CASE REPORT

Multifocal Epstein–Barr virus-associated miliary post-transplant smooth muscle tumors

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ABSTRACT

Epstein–Barr virus (EBV) promotes the development of undifferentiated carcinomas of the upper aerodigestive tract and different types of lymphomas. This ability of tumorigenesis is heightened in many immunocompromised patients who have an increased incidence of lymphoproliferative disorders. The virus also induces smooth muscle proliferation, and those occurring following transplantation are designated as EBV-associated post-transplant smooth muscle tumors. We report multifocal miliary-sized leiomyomas in the lungs in a renal transplant recipient as an incidental finding.

KEY WORDS: Epstein–Barr virus, smooth muscle tumors, transplantation

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INTRODUCTION

Several diseases have been effectively treated by bone-marrow and solid organ transplantation, and in such circumstances long-term immunosuppression is inevitable. The fallout of this practice is not only the development of opportunistic infections, but also malignant neoplasms in these patients. Epstein–Barr virus (EBV), a common human pathogen, is instrumental in the genesis of different types of lymphomas and undifferentiated carcinomas of the upper aerodigestive tract. This ability of tumorigenesis is heightened in transplant recipients, who tend to develop post-transplant lymphoproliferative disorders.[1] In other immunocompromised states, such as acquired immunodeficiency syndrome, autoimmune disorders, or congenital immunodeficiency syndromes, the virus also promotes smooth muscle proliferation, designated as EBV-associated smooth muscle tumors.[2] Similar lesions following transplantation, i.e., EBV-associated post-transplant smooth muscle tumors (PTSMT) are relatively uncommon. We report multifocal miliary-sized leiomyomas in the lungs in renal transplant recipient as an incidental finding.

CASE REPORT

A 31-year-old kidney transplant recipient developed fatal pulmonary edema and hemorrhage during hemodialysis. He had undergone a living-donor renal transplantation in the year 2000 for chronic kidney disease; details of the primary disease were not available. He had been on immunosuppressive therapy (azoran, wysolone, and byoral) with serum creatinine ranging from 1.2 to 1.8 mg/dl. The patient had been diagnosed as a case of pancytopenia in 2009 with recurrent hospital admissions for fever, loose motions, and boils over the body. The current admission was for acute febrile illness of 7 days' duration with chills, headache, and boils over the buttocks. He was admitted to private healthcare center where hypotension (90/70 mm Hg), right gluteal region abscess, multiple sebaceous cysts over scrotum, and severe azotemia (serum creatinine of 6 mg/dl) with progressive oliguria was also noted. In view of these clinical features, he was transferred to our center for further management.

At autopsy, multiple small well -circumscribed firm glistening nodules [Figure 1a and b] were seen scattered in the edematous and hemorrhagic pulmonary parenchyma; some could even be easily shelled out. On histology, these were present close to the bronchovascular bundle and were composed of interlacing bundles of spindle-shaped cells. These had the morphology of smooth muscle cells [Figure 1c-e], which did not display pleomorphism or nuclear hyperchromasia. Occasional nodules showed significant hyalinization, while a nodule appeared

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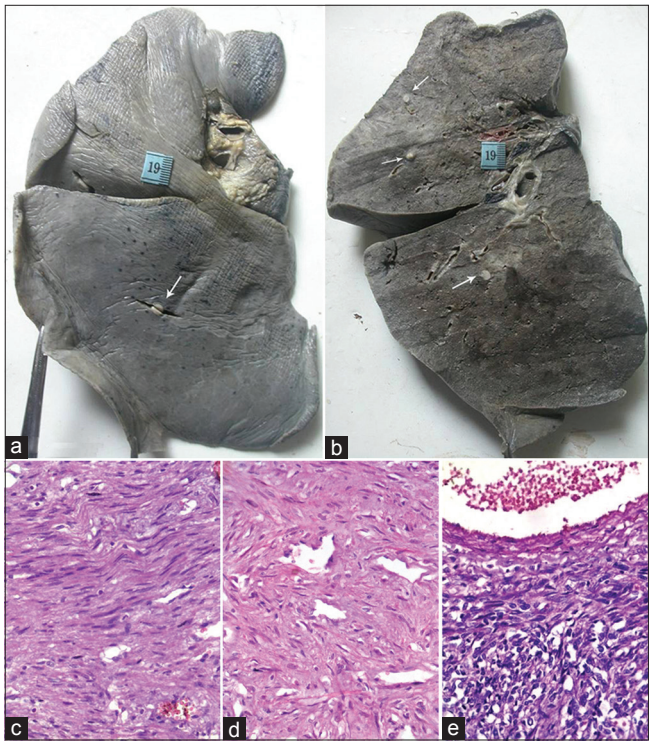

Figure 1: (a) The external and (b) the cut surface of the left lung shows well spaced out sub-pleural and intra-parenchymal (arrows) well-circumscribed grey white slightly glistening nodules, respectively; (c) Interlacing bundles of benign smooth muscle cells; (d) Foci of hyalinization observed in few nodules; (e) Hypercellularity emanating from the periphery of a vein (H and E ×400)

to arise from the adventitial aspect of a muscular artery; it showed cellular pleomorphism devoid of mitoses. On immunohistochemistry (IHC), the cells were positive for desmin, smooth muscle actin [Figure 2a], and also for EBV-encoded early RNA (EBER, [Figure 2b]. A diagnosis of EBV-associated smooth muscle proliferation was made.

DISCUSSION

Though the association of immunosuppression and occurrence of smooth muscle tumors initiated by EBV was recognized several decades ago, they still remain uncommon neoplasms.[3] They occur basically in three clinical settings, i.e., HIV-positive patients, transplant recipients, and patients with congenital immunodeficiency, in whom there are differences in the incidence, sites, morphology, and clinical behavior.[4] Majority of the patients are transplant recipients, especially with the liver, kidney, or heart transplantations, wherein unifocal or multifocal/multicentric tumors occur late after transplant (median duration of 48 months).[5] The liver and the respiratory system are most frequently involved and patients present usually with pain and/or organ dysfunction; the symptoms depend on the size and site of tumors. Our patient developed asymptomatic, multicentric, miliary-sized nodules, 13 years after the renal transplant.[3,5]

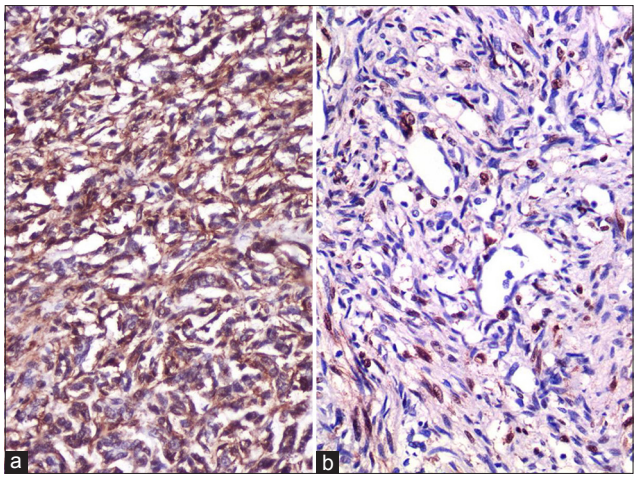

Figure 2: (a) Cytoplasmic strong positivity for smooth muscle actin; (b) Nuclear EBER positivity (IHC ×400)

PTSMTs are thought to be derived from aberrant myogenous perivascular cells, a feature well depicted in one of the nodules sampled in our patient. The EBV infection is derived either from the donor or the recipient; multiple infections leads to the development of multifocal tumors.[5] The infection and transformation is mediated through CD21 receptor or fusion of the smooth muscle cell with an infected B-cell. In contrast to the tumors developing in other immunodeficient states, PTSMT histomorphology is characterized by a well-differentiated phenotype with mild atypia, low-mitotic counts, and lack of tumor necroses.[3,4] On IHC, the tumor cells are diffusely and strongly positive for smooth muscle actin, while desmin is positive in half the cases. Sampling of the multifocal tumors in our case, however, did not reveal primitive round cell areas or intra-tumoral lymphocytes (T-cells on IHC), which are said to be the unique features of these tumors.[4] Demonstration of EBER shows nuclear positivity in the spindle cells with a diagnostic accuracy of 96%.[6] Presence of high copy numbers of EBV in tumor cells by quantitative polymerase chain reaction (PCR) is also reliable for diagnosis.[6] The other methods of EBV detection like EBV seropositivity and EBV DNA detection by PCR may provide spurious results. Over-expression of *myc* proto-oncogene has been expressed in some of the tumors.[2,4]

Depending upon the symptomatology, size, site, and high-grade nature (if present), the treatment modalities are reduction in immune-suppression, surgical resection, anti-viral therapy, or even chemotherapy. Our patient may not have required treatment since all lesions were miliary-sized and had a bland morphology. But such a manifestation of pulmonary PTSMTs should be borne in mind as a differential diagnosis of miliary or nodular shadows on imaging in transplant recipients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand

that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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