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Case Report
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A Case Report of Two Concurrent EBV-Associated Primary Malignancies in the Nasopharynx: Extranodal NK/T-Cell Lymphoma and Squamous Cell Nasopharyngeal Carcinoma

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Clinical Presentation

In October 2018, a 41-year-old Asian male, native of Fujian Province of China, presented to the otolaryngologist's office with progressive right ear fullness of several months' duration, accompanied by right-sided epistaxis, decreased hearing, and nasal sinus fullness. Physical exam revealed right nasal mucosal fullness and erythema with bilateral bulging tympanic membranes. Nasopharyngoscopy showed symmetric nasopharyngeal fullness but no masses or lesions. He had bilateral myringotomy tubes placed and the physician prescribed a course of nasal spray and local treatment for upper respiratory infection, resulting in partial relief of symptoms. In November, the patient returned to the office with persistent symptoms; a repeat scope showed right-sided nasopharyngeal fullness, and a biopsy showed reactive lymphoid tissue on pathology. MRI of the neck at the time was unremarkable.

The patient visited China for vacation in January 2019, where another biopsy of the right nasopharynx was performed. Pathology from the procedure was reported as NK/T-cell lymphoproliferative disorder - however, slides were not made available to us for confirmation. Upon his return to the United States, the patient's otolaryngologist performed repeat biopsies of the left and right nasopharynx. The pathology from the left nasopharynx biopsy revealed Epstein-Barr Virus-encoded small RNA (EBER) positive poorly-differentiated squamous cell carcinoma. Pathology from the right nasopharynx was consistent with EBV-associated NK/T-cell lymphoproliferative disorder. Among 29.8% lymphocytes detected, 14.9% NK cells were detected, with a phenotype of CD2+, CD3-, CD4-, CD8-, CD16+, CD56+, CD57. The Ki-67 proliferative index for the atypical lymphoid cells was approximately 2% to 3%. No features of aggressive lymphoma such as necrosis, vasculocentricity, or a high proliferation index were present. The pathology slides were sent to two other pathologists from other centers who concurred with the diagnosis. The patient's work-up and treatment plan were co-managed by a hematologist who specializes in lymphomas and a medical oncologist who specializes in head and neck malignancies. Further staging with a Fluorodeoxyglucose Positron-Emission Tomography-Computerized Tomography (FDG PET-CT) scan showed intense uptake in the bilateral nasopharynx, left greater than right, with a Standard Uptake Value (SUV) of 7.3 on the left and 4.0 on the right. The scan also showed uptake in the bilateral cervical lymph nodes, with the most FDG-avid node demonstrating an SUV of 5.1. However, a fine-needle aspiration of the most FDG-avid node in level II of the right neck showed reactive cells with no evidence of lymphoma or carcinoma. Bone marrow biopsy was performed to complete staging for NK/T-cell lymphoma and was found to be negative. The patient's final diagnosis and clinical staging was one that is quite rare: Stage I squamous cell nasopharyngeal carcinoma with concurrent Stage I extranodal NK/T-cell lymphoma, both Epstein-Barr-Virus (EBV) associated. EBV was undetectable by Polymerized Chain Reaction test (PCR) in peripheral blood at baseline. The case was discussed at hematology and head and neck tumor boards. Based on consensus opinion, a decision was made to treat both early-stage cancers with radiation therapy alone.

The patient successfully underwent radiation to the nasopharynx and bilateral neck of 70 gray in 35 fractions, completing therapy in July 2019. The patient tolerated this very well with grade 1 mucositis as the main side effect - during therapy, the patient experienced orophyarngeal pain, which was mildly improved with an antiseptic mouthwash. He continued to have right-sided tinnitus.

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Approximately one month after the completion of treatment, the patient also presented with new-onset right-sided facial droop, which improved to baseline after a course of steroids and Valtrex. A PET-CT in October 2019 showed complete resolution of the right and left nasopharyngeal FDG avidity, and repeat nasopharyngoscopy showed no evidence of tumor. Repeat imaging in January showed no concerns for disease recurrence. At the time of this report, both clinically and radiologically, the patient has no evidence of disease. Repeat imaging and close follow-up with otolaryngology, hematology-oncology, and radiation oncology will continue to monitor his progress.

Discussion

Here, we present a rare case of two EBV-mediated primary malignancies of the nasal cavity/nasopharynx occurring synchronously in the same individual: Squamous cell nasopharyngeal carcinoma in the left nasopharynx with extranodal NK/T-cell lymphoma in the right nasopharynx. In our review of the literature, we came across only two previously reported cases of EBV-associated NK/T-cell lymphoma diagnosed concurrently with EBV-positive NPC. However, unlike in our patient, both of these cases initially presented at extra-nasal sites [1,2].

EBV has been widely implicated in the pathogenesis of various malignancies, including Burkitt's lymphoma, Hodgkin's disease, nasopharyngeal carcinoma, gastric adenocarcinoma, and a subset of non-Hodgkin's lymphoma [3]. EBV is consistently linked with NK/T-cell lymphoma [4], as well with a large subset of nasopharyngeal carcinomas suggesting a key role in tumorigenesis.

Given that the nasal cavities are a known site of significant EBV proliferation and mutagenesis, it is not surprising that EBV is implicated in the pathogenesis of these tumors. However, ethnic and dietary predispositions to tumorigenesis are still not completely known. Given the ubiquitous association of EBV with both extra-nodal NK/T-cell lymphoma (ENKL) and the non-keratinizing subtype of Nasopharyngeal Carcinoma (NPC), the rarity of cases of concomitant malignancies in EBV-infected patients may seem counterintuitive. However, the two tumors have several clinical and etiopathogenetic differences that may explain this observation. While NPC starts exclusively in the nasopharynx, ENKL can affect the nasal cavity, mid-facial bones, and upper aerodigestive tract [5]. Different pathways of EBV-induced tumorigenesis with a unique set of activated cofactors are linked to NPC and ENKL. For example, among the nuclear factor kB-pathway, p50 homodimers are activated in the pathogenesis of NPC [6] while the p52 subunit is preferentially activated in the pathogenesis of ENKL [7]. Overexpression of p53 *via* an EBV-induced p53 gene mutation may be a key driving factor in NK/T-cell lymphoma but has not been implicated in NPC [8,9]. In addition, unique environmental and occupational exposures may play a role as co-factors in the pathogenesis of these malignancies. For example, consumption of salt-cured fish and smoking has been strongly associated with NPC [3]; however, no such associations have been reported for ENKL. These differential tumorigenesis pathways and risk factors may help to explain the rarity of cases of multiple concomitant primary EBV-associated malignancies. There are also some epidemiological differences between the two tumors. ENKL is highly prevalent in Asian and South American populations, with the majority of cases being reported from China, Taiwan, Japan, and Korea [10]. The disease most commonly presents in the fourth or fifth decade of life, preferentially affecting men, with a sex ratio between 2 and 4.5 in the literature [5]. Nasopharyngeal Carcinoma (NPC) is highly endemic in Southern China, Southeast Asia, the Arctic, and the Middle East/North African regions [11]. It is 2-3 times more common in men than women, with a peak incidence between 50 years to 59 years of age. The World Health Organization (WHO) classification of NPC includes two major types-keratinizing squamous cell carcinoma and non-keratinizing carcinoma. Non-keratinizing NPC is almost always associated EBV, suggesting that the virus plays an important role in the formation of these tumors, whereas keratinizing squamous cell NPC is frequently tobacco related [11].

Early diagnosis and treatment of both ENKL and NPC are paramount to increase survival, as both malignancies can be highly aggressive. The treatment of localized Stage I or II ENKL includes radiotherapy alone for localized cancers, chemotherapy, or chemoradiation based on various patient factors. Active chemotherapy regimens include asparaginase-based regimens such as P-GEMOX (pegaspargase, gemcitabine and oxaliplatin) [12] or AspaMetDex (pegaspargase, methotrexate, dexametheasone) [13] for patients who are undergoing chemotherapy alone, and DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin) for patients undergoing chemoradiation [14]. A modified-SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, etoposide) regimen can be used for patients with more advanced stage, relapsed, or refractory ENKL [15]. NPC is an exquisitely chemosensitive and radiosensitive malignancy. Treatment for Stage I NPC is radiotherapy alone, while Stages II-IV is often treated with concurrent cisplatin with radiation followed by adjuvant cisplatin-based chemotherapy combinations such as cisplatin and 5-FU or cisplatin and gemcitabine [16]. While waiting for completion of staging, we considered a regimen of concurrent cisplatin and radiation followed by adjuvant treatment with gemcitabine and oxaliplatin, since these drugs have activity in both cancers [12,14]. However, since both malignancies were clinically Stage I, we decided to employ curative-intent radiation therapy alone which resulted in a complete response for both tumors.

Conclusion

Concurrent EBV-associated malignancies are extremely rare but can co-exist. Their rarity may be attributed to a variety of different tumorigenesis pathways, further modified by unique ethnic, dietary, and occupational risk factors. Our report highlights the occasional need for multiple, bilateral biopsies in EBV-related sinonasal malignancies. As ENKL and NPC are highly aggressive and destructive malignancies, timely diagnosis and treatment are crucial in improving survival. When diagnosed at an early stage, the sensitivity of both malignancies to radiotherapy allows for the successful use of radiation for curative intent for both cancers, as in our patient. Regardless of stage, treatment of concurrent ENKL and NPC will require multidisciplinary input and creative regimens that treat both malignancies and the unique challenges that arise with them.

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