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Diagnostic challenges in a case of an isolated third nerve palsy

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ABSTRACT

Purpose: Neuro-ophthalmic manifestations may be the first and sole presenting feature of a nasopharyngeal carcinoma. Peri-neural spread is an emerging phenomenon that explains the distant spread of tumour cells well beyond the local extent of invasion. This under recognized route of tumour spread often results in delayed diagnosis and reduced life expectancy. The authors report a case of an isolated third nerve palsy as the only initial manifestation of nasopharyngeal carcinoma and emphasize the need for a high index of suspicion.

Observation: The patient presented with left painful pupil involving complete third nerve palsy. Contrast enhanced imaging was initially deferred due to renal impairment. Plain MRI with MRA brain was normal. Hematology was suggestive of giant cell arteritis which is a rare but well documented cause of painful nerve palsies in the elderly. Unresponsiveness to steroids prompted contrast imaging with a reduced gadolinium dosing and hemodialysis backup which finally revealed a nasopharyngeal carcinoma.

Conclusion and importance: This report is the journey of a third nerve palsy from a clinical diagnosis of an aneurysm (pupil involving palsy) to a probable diagnosis of giant cell arteritis (based on hematology) and to a final diagnosis of nasopharyngeal carcinoma (based on contrast imaging and immunohistochemistry)

Nasopharyngeal carcinoma can be successfully cured if detected early. This report highlights the various manifestations of nasopharyngeal carcinoma and challenges faced in diagnosing this elusive tumor.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a rare tumor involving the posterolateral nasopharynx, extending to the skull base. A cervical mass is the initial presentation, followed by nasal obstruction and otitis media. NPC may also present with neuro-ophthalmic features. Most patients manifest multiple cranial nerve dysfunction. We report a case of an isolated pupil involving third nerve palsy as the only initial manifestation of NPC.

2. Case description

A 78-year-old male presented with a 2-week history of headache and drooping of left upper lid (Fig. 1). Patient is a known diabetic on oral hypoglycemics for the past 10 years. He also suffers from mild renal impairment for the past 3 years. On examination, an isolated left pupil involving third nerve palsy was noted. BCVA was 6/9 in both eyes. Intraocular pressures, fundoscopy, general physical, systemic and rest of the cranial nerves and central nervous system examination were normal. Routine hematology demonstrated thrombocytosis, elevated ESR of 77 mm/hour and positive CRP of 4.7 mg/dl. No temporal artery thickening or tenderness, scalp tenderness, or jaw claudication were noted. Magnetic resonance imaging and angiography (MRI & MRA) of the brain and orbits were normal (Fig. 2), followed by a lumbar puncture which was normal. Chest radiography was normal. The patient was started on oral steroids for pain management. Temporal artery biopsy was performed to rule out atypical presentation of giant cell arteritis (GCA). It revealed hypertensive changes and was negative for GCA. On review, pain was unresponsive to oral steroids and along with the third nerve, the left ophthalmic division of trigeminal nerve involvement was noted suggestive of a progressive pathology. Contrast enhanced imaging of the head and neck (in a center with hemodialysis facility if need arise) revealed nasopharyngeal carcinoma (Fig. 3A and B). Histopathology (Fig. 4A) and immunohistochemistry (Fig. 4B) proved poorly differentiated squamous carcinoma.

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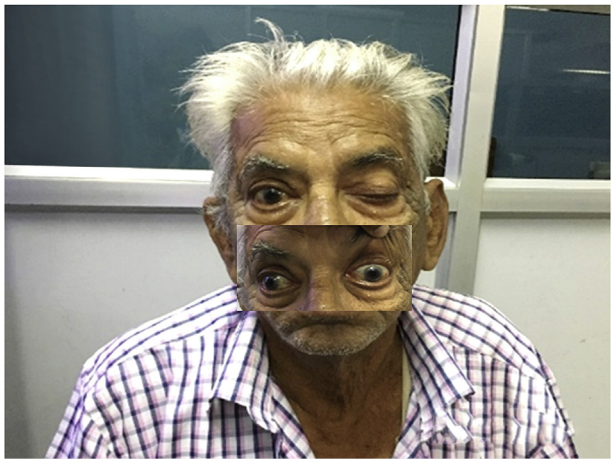

Fig. 1. Patient profile showing left complete ptosis and pupil involving third nerve palsy.

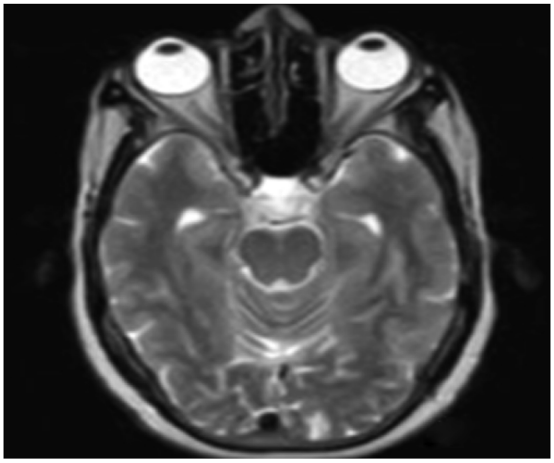

Fig. 2. Initial plain MRI brain T2 axial view showing a normal section.

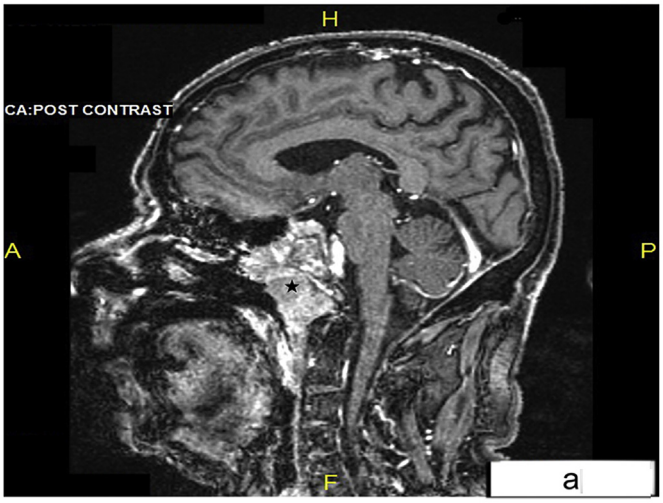

Fig. 3A. Final contrast enhanced MRI of head and neck T1 fat suppressed sagital view showing mass from nasopharynx extending into middle cranial fossa.

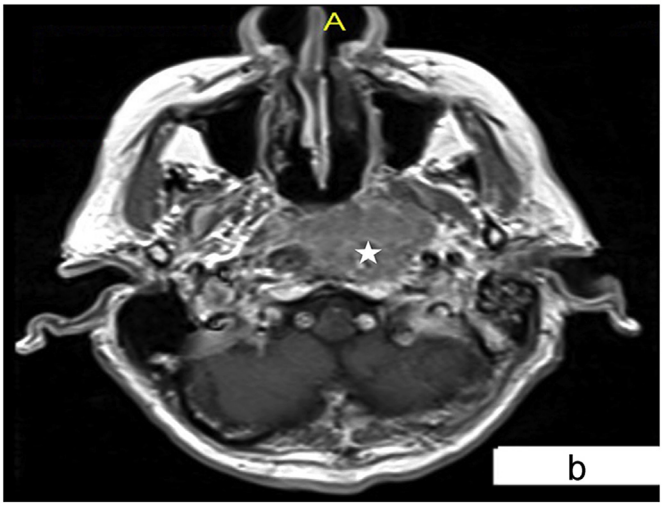

Fig. 3B. Heterogenously enhancing mass in contrast enhanced head and neck skull base view showing tumor extension into cavernous sinus (arrow head).

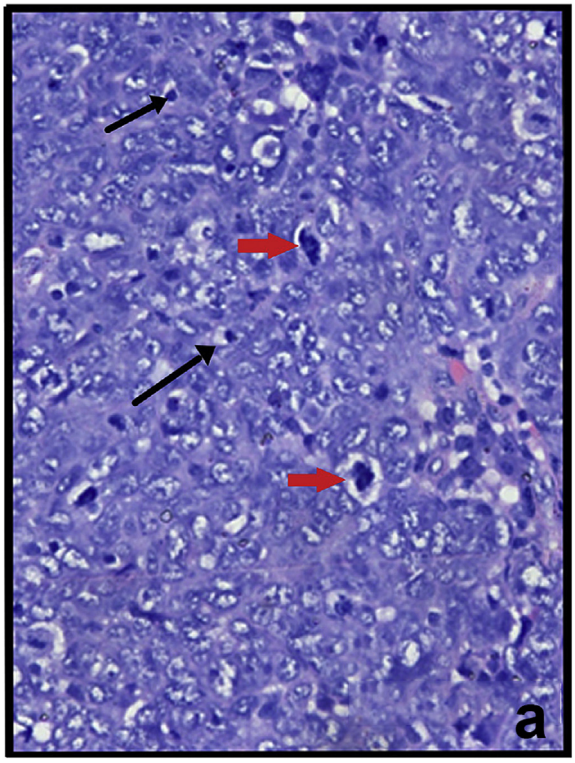

Fig. 4A. Histopathology suggestive of poorly differentiated squamous carcinoma. Red arrows indicate the mitotic figures and black arrows the scattered lymphoid cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

Painful pupil-involving third nerve palsy is a neuro-ophthalmic emergency. The differential diagnosis includes posterior-communicating artery aneurysm, ruptured aneurysms causing subarachnoid hemorrhage, compressive tumors, midbrain injury, uncal herniation, raised intracranial pressure (ICP) or rarely giant cell arteritis.[1] Pupillary sparing, on the other hand, is the hallmark of an ischemic oculomotor palsy, as seen classically in diabetes.[2] There are few exceptions to the rule which will be discussed in this case report.

Normal MRI & MRA in our patient excluded aneurysms, tumors, midbrain injury and uncal herniation as causes of pupil involving oculomotor palsy. Lumbar puncture failed to demonstrate raised intracranial pressure, blood, or xanthochromia ruling out subarachnoid hemorrhage. Negative neuroimaging along with positive hematological

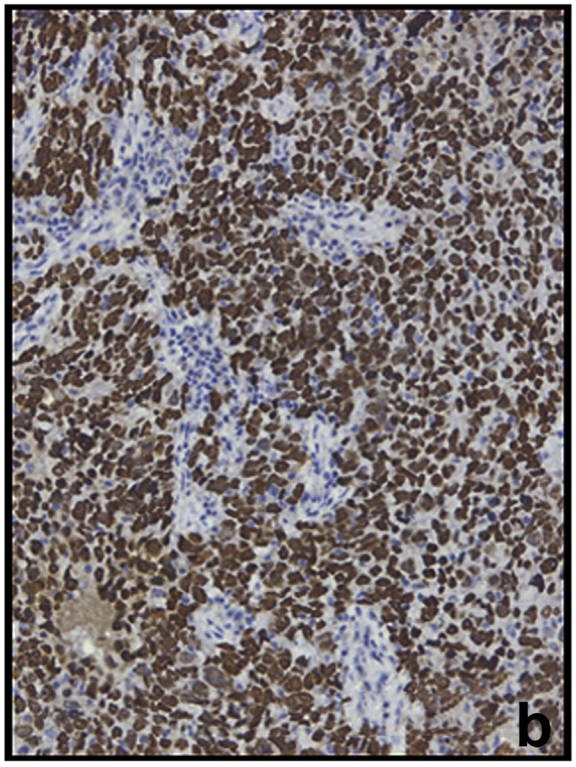

Fig. 4B. Immunohistochemistry shows tumor cells with diffuse strong nuclear positivity for p63 IHC indicating squamous differentiation of nasopharyngeal carcinoma.

indicators like raised ESR, thrombocytosis, and raised CRP in an elderly patient with painful ophthalmoplegia pointed towards a clinical diagnosis of GCA. Ophthalmoplegia is a recognized manifestation in GCA.[3] It occurs due to posterior cerebral arteritis (blood supply of third nerve) or ocular muscle ischemia.[4,5] Usually GCA-induced pain dramatically responds to steroid therapy.[4] In contrast, our patient was unresponsive to steroids. Temporal artery biopsy was also negative for GCA, prompting us to investigate further. Contrast enhanced imaging of the head and neck was initially deferred due to patient's age and pre-existing diabetic nephropathy, but as it was absolutely necessary at this stage of work up, it was performed under high-risk consent in a multispecialty center equipped for hemodialysis if necessary. Gadolinium dosage was restricted to 0.05 mmol/kg. Contrast imaging revealed nasopharyngeal carcinoma.

NPC is one of the most confusing, commonly misdiagnosed, and poorly understood diseases due to its location of origin from the fossa of Rosenmuller, extending superiorly through foramen lacerum into the middle cranial fossa, cavernous sinus and skull base. Initial presentation comprises nasal obstruction, cervical lymphadenopathy and hearing loss. Lateral and posterior extensions lead to multiple cranial nerve palsies. The incidence of cranial nerve palsy in NPC is approximately 20%.[6]

Ophthalmic manifestations usually occur at the late stage of the disease. Isolated oculomotor involvement as an initial manifestation is very rare. Patients of NPC with ocular manifestations are reported to have lower survival rates and poor prognosis.[7]

A retrospective study of 79 patients with NPC in Africa revealed that 25% of these patients have neuro-ophthalmic manifestations.[8] In a group of 564 patients, cranial nerve dysfunction was reported in 12% in Hong Kong.[9] A 9-year study in Israel revealed that in 92% of the patients, neurologic deficits were confined exclusively to cranial nerves, the most frequently affected nerves being the fifth and sixth.[10]

The present report emphasizes that NPC can present as isolated cranial nerve palsies. The initial negative radiological findings are likely due to its paraneoplastic effect[11] or perineural spread. A similar case was reported by Beckam et al., in 2010 which states that the extent of the tumor on MRI fails to indicate why the third cranial nerve was the only affected cranial nerve.[12] More than 260 cases of NPCs associated with paraneoplastic syndrome (PNS) affecting various organ systems have been reported.[13] PNS occurs due to immune cross-reactivity between tumor cells and normal tissue. It can present weeks to months before or after the diagnosis of malignancies. Previously documented ocular paraneoplastic manifestations of NPC include isolated unilateral or bilateral optic neuritis.[14–16]

Perineural invasion (PNI) is an emerging phenomenon that explains the process of neoplastic invasion of nerves and is an under-recognized route of metastatic spread in head and neck malignancies. PNI can occur in the absence of lymphatic or vascular invasion. It can be a source of distant tumor spread well beyond the extent of any local invasion.[17]

The initial isolated involvement of oculomotor nerve in our patient could be a result of paraneoplastic or perineural spread.

Normal radiography at the time of presentation, like in our patient, can be misleading. Complex human anatomy, a variety of soft tissues with abundant fat in the head and neck and the tumor's propensity to infiltrate skull base make accurate radiological interpretation of NPC a diagnostic challenge. The imaging sequence for NPC as recommended by Kam Y et al. based on a 6 years retrospective study is a combination sequence of non-enhanced and contrast-enhanced T1 axial, fat suppressed sections of MRI head and neck.[18] Single sequence imaging has less diagnostic accuracy, particularly at early stages of the disease.

To conclude, the classical manifestations of NPC includes cervical mass, nasal obstruction, dysphagia, epistaxis, hearing loss, and multiple cranial nerve palsies. At times it can also present with isolated cranial nerve palsies due to its perineural spread. This case is presented to highlight a rare, unexpected manifestation of a life threatening occult malignancy which is potentially curable if diagnosed early.

Patient consent

Consent to publish this case report has been obtained from the patient in writing.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

Nil.

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