Case report of concurrent primary malignancies of the breast and nasopharynx

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Abstract. The aim of this study was to report a case of concurrent primary malignancies of the breast and nasopharynx and discuss the potential relationship between Epstein-Barr virus (EBV) infection and breast cancer. A 39-year-old female presented with a palpable mass present for 1 year in her left breast. Immunohistochemical staining was performed and the results showed that the tumor cells were immunopositive for the estrogen receptor, progesterone receptor and p53 protein, and markedly positive for C-erb B2. In addition, 30% of the tumor cells were positive for the Ki-67 antigen. Blood test results revealed that EBV-CA-IgG was present and EBV-EA-IgG was reactivated. The patient was diagnosed with breast cancer (T1N0M0) and EBV infection. A mastectomy with axillary clearance was performed on the left breast. Histopathological examination provided evidence of invasive ductal adenocarcinoma. Further evaluation due to epistaxis following the breast surgery resulted in a diagnosis of nasopharyngeal carcinoma (T2N1M0). Histopathology showed a non-keratinizing undifferentiated carcinoma. The patient was treated with chemoradiotherapy for nasopharyngeal carcinoma. Twelve months following surgery and chemoradiotherapy the patient was assessed at the Cancer Hospital of Guangxi Medical University outpatient clinic and no evidence of relapse or metastasis was found. Thus, EBV infection may be involved in the pathogenesis of breast cancer, as observed in nasopharyngeal carcinoma.

Introduction

The mechanisms responsible for the appearance of multiple primary cancers remain unclear. Among the factors most frequently involved are genetic susceptibility, the immune system and intensive exposure to carcinogens, including chemical and biological carcinogens and radiation.

Breast cancer is the most common neoplastic disease of women in the Western world. In developed countries, more than 200 cases are diagnosed annually per 100,000 women. The etiology and mechanisms of breast cancer are poorly understood. Well-known risk factors, including those that affect circulating sex hormones and genetic background can only explain approximately 50% of all breast cancer cases. Among the remaining 50% of cases, findings of numerous studies have suggested that Epstein-Barr virus (EBV) infection may be a causal factor (1-4).

EBV is a ubiquitous γ herpes virus and infects 90% of the population. In the majority of individuals, the virus persists for life in the memory B-cell pool (5) with no adverse health consequences. The virus is essentially a B-lymphotropic agent and is associated with malignancies of B-cell origin, including Burkitt's lymphoma. However, epithelial cell infection clearly occurs *in vivo*, as EBV is also associated with malignancies of epithelial origin, such as nasopharyngeal carcinoma (NPC). In Burkitt's lymphoma and NPC, epidemiological and molecular virological data favor the role of the virus as a cofactor in tumor initiation and/or development. The involvement of EBV has been demonstrated by the findings of EBNA-1 expression in Burkitt's lymphoma, and EBNA-1, LMP1 and LMP2 expression in NPC (6).

The list of malignancies reportedly associated with EBV continues to grow and includes Hodgkin's disease, sino-nasal T-cell lymphoma, lymphoepithelioma, certain sarcomas and breast cancers, cancers of the head and neck, and lymphomas arising in patients with immune dysfunctions. Evidence of a role for EBV in the pathogenesis of a tumor includes: i) elevated antibody titers to EBV preceding the development of a neoplasm; ii) the presence of the viral genome in a large majority (if not all) of tumor cells; iii) clonality of the viral genome; and iv) expression of viral genes in neoplastic cells. Elevated antibody titers to EBV have been found in patients with breast cancer, but the presence of the EBV genome or its products at the cellular level remains controversial (4,7). The possible contribution of EBV to the development and/or progression of breast cancer may be as a putative 'non-traditional' infection, as observed in NPC or Burkitt's lymphoma.

We report a rare case of multiple concurrent primary malignancies of the breast and nasopharynx with EBV infection

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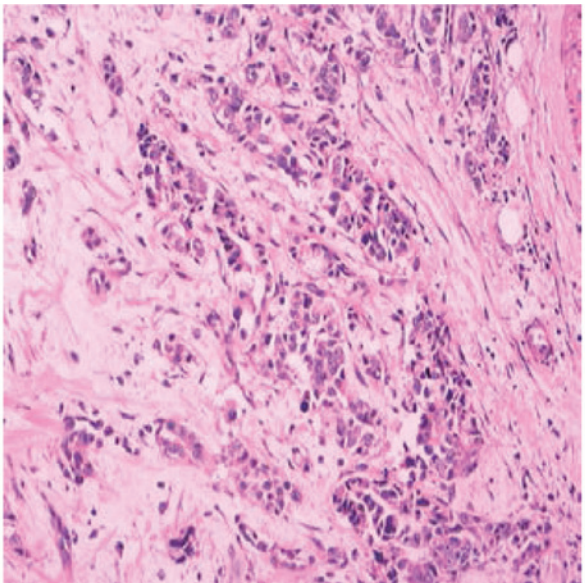

Figure 1. Histopathology of breast mass revealed invasive ductal adenocarcinoma (H&E; magnification, x100).

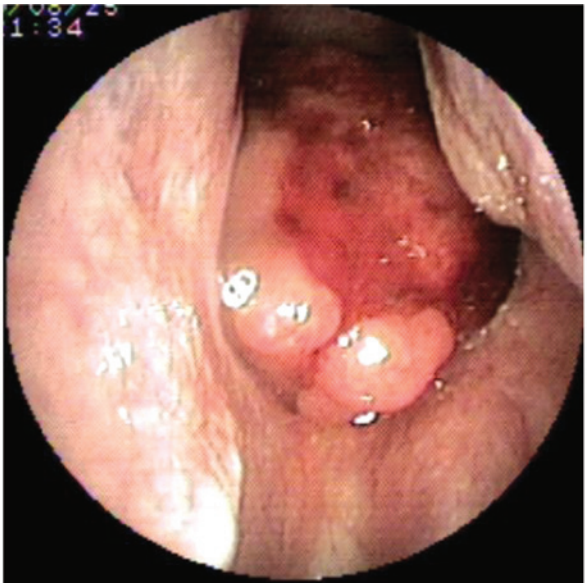

Figure 2. Nasopharyngoscopy revealed a mass with active mucosal bleeding located in the nasopharynx.

and discuss the possible association between EBV infection and breast cancer. This study was endorsed by the Ethics Committee of the Guangxi Medical University. The patient received an explanation of the aims of the study, provided signed informed consent, and understood that withdrawal from the study was allowed at any time without influencing her oncological or general medical treatment.

Case report

Patient history. A 39-year-old female visited our hospital after a palpable lesion of 1-year duration had been removed from her left breast at a community hospital. The lump in the patient's left breast, which measured 2x2x1 cm according to the report, had been resected for diagnosis. The histopathological report revealed invasive ductal adenocarcinoma. The patient refused any treatment at the community hospital and presented to our breast unit for further evaluation. Physical examination of the left breast revealed a 3-cm scar on the lower inner quadrant. The skin of the breast, including the nipple and areola, was not invaded and was without redness, erosion or ulcer. Multiple lymph nodes were felt in the left axilla; the largest node, measuring about 1x1x0.5 cm, was mobile and non-tender. The right breast yielded negative findings.

Carcinoma specimen analysis. The pathological specimen provided by the community hospital showed an invasive ductal adenocarcinoma. According to an immunohistochemical analysis, the cells were positive for the estrogen receptor, progesterone receptor and p53 protein, and negative for vascular endothelial growth factor and epidermal growth factor receptor. The cells were markedly positive for C-erb B2 (also known as HER-2/neu), and 30% of the tumor cells were positive for the Ki-67 antigen (Fig. 1).

Patient examination. Electron beam computed tomography showed a positive sentinel lymph node located at the upper outer quadrant. A chest X-ray and ultrasound did not reveal any metastases. Routine blood test results were within normal limits, except that EBV-CA-IgG was present and EBV-EA-IgG was reactivated.

Lymph node examination. A simple mastectomy with sentinel lymph node biopsy and axillary clearance was performed on the left breast. Six sentinel lymph nodes, including the one positive on electron beam computed tomography, were found. All presented non-specific inflammation. Pathology revealed a total of 12 lymph nodes of the left axilla also had non-specific inflammation. The diagnosis was pT1N0M0/stage I breast carcinoma (UICC, 2002).

Nasopharyngeal carcinoma. Three days following surgery, the patient experienced epistaxis and was sent for an endoscopic nasopharyngeal examination. A mass with active mucosal bleeding was found and biopsied (Fig. 2). Histopathology revealed a non-keratinizing undifferentiated carcinoma. MRI showed an enlarged lymph node in region II of the right neck and an invasive mass in the parapharyngeal space (Fig. 3A and B). The patient was diagnosed with nasopharyngeal carcinoma, T2N1M0/stage II (UICC, 2002).

Treatment and follow-up. Two weeks following breast surgery, the patient was treated with chemoradiotherapy for nasopharyngeal carcinoma. A planned dose of 70 Gy was to be delivered in 2.0-Gy fractions over seven weeks to the primary tumor, with 6-MV photons. The neck was treated with 54 Gy. The positive node was boosted to a total dose of 64 Gy. The chemotherapy regimen was delivered for three cycles, on days 1, 22 and 43 during the course of radiotherapy, as concurrent chemotherapy. The patient was followed up 12 months after the completion of treatment. Physical examination, CT of the chest, MRI of the nasopharynx and neck, ultrasound imaging of the abdomen and a bone scan were performed. There was no evidence of relapse or metastasis.

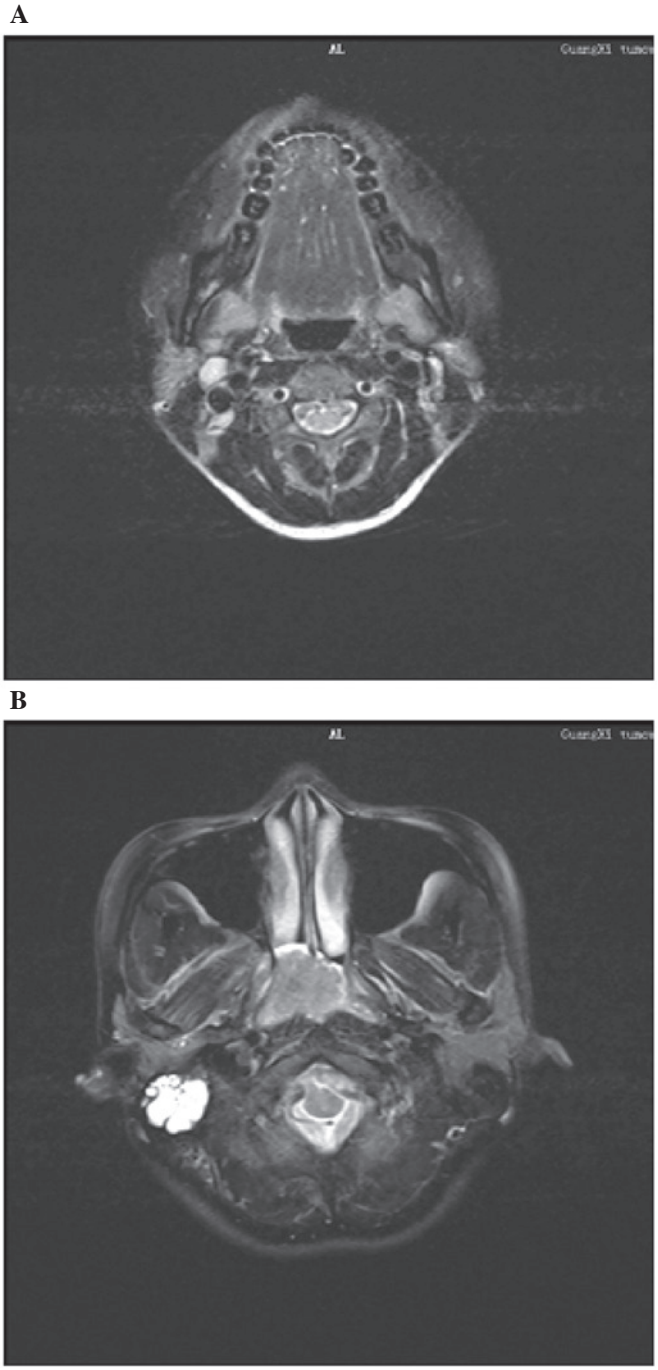

Figure 3. (A) An axial MR image showed an enlarged lymph node with high signal intensity in the right neck region. (B) The enhanced mass had invaded the pharyngeal space. MR, magnetic resonance.

Discussion

Previous studies have shown that individuals with one malignant neoplasm have a 1.29-fold risk of developing a new independent primary tumor, compared with individuals who have no cancer (8). Additional primary cancers occurring simultaneously with breast cancer have been reported in the opposite breast, salivary glands, uterine corpus, ovary and thyroid (9). To the best of our knowledge, the present case is the first report of concurring multiple primary malignancies of the breast and nasopharynx.

Epidemiological and molecular virological data have shown that EBV is a cofactor in tumor initiation and/or development in NPC. Almost 100% of anaplastic or poorly differentiated nasopharyngeal carcinomas contain EBV genomes and express EBV proteins (10). Although the etiology of breast cancer is poorly understood, genetic background and hormonal effects are believed to be important in its development. Our patient did not have a family history for breast cancer or NPC, suggesting that genetic susceptibility was a weak factor in breast cancer pathogenesis in this case. However, epidemiological data on breast cancer indicate that delayed infection with EBV may be a risk factor for breast cancer (2). Our patient was positive for EBV-CA-IgG and EBV-EA-IgG, showing that the patient was infected with EBV. Thus, we suggest that EBV infection causes NPC and may simultaneously be the cause of breast cancer.

No definitive consensus has yet been achieved regarding an association between EBV and breast cancer (11,12). Detection of the EBV genome or its products in breast cancer cells would provide strong evidence of this association. In 2001, Fina *et al* (4)reported the frequency and genome load of EVB in 509 breast cancers from different geographical areas. EBER-1 has been identified in 31.8% of frozen sections from different breast cancers (4). By contrast, a study conducted in 2002 found no evidence of EBV infection in breast cancer, as no EBERs, EBNa1, LMP1 or LMP2A was detected in 43 frozen sections of breast cancer (7).

A few studies have demonstrated a new way in which EBV infects breast epithelial cells (13,14). This finding may lead to an explanation for the pathogenesis of breast cancer caused by EBV. Contact between lymphoid and epithelial cells appears to provide a mechanism for EBV transfer from lymphoid to epithelial cells. This idea is supported by Imai *et al*, who showed that co-culturing target cells with semi-permissive B-cells leads to the infection of epithelial cells (13). As further evidence, a study by Speck *et al* suggested that breast epithelial cells became infected with EBV following direct contact with lymphoid cells (14).

A model for the putative role of EBV in the progression of breast cancer has been provided by Hippocrate *et al* (15). A limited number of previously transformed epithelial cells may become infected with EBV via direct contact with infiltrating EBV-positive B cells. The inflammatory milieu of the tumor may activate the virus, leading to an increased expression of factors involved in angiogenesis and cell invasion, which favors tumor progression. Alternatively, EBV-positive infiltrating B cells may provide EBV-induced or EBV-encoded products such as cytokines and microRNA, which could alter the cellular environment to influence the growth of transformed epithelial cells.

There are no established therapeutic rules for multiple primary cancers. The tumor type, location, stage and progression, as well as the patient's general health status should be considered. The treatment of choice involves curative surgical resection of each cancer, followed by radiotherapy and chemotherapy (16-18). The prognosis should be determined independently as a function of the tumor stage and treatment results for each cancer. When the two cancers present the possibility for a cure, radical therapy is indicated. However, when radical therapy of the primary cancer is impossible, conservative therapy is indicated for the second cancer. In the

present case, radical surgery for the breast cancer and radical concurrent chemoradiotherapy for the nasopharyngeal carcinoma were performed, in anticipation of a better prognosis.

In conclusion, EBV infection may be involved in the pathogenesis of breast cancer, as observed in nasopharyngeal carcinoma. This possibility must be taken into account, even though this association may not reflect a 'traditional infection' as observed in EBV-associated tumors.

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