results, and management. A brief literature review was performed to analyze the prevalence of orbital lymphomas as compared to prostate cancer metastases in the orbit.

Results

Patient 1

A 79-year-old male presented to the Ophthalmology service with a 1-month history of gradually progressive proptosis of the right eye. Neuroimaging confirmed a 5 mm mass in the superotemporal orbit without bone erosion. Nine months' prior the patient had been diagnosed with locally advanced prostate cancer, at which point he had decided to forgo biopsy confirmation. The patient opted for androgen deprivation therapy to treat his prostate cancer, which was discontinued after 8 months due to intolerable side effects. Upon discovering the patient's orbital mass, he underwent further testing including computed tomography (CT), which revealed a large prostate gland invading the bladder base, multiple ring-enhancing hepatic lesions, a 3 cm splenic lesion, and a 5 cm infrahilar mass with bilateral hilar lymphadenopathy and endobronchial disease.

Given the patient's history, the urology oncology team felt that the new orbital mass causing his right proptosis was most consistent with metastatic prostate carcinoma and he was thus referred to radiation oncology for localized treatment. It was at this time that the radiation oncologist recommended a biopsy of the right orbital mass and liver lesion to rule out other potential underlying etiologies. The liver biopsy revealed metastatic carcinoma consistent with a prostate primary. The orbital biopsy, however, revealed follicular lymphoma Grade 2/3 (Figs. 1–3). It was therefore treated with radiation therapy of 2975 CGY. The patient also received palliative radiotherapy for his liver and subsequent bone metastases. He was restarted on androgen deprivation therapy with continued disease progression. The patient's course was one of relentless progression of disease and he died 3 years after the diagnosis of the orbital lymphoma.

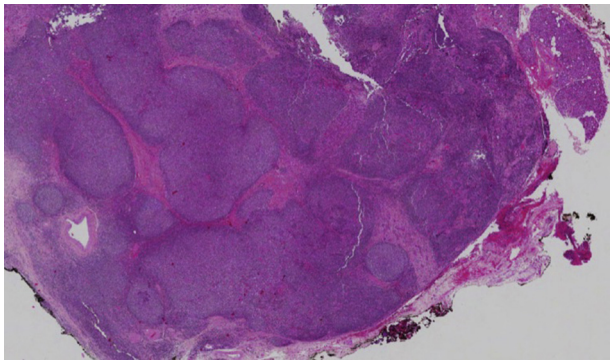

Fig. 1. Patient 1 – Low Power H&E Stain of Orbital Mass. Low power magnification of the orbital biopsy shows a mass arising out of the lacrimal gland with a follicular configuration (25×).

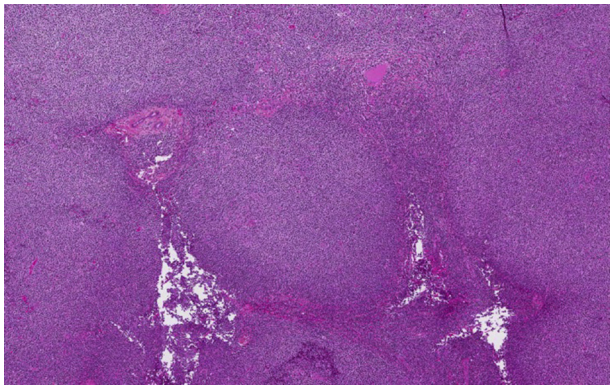

Fig. 2. Patient 1 – Medium Power H&E Stain of Orbital Mass. Medium power magnification of the orbital biopsy shows the nodular (follicular) architecture and the absence of any glandular or epithelial structures (100×).

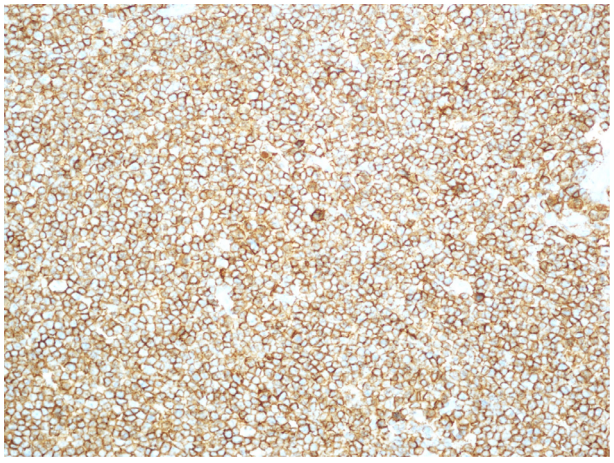

Fig. 3. Patient 1 – Medium Power B Cell Marker CD20 of Orbital Mass. Medium power magnification of the orbital biopsy shows diffuse positivity for the pan B cell marker CD20 (100×).

Patient 2

A 53-year-old man presented to the Ophthalmology service with a 3- to 4-week history of swelling of the left eyelid without a palpable mass. CT scan of the orbits revealed a 2 .1 × 2.3 × 0.9 cm left superotemporal orbital mass with local

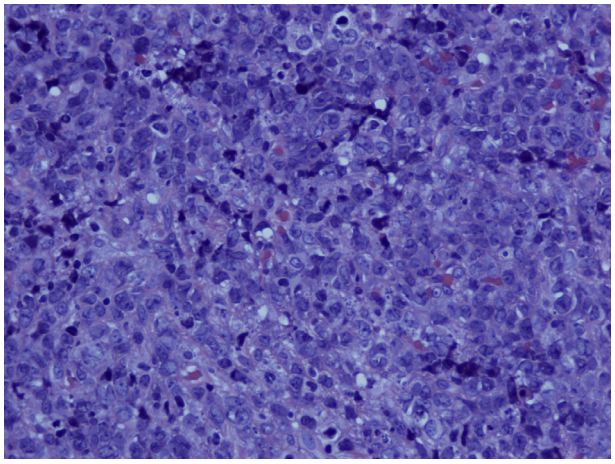

Fig. 4. Patient 2 – High Power H&E Stain of Orbital Mass. High power magnification of the orbital biopsy shows large atypical lymphocytes with brisk mitotic activity and apoptosis (400×).

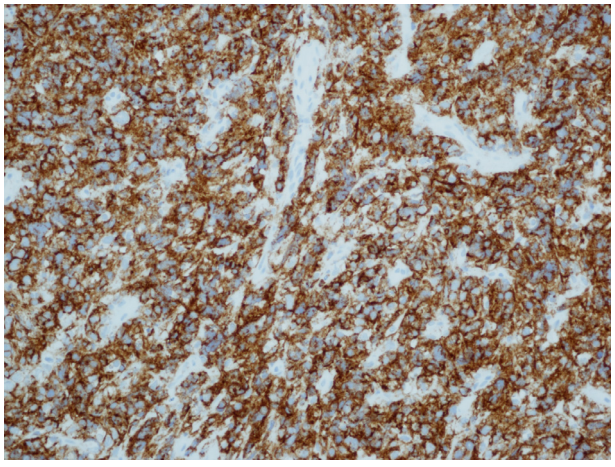

Fig. 5. Patient 2 – High Power B Cell Marker CD20 of Orbital mass. High power magnification of the orbital biopsy shows diffuse positivity for the pan B cell marker CD20 (100×).

bone erosion. Four years' prior, this patient had also been diagnosed with locally advanced prostate cancer. An ultrasound-guided prostate biopsy done at the time had revealed prostatic adenocarcinoma, Gleason Grade 6. After clinical evaluation and staging was done, he was diagnosed as high risk prostate carcinoma with locally advanced disease. External beam radiation with adjuvant hormonal treatment was undertaken and successfully completed over a 3-year period, with no evidence of local or metastatic disease. His PSA remained undetectable at the time of the orbital mass.

Given his history of prostate cancer, the newly discovered left orbital mass was highly suspicious for metastatic disease; however, the neuroradiologist suggested a differential diagnosis that also included lymphoma and orbital inflammatory disease. The differential prompted an orbital biopsy which revealed a diffuse large B-cell lymphoma of the ABC phenotype and no evidence of metastatic prostate carcinoma (Figs. 4 and 5). He is currently undergoing chemotherapy to treat the lymphoma.

Discussion

Orbital space-occupying lesions have a wide differential. They may be congenital, inflammatory, autoimmune, infectious, vascular, neural, neoplastic, or malignant in origin. Each of these categories contains multiple possible sub-etiologies. In older patients presenting with orbital lesions, malignancies and metastases must always be considered. Bonavolonta et al. analyzed 2480 cases of space-occupying lesions at one center in Italy over a 35-year period. Sixty-eight percent of these lesions were found to be benign, and the remainder malignant. Of the malignant tumours, non-Hodgkin lymphoma was found to be the most common, representing 12% of all masses. Metastases made up only 3% of all masses.[6] Over a 12-year period, Shinder, Al-Zubidi, and Esmali analyzed 268 cases of orbital lesions seen in a comprehensive cancer center in the United States. Given the parameters of the study, there was a preponderance of malignant lesions. Twenty-three percent of the orbital lesions were lymphomas and plasmacytomas and 10% were metastases.[7] Kim et al. analyzed 6328 consecutive patients with orbital disease in South India over an 11-year period, and found that 20% were neoplastic. Of these neoplastic lesions, 10.2% were lymphoid or leukemic and 3% were metastatic.[8] Shields et al. examined 1264 consecutive patients with orbital tumours over a 30-year period and discovered that 10% were lymphoma or leukemia lesions and 7% were metastatic tumours.[9]

As demonstrated in the studies mentioned above, only 3–10% of orbital tumours are metastatic in origin. Comparably, metastatic orbital tumours have only been shown to occur in 2–3% of the general cancer population who have metastatic disease.[10] Prostate cancer can infrequently metastasize to the orbit. In the context of a known metastatic orbital lesion, 12–13% have been shown to be caused by a prostate cancer primary.[11,12] Metastatic orbital lesions will most often present as unilateral masses (90% of the time), with limited ocular motility in 54% of cases, proptosis in 50% of cases, and a palpable mass in 43% of cases.[11] Treatment for these patients includes surgery, chemo- or hormonal therapy of the primary cancer, and orbital radiation. Prognosis is often poor, with up to 95% of patients dying secondary to metastases within 15–18 months.[11,12]

Conversely, 10–23% of orbital lesions have been shown to be lymphoid or leukemic/plasmacytic in nature, making lymphoma the most common orbital malignancy.[13] Lymphoma is the fifth most common cancer in both men and women, and its incidence doubled from 1975 to 2001 in the United States.[14] One to 2% of all lymphomas manifest in the ocular adnexa[15] and up to 8% of extranodal lymphomas arise here.[16] The most common ocular adnexal location for lymphoma is the orbit, comprising approximately 40% of all ocular adnexal lymphomas (OALs).[17] In comparison, 35–40% of OALs occur in the conjunctiva, 10–20% occur in the lacrimal gland, and approximately 10% occur in the eyelids.[17] Ninety-five to 100% of OALs are of B-cell origin, and the majority are low grade.[18] In contrast to patients with metastatic orbital lesions, ocular adnexal lymphomas have a 5-year overall survival rate of between 50% and 94%[19], with likely a much better rate for the purely low grade OALs that predominate.[17]

As cancer-treating modalities continue to make advancements, the number of people living with a previous diagnosis

of cancer is increasing rapidly. In 2014, there were 14.5 million people living beyond a cancer diagnosis in the United States. This number is projected to increase to nearly 19 million by 2024.[20] Consequently, a medical history that includes cancer is becoming increasingly frequent. However, a history of this nature does not preclude the possibility of having a new cancer diagnosis in the setting of a malignant lesion. One in 6 incident cancers reported to the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results Program in 2003 were independent malignancies in the setting of multiple primary cancers.[21] In one study, prostate cancer was found to be the most commonly identified cancer in cases of multiple primary malignancies.[22] In another study looking at over 700,000 patients diagnosed with more than one primary cancer between 1975 and 2001, prostate cancer accounted for 13% of cases. Of these prostate cancer patients, 8% had a concurrent diagnosis of non-Hodgkin's lymphoma.[21] The underlying etiology for having multiple primary cancers is not clear. There is a presumed role of prior treatments for the initial primary cancer, such as radiation and chemotherapy, in causing mutations leading to a second primary cancer.[23] Genetic predisposition or syndromic presentations may also play a role.[24] Shared etiologic features for multiple different malignancies, which persist in the patient and include lifestyle, environmental exposures, and age, may be contributing factors.[24]

The importance of establishing the correct diagnosis in cases of metastatic cancer to the orbit is also underscored by the potential different therapies and prognostic implications. The management of metastatic tumours of the orbit and ocular adnexa has changed in recent decades because of the availability of novel targeted treatments and advances in radiotherapy techniques.[25] With respect to prostate cancer, external beam radiotherapy (EBRT) plus hormonal therapy is recommended.[25] The treatment for orbital lymphomas has also advanced in recent years and includes EBRT, rituximab, systemic chemotherapy, combined modality therapy and radioimmunotherapy.[26] However, the doses of radiation used for metastatic disease is often much greater than for lymphomas[27] and is not combined with other novel targeted systemic treatments. Therefore, it is vital to establish the appropriate diagnosis to avoid a major error in treatment.

The prognosis for orbital metastases overall despite treatment is unfortunately poor. In the series by Shields[11], 95% of patients died of metastases, with overall mean survival of 15 months after orbital diagnosis. However, the prognosis for ocular adnexal lymphoma is usually excellent with overall 5-year survival rates of 90–95% and 5-year disease-free survival rates of up to 100%.[26]

In *Patient 1*'s case, the radiation oncologist avoided the anchoring bias of the urological oncology team by noting the lack of bone erosion associated with the orbital tumour (which is unusual in prostate cancer metastatic to the orbit) and the overall rarity of orbital metastases in the patient's clinical setting. In *Patient 2*'s case, prostate cancer metastasis was highest on the differential for the orbital mass, especially given the bone erosion seen on neuroimaging. However, the anchoring bias was avoided by recognizing the lack of other metastatic disease at 3 years post successful treatment, and normal PSA at the time of the presentation of the proptosis. Orbital biopsy and histopathological examination successfully identified the problem and directed appropriate therapy.

Conclusions

The two cases presented here demonstrate anchoring bias, in which knowledge of the patients' primary prostate cancer skewed the clinicians' diagnostic algorithm in favour of a metastatic orbital lesion of prostate cancer origin. In reality, both patients had two separate diagnoses, prostate cancer and orbital lymphoma. Orbital lymphoma is a more common disease entity than a prostate cancer metastasis to the orbit. Therefore, the simultaneous diagnosis of prostate cancer and orbital lymphoma is statistically more likely than the single diagnosis of metastatic prostate cancer to the orbit. While it may seem unlikely to have two separate but concurrent malignant processes in one patient, it is important to consider that this may still be statistically more probable than having a metastatic lesion in an infrequently identified location. Most significantly, the therapeutic and prognostic implications of a misdiagnosis demand proper investigation and tissue confirmation to avoid cognitive bias.

Conflict of interest

The authors declared that there is no conflict of interest.

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