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Epstein-Barr Virus-Associated Leiomyomatous Tumors in Immune Compromised and Immune Suppressed Children: Histopathologic and Ultrastructural Features

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Background: Epstein-Barr virus-associated malignancies are well described and are linked to Burkitt's lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, nasopharyngeal carcinoma and lymphoepithelial carcinoma. Not until the AIDS epidemic affected children did the relationship between immune compromise and EBV-associated leiomyomatous tumors become known. With HIV-infected children, EBV-associated smooth muscle tumors are the second most common neoplasm. More recently, it has been noted that children on immunosuppressive medications or with immune compromise are at increased risk for development of EBV-associated leiomyomatous tumors.

Design: 4 children with EBV-associated smooth muscle tumors were identified at Texas Children's Hospital. Tissue was available for immunocytochemical (smooth muscle actin), in situ hybridization (EBER-1) and electron microscopic evaluation.

Results: The children ranged in age from 3 to 19 years of age. There were 3 females, 1 male, 3 Hispanics and 1 Caucasian. Two children were HIV-infected secondary to vertical transmission. One child had undergone renal transplantation due to prune belly syndrome with ensuing kidney failure. Another child had ataxia-telangiectasia with associated immune compromise. The presenting sites of involvement for the leiomyomatous tumors were: liver, larynx, subcutaneous tissue, and lung. Multiple sites of involvement were identified in the children after the diagnosis of EBV-associated smooth muscle tumor was made. The tumors were composed of spindle cells with variable amounts of eosinophilic cytoplasm, and had a high degree of cellularity. The tumor cells readily immunoreacted with smooth muscle actin. EBER-1 was detected by in situ hybridization. In 2 cases, the tumors were considered to be cellular leiomyomas. With the other 2 children, the tumors were determined to be leiomyosarcomas. Ultrastructural examination revealed spindle cells with characteristic features consistent with smooth muscle origin. Cytoplasmic thin filaments, electron dense bands and plaques along the plasma membranes, basement membranes, and pinocytotic vesicles were readily appreciated. Three patients died shortly after their initial diagnosis with disseminated disease and opportunistic infections (CMV).

Conclusions: Over the past several years, it has been demonstrated that smooth muscle cells possess CD21 receptors. It is via CD21 receptors that EBV can infect B-lymphocytes, oropharyngeal epithelial cells, cervical epithelial cells, and smooth muscle cells. In HIV-infection, CD21 receptors are upregulated on the cytoplasmic membranes of smooth muscle cells. The oncogenic ability of EBV is reinforced by the fact that several smooth muscle tumors have been shown to contain clonal EBV strains. In children with immune suppression or immune compromise, EBV infection may lead to smooth muscle tumor development and progression to malignant transformation.

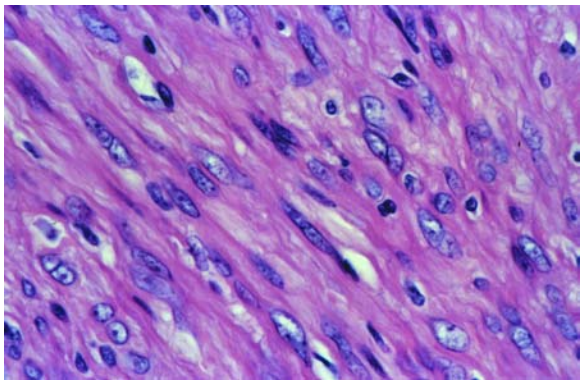

Figure1: EBV-Associated Leiomyoma (H&E, 400x original magnification)

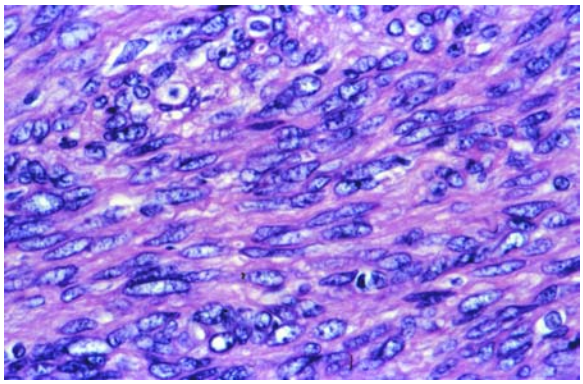

Figure 2: EBV-Associated Leiomyosarcoma (H&E, 400x original magnification)

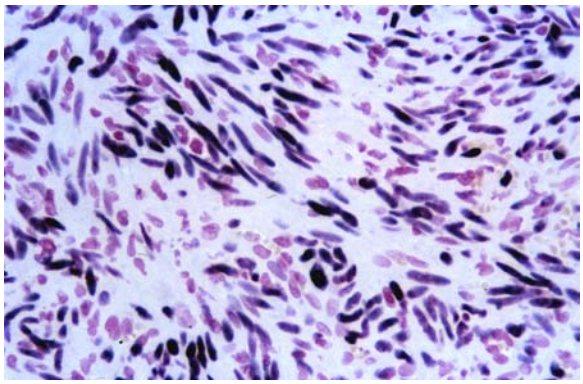

Figure 3: EBV In Situ Hybridization with Leiomyoma (200x original magnification)

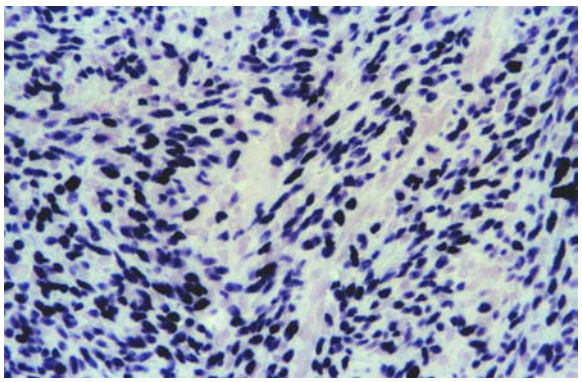

Figure 4: EBV In Situ Hybridization with Leiomyosarcoma (200x original magnification)

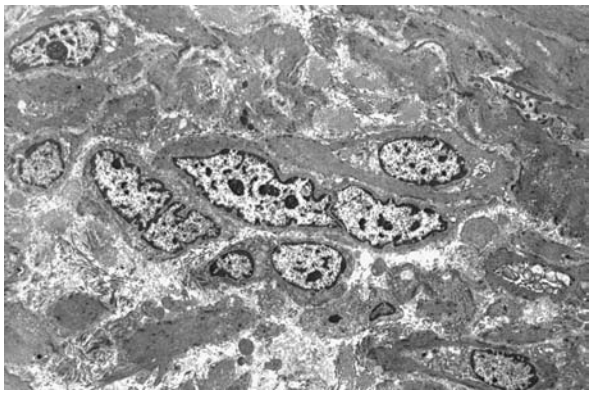

Figure 5: EBV-Associated Leiomyomatous Tumor (1,500 x original magnification)

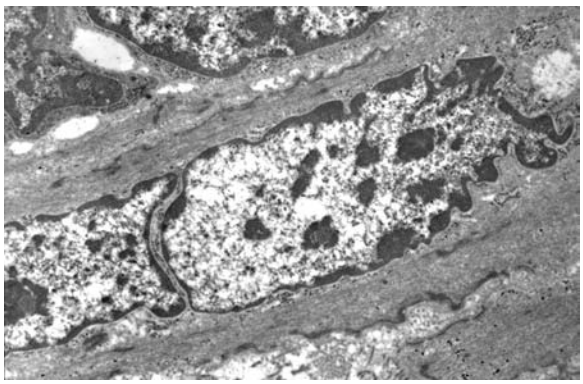

Figure 6: EBV-Associated Leiomyomatous Tumor (5,000x original magnification)

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