Sequential occurrence of diffuse large B-cell lymphoma and carcinoma in the nasopharynx
A case report

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Abstract

Background: The sequential occurrence of the 2 malignancies development of nasopharyngeal carcinoma (NPC) and lymphoma is extremely rare and their coexistence raises the question of a common etiologic factor.

Clinical findings/clinical concerns: A 71-year-old previously healthy man presented with diffuse large B-cell lymphoma (BCL) followed by NPC almost 2 years later with Epstein–Barr virus (EBV) positive.

Diagnosis: Endoscopic examination characterized a fixed, hard and nontender mass in the nasopharynx and biopsies were done.

Intervention: A patient successfully underwent chemotherapy for lymphoma and chemoradiation for carcinoma sequentially.

Outcomes: He was followed up every 3 months for 1 year with endoscopic and radiological examinations. The nasopharynx mass was completely resolved after chemoradiation therapy.

Conclusion: The presentation with diffuse large B-cell lymphoma (BCL) and NPC in this patient was perhaps caused by dual EBV infection or a different oncogenic mechanism.

Abbreviations: BCL = B-cell lymphoma, CR2 = conserved region 2, DLBC = diffuse large cell lymphoma, EBER = Epstein–Barr encoding region, EBV = Epstein–Barr virus, FDG = fluoro-deoxyglucose, NPC = nasopharyngeal carcinoma, PET-CT = positron emission tomography-computed tomography, RNA = Ribonucleic acid.

Keywords: carcinoma, lymphoma, nasopharynx

1. Introduction

Nasopharyngeal carcinoma (NPC) is a rare malignancy that occurs worldwide with a marked geographic and racial variation in incidence. The major etiological factors proposed for NPC pathogenesis include genetic susceptibility, environment factors and Epstein–Barr virus (EBV) infection. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of malignant lymphoma. EBV-positive DLBCL of the elderly accounts for 8.7% to 11.4% of all DLBCL cases in Asian countries, but less than 5% in western nations. EBV-positive patients, especially elderly patients, have an inferior prognosis compared with EBV-negative cases.

EBV is a ubiquitous human herpes virus infecting over 90% of the adult population worldwide. EBV has been classified as a group I carcinogen by the International Agency for Research on Cancer, with conclusive evidence with respect to carcinogenicity in NPC and in causing lymphoproliferative diseases, most of which are polyclonal B-cell proliferations classified as diffuse lymphomas. Primary EBV infection usually occurs early in life and is asymptomatic; 95% of the adults latently harbor the virus within B cells. Latent EBV infection is believed to be involved in tumorigenesis as lytic reactivation of EBV infection in infected cells will lead to cell death. Latent EBV infection is associated with several lymphoid and epithelial malignancies.

There are some published case reports of patients who develop NPC and Hodgkin’s lymphoma separated by several years or presenting concurrently at diagnosis. Here, we describe the case of sequential presentation of NPC and DLBCL. Sequential occurrence of the 2 malignancies is rare and their coexistence raises the question of a common etiologic factor.

2. Case report

A 71-year-old man with no significant past medical history presented with an enlarged right cervical lymph node involved at levels IB and II. Examination in an ENT department characterized a fixed, hard, and nontender mass. Nasal endoscopy revealed a necrotic portion on right level II. There were no active pulmonary parenchymal lesions in both lungs. A nasopharyngeal mass
punch biopsy led to a diagnosis of DLBCL, not otherwise specified, with germinal center B-cell immunophenotype. According to the Ann Arbor system [8], the patient was classified with stage IIIE. He was treated with a course of 6 cycles of combination chemotherapy. His symptoms resolved within a couple of months after treatment. He was checked with PET-CT after 3 cycles and after the last cycle of treatment, which always defined no demonstrable fluoro-deoxyglucose (FDG)-avid residual lymphoma. He was followed up every 3 months for 1 year with radiological examinations, which showed no evidence of FDG-avid recurrent lymphoma.

A follow-up PET-CT study at 18 months after chemotherapy for lymphoma (Fig. 2) revealed hypermetabolic thickening and an obliteration at the right Rosenmüller fossa. Nasal endoscopy revealed a protrusion on the posterolateral wall of the nasopharynx. Neck CT showed a mildly enhanced mass on posterolateral wall of the nasopharynx. Our first impression was recurrent lymphoma. A punch biopsy was done. Histopathological findings confirmed a nasopharyngeal nonkeratinizing carcinoma, undifferentiated (World Health Organization type 3). According to the American Joint Committee on Cancer Staging, the patient was diagnosed with stage I (T1N0) nasopharyngeal carcinoma. Laboratory tests were positive CD20 on B-cell and positive reactions for BCL-2, BCL-6, and EBV encoded small RNA. The patient was offered a course of cisplatin-based chemotherapy with radiation therapy. The nasopharynx mass was completely resolved after chemoradiation therapy. A patient was informed of the right to abstain from participation in the study and was not found to be ethically incompetent. We reviewed an institutional review board approval from Chonbuk National University Hospital and obtained proper consent from a patient (Fig. 3).

3. Discussion

Only 3 cases of NPC and Hodgkin’s lymphoma occurring in the same patients have been reported, either separated by several years (2 and 8 years), or concurrently at diagnosis.[4] To the best of our knowledge, we report here the 1st case of the occurrence of 2 cancers: a patient with DLBCL followed by NPC almost 2 years later.

EBV is an omnipresent B-herpes virus that infects the majority of the human population by adulthood.[5] It is transmitted through saliva, infecting oropharyngeal epithelial cells, and B-lymphocytes, and results in life-long persistence of the viral genome. The virus initially give rise to the lytic form of infection and then to the latent form of infection. The EBV latent proteins are important in mediating transformation and promoting
The underlying pathogenesis for EBV-related cancers has not been completely defined, but appears to be mediated through activation of various cell signaling pathways by EBV nuclear antigens and latent membrane proteins. Indeed, an association has been found between the malignancies and the different types of latent EBV expression profiles in which they develop. A type I latency pattern is typical of Burkitt lymphoma, type II is seen in NPC and HL, and type III is seen in DLBCL.

DLBCL is the most common subtype of malignant lymphoma accounting for 30% to 40% of new lymphoma cases, and only 40% to 50% of patients achieve durable remissions. Over 30% of DLBCL will ultimately relapse. The role of EBV infection in the pathogenesis of DLBCL is not known. EBV can infect resting B lymphocytes efficiently and drive it out of the resting state to become an activated lymphoblastoid cell line. These transforming effects are associated with the restricted expression of the EBV-encoded latent genes, such as latent infection membrane protein 1. DLBCL harboring EBV positive monoclonal B-cell proliferation in patients older than 50 years of age without any known immunodeficiency. Genetic factors could also play a role in the development of EBV-associated lymphoma.

NPC presents as an epithelial cancer with histology that ranges from well-differentiated to undifferentiated squamous cell carcinoma, and includes both keratinizing and nonkeratinizing forms. The disease is rare in the United States and Europe, but is endemic to parts of China and elsewhere in Asia. The undifferentiated variant of NPC is universally associated with EBV infection, viral genomes within the tumor are clonal and exhibit EBV gene products typical of a type II latency pattern.

This study describes a patient with DLBCL followed by NPC almost 2 years later. The presentation with DLBCL and NPC raises the possibilities of dual EBV infection or a different oncogenic mechanism. Human epithelial cells can be infected in vitro through the formation of specialized B cell-epithelial cell conjugates involving the GP350 EBV viral envelope glycoprotein and the CR2 receptor of B lymphocytes. This cell-to-cell method of EBV infection of nasopharyngeal epithelium may take place in vivo. EBV-infected B cells invariably may be present in the nasopharyngeal mucosa and can come into close contact with the polarized nasopharyngeal epithelial cells to transmit EBV.

In the present case, the serologic results revealed positive CD20 on B-cell and Epstein–Barr encoding region positive, illustrating a type III latency pattern.

4. Conclusion

Our observations support the possibility of multiple EBV infections in a single patient, which can lead to distinct
malignancies. Since the 2 tumors in the same patient will contain different clonal viral genomes, it suggests that the 2 different EBV strains could activate different oncogenic pathways, leading to the occurrence of malignancies of lymphoid and epithelial cell origin, respectively. Further evaluation of EBV protein expression and cellular immune response in this patient could lend additional insight into the development of EBV-associated neoplasia.

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References

[1] Tsao SW, Yip YL, Tsang CM. Etiological factors of nasopharyngeal carcinoma. Oral Oncol 2014;50:330–8.
[2] Niedobitek G. Epstein-Barr virus infection in the pathogenesis of nasopharyngeal carcinoma. J Clin Pathol: Mol Pathol 2000;53:248–54.
[3] Jia WH, Qin HD. Non-viral environmental risk factors for nasopharyngeal carcinoma: A systematic review. Seminars Cancer Biol 2012;22:117–26.
[4] Rey J, Xerrè L, Bouabdallah R, et al. Detection of different clonal EBV strains in Hodgkin lymphoma and nasopharyngeal carcinoma tissues from the same patient. Brit J Haematol 2008;142:79–81.
[5] Morrison JA, Golley ML, Pathmanathan R. Differential signaling pathways are activated in the Epstein-Barr virus-associated malignancies nasopharyngeal carcinoma and Hodgkin lymphoma. Cancer Res 2004;64:5251–60.
[6] Elizabeth AS, Bradford CR, Carey TE. Epstein-Barr virus detected in a head and neck squamous cell carcinoma cell line derived from an immunocompromised patient. Arch Otolaryngol Head Neck Surg 2003;129:1115.
[7] Stokken J, Manz RM, Flagg A, et al. Synchronous occurrence of nasopharyngeal carcinoma and Hodgkin lymphoma. Int J Pediatr Otorhinolaryngol 2014;78:154–6.
[8] Tilly H, Vitolo U, Waleyki J, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23:78–82.
[9] Lu TX, Liang JH, Miao Y, et al. Epstein-Barr virus positive diffuse large B-cell lymphoma predict poor outcome, regardless of the age. Sci Rep 2015;5:12168.
[10] Beltran B, Salas R, Quinones P, et al. EBV-positive diffuse large B-cell lymphoma in a human T-lymphotropic virus type I carrier. Infect Agent Cancer 2009;4:10.
[11] Breida E, Catarino RJ, Azevedo I. Epstein-Barr virus detection in nasopharyngeal carcinoma:implications in a low-risk area. Braz J Otorhinolaryngol 2010;76:310–5.