Metastatic Adenocarcinoma Presenting as an Orbital Mass with Orbital Apex Involvement: Application of Immunohistochemistry in Diagnostic Ophthalmic Pathology

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ABSTRACT

Objective: To report a case of orbital apex syndrome due to metastatic adenocarcinoma of the orbit in an adult male.

Methods: This is a case report.

Results: A 52-year-old male presented with a subacute onset of ophthalmoplegia, ptosis, and vision loss secondary to an optic neuropathy. Orbital apex syndrome was the primary consideration. Laboratory workup ruled out infectious and inflammatory etiologies. Neuroimaging revealed an irregular, intraconal mass in the left orbit. During the disease course, a new supraorbital mass lesion was noted. Incisional biopsy, histopathology and immunohistochemistry (IHC) revealed positive Cytokeratin 7 and negative Cytokeratin 20 expression, suggestive of metastatic adenocarcinoma.

Conclusion: Diagnosis of orbital apex syndrome requires careful integration of clinical evaluation, laboratory testing, and imaging. When a mass lesion is present, biopsy and IHC staining can be critical in determining the primary origin of a malignancy.

Keywords: Ophthalmoplegia, orbital apex syndrome, metastatic carcinoma, immunohistochemistry, adenocarcinoma, vision loss

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Orbital apex syndrome (OAS) is a constellation of neuro-ophthalmic signs and symptoms resulting from lesions affecting the neurovascular structures at the orbital apex area. These disorders may be inflammatory, infectious, malignant, traumatic, iatrogenic, or vascular in nature.[1] Clinically, OAS may manifest as visual loss, ophthalmoplegia, facial paresthesia, or anisocoria. Visual loss is typically from optic nerve involvement due to its course through the optic canal. Ophthalmoplegia, anisocoria, and facial paresthesia arise from involvement of the other cranial nerves that are located proximal to the superior orbital fissure, including the oculomotor, trochlear, abducens, as well as the ophthalmic and maxillary branches of the trigeminal nerve.

This case report describes the clinical presentation and diagnostic work-up of a male adult with OAS.

CASE PRESENTATION

A 52-year-old male consulted for one-month history of blurring of vision in the left eye, associated with severe, intermittent, ipsilateral, pulsating orbital pain. He initially self-medicated with mefenamic acid 500 mg tablet which provided only partial and temporary relief of pain. He had no other constitutional symptoms such as fever, weight loss, cough, dyspnea, change in appetite, change in bowel habits, or abdominal discomfort.

The patient had an unremarkable past medical history. He was a farmer, smoked for eight pack-years and occasionally drank alcoholic beverages. There was no known heredofamilial disease or cancer history.

On neuro-ophthalmic examination, visual acuity was 20/30 in the right eye, improving to 20/25 with pinhole, and 5/200 in the left eye, improving to 20/70 with pinhole. Peripheral fields were full on the right eye while an inferonasal quadrant defect was present in the left eye. Automated visual field testing, performed with good reliability, demonstrated a central scotoma on the left eye (**Figure 1A**). Pupil exam showed a 3 mm, briskly reactive pupil in the right and a 5 mm, sluggishly reactive pupil in the left with a left relative afferent pupillary defect (RAPD). The right eye had unremarkable anterior and posterior segments, normal adnexa and full ocular motility. Intraocular pressures were normal in both eyes. On the left side, there was mild ptosis and ocular motility deficits in all directions (**Figure 1B**). Slit-lamp examination disclosed ciliary injection, clear cornea, deep and quiet anterior chamber, and a mild nuclear sclerosis cataract. Dilated fundus examination showed a hyperemic optic disc with indistinct disc borders, and retinochoroidal folds temporal to the optic nerve head extending to the macula (**Figure 1C**). There was no gross proptosis in both eyes on Hertel's exophthalmometry. The rest of the neurological and cranial nerve examination was unremarkable.

Orbital apex syndrome (OAS) was considered given the presence of unilateral optic neuropathy, as evidenced by decreased visual acuity, a central scotoma, and a positive RAPD, in combination with multiple cranial nerve palsies involving cranial nerves III, IV, VI resulting in ophthalmoplegia.

A systemic diagnostic work-up was conducted. Vital signs were within normal limits. There were no palpable masses or lymphadenopathies noted. Laboratory testing showed unremarkable erythrocyte sedimentation rate (20 mm/hr), C-reactive protein (1.34 mg/dL), lactate dehydrogenase, thyroid panel, complete blood counts and peripheral blood smear. Serologic testing for syphilis, hepatitis B, anti-HCV, and HIV were non-reactive. Urine culture, blood cultures, and fecal analysis were unremarkable. Ultrasound of the abdomen and chest X-ray were normal. Carcinoembryonic antigen (CEA) was elevated at 64.7 ng/mL.

A plain computed tomography (CT) scan of the brain and orbits revealed an ill-defined, irregular, intraconal, soft tissue lesion with loss of definition of the optic nerve sheath complex (**Figure 2**). Magnetic resonance imaging (MRI) showed peripherally enhancing soft tissue signals in the left intraconal retrobulbar space with lateral displacement of the optic nerve (**Figure 3A**). Numerous small enhancing nodules with peripheral enhancement were present in the supratentorial and infratentorial brain parenchyma ranging from 2 mm to 12 mm (**Figure 3B**).

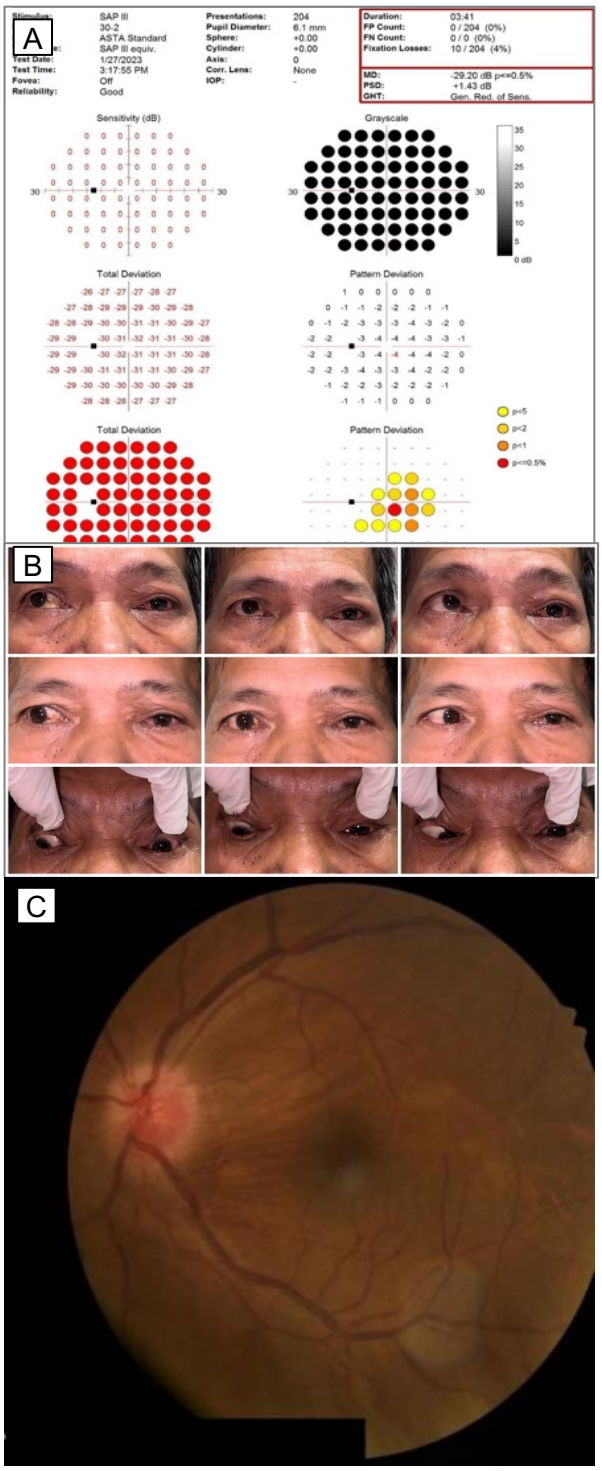

Figure 1. (A) Formal visual field testing of the left eye demonstrates central scotoma. (B) Photographs of the nine-cardinal gazes show full ocular motility in the right eye and restriction in extraocular muscle movements in all gazes and ptosis on the left side. (C) Color photo of the left fundus show a hyperemic optic disc with indistinct disc borders and retinochoroidal folds temporal to the optic nerve head extending toward the macula.

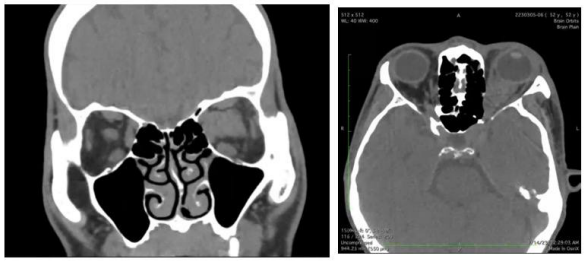

Figure 2. CT scan of the brain and orbits showed an ill-defined, irregular, intraconal soft tissue lesion with loss of definition of the optic nerve sheath complex.

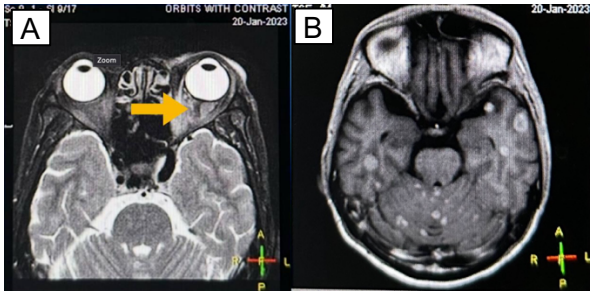

Figure 3. (A) Axial T2-weighted MRI demonstrating peripherally enhancing soft tissue signals in the left intraconal retrobulbar space, with lateral displacement of the left optic nerve. (B) Axial T1-weighted MRI showing numerous small enhancing nodules with peripheral enhancement in the supratentorial and infratentorial brain parenchyma, ranging from 2 mm to 12 mm in size

On the 12th hospital day, a firm, erythematous, tender, supraorbital mass measuring 17 x 12 mm was observed (**Figure 4**). Other ophthalmologic findings remained the same. An incision biopsy of the supraorbital mass was performed under local anesthesia, yielding a pale tan to dark ovoidal firm tissue fragment measuring 1.5 x 0.9 cm. Microscopic examination showed a malignant neoplasm composed of atypical cells in small trabeculae and nests invading a desmoplastic stroma, with pleomorphic hyperchromatic polygonal nuclei and areas of necrosis, consistent with metastatic carcinoma (**Figure 5**). Hematoxylin and eosin–stained slides and paraffin block were subjected to immunohistochemistry, which revealed cytokeratin 7 (CK7) positivity with strong diffuse cytoplasmic expression, and cytokeratin 20 (CK20) negativity. A diagnosis of metastatic adenocarcinoma was made. Additional immunohistochemical studies for thyroid transcription factor-1 (TTF-1) and p40 were recommended.

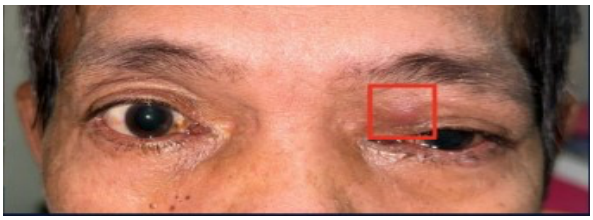

Figure 4. Gross clinical photograph of the patient in primary gaze demonstrating a mass located at the superior left periorbital area.

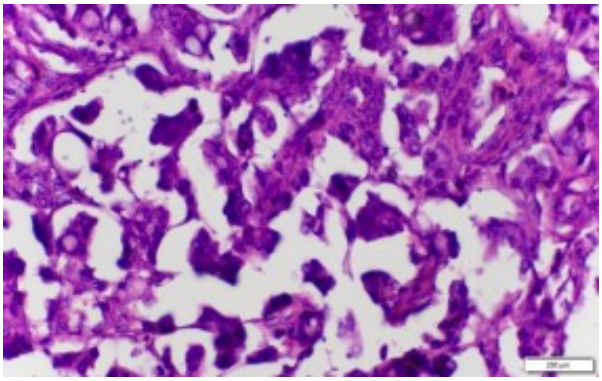

Figure 5. Hematoxylin and eosin–stained section of the supraorbital mass at low-power magnification demonstrating a malignant neoplasm composed of atypical small to medium-sized cells with pleomorphic hyperchromatic polygonal nuclei, arranged in small trabeculae and nests invading a desmoplastic stroma with areas of necrosis, consistent with metastatic carcinoma.

Following discharge, the patient developed progressive generalized weakness, poor appetite, significant weight loss, and decreased sensorium. The patient was advised oncology referral and palliative care, but the family opted for home care. The patient expired two months after the initial consult without further workup or treatment.

DISCUSSION

This report describes a 52-year-old male who presented with the characteristic signs of OAS, including vision loss associated with central scotoma and an ipsilateral RAPD along with ophthalmoplegia, and ptosis, reflecting involvement of multiple cranial nerves, particularly cranial nerves II, III, IV, and VI. The diagnostic work-up systematically excluded traumatic, vascular, infectious, and inflammatory causes. Although the patient presented clinically with orbital apex syndrome, imaging studies showed the lesion was not confined to the orbital apex but rather represented an orbital mass extending to the orbital apex. This distinction is important, as lesions presenting with orbital apex syndrome may originate within the apex itself (e.g. meningioma, schwannoma, inflammatory pseudotumor) or may extend secondarily to the apex, as in this case.

Our findings highlight that careful radio-pathologic correlation is crucial to avoid mislocalization. The role of immunohistochemistry remains central. Thus, incisional biopsy and histopathologic examination of a surgically-accessible supraorbital mass led to a diagnosis of metastatic adenocarcinoma.

OAS arises from pathologies affecting the structures within the orbital apex, notably the optic nerve (cranial nerve II), oculomotor (cranial nerve III), trochlear (cranial nerve IV), abducens (cranial nerve VI), and the ophthalmic division of the trigeminal nerve (cranial nerve V). This anatomical complexity often makes differentiation between OAS, cavernous sinus syndrome, and superior orbital fissure syndrome essential, as these conditions share overlapping clinical features but differ in the specific structures involved and consequent management strategies.[1,2] In superior orbital fissure syndrome and cavernous sinus syndrome, multiple cranial nerve involvement is seen, similar to OAS, but the optic nerve is generally spared. Visual loss and ophthalmoplegia are commonly reported initial symptoms in OAS, consistent with the patient's presentation in this case.[3]

Diagnostic evaluation of OAS requires thorough neuroimaging and laboratory investigations to determine the underlying cause. In this patient, contrast-enhanced MRI revealed a left intraconal retrobulbar mass along with multiple nodules in the brain parenchyma, possibly metastatic in nature. Work-up ruled out any infectious etiology, but showed increased CEA levels, warranting further investigation for possible neoplastic etiology. Histopathology and immunohistochemistry of the supraorbital mass provided critical diagnostic information, establishing the mass as metastatic adenocarcinoma with a cytokeratin profile of CK7-positive and CK20-negative expression.[4] This staining pattern narrows possible primary sites, frequently pointing toward cancers of lung, breast, thyroid, or upper gastrointestinal origin, though in many cases the primary tumor remains unidentified, as summarized in **Table 1**.[4-8]

Table 1. Common primary tumor sites associated with carcinomas of unknown primary (CUP) based on cytokeratin 7 (CK7) and cytokeratin 20 (CK20) immunohistochemical staining patterns.

Staining pattern	Common primary tumor sites associated with carcinomas of unknown primary
CK7+/CK20-	Breast carcinoma, lung adenocarcinoma, endometrial adenocarcinoma, endocervical adenocarcinoma, ovarian (serous) carcinoma, cholangiocarcinoma, small cell lung carcinoma, mesothelioma, thyroid carcinoma, salivary gland tumors, kidney (papillary) urothelial carcinoma (subset), pancreatic adenocarcinoma, gastric adenocarcinoma
CK7+/CK20+	Urothelial carcinoma, pancreatic adenocarcinoma, ovarian mucinous carcinoma, bladder adenocarcinoma, gastric adenocarcinoma, cholangiocarcinoma
CK7-/CK20+	Colorectal adenocarcinoma, Merkel cell carcinoma, gastric adenocarcinoma
CK7-/CK20-	Prostate adenocarcinoma, clear cell renal cell carcinoma, hepatocellular carcinoma, adrenocortical carcinoma, non-seminoma germ cell tumors, mesothelioma small cell lung carcinoma, gastric adenocarcinoma

Carcinoma of unknown primary (CUP) remains a rare and diagnostically challenging entity, comprising about 3% of all malignancies, and often requiring extensive IHC panels to help determine the tissue of origin.[4,7] In this case, additional IHC markers, including GATA3, thyroid transcription factor-1 (TTF-1), and p40, were recommended to further refine the search for the primary site, underlining the importance of advanced pathology tools in the modern diagnostic approach to metastatic disease. Identifying the primary tumor site has prognostic and therapeutic implications, as site-directed therapies can significantly impact patient outcomes.[9, 10]

One limitation in this case was the patient's progressively declining clinical status, which precluded further investigations and comprehensive oncologic management. This underscores the aggressive nature and poor prognosis associated with CUP, particularly when presenting as OAS, and highlights the necessity of rapid diagnostic work-up and interdisciplinary coordination to optimize patient care. Despite this limitation, this case emphasizes that early biopsy and IHC analysis are critical steps in elucidating the etiology of OAS when initial imaging and systemic evaluations are inconclusive. Proper identification of the underlying pathology allows for appropriate management strategies.[3]

In conclusion, OAS represents a diagnostic challenge requiring a systematic approach integrating clinical, imaging, laboratory, and histopathological assessments. This case demonstrates that metastatic adenocarcinoma should be considered in the differential diagnosis of OAS, even in the absence of an identifiable primary tumor. Early detection and tissue diagnosis through biopsy and IHC are essential to guide clinical decisions and improve patient outcomes, although prognosis remains guarded in metastatic cases presenting as OAS.

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