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Leptomeningeal Metastases in Nasopharyngeal Carcinoma: A Rare Case Report and a Review of Literature

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Abstract

Introduction: The most common sites for distant nasopharyngeal carcinoma metastases are the bone, lung, and liver. Leptomeningeal metastases LM in undifferentiated nasopharyngeal carcinoma are rare.

Case and outcomes: We present a case report of a 36 years old patient treated initially for undifferentiated nasopharyngeal carcinoma (T2N3M0, stage III of AJCC 7th edition) by association of chemotherapy and radiotherapy. Two years and half later, the patient developed a frontal leptomeningeal metastasis in association with subcutaneous and left parotid relapses on MRI. The patient was treated by resection of the leptomeningeal and subcutaneous lesions. These masses turned out to be an undifferentiated carcinoma consistent with nasopharyngeal carcinoma metastasis. The patient refused parotidectomy and adjuvant radiotherapy of leptomeningeal metastasis was performed. She is now being treated with chemotherapy.

Discussion: Leptomeningeal metastases from nasopharyngeal carcinoma are rare and occur in almost 3% of patients. Multifocal neurologic signs are common and indicate multilevel involvement. The treatment of LM is based on chemotherapy and radiation therapy. Even with chemotherapeutic agents active on central neurologic system, the median survival was up to four months.

Conclusion: Leptomeningeal metastases from NPC are rare. The prognosis of patients with LM is poor. However a small subset of patients with low tumor burden and good performance status could be treated more aggressively with multimodal strategy.

Keywords: Leptomeningeal metastases • Undifferentiated nasopharyngeal carcinoma • Case report

Abbreviations

NPC: Nasopharyngeal carcinoma; LM: Leptomeningeal Metastasis; IC: Intrathecal Chemotherapy; RT: Radiation Therapy; CSF: Cerebrospinal Fluid; UCNT: Undifferentiated Nasopharyngeal Carcinoma; MRI: Magnetic Resonance Imaging, FDG PET-CT: Fluorodeoxyglucose Positron Emission Computed Tomography.

Introduction

Nasopharyngeal carcinoma NPC is an uncommon cancer in most parts of the world. There is a distinct geographical distribution with low incidence in Europe and the United States [1]. Intermediate incidence rates are found in the Mediterranean Basin and the Arctic and in certain places such as southern China and Southeast Asia, the incidence rises significantly and these areas are considered endemic for NPC with 80% of the global burden in Asian countries [2].

The standard of care for these patients consists of concurrent chemoradiotherapy with cisplatin-based regimens, generally followed by adjuvant chemotherapy. This treatment approach results in cure for the vast majority of patients, with 3-year disease-free and overall survival rates of approximately 70% and 80%, respectively [3]. Distant metastases are present in 3% to 6% of the cases and may occur in 18% to 50% of cases during the disease course [4]. The most common sites for distant NPC metastases are the bone, lung, and liver [5]. Brain and skin metastases rarely occur [6,7].

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A PubMed database search of existing English literature regarding leptomeningeal metastasis LM metastases of NPC revealed few well-described cases. A case of LM of NPC and related literature is discussed.

Case Description

Case and outcomes

A 36 years old female patient with no history of chronic disease, presented in November 2015 for 18 months history of progressively growing left mass of the neck. Ear, nose and throat evaluation included fiberoptic endoscopy, which indicated a bulb in the right side of nasopharynx. Biopsy was positive for undifferentiated nasopharyngeal carcinoma UCNT. Magnetic resonance imaging MRI revealed an infiltrative mass in the nasopharynx extending into left parapharyngeal space and bilateral lymphadenopathy including level IV. Additional workup revealed no distant metastases. The disease was staged T2N3M0 (AJCC 7th edition). Thereafter, the patient received three cycles of Induction chemotherapy followed by radiotherapy using intensity-modulated radiation therapy (total dose of 69.96 Gy (2.12 Gy/fraction in 33 fractions) with concomitant weekly cisplatin. Six months after completion of treatment, MRI showed disease resolution.

In March 2018, the patient complained of headache and left temporal swelling. This subcutaneous mass was painless and firm. Physical exam was otherwise unremarkable. Head and Neck MRI revealed a left frontal enhancing lesion measuring 23 mm in greatest dimension with limited leptomeningeal enhancement (Figures 1 and 2). Three other enhancing lesions were found in left subcutaneous temporal area (01 mass) and in left parotid gland (02 masses) (Figures 1-3). Brain and spine MRI revealed no additional lesions. Fluorodeoxyglucose positron emission computed tomography FDG PET-CT scan showed pathological uptakes corresponding to subcutaneous and parotid masses. No distant metastases were found.

Considering the high probability of metastatic disease and with the patient's consent, the neurosurgeon performed a macroscopic total excision of the frontal mass and a total excision of the subcutaneous lesion with frozen examination. The tumor turned out to be an undifferentiated carcinoma

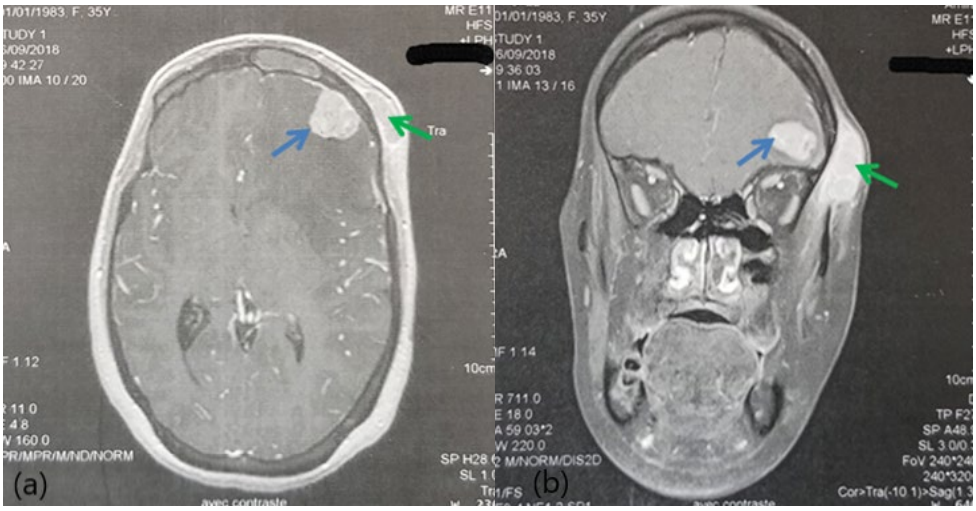

Figure 1. Gadolinium-enhanced T1-weighted sequence MRI showing an enhancement of both intracranial nodular (blue arrow) and extra cranial subcutaneous (green arrow) lesions (a: Axial view; b: Coronal view).

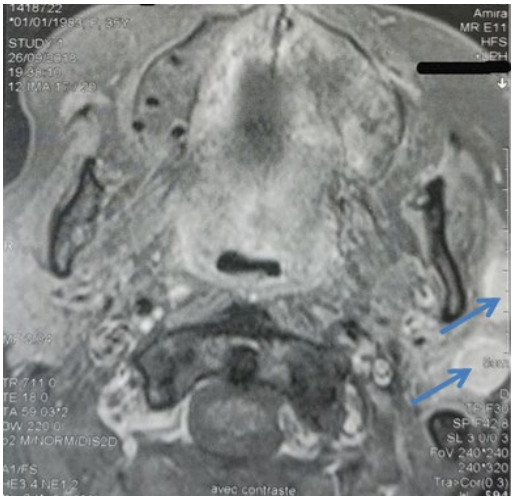

Figure 2. Gadolinium-enhanced T1-weighted sequence MRI showing two enhanced lesions in left parotid gland (blue arrows) (axial view).

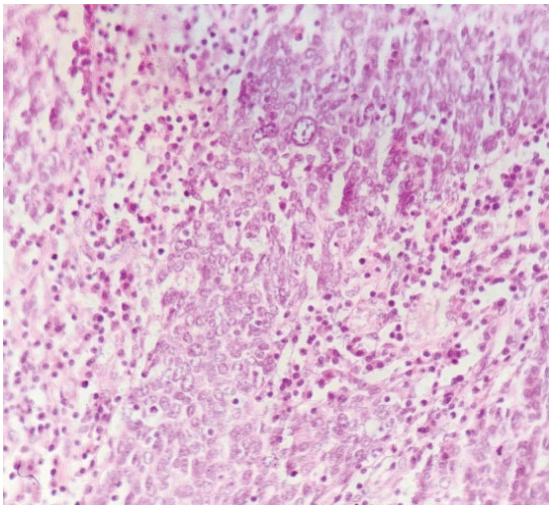

Figure 3. Hematoxylin and eosin HE stain: Brain metastatic UCNT, tumor cells showing vesicular nuclei with prominent nucleoli.

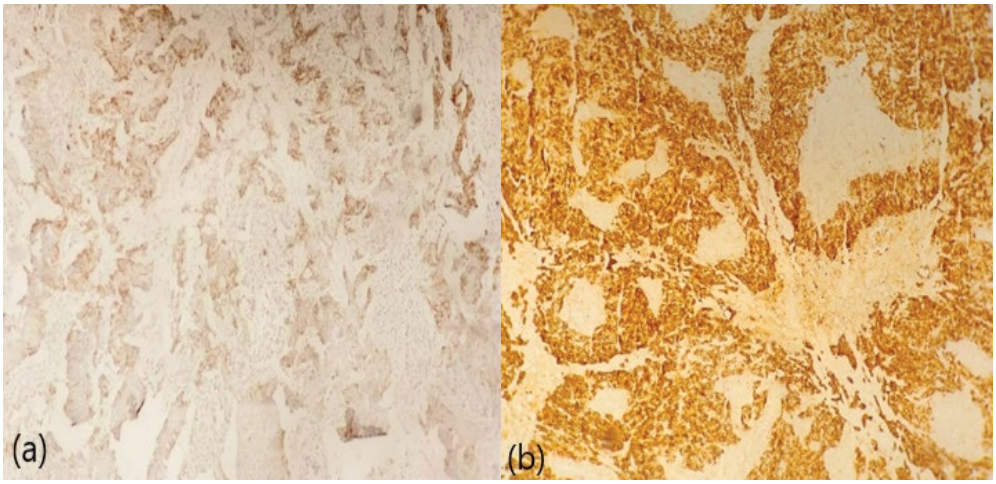

Figure 4. Immunohistochemistry IHC : (a) Cytokeratin 34 Beta E12 stain showing positivity on tumor cells (b) Epithelial myoepithelial antigen EMA stain showing diffuse positivity on tumor cells.

consistent with nasopharyngeal carcinoma metastasis (Figures 4). Epstein-Barr virus staining using *in situ* hybridization was unavailable in pathology department at this time. The disease was classified stage IV (AJCC 7th edition).

A small residual enhancement persisted on post-operative brain MRI. Hypo fractionated brain radiotherapy was initiated. A total dose of 50 Gy (2 Gy/fraction) was delivered in preoperative leptomeningeal site with integrated boost of 67.5 Gy (2.7 Gy/fraction) to residual mass. The patient refused parotidectomy due to significant risk of facial paralysis. In order to obtain parotid masses shrinkage, a systemic chemotherapy was initiated. After 03 cures of systemic chemotherapy, head and neck MRI revealed a slight shrinkage of

parotid lesions. Whereas Brain MRI showed no active disease. Once again, the patient refused surgery. We decided to continue chemotherapy. After the 6th cures, she complained lumbar and left thigh pain. FDG PET-CT scan showed a disease progression with pathological uptakes in left parotid gland, left cervical lymphadenopathies and bones (7th dorsal vertebrae, 4th lumbar vertebrae, and left femoral shaft). The patient is now being treated with palliative chemotherapy.

Results and Discussion

Leptomeningeal metastases are broadly defined as the deposits of tumor cells with invasion of the meninges. The most common solid tumors known to cause this are breast cancer (12%-35%), lung cancer (10%-26%) and melanomas (5%-25%) [8]. Leptomeningeal metastases from nasopharyngeal carcinoma are rare and occur in almost 3% of patients [9,10]. LM is often multifocal with simultaneous involvement of multiple areas of the craniospinal axis [8]. Isolated LM is extremely rare. This is in sharp contrast to the frequent occurrence of direct intracranial extension.

There are three membranes surrounding the brain and spinal cord: the dura mater, the arachnoid, and the pia mater. The arachnoid and pia mater are collectively called the leptomeninges. Tumor involvement of the leptomeninges, which is distinguished from tumor involving the dura mater, allows malignant cells to spread throughout the subarachnoid space, travel to distant sites, and grows.

Patients with LM develop clinical manifestations over days to weeks. Multifocal neurologic signs are common and indicate multilevel involvement [8]. The most common presenting symptoms were headache (39%), nausea and vomiting (25%), Seizures (25%), leg weakness (21%), cerebellar dysfunction (17%), altered mental status (16%), diplopia (14%), and facial weakness (13%). Of note, only 1% of patients with solid tumor LM were asymptomatic at time of diagnosis [11-13].

Gadolinium enhanced MRI of the brain and spine often provides evidence of LM. The brain MRI typically showed a thin, diffuse leptomeningeal enhancement following the contours of the gyri and sulci or nodular deposits in the subarachnoid space. Common sites of leptomeningeal enhancement are the cerebellar folia, the cortical surface, and the basal cisterns [14]. Linear or nodular enhancement can be showed along the surface of the cord or the cauda equina on spine MRI.

The analysis of cerebrospinal fluid CSF (biochemical analysis, cytology) is often considered to be complementary to MRI findings. MRI is more sensitive while CSF is more specific [3]. However, CSF cytology is persistently negative in as much as 20% of patients with clinically or radiographically unequivocal LM [11-15]. A typical MRI, in the appropriate clinical setting is sufficient for establishing the diagnosis without lumbar puncture.

The treatment of LM is based on systemic or intrathecal chemotherapy IC and radiation therapy RT. Systemic chemotherapy offers several advantages compared with IC. It could allow the simultaneous treatment of active systemic and leptomeningeal disease. Moreover, there are no randomized trials establishing the superiority of IC compared to systemic chemotherapy [8]. RT is often palliative and appears to be more effective at relieving symptoms than IC. Focal rather than craniospinal RT is preferred to avoid excess myelosuppresion and other toxicity. Without treatment, the median survival of patients with leptomeningeal disease is approximately four to six weeks, and death occurred from progressive neurologic dysfunction [16]. Even with chemotherapeutic agents active on central neurologic system, the median survival was up to four months [17,18]. Despite the poor prognosis of patients with LM, sustained tumor control is reported in a small subset of patients with low systemic tumor burden, a Karnofsky Performance Score of 60 or above, modest or no fixed neurologic deficits [8]. Aggressive treatment strategy could be offered to these patients.

Conclusion

Leptomeningeal metastases from NPC are rare. Often, multiple areas of craniospinal axis are involved simultaneously. The diagnosis is based on neuroimaging modality and CSF analysis. The chemotherapy is the mainstay of treatment and radiotherapy is often palliative. The prognosis of patients with LM is poor. However a small subset of patients with low tumor burden and good performance status could be treated more aggressively.

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