Quiz Case

A case of neck swelling with an unusual presentation

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A 25-year-old female with headache for 8 months with nasal obstruction, diplopia, and diffuse mildly tender swelling in the left periorbital and frontal region for 2 months. There was a left cervical, firm, slightly mobile, non-tender 2 × 2 cm swelling. Patient had left lateral rectus palsy with decreased temporal field vision. Fine needle aspiration (FNA) of left cervical swelling was performed [Figures 1].

Figure 1: (a) Aspirates were high cellularity with loosely cohesive clusters and dispersed population of atypical cells (Giemsa; x100), (b) Markedly pleomorphic, oval to spindled cells with plump elongated nuclei, vesicular chromatin, prominent nucleoli and ill-defined cytoplasm (Giemsa; x400), (c) Few reactive lymphoid cells in background (Papanicolaou; x400), (d) The biopsy showed sheets of large atypical cells with brisk mitoses (H and E; x400), inset: nuclear p63 in atypical cells (DAB; x400).

QUESTION
What is your interpretation?
A. Granulomatous lesion
B. Olfactory neuroblastoma
C. Metastatic nasopharyngeal carcinoma (NPC), undifferentiated type
D. Metastasis from CNS tumor
E. Malignant melanoma.
ANSWER

The correct cytopathological interpretation is:
C. Metastatic nasopharyngeal carcinoma (NPC), undifferentiated type.

EXPLANATION

NPC is a high-grade epithelial malignancy which is usually seen in the elderly age group. Propensity for lymph node metastases particularly jugulodigastric lymph nodes has been commonly reported in the advanced stages.[1] NPC arising from fossa of Rosenmuller has a tendency to invade parapharyngeal space with frequent spread to trigeminal perineural space.[2] Hematogenous dissemination to bone marrow, liver, lung, etc., has been observed consistently, however rarer. The usual symptoms of NPC include cervical lymphadenopathy, nasal obstruction, epistaxis, hearing loss, and tinnitus.[3]

The fine-needle aspiration smears were highly cellular comprising of loosely cohesive clusters and dispersed population of markedly pleomorphic oval to spindled cells with plump elongated nuclei, vesicular chromatin, prominent nucleoli, and ill-defined cytoplasm. Few bizarre giant cells with binucleate and multinucleate forms including occasional atypical mitotic figures were noted. Background revealed presence of few reactive lymphoid cells. Based on cytological findings, a possibility of metastatic epithelial malignancy was considered. The differential diagnoses of masses which need to be excluded are summarized in Table 1.

Contrast-enhanced computed tomography and magnetic resonance imaging (MRI) of brain showed an extra-axial isointense rounded solid mass lesion measuring 2.5 × 2.2 × 1.6 cm in the left temporal lobe invading cavernous sinus and encasing internal carotid artery with mild erosion of medial aspect of petrous temporal bone and extension into nasopharynx [Figure 2]. MRI of neck revealed a discrete well-defined homogenously enhancing soft-tissue lesion in posterior aspect of the left carotid sheath measuring 3.5 × 3 × 2.5 cm, along with few subcentimetric lymph nodes in the cervical region at Level II, III, IV, and V of the left side, largest measuring 5 mm.

An immediate endoscopic biopsy was done from the nasopharyngeal mass as this was easily accessible in comparison to the intracranial lesion. Paraffin-embedded sections were studied which comprised of multiple fragments partly lined by respiratory epithelium with an underlying tumor composed of sheets of monomorphic round to oval cells with high nucleocytoplasmic ratio, round nuclei, prominent eosinophilic nucleoli, and scant cytoplasm with the presence of brisk mitoses and focal areas of fascicles of spindle cells [Figure 1d]. At places, infiltration by lymphocytes and plasma cells was seen in the stroma. Immunohistochemistry (IHC) revealed p63, cytokeratin (CK) 19, and 5/6 positivity with negative CK7 and 14 [Figure 3]. Henceforth, a final histopathological diagnosis of NPC, undifferentiated type was rendered in conjunction with IHC findings, showing extension into brain, and presenting as a huge neck mass. The prospective plan of action of operating the brain tumor could not be executed because of the widespread extension of the tumor and the patient was referred to oncology department. The patient has received 3 cycles of cisplatin and 5_FU chemotherapy with a favorable treatment response.

ADDITIONAL QUIZ QUESTIONS

Q1. What is the incidence of NPC, undifferentiated type?
   a. <1 case/100,000 population
   b. 5–10 cases/100,000 population
   c. 15–20 cases/100,000 population
   d. 20–25 cases/100,000 population.

Q2. Which of the following is true regarding NPC, undifferentiated type?
   a. Epstein–Barr virus (EBV) association is less frequently seen in NPC, undifferentiated type as compared to keratinizing NPC.
   b. Subclassification into undifferentiated and differentiated types has no prognostic significance.
   c. Undifferentiated NPC has a high propensity for locally advanced tumor growth and a lower propensity for lymph node spread.
   d. HPV infection is not associated with undifferentiated NPC.

Q3. Which IHC marker is not expressed in NPC?
   a. CK 5/6
   b. CK 19
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ANSWERS TO ADDITIONAL QUIZ QUESTIONS

Answers: Q1-a, Q2-b, Q3-d.

Q1– NPC is an uncommon tumor with annual incidence of <1 case/100,000 population.[4]

Q2– It has been shown in many studies that non-keratinizing NPC (NK-NPC), especially undifferentiated type has a strong association with EBV infection.[5] Moreover, EBV is generally absent in keratinizing NPC (K-NPC). Subclassification of NPC into differentiated and undifferentiated types carries no clinical or prognostic significance.[6] Undifferentiated NPC has a high propensity for locally advanced tumor growth along with higher propensity for LN spread.[7] Conversely, K-NPC has a lower propensity for LN metastasis, however, local advancement is high. HPV-related NPC is likely to be undifferentiated type, especially in non-endemic region.[7]

Q3– NPC stains strongly for p63, panCK, and CK19. Immunohistochemical staining for CK 7 and 14 is negative.[8]

BRIEF REVIEW OF THE TOPIC

NPC is a rare malignant disease with complex and unique etiology. It usually presents as nasal obstruction or cervical lymphadenopathy as an early manifestation. In advanced cases, tumor can invade the orbital fissure or the orbital apex and can result in compressive optic neuropathy or direct infiltration of the optic nerve.[9] Wong et al. described a series of 354 patients who had been diagnosed with NPC and found that 27 out of these 354 had ophthalmic involvement but only eight of these 27 had ocular signs without orbital invasion.[9] Most of the patients had infiltration of cavernous

Table 1: Cytomorphological differentials of masses in NPC.

| Diagnosis                           | Age       | Cytomorphology                                                                 | Anaplasia | Mitoses | Immunohistochemistry |
|-------------------------------------|-----------|---------------------------------------------------------------------------------|-----------|---------|----------------------|
| Squamous cell carcinoma             | 55–65 years | Malignant cells with vesicular nuclei, large nucleoli, with evidence of keratinization | Common    | Variable | EMA, CK5/6, CK14, p63+ |
| NPC                                 | 40–60 years | Spindly cells with vesicular nuclei, prominent central nucleoli, Background shows lymphoid cells and plasma cells | Common    | Frequent | Pan CK, p63, EMA, CK5/6, CK14, CK 19+ |
| Sinonasal undifferentiated carcinoma | 50–60 years | Medium to large sized cells with scant cytoplasm and well defined borders | Little    | Frequent | PanCK, CK 7, CK8, CK 18+, (CK5/6, p63 variable, p40) |
| Olfactory neuroblastoma             | 2–90 years | Round cells with fragile cytoplasm and delicate chromatin, rosetting present   | Variable  | Frequent | NSE, synaptophysin, CD 56, chromogranin+, (CD 99 and FLI1-) |
| Ewing sarcoma/PNET                   | 2–20 years | Loosely dispersed small to medium sized cells, scant cytoplasm, fine chromatin, rosetting present | Uncommon  | Common   | Synaptophysin, CD99, FLI1, Vimentin+ |
| Malignant melanoma                   | 40–70 years | Large plasmacytoid cells with inclusion like nucleoli, melanotic cytoplasm     | Common    | Frequent | HMB 45, S 100, Vimentin, Melan A+ |

EMA: Epithelial membrane antigen, CK: Cytokeratin, NSE: Neuron-specific enolase, PNET: Primitive neuroectodermal tumor, FLI1: Friend leukemia integration-1, HMB: Human melanoma black, CD: Cluster of differentiation, NPC: Nasopharyngeal carcinoma

Figure 3: (a) p63 positivity in atypical cells (DAB; x400), (b) some cells reveal CK5/6 positivity (DAB; x400), (c) many cells reveal CK 19 positivity (DAB; x400), (d) cells are negative for CK 7 (DAB; x400).

c. Pan CK
d. CK 7.
sinus and sphenoid sinus with associated third and sixth cranial nerve palsy. This is dissimilar to the present case, as our patient had involvement of the second and sixth cranial nerves, sparing all the other cranial nerves without any intraorbital spread.

This case is interesting from pathologist’s point of view because of the broad differential in the head and neck area. Histopathological findings and IHC played a key role here to help us reach a definite diagnosis.

SUMMARY

The present case highlights the importance of ocular symptoms as the rare and first manifestation of NPC. We should be aware that NPC should be added to the list of differential diagnosis in patients with intracranial disease where the exact location of primary tumor is unclear.

COMPETING INTEREST STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interest.

AUTHORSHIP STATEMENT BY ALL AUTHORS

Each author has participated sufficiently in the work and takes public responsibility for the appropriate portions of the content of this article. SJ: Conceptualization, drafting of the manuscript, literature review. MK: Data acquisition, revising it critically for important intellectual content. MB: Critical review, finalization of the manuscript. Each author acknowledges that this final version was read and approved.

ETHICS STATEMENT BY ALL AUTHORS

As this is a quiz case without identifiers, our institution does not require approval from Institutional Review Board (IRB).

LIST OF ABBREVIATIONS (IN ALPHABETIC ORDER)

CK – Cytokeratin
EBV – Epstein–Barr virus
FNA – Fine-needle aspiration
FNAC – Fine-needle aspiration cytology
IHC – Immunohistochemistry
K-NPC – Keratinizing nasopharyngeal carcinoma
NK – Non-keratinizing
NPC – Nasopharyngeal carcinoma.

EDITORIAL/PEER-REVIEW STATEMENT

To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a double-blind model (authors are blinded for reviewers and vice versa) through automatic online system.

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