Epstein-Barr virus associated smooth muscle tumors

Synchronous liver and lung involvement

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ABSTRACT

Epstein-Barr virus associated smooth muscle tumors (EBV-SMT) are rare neoplasms that can occur in various anatomical locations. They mainly affect immunocompromised patients, and their clinical presentation is variable depending on size and organ involvement. They can pose diagnostic challenges, therefore if they are not considered in the differential diagnosis, they can be definitely misdiagnosed. Synchronous and multifocal involvement has been reported. Although malignant behavior maybe rarely seen; most behave in a benign fashion with favorable clinical outcome. We herein report an unusual case of synchronous EBV-SMT that occurred in the lung and liver in a 44-year-old female patient 7 years after renal transplantation. Both lesions were histologically examined revealing benign appearing spindle cell neoplasm that was positive on immunohistochemical staining for smooth muscle actin, desmin, and caldesmon with strong nuclear staining for EBV RNA by in situ hybridization. A brief pertinent literature review and discussion of EBV-SMT pathogenesis is offered.

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Smooth muscle tumors in organ transplant recipients were first described in 1970.1 Co-infection with Epstein-Barr virus (EBV) seems to be an essential co-factor for development of these tumors in these immunocompromised patients. However, the relationship and the association between these tumors and EBV was not discovered until 1995.2 Epstein Barr virus associated smooth muscle tumors (EBV-SMT) was the name that these tumors were given since then. The EBV-SMT is a rare tumor that can be multicentric with a predilection of unusual sites such as liver, lung, heart, spleen, lumen of the gastrointestinal tract, and other sites. The clinical features of EBV-SMT vary depending on their location and size.3 Radiologically, these tumors are usually well-defined and intensely enhancing by CT scans or magnetic resonance imaging studies. On gross examination, these tumors are usually well-demarcated and histologically, they resemble benign SMTs without significant atypia, increased mitosis, or necrosis.4 These tumors have been proven to be clonal and their DNA harbor EBV material. The scenario of metastasis or
multicentric synchronous involvement is still uncertain, yet most investigators believe that metachronous and synchronous EBV-SMT is the result of EBV infection rather than metastasis. We are describing an unusual case of multicentric EBV-SMT that involved the lung and liver simultaneously. The reason for presenting the case is to increase awareness regarding the entity so that it will be considered in the differential diagnosis.

**Case Report.** The patient is a 44-year-old Saudi female, suffering from type-I diabetes mellitus, complicated by diabetic nephropathy, which ended in end-stage renal disease. Consequently, she underwent living unrelated renal transplant 6 years prior to her latest admission. Since then, she was receiving routine anti-rejection protocol. However and despite aggressive anti-rejection treatment, her transplant failed, and she was maintained on hemodialysis. She presented to our emergency room with non-productive cough, progressive dyspnea, and shortness of breath at rest with orthopnea for several days. No hemoptysis, anorexia, night sweats, or weight loss was reported. Physical examination revealed significant diminished breath sounds and dullness to percussion on the right chest. Laboratory tests were significant for leukocytosis with neutrophilia and her liver function test only showed elevated alkaline phosphatase. Chest radiograph showed right sided opacification, tracheal and mediastinal deviation towards the right, while the CT scan examination revealed complete right lung collapse due to right main stem bronchial hypo-dense filling defect (Figure 1A). No significant hilar mediastinal lymphadenopathy was noted. There were no pulmonary nodules or significant pleural effusion identified. The upper abdominal cuts showed 2 hypodense liver lesions (Figure 1B). Initial bronchoscopy evaluation was non-conclusive, but this was followed by an open lung biopsy, where most of the lesion obstructing the main stem bronchus was removed and sent for histological examination. Histological sections revealed benign appearing spindle cell neoplasm composed of short intersecting fascicles of spindle cells with elongate bland nuclei and slightly pale to eosinophilic cytoplasm. Intersecting fascicles of these spindle cells were also noted. The mitotic figures were very rare and abnormal forms were not seen. There was no cellular or nuclear atypia, and tumor necrosis was completely absent (Figures 2A-2D). Well-controlled immunohistochemical stains were positive for smooth muscle actin, caldesmon, vimentin and desmin but were negative for S 100 protein, pankeratins, CD 117, CD 34, Alk-1, and P 53 (Figures 3A-3C). Interestingly, the initial immunostaining for EBV by our routine immunohistochemistry was completely negative (EBV, ventana, Clone CSI-4, Tuscon AZ, USA). Special stains for acid fast bacilli and fungi were performed, and were negative. The initial impression was consistent with inflammatory myofibroblastic pseudotumor. To further characterize this process an ultrasound-guided liver biopsy was carried out to examine these lesions and rule out metastasis. The histology of the liver lesion was exactly the same as those seen in the lung. The lung and liver tissue material was sent for EBV-RNA examination by in situ hybridization to a referral laboratory and it was strongly and diffusely positive (Figure 3 D). Therefore, the diagnosis of EBV associated SMT was made. The patient had a prolonged postoperative course, where she developed pulmonary cutaneous fistula followed by fatal gram-negative sepsis. She died 2 months after thoracotomy.

**Discussion.** Immunosuppression due to any etiology is a well-known risk factor for the development of malignancies. These malignancies are most
Figure 2 - Histological sections of the mass from the lung A & B) and liver C & D) showing bland smooth muscle neoplasm that lacks significant atypia, necrosis or increased mitosis (low and high power views, hematoxylin & eosin).

Figure 3 - Immunohistochemical stains for A) caldesmon, B) smooth muscle actin, and C) vimentin are all positive. RNA in situ hybridization for D) Epstein-Barr virus is strongly positive.
commonly epithelial or lymphoproliferative in nature. The lymphoproliferative ones are usually associated with opportunistic infections, the most common of which are those associated with viruses. Viruses are known to cause malignancies in animals and humans. A large number of DNA and RNA viruses have proved to be oncogenic in a wide range of animals. Of interest, there are a group of DNA viruses that are known to cause human cancer in their infected host cells. This list includes human papillomavirus, EBV, hepatitis B virus, and Kaposi sarcoma herpes virus. In addition, hepatitis C virus, not a DNA virus, is implicated in the development of human hepatocellular carcinoma. These viruses infect human cells, and their nucleic acids integrate into host DNA and exhibit oncogenic transformations that take variable amount of time.

The EBV, is a member of the herpes virus family, and is known to be implicated in the pathogenesis of different types of human cancer; nasopharyngeal carcinoma, the African form of Burkitt lymphoma, Hodgkin lymphoma and other types B-cell non-Hodgkin lymphoma. The mechanism of action of EBV associated oncogenesis is complex. In brief, it usually requires infection of nasopharyngeal epithelial cells or B lymphocytes, where the virus integrates itself in the nucleus, in which these cells become immortalized and acquire the ability to proliferate in malignant fashion.

Despite the rarity of benign and malignant mesenchymal tumors in the immunocompromised host, they can occur and recently have been reported in association with EBV infection. These tumors were found to be smooth muscle in nature and the term EBV-SMT has been given since then, and reports of such tumors in immunocompromised patients started to appear in the literature. These tumors are characteristically multicentric and can occur in unusual sites whether in a synchronous or metachronous fashion. In our patient, the tumor involved the main stem bronchus with almost complete obstruction, and simultaneously had 2 separate liver lesions. Histological examination of both lesions was identical. Therefore, the question of malignancy and metastasis arose. Whether the scenario of our patient, and the similar (approximately 86 cases) cases that were reported in the literature represent metastasis or multicentric synchronous benign involvement, is uncertain. Since the histological examination of these lesions is the same, it is extremely difficult to predict the behavior based only on microscopic grounds. Most investigators strongly believe that metachronous and synchronous EBV-SMT is the result of multiple EBV infections rather than malignancy and metastasis. One additional point that is worth mentioning is that routine immunohistochemical stains for EBV antigens is not sensitive, and EBV-encoded RNA (EBER) in-situ hybridization is always recommended. In our case, the routine immunohistochemical stain for EBV was completely negative, however as shown above, the EBER was strongly positive. The appropriate management of these tumors varies and includes surgical excision, prolonged antiviral treatment, and reducing both the immunosuppressive and chemotherapy. In our patient, the obstructing bronchial lesion was removed surgically without removing the 2 hepatic lesions.

In conclusion, EBV-SMTs are histologically benign SMTs that harbor EBV in their nucleus. These tumors are often multicentric, and the multicity is believed to be due to multiple infections with EBV, rather than metastasis. To confirm the diagnosis, EBER in-situ hybridization is recommended.

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References