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LETTER TO THE EDITOR

Epstein–Barr virus-associated smooth muscle tumor in a female with ataxia telangiectasia: A case report

To the Editor:

Ataxia telangiectasia (AT) is a rare disorder caused by pathogenic variants in the *ataxia telangiectasia-mutated (ATM)* gene, characterized by progressive neurological involvement, oculocutaneous telangiectasia, variable degrees of immunodeficiency, radiosensitivity and increased susceptibility to tumors.[1] The ATM kinase plays a role in detecting DNA lesions and in regulating the cell cycle progression, and its impairment is responsible for the instability of the genome and radiation sensitivity.[2] Immunodeficiency may contribute to neoplasms development, particularly those associated with Epstein–Barr virus (EBV).

EBV-associated smooth muscle tumor (EBV-SMT) is a rare mesenchymal tumor that generally occurs in immunocompromised individuals.

To our knowledge, a single case report of EBV-SMT (laryngeal leiomyosarcoma) has been reported in the literature in a patient with AT.[3]

We present the case of a 9-year-old Romanian female from consanguineous parents frequently hospitalized for arthritis and pneumonia confirmed by serial chest radiographs. She was admitted to our hospital at the age of 7, for pneumonia and acute respiratory distress syndrome, displaying bulbar telangiectasias, ataxic gait, failure to thrive, and recurrent infections. Immunological evaluation revealed IgA deficiency, reduced naïve CD4 and CD8 T-cell counts, elevated alpha-fetoprotein, and sustained EBV replication (Table 1). Genetic testing identified a homozygous *ATM* gene deletion (c.8831_8832del).[4–6] Both parents and her brother, diagnosed with acute myeloid leukemia, were heterozygous for this variant. Despite initial improvement with antibiotic prophylaxis and immunoglobulin replacement treatment, the patient continued to experience episodes of pneumonia. Clinical deterioration prompted bronchoalveolar lavage confirmed EBV pneumonia, with other microbiological tests negative. In light of persistent EBV replication, the patient received four weekly doses of rituximab. The radiosensitivity required a cautious approach to imaging. However, a computed tomography (CT) scan, considered essential due to the progressive decline in lung function, showed atelectasis in the lower left lobe and multiple bronchiectasis (Figure 1A). Her respiratory symptoms continued to worsen with frequent need for oxygen therapy despite antibiotic and asthma treatment. Lung ultrasound and magnetic resonance imaging (MRI) performed for follow-up showed fibrosis and dystelectasis in the left lower lobe (Figure 1B), leading to a recommendation for lobectomy. The histology of the removed lobe showed congestion and hepatization with extensive bronchial ectasias. Notably, a 1-cm nodular whitish mass was incidentally found (Figure 1D). Microscopic examination revealed a tumor composed of spindle cells with eosinophilic cytoplasm and oval nuclei, arranged in a fascicular pattern within a sparse stromal collagen matrix and accompanied by a lymphocytic infiltrate (Figure 1E). The surrounding lung parenchyma displayed pronounced congestion and severe inflammation, including bronchial abscesses filled with neutrophils, lymphocytic infiltration, and multiple foci of alveolar hemorrhage. The spindle cells were positive for α-smooth muscle actin (α-SMA) and negative for desmin, CD34, anaplastic lymphoma kinase (ALK, D5F3), and CD21. In situ hybridization for EBV-encoded RNA (EBER) was positive in the tumor cells, displaying nuclear localization (Figure 1F,G). These findings were diagnostic of EBV-SMT. Whole-body MRI showed no metastatic lesions or in situ macroscopic recurrence. Respiratory symptoms improved, although residual bronchiectasis persisted in the basal segments of the left lung (Figure 1C).

EBV-SMT is a rare neoplasm associated with immunodeficiency, described in patients infected with human immunodeficiency virus (HIV),[7] in the post-transplant setting,[8] and in those with congenital immunodeficiency.[9] It can manifest at any age, but rarely in pediatric patients with primary immunodeficiency.

EBV-SMT typically manifests either as a single mass or multiple nodules often found in the liver, but can occur anywhere in the body.[10] Although locally aggressive, metastasis are rarely reported.[11]

To the best of our knowledge, the literature has documented only a single case of EBV-SMT manifesting as laryngeal leiomyosarcoma in an AT patient.[11] The case we present is notable for being an instance of pulmonary EBV-SMT. The differential diagnosis initially included inflammatory myofibroblastic tumor, but the presence of a monotypic T-lymphocyte infiltrate and EBER nuclear positivity suggested EBV-SMT.

The pathogenesis of EBV-SMT remains a subject of scientific inquiry. The oncogenic role of EBV is well recognized, particularly

TABLE 1 Immunological findings.

Test	Result	Normal range
Total IgG (mg/dL)	1009	[514–1672]
IgG subclasses (mg/dL)		
IgG1	907	[363–1276]
IgG2	0.42	[26–397]
IgG3	0.5	[17–169]
IgG4	**0.01**	[0.42–167]
IgM (mg/dL)	135	[26–187]
IgA (mg/dL)	**<4**	[52–225]
IgE (Kμ/L)	<2	[<100.0]
EBV IgG anti-VCA (Index)	**57.34**	[absent to <0.75]
EBV IgM anti-VCA (Index)	**0**	[absent to <1.00]
EBNA IgG (Index)	**0**	[absent to <0.5]
EBV-PCR on whole blood (copies/mL)	**208,000**	
EBV-PCR on BAL (copies/mL)	**250,000**	
AFP (ng/L)	**338**	[<12]
Lymphocytes (/mmc)	3950	[1040–6480]
$CD3^+$ (% of lymphocytes)	59.8	[55–97]
$CD19^+$ (% of lymphocytes)	7.6	[4–33]
$CD3^-/CD16^+CD56^+$ (% of lymphocytes)	32.6	[2–31]
$CD3^+CD4^+$ (% of lymphocytes)	**17.6**	[26–61]
$CD3^+/CD4^+/CD27^+CD45RA^+$ (% of $CD4^+$)	**1.0**	[46–99]
$CD3^+/CD4^+/CD27^+CD45RA^-$ (% of $CD4^+$)	68.0	[16–100]
$CD3^+/CD4^+/CD27^-CD45RA^-$ (% of $CD4^+$)	29.4	[0.35–100]
$CD3^+/CD4^+/CD27^-CD45RA^+$ (% of $CD4^+$)	1.60	[0.27–18]
$CD3^+/CD4^+/CD31^+/CD45RA^+$ (% of $CD4^+$)	**0.9**	[0.0031–1.8]
$CD3^+/CD4^+/CD45RO^+/CXCX5^+$ (% of $CD4^+$)	**1.1**	[7–85]
$CD3^+/CD8^+$ (% of lymphocytes)	36.2	[13–47]
$CD3^+/CD8^+/CCR7^+/CD45RA^+$ (% of $CD4^+$)	**0.18**	[16–100]
$CD3^+/CD8^+/CCR7^+/CD45RA^-$ (% of $CD4^+$)	0.54	[1–6]
$CD3^+/CD8^+/CCR7^-CD45RA^-$ (% of $CD4^+$)	69.3	[5–100]
$CD3^+/CD8^+/CCR7^-CD45RA^+$ (% of $CD4^+$)	30.0	[15–41]
$CD3^+$TCR alfa/beta (% of $CD3^+$)	92.4	[44–92]
TCR gamma/delta (% of $CD3^+$)	7.4	[2–24]
$CD3^+CD4^-CD8^-$(DN) TCR alfa/$beta^+$ (% of $CD3^+$)	0.6	[<2.5]
$CD27^+IgD^+IgM^+$ (% of $CD19^+$)	**31.4**	[7.5–12.4]
$CD27^+IgD^-IgM^-$ (% of $CD19^+$)	**20.6**	[5.2–12.1]
$CD27^-IgD^+IgM^+$ (% of $CD19^+$)	**39.1**	[69.4–80.4]
$CD27^-IgD^-IgM^-$ (% of $CD19^+$)	8.9	[3.5–6.6]
$CD21^{low}CD38^-$ (% of $CD19^+$)	**18.0**	[0.9–3.5]
Transitional $CD38^{++}IgM^{++}$ (% of $CD19^+$)	1.0	[0.7–3.5]

Note: Range values[18–20] in brackets. Values outside the range highlighted in bold.

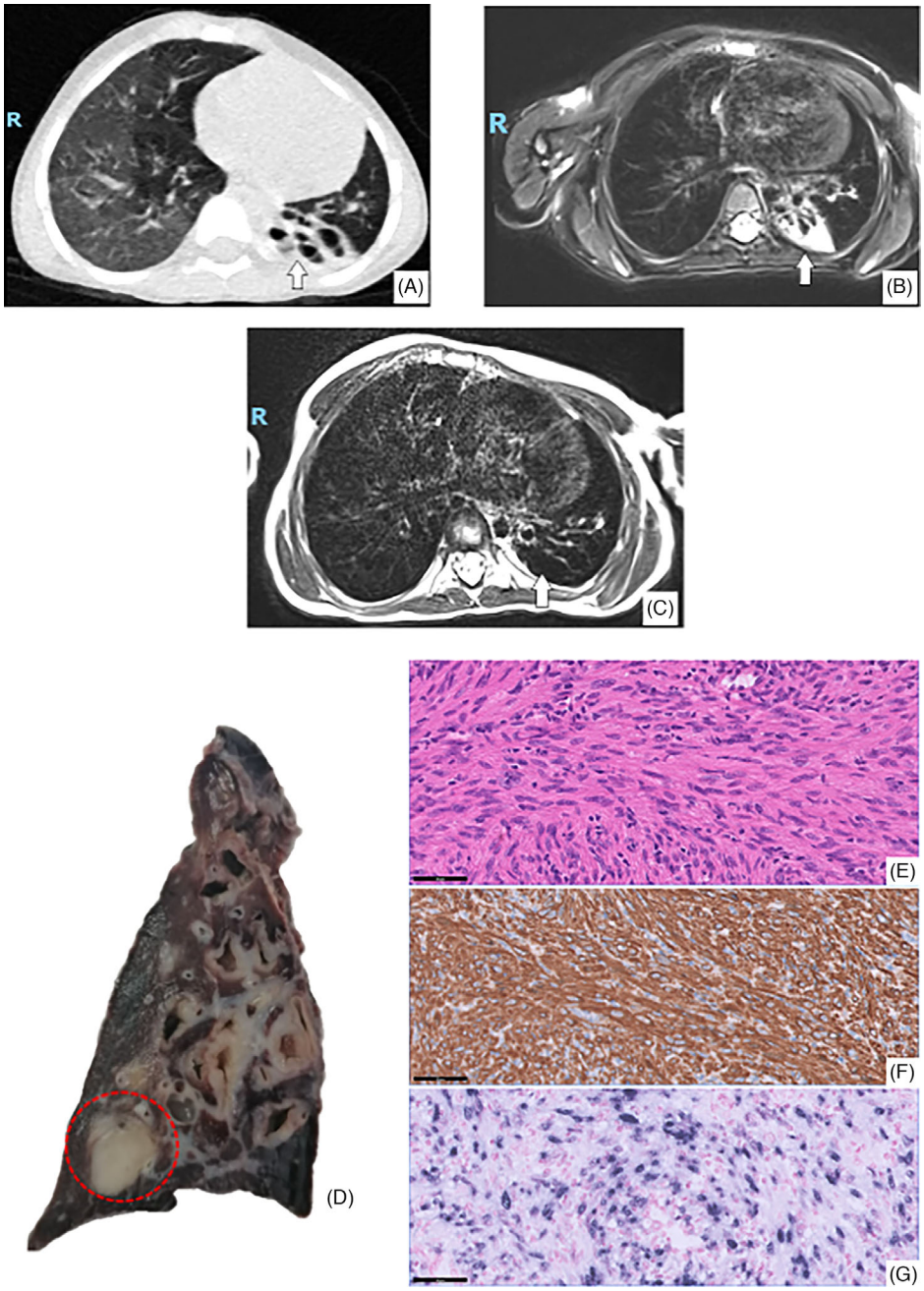

FIGURE 1 Pulmonary radiological findings. (A) Pulmonary computed tomography (CT) showing atelectasis of the lower left lobe with varicoid bronchiectasis. (B) Pulmonary magnetic resonance imaging (MRI) pre-lobectomy shows persistence of the left posterior-basal fibro-dystelectasis area with bronchiectasis. (C) MRI post-lobectomy thorax evidenced the absence of macroscopic residues. Macroscopic and microscopic pictures of Epstein–Barr virus-associated smooth muscle tumor (EBV-SMT). (D) Pulmonary parenchyma (7 × 5 × 4 cm) showing congestion and hepatization with multiple bronchial ectasias. A nodular whitish mass measuring 1 cm was found (red circle). (E) The tumor was composed of spindle cells with long eosinophilic cytoplasm and ovoidal nuclei disposed in a fascicular growth pattern in a background of scarce stromal collagen. A rich inflammatory lymphocytic infiltrate was also present. (F) Immunohistochemical staining for smooth muscle actin (SMA) shows cytoplasmic staining on the spindle cells. (G) EBV-encoded RNA (EBER) in situ hybridization was performed. The tumoral cells resulted positive with nuclear signal.

in hematological malignancies.[12,13] Both EBV infection and immunodeficiency are critical factors in tumor development. In AT, thymic hypoplasia and restricted T-cell receptor repertoire led to T-cell lymphopenia mainly affecting naive T-cell impairing the control of EBV infection, allowing persistence in B cells. Additionally, the ATM protein is involved in the EBV lytic cycle, promoting its replication. However, the mechanism by which *ATM* mutation enhances EBV's oncogenic potential remains unclear.[14] Finally, the intrinsic predisposition to cancer in AT may contribute to the pathogenesis of EBV-SMT.[15]

Therapeutic approach for EBV-SMT focuses on restoring T-cell function controlling EBV replication including antiretroviral therapy (ART) in HIV patients or reducing immunosuppression

after transplant.[9] Surgery is required for organ-compromising tumor masses. Despite the rarity of metastasis in EBV-SMT, strict follow-up is essential for timely intervention.[16] Sirolimus, an mTOR-inhibitor, offers a potential therapeutic option, though its efficacy remains debated.[17]

In our AT patient, the coexistence of immunodeficiency (Table 1), EBV active replication, repeated chest x-rays for recurrent pneumonia, along with cancer predisposition and increased radiosensitivity may have collectively contributed to the cancer pathogenesis.

In summary, EBV-SMT should be considered in the differential diagnosis of solid tumors, particularly in patients with primary immunodeficiency such as AT. Prompt diagnosis is crucial, as prognosis can be poor without appropriate treatment.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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