

Case Report

Nasopharyngeal primitive neuroectodermal tumor after concurrent chemoradiotherapy for nasopharyngeal carcinoma: a case report

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Abstract: *Objectives* Primitive neuroectodermal tumors (PNETs) belong to the class of malignant small round cell tumors and are highly aggressive with rapid growth. PNETs occurring in the nasopharynx are extremely rare. *Methods* This article reports a case of a 39-year old male patient who had been cured of nasopharyngeal carcinoma (NPC) by concurrent chemoradiotherapy (CCRT). Fifteen years later, at the age of 54, he had a nasopharyngeal PNET and subsequently underwent endoscopic resection and chemoradiotherapy. *Results* The patient tolerated the treatment well and has had symptom resolution. Tumor recurrence was not observed in a follow-up (at 6 months) magnetic resonance imaging study after therapy. *Conclusion* Based on our research, this is the first case of a nasopharyngeal PNET developing after CCRT for NPC. This report highlights the importance of considering the impact of prior CCRT on predisposition to future PNETs and expands the spectrum of reported radiation-induced neoplasms in the nasopharynx.

Keywords: Primitive neuroectodermal tumor, Ewing sarcoma, concurrent chemoradiotherapy, nasopharyngeal carcinoma, post radiation neoplasia

Introduction

Primitive neuroectodermal tumors (PNETs) belong to the class of malignant small round cell tumors, presumably of neural crest origin. These tumors are highly aggressive with high mortality [1, 2]. The incidence of PNETs occurring in the head and neck region is 2%-7% [3]. PNETs at different sites of the head and neck region, including the maxilla [4], mandible [4], retina [5], thyroid [6], vagus nerve [2], masseter muscle [7], sinonasal tract [3, 8, 9] and nasopharynx [9], have been reported. The maxilla and mandible are the most common sites, whereas involvement of the nasopharynx is extremely rare [3]. Herein, we report the case of a patient with a nasopharyngeal PNET who had received concurrent chemoradiotherapy (CCRT) for nasopharyngeal carcinoma (NPC) 15 years previously.

Case report

At 39 years of age, a Taiwanese man was found to have stage III (T2bN2M0, American Joint

Committee on Cancer TNM staging system, 6th edition) NPC (pathology: nonkeratinizing carcinoma). He was subsequently treated with CCRT. The chemotherapy regimen of CCRT was Cisplatin (30 mg/m² on Mondays, for 7 weeks). The radiotherapy of CCRT involved applying irradiation at a dose of 70 Gy (2 Gy/fraction; daily Mondays-Fridays, for 7 weeks) to the primary tumor and gross adenopathy and application of radiation at a dose of 63 Gy (1.8 Gy/fraction) to the uninvolved nodal stations. Three months after finishing CCRT, adjuvant intracavitary brachytherapy was applied at a dose of 10.5 Gy (3.5 Gy/fraction). In April 2017; nasopharyngoscopy conducted during routine follow-up revealed no evidence of recurrence.

In June 2017, at 54 years of age, he visited our hospital for a fetid odor in the nose for 2 weeks. Nasopharyngoscopic examination identified a whitish mass in the nasopharynx (**Figure 1A**). Contrast-enhanced magnetic resonance imaging (MRI) revealed a poorly enhanced tumor measuring 1.5 cm in diameter in the right naso-

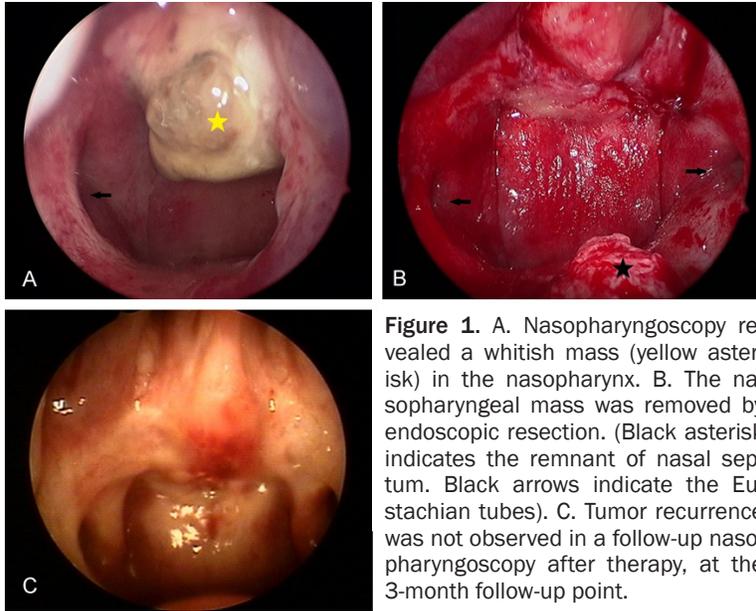


Figure 1. A. Nasopharyngoscopy revealed a whitish mass (yellow asterisk) in the nasopharynx. B. The nasopharyngeal mass was removed by endoscopic resection. (Black asterisk indicates the remnant of nasal septum. Black arrows indicate the Eustachian tubes). C. Tumor recurrence was not observed in a follow-up nasopharyngoscopy after therapy, at the 3-month follow-up point.

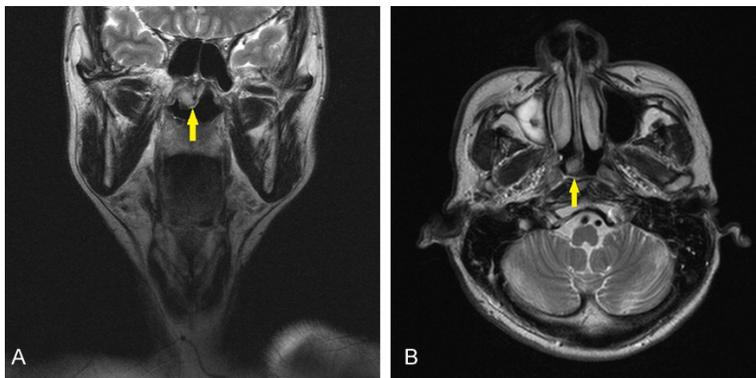


Figure 2. Coronal (A) and axial (B) images of contrast-enhanced MRI revealed a poorly enhanced tumor measuring 1.5 cm in diameter in the right nasopharynx (yellow arrows). Moreover, mucoperiosteal thickening of the right maxillary sinus was observed and was suggestive of sinusitis.

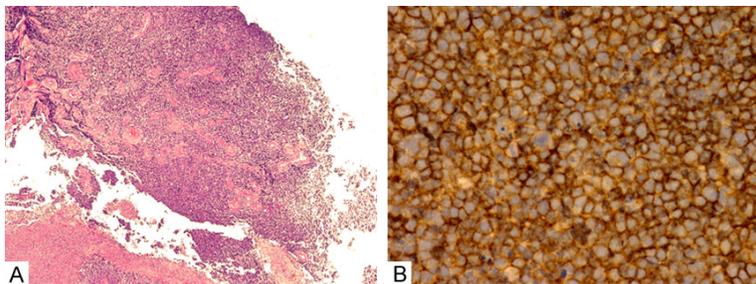


Figure 3. Histopathological sections of the mass of the nasopharynx. A. The section revealed pieces of nasopharyngeal mucosa infiltrated with many uniform small round cells with hyperchromatic nuclei and scanty cytoplasm. Moreover, large areas of necrosis were observed (H&E 40 \times). B. The section revealed the neoplastic cells were diffuse positive for CD99 immunostain (CD99 400 \times).

pharynx (**Figure 2**). Subsequently, biopsy of the nasopharyngeal mass was performed. Histopathological sections revealed pieces of nasopharyngeal mucosa infiltrated with many uniform small round cells with hyperchromatic nuclei and scant cytoplasm. The neoplastic cells were diffuse positive for CD99, vimentin, synaptophysin, and CD56 immunostain, and some were positive for CK with a dot-like pattern and negative for S100, CD3, and CD20 immunostains. Combined with the histologic features and the results of immunostains, the tumor was consistent with a PNET (**Figure 3**). Moreover, a bone scan and computerized tomography scan of the chest, abdomen, and pelvis were negative for metastatic disease.

The patient subsequently underwent endoscopic resection of nasopharyngeal mass (**Figure 1B**), followed by adjuvant chemotherapy and radiotherapy. The chemotherapy regimen was etoposide (100 mg/m²; daily Monday-Wednesday) and cisplatin (75 mg/m² on Monday) every 3 weeks for 3 months (4 courses totally). Radiotherapy involved applying radiation at a dose of 66 Gy (2 Gy/fraction; daily Mondays-Fridays, for 7 weeks) to the surgical bed of the nasopharynx. The patient tolerated the treatment well and has had symptom resolution. Tumor recurrence was not observed in follow-up nasopharyngoscopy (**Figure 1C**) and MRI, after therapy, at the 3-month follow-up point, and the patient has resumed a normal life. However, longer-

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Table 1. Summary of reported cases of PNETs developing after radiotherapy

Authors	Age/sex	Site	Past history
Klein et al. (1992)	19/F	Sinonasal cavity	Unilateral retinoblastoma underwent radiotherapy and enucleation at 1 y/o
Chan et al. (2011)	20/M	Right basal ganglia	Craniopharyngioma underwent resection and radiotherapy at 12 y/o
Fujisawa et al. (2011)	65/M	Spinal cord (C5-T1)	Pineal tumor underwent radiotherapy at 45 y/o
Cole et al. (2014)	51/F	Dura	Breast cancer underwent modified radical mastectomy, chemotherapy, and radiotherapy at 41 y/o, followed by endocrine therapy
Sato et al. (2014)	30/M	Left frontal lobe	Medulloblastoma of the cerebellum underwent resection and radiotherapy at 5 y/o
De Menezes et al. (2015)	38/F	Left kidney	Nasopharyngeal non-Hodgkin's lymphoma underwent chemotherapy and radiotherapy at 27 y/o
Sedney et al. (2015)	16/M	Cerebellum	Non-Hodgkin's lymphoma underwent chemotherapy and radiotherapy

term follow-up is required to assess for late recurrence.

Discussion

PNETs are broadly classified to include poorly differentiated or undifferentiated small round cell tumors of neuroectodermal origin. PNETs mostly originate from the central and autonomous nervous system and are called central PNETs (cPNETs) [10-12]. However, PNETs may originate from peripheral tissues and are called peripheral PNETs (pPNETs) [7]. pPNETs and Ewing sarcoma represent different manifestations of the same entity. Ewing sarcoma describes tumors that lack evidence of neuroectodermal differentiation, whereas pPNETs describe tumors that demonstrate neuroectodermal features [9, 13]. Immunohistochemical and cytogenetic studies have suggested that these two tumor types have a common origin. Therefore, these two tumor types are grouped as the Ewing family of tumors [9, 14]. Ewing sarcoma is more common in bone, whereas pPNETs are more common in soft tissues [6]. A specific chromosomal translocation (EWS-FLI1 gene, t(11;22) (q24;q12)) has been reported in pPNETs and ascribed to genetic mechanisms. The chromosomal translocation t(11;22) (q24;q12) is apparent in 80%-95% of pPNETs [9, 13, 14]. PNETs belong to the class of malignant round cell tumors and may be difficult to diagnose because PNETs display significant histologic overlap with other more common undifferentiated malignant round cell tumors. Thus, immunohistochemistry plays a pivotal

role in differentiating this tumor entity [9]. A pPNET is positive for CD99, synaptophysin, NSE, vimentin, S100, and neurofilament immunostains [13].

Radiotherapy could potentially lead to unrecognized mutations, predisposing a patient to a second malignancy. Secondary, radiation-induced PNETs are extremely rare entities that may present in survivors of cancers after radiotherapy. Few cases of PNETs developing after radiotherapy for malignancy have been reported in the literature (**Table 1**) [13-19].

Although CCRT is currently the gold standard of treatment for locoregionally advanced NPC, such "cured" patients are at risk of developing a second tumor. The risk of radiation treatment should be clearly communicated to the patients and their families before starting such a treatment. The present case, a nasopharyngeal PNET, was suspected as a second nasopharyngeal malignancy induced by radiotherapy previously used to treat the patient's NPC. This thus represents a rare late-onset complication of radiotherapy.

The long-term prognosis (5-7.5 years) in terms of overall survival is 33% for cPNETs and 45%-60% for pPNETs [13]. However, because of the rarity of nasopharyngeal PNETs, their outcomes and prognostic variables are not well characterized. In a study by Ghosh et al. pertaining to the prognostic outcomes of PNETs of the head and neck region, these tumors were determined to be aggressive and associated with high mortality rates. Chemoradiotherapy was attempted,

but local and systemic spread occurred early and had poor prognosis [9]. In a study by Bakhshi et al. pertaining to the prognostic outcomes of jaw PNETs, no difference in outcomes was observed, regardless of whether surgery was performed. This result suggests the use of chemoradiotherapy as the initial modality of treatment, rather than extensive and mutilating surgery [4]. However, a study by Biswas et al. pertaining to the outcomes and prognostic factors of thoracic PNETs suggested that all efforts should be made to resect the primary tumor after neoadjuvant chemotherapy, because radical radiation therapy results in inferior 5-year event-free survival and local control rates, despite good responses to neoadjuvant chemotherapy [20]. A study by Gerber et al. pertaining to the prognosis of cPNETs suggested that postoperative hyperfractionated radiation therapy with local dose escalation followed by maintenance chemotherapy was feasible without major acute toxicity [21]. However, the overall prognosis of spinal PNETs is very poor, even with adequate surgery, radiotherapy, and chemotherapy [1].

Local recurrence is the primary pattern of treatment failure for PNETs [22]. The most common sites of metastases from PNETs include the lungs, bone, and bone marrow [9]. In the present patient, because the tumor occurred at the same site where radiotherapy had been previously administered to treat his NPC, an additional dose of radiotherapy was limited in favor of endoscopic resection of the nasopharyngeal PNET. Among selected low-stage sinonasal malignancies (T1-2 or Kadish A-B), endoscopic and open approaches demonstrated no statistically significant difference in outcome results [23, 24].

A combination of ifosfamide and etoposide was highly effective in patients with a PNET of bone who had a relapse after standard therapy. However, in patients with a newly diagnosed PNET of bone, addition of ifosfamide and etoposide to a standard regimen did not affect the outcomes for patients with metastatic disease, but did significantly improve the outcomes for patients with nonmetastatic disease [25]. Moreover, magnetic resonance-guided laser-induced thermal therapy and proton radiation for supratentorial PNETs have been reported as alternative therapies [10, 11]. Proton radiation

after chemotherapy resulted in favorable disease outcomes for very young patients with supratentorial PNETs [11].

Based on our research, this is the first case of a nasopharyngeal PNET developing after CCRT for NPC. This report highlights the importance of considering the impact of prior CCRT on predisposition to future PNETs and expands the spectrum of reported radiation-induced neoplasms in the nasopharynx.

Disclosure of conflict of interest

None.

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