

An Unusual Clinical Manifestation of Nasopharyngeal Cancer Treatment: The Curious Case of Hiccups

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Abstract

Nasopharyngeal carcinoma (NPC) is a rare malignancy with distinct racial and geographic distribution. Due to its proximity to critical structures, NPC presents with a diverse range of symptoms and is best treated with conformal concurrent chemoradiotherapy. We report the case of a 45-year-old male diagnosed with NPC, referred for radiation therapy after receiving three cycles of neoadjuvant chemotherapy. The patient was planned for volumetric arc radiotherapy with concurrent cisplatin, following the current standard of care. The initial phase of treatment was well tolerated; however, by the 4th week, the patient developed persistent hiccups unresponsive to conservative management. A re-evaluation of the treatment plan revealed a maximum brainstem dose of 54.32 Gy. It was hypothesized that radiation-induced edema may have stimulated the vagus nerve, leading to hiccups. The patient was treated with chlorpromazine and injectable steroids, resulting in rapid symptom resolution within 5 days.

Keywords: Chemoradiotherapy, hiccups, nasopharyngeal carcinoma, volumetric-arc radiation treatment

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a relatively uncommon malignancy among head-and-neck cancers^[1] with a higher prevalence in the northeastern regions of India.^[2] Due to its anatomical proximity to several critical structures, patients may present with diverse symptoms, including nasal obstruction, nasal discharge, facial discomfort, and facial numbness. Studies have shown that patients undergoing concurrent chemo-radiotherapy (CRT) and conformal radiotherapy (RT) experience improved overall survival rates with fewer adverse effects.^[3] This case report highlights a rare presentation of recurrent hiccups in a patient with NPC during CRT, posing a significant clinical challenge. A rare underlying etiology was later identified and effectively managed.

CASE SUMMARY

The patient was referred to our department from the Medical Oncology unit after completing three cycles of neoadjuvant chemotherapy (NACT). A detailed medical history revealed persistent nasal congestion and upper neck swelling for 6 months, with gradual onset and progressive worsening over the past 1 month. Fine-needle aspiration cytology of the neck

swelling confirmed metastatic squamous cell carcinoma. A baseline contrast-enhanced computed tomography (CT) scan of the face and neck identified a mass lesion measuring 35 mm × 48 mm × 64 mm in the nasopharynx, with infiltration into the pharyngeal wall, medial pterygoid muscle, uvula, and prevertebral muscles. Multiple bilateral enlarged lymph nodes were noted at levels II, III, IV, and V, with superior extension to the skull base. No distant metastases were detected. Based on the AJCC 8th edition staging system, the patient was diagnosed with carcinoma of the nasopharynx, cT3N3M0, Stage IVA.

The patient subsequently underwent 3 weekly cycles of NACT with paclitaxel and carboplatin, which were well tolerated. A post-NACT whole-body 18F fluorodeoxyglucose (FDG) positron emission tomography-CT scan showed bilateral cervical lymphadenopathy at levels Ib, II, III, and V, along with non-FDG avid ill-defined thickening in the naso-oropharyngeal region. The patient was then referred for radical concurrent

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chemo-radiotherapy (CRT). Upon presentation to our department post-NACT, the Karnofsky Performance Score was 90%. Clinical examination revealed small, ill-defined palpable nodes only in the contralateral Level II region of the neck, with no residual disease observed on nasopharyngoscopy. A systemic examination was unremarkable, and baseline ocular and audiometric assessments were within normal limits.

The patient was planned for CRT using the volumetric arc therapy approach with a simultaneous integrated boost. A total radiation dose of 70 Gy was prescribed to the high-risk volume, including the prechemotherapy disease site, and 59.4 Gy to the low-risk regions, delivered in 35 fractions. Concurrent cisplatin (40 mg/m²) was administered weekly. Target volume and organ-at-risk contouring were performed in accordance with contemporary research guidelines.^[4] The initial phase of treatment was uneventful. However, during the 4th week of CRT, the patient developed severe and persistent hiccups. Oral medications, including baclofen and metoclopramide, were prescribed, but no improvement was observed. Neurological evaluation was normal, and brain magnetic resonance imaging revealed no significant abnormalities. Despite continued medical management, the hiccups persisted.

Given the clinical presentation, it was hypothesized that radiation-induced medullary inflammation led to edema affecting the vagal nucleus. Consequently, the treatment plan was reassessed, and CRT was temporarily halted. The brainstem had received a maximum radiation dose of 54.32 Gy (Dmax) [Figure 1], D1% was 49.75 Gy, D0.1% - 53.04 Gy and the dose-volume histogram displayed data for the brainstem and the planning target volume

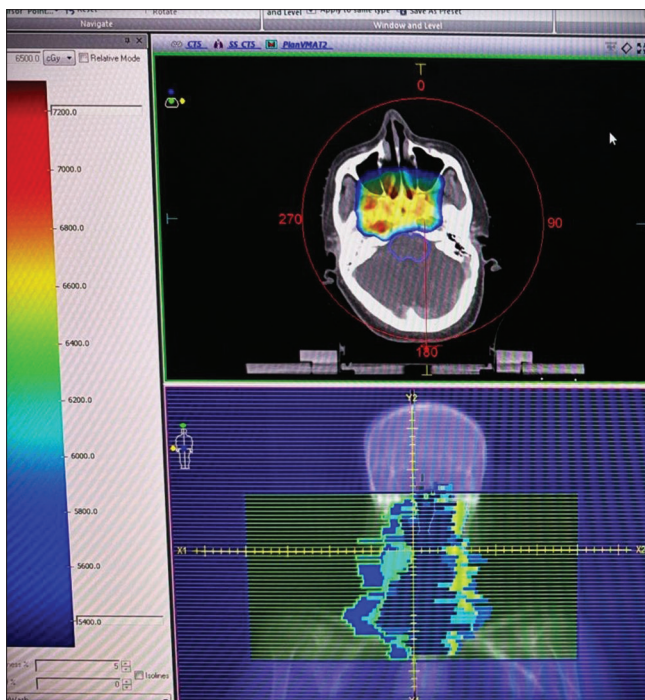


Figure 1: An isodose distribution of 54 Gy that displays the dose that the brainstem received

(PTV) [Figure 2]. The patient was administered injectable chlorpromazine along with high-dose dexamethasone (16 mg initially, followed by 4 mg every 8 h). This resulted in rapid symptomatic relief, with complete resolution of hiccups within 5 days. CRT was then resumed, and the patient successfully completed the planned course of treatment. chlorpromazine and steroids were gradually tapered and discontinued during CRT. At the 2-year follow-up, no evidence of disease recurrence or persistent symptoms was observed. In addition, there were no further episodes of hiccups posttreatment.

DISCUSSION

Hiccups, or involuntary myoclonic contractions of the diaphragm and intercostal muscles, can originate from either central or peripheral sources. The hiccup reflex arc comprises an afferent limb—including the phrenic, vagus, and sympathetic nerves that transmit somatic and visceral sensory signals—and an efferent limb, which consists of motor fibers from the phrenic nerves to the diaphragm and accessory nerves to the intercostal muscles. Central processing of this reflex occurs in the brainstem.^[5] Accurately identifying the underlying etiology before initiating treatment is essential for effectively managing persistent hiccups and preventing severe complications. However, due to the complexity of this reflex pathway, determining the precise cause and pathophysiology can be challenging.

NPC, frequently associated with Epstein–Barr virus, is prevalent among the Chinese population. In India, NPC is relatively rare, with a higher incidence in the northeastern regions.^[2] The clinical presentation varies depending on disease severity, often involving a constellation of symptoms due to its anatomical proximity to critical structures. While cranial neuropathy—including late-onset radiation-induced neurotoxicity following conventional RT—has been well-documented,^[2,6–8] the occurrence of hiccups due to vagus nerve nucleus stimulation during concurrent

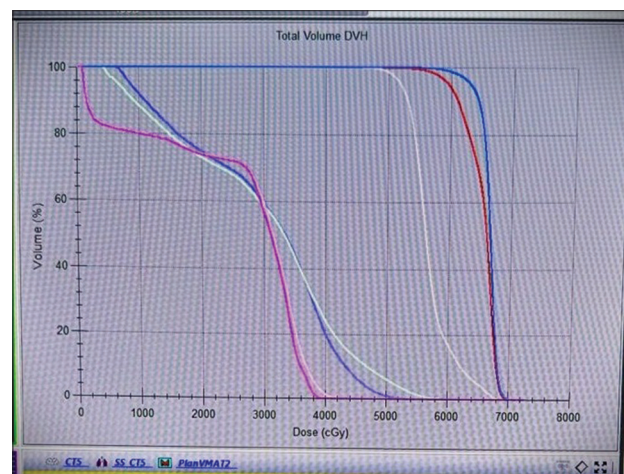


Figure 2: Dose-volume histogram illustrating dose distribution for the brainstem Light blue line and target volumes (PTV 65 - Blue line, PTV 60 - Redline, and PTV 54 - White line). PTV: Planning target volume

chemoradiotherapy (CRT) has not been previously reported. Although Nardone *et al.* described a similar case,^[9] their report documented hiccups occurring 4 weeks after CRT completion. To our knowledge, this is the first case report describing hiccups as an adverse event occurring during CRT.

In our case, the patient was classified as high-risk before chemotherapy. Due to the extensive disease burden at presentation, sparing the brainstem and cochlea was challenging. The patient received three cycles of NACT with carboplatin and paclitaxel, which can sometimes cause hiccups, but patient tolerated the treatment without any issues. However, hiccups developed 4 weeks after the initiation of RT. We postulate that radiation-induced brainstem edema, likely due to localized hotspots near the vagus nerve nuclei, contributed to the persistent hiccups, which were refractory to conventional medical management. The rapid resolution of symptoms following corticosteroid administration supports this hypothesis. Notably, corticosteroids, including dexamethasone, have also been implicated in triggering hiccups.^[10] In addition, 5HT3 antagonists and corticosteroids are commonly used both prophylactically and therapeutically for chemotherapy-induced hiccups,^[5] highlighting their paradoxical role in symptom modulation.

Given the rarity of this adverse event, our case highlights the diagnostic and therapeutic challenges associated with radiation-induced hiccups. A thorough clinical evaluation and a high index of suspicion are essential for identifying and managing this complication effectively. Our report aims to contribute to the existing literature by providing insights into the recognition and treatment of this uncommon but clinically significant side effect.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be

reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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