

Epstein-Barr Virus-associated Pulmonary Tumor: A Pediatric Case and Discussion of the Literature

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Summary: Epstein-Barr virus-associated smooth pulmonary tumor is a rare condition that mostly affects immunosuppressed patients. This case describes a young boy with a history of kidney transplantation who presented recurrent pneumonia. Multiple endobronchial soft tissue tumors affecting both right and left bronchial tree were found and partially removed by bronchoscopy. Immunohistologic analysis demonstrated Epstein-Barr virus-associated smooth pulmonary tumor. Immunosuppressive therapy was changed from tacrolimus to sirolimus. A few months later, new right upper lobe and inferior left lobe tumors were found. Recurrent left lower lobe pneumonia prompted lobectomy. In the present case, complete resection and change of immunosuppressive treatment were effective.

Key Words: viral infection, bronchiectasis, renal transplant, immunodeficiency, lung cancer, pediatric lung disease

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Epstein-Barr virus (EBV) is associated with a spectrum of diseases, ranging from asymptomatic infections to pre-malignant lymphoproliferative diseases and tumors, including Epstein-Barr virus associated smooth muscle tumor (EBV-SMT). Although EBV-SMT are EBV-driven, they are not considered a posttransplantation lymphoproliferative disorder.

EBV-SMT are tumors with the histologic features of smooth muscle. They show a immunohistology profile compatible with EBV. EBV is found in these tumors.

EBV leiomyosarcoma is the malignant form of EBV-SMT. However, the malignant potential of these forms is difficult to assess. It can be differentiated from primary leiomyosarcoma in which EBV DNA is not found.

Most reported cases of EBV-SMT concern immunodeficient patients with acquired HIV-related immunodeficiency syndrome or after organ transplantation, that is, patients with impaired T-cell immunity functions.

Thirty-five pediatric cases of EBV-SMT post-transplantation have been reported (before our case) and about 70 cases in the adult population. We describe the case of a young boy who developed airway EBV-SMT after kidney transplantation and propose a literature review regarding EBV-SMT after transplantation in the pediatric population.

CASE PRESENTATION

The antenatal history of the boy was marked by a diagnosis of cardiopathy (double outlet right ventricle). A blalock shunt was performed at 1 month of life. At 4 months, he underwent surgical cardiac correction. He developed progressive hypertension and chronic tubulointerstitial nephritis. Genetic analysis for suspected ciliopathy revealed 1 mutation of the inversin gene and his nasal ciliary biopsy was normal.

He progressed to end-stage renal disease at the age of 3 years and benefited from a kidney transplant from a deceased donor at the age of 4. The immunosuppressive treatment consisted of tacrolimus, mycophenolate mofetil and methylprednisolone. He was not immunized against EBV before the transplantation and a mild EBV viral load appeared 6 months after transplantation (polymerase chain reaction of about 2000 copies/μg DNA).

At that time, he developed recurrent respiratory tract infections, including pneumonia of the middle lobe justifying a reduction of the doses of mycophenolate mofetil by half. Despite maintenance treatment with fluticasone propionate for bronchial hyperreactivity, the frequency of respiratory infections did not change and he also presented recurrent right and left inferior lobe pneumonia.

A chest computed tomography showed bronchiectasis of the left inferior lobe. Prophylactic azithromycin and intensive chest physiotherapy were added but lower respiratory infections persisted.

At the age of 8 years, that is, 4 years after the transplant, flexible bronchoscopy showed multiple endobronchial soft tissue tumors affecting the right primary bronchus, occluding the left primary bronchus and a last one in the left superior lobe (LB2). The immunohistochemical profile was compatible with EBV associated tumor: low marker of proliferation (Ki67 2%), negative marker for CK1/3, CD34, STAT6, PS100, ALK, and fluorescence in situ hybridization was positive for EBV. EBV viral load was about 10,000 copies/μg of DNA at this time. All tumors but one was subsequently removed by rigid bronchoscopy. The left basal lobe tumor did not have a pedicle and therefore could not be removed by bronchoscopy. Tacrolimus was switched to sirolimus in an attempt to benefit from its antiproliferative properties. A liver ultrasound was performed to exclude other tumors.

Nevertheless, new episodes of left lower lobe pneumonia happened. Since the inferior left lobe was unreachable by bronchoscopy, a left lobectomy was performed ~6 months after the reduction of the immunosuppressive treatment. EBV viral load was about 25,000 copies/μg of DNA. Maximum EBV viral load appeared 5 months later and was about 500,000 copies/μg of DNA.

Six months after the lobectomy, the child presented an episode of stridor for which a control bronchoscopy was performed and showed no new tumors.

One year, after the control bronchoscopy, the evolution of the child stabilized, except for exercise-induced wheeze. Nocturnal oximetry and 6-minute walk test were normal. EBV viral load has dipped to 100,000 copies/μg of DNA.

CASE DISCUSSION AND REVIEW OF THE LITERATURE

Methods

Literature review was performed by PubMed and Science Direct research on all the articles published before March 2020 with the keywords “EBV associated smooth muscle tumors.”

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TABLE 1. Review of the Literature Pulmonary EBV-SMT Affecting the Airways

References	Sex	Age at Time of Transplant	Immunosuppressive Treatment at Time of Diagnosis	Delay Between Transplant and SMT	Localization	Organ Transplant	Treatments				Length of Follow-up Outcome (Follow-up After EBV-SMT)
							Reduced Immunosuppression	Surgery	Chemotherapy	Others	
Lee et al ¹	Male	15 mo	Cyclosporine Methylprednisolone Azathioprine	66 mo	Liver+lung	Liver	Reduction immunotherapy not specified	—	Vincristine sulfate Dactinomycin Cyclophosphamide	Acyclovir	Death
Boudjemaa et al ²	Male	2 y	Cyclosporine Methylprednisolone Mycophenolate mofetil	3 y	CNS Pulmonary—hepatic—splenic lymph nodes	Kidney	Prednisolone	—	Temozolomide	—	Death
Suzuki et al ³	Female	4 y	Methylprednisolone Mycophenolate mofetil	5 y	Lung	Kidney	Sirolimus	Surgery	—	Ganciclovir	Alive (2 y)
Jonigk et al ⁴	Female	7 y	Tacrolimus Unknown	68, 75 mo	Liver, bronchus	Liver	Unknown				Unkown
Jonigk et al ⁴	Female	10 y	Unknown	54 mo	Pharynx	Heart	Unknown				Unkown
Jericho et al ⁵	Female	15 mo	Cyclosporine Prednisone Tacrolimus	15, 26 mo	Liver, lung, spleen	Liver	Sirolimus	Surgery	Rituximab	—	Alive (2 y)
Stubbins et al ⁶	Female	4 mo	Tacrolimus Sirolimus Mycophenolate mofetil	20, 38 mo	Lung—liver—GI tract	Heart	Sirolimus	Surgery	Gemcitabine Taxotere (2 cycles)	Ganciclovir Famciclovir	Death
Stubbins et al ⁶	Female	23 mo	Methylprednisolone Tacrolimus Mycophenolate mofetil Methylprednisolone	47 mo 50 mo	GI tract+ CNS+ lymph node Lung+liver Lung	Heart	Reduction immunotherapy not specified	Surgery	Vincristine Doxorubicin Cyclophosphamide Prednisone	Immunoglobulin Rituximab Ganciclovir	Death
Lecoq (current study)	Male	4 y	Tacrolimus Mycophenolate mofetil Methylprednisolone	4 y	Lung	Kidney	Sirolimus	Bronchoscopy resection and surgery	—	—	Alive (1 y)

CNS indicates central nervous system; EBV-SMT, Epstein-Barr virus-associated smooth pulmonary tumor; GI, gastrointestinal.

TABLE 2. Review of the Literature EBV-SMT Affecting Children

References—Sex—Age at the Time of the Transplant	Delay Between Transplant and SMT	Localization	Organ Transplant	Treatments	Outcome (Follow-up After EBV-SMT)
Lee et al ¹ —female—18 mo	36 mo	Liver	Liver	Surgery	Alive (3 y)
Lee et al ¹ —male—15 mo	66 mo	Liver+lung	Liver	Reduction IT—CTX	Death
Lee et al ¹ —female—20 mo	12 mo	Colon	Liver	Reduction IT	Death
Timmons et al ⁷ —male—7 y	2 y	Liver	Liver	CTX	Death
Timmons et al ⁷ —female—7 y	5 y	Retroperitoneal (superior mesenteric vein)	Liver	Surgery	Alive (2 y)
Kingma et al ⁸ —female—23 mo	27 mo		Heart	Reduction IT—CTX	Death
Davidoff et al ⁹ —male—1 y	4 y		Heart	Surgery	Alive (10 mo)
Sadahira et al ¹⁰ —female—15 y	65 mo	Liver	Heart	Postmortem diagnosis	Death
Somers et al ¹¹ —male—11 y	41 mo	Liver	Heart lung	Reduction IT	NA
Ferlicot et al ¹² —male—2 y	5 y	Mesenteric	Liver	Reduction IT	Death
Collins et al ¹³ —female—18 d	58, 78 mo	CNS intracranial, endobronchial	Heart	Reduction IT—Surgery	Alive (2 y)
Brichard et al ¹⁴ —female—3 y	22 mo		Liver	CTX—reduction IT	Alive (12 y)
Debiec-Rychter et al ¹⁵ —male—8 y	25 mo	Liver	Kidney	Surgery	Alive (2 mo)
Boudjema et al ² —male—2 y	3 y	CNS	Kidney	Reduction IT—CTX	Death
Dionne et al ¹⁶ —male—2 y	60 mo	Renal	Kidney	Surgery	NA
Rougemont et al ¹⁷ —female—14 y	30 mo	Small bowel	Kidney	Surgery—reduction IT	NA
Rougemont et al ¹⁷ —male—7 y	5 y	Mesenteric tumor	Liver	Reduction IT	Death
Suzuki et al ³ —female—4 y	5 y	Lung	Kidney	Surgery, reduction IT, antiviral therapy	Alive (2 y)
Jonigk et al ⁴ —female—13 y	52 mo	CNS	Bone marrow		NA
Jonigk et al ⁴ —female—6 y	16 mo	Liver	Liver	NA	NA
Jonigk et al ⁴ —female—7 y	68, 75 mo	Liver, bronchus	Liver	NA	NA
Jonigk et al ⁴ —female—10 y	54 mo	Pharynx	Heart	NA	NA
Jonigk et al ⁴ —female—15 y	28 mo	Cerebral sinus, spleen	Bone marrow	NA	NA
Kazmi et al ¹⁸ —female—8 y	5 y	CNS	Kidney	Surgery—reduction IT	Alive (3 y)
Elawabdeh et al ¹⁹ —female—10 y	3 y	Colon	Liver	Surgery	NA
Elawabdeh et al ¹⁹ —female—12 y	2 y	Orbit	Liver	Surgery	NA
Conrad et al ²⁰ —female—3 y	2 y	Upper digestive tract	Liver	Reduction IT	Alive (4 y)
Jericho et al ⁵ —15 mo	15, 26 mo	Liver, lung, spleen	Liver	Reduction IT, CTX	Alive (2 y)
Jossen et al ²¹ —male—11 y	22 mo	Liver	Kidney	Surgery—reduction IT	Alive (15 mo)
Arva and Schafernak ²² —male—14 mo	10 mo	Spleen	Liver	Postmortem diagnosis	Death
Liu et al ²³ —female—6 wk	8 y	Liver	Heart	Surgery—reduction IT	NA
Penney et al ²⁴ —female—5 y	3 y	Liver	Bone transplant	Reduction IT	Alive (10 y)
Stubbins et al ⁶ —female—4 mo	20, 38 mo	Lung—liver—GI tract	Heart	Surgery—reduction IT—CTX	Death
Stubbins et al ⁶ —female—8 mo	16, 21 mo	GI tract—adrenal	Heart	Surgery—reduction IT—CTX	Alive (6, 2 y)
Stubbins et al ⁶ —female—23 mo	47, 50 mo	GI tract—lung—liver—lymph node—CNS	Heart	Reduction IT—CTX	Death
Lecoq (current study)—male—4 y	4 y	Lung	Kidney	Reduction IT—Surgery	Alive (1 y follow-up)

CNS indicates central nervous system; CTX, chemotherapy; EBV-SMT, Epstein-Barr virus-associated smooth pulmonary tumor; GI, gastrointestinal; IT, immunosuppressive treatment; NA, not available.

All posttransplant pediatric cases (age at transplant below 18 y) were included. We excluded adult case reports and patients with other causes of immunodeficiency (or unknown causes).

The search was then refined by using the keywords: “leiomyoma or leiomyosarcoma EBV associated.” Additional articles were found by reference check.

We found 8 pediatric cases of EBV-SMT affecting the airways (Table 1) among a total of 36 cases of EBV-SMT affecting children (Table 2).

Review of the Literature

The first pediatric cases of airway EBV-SMT were described by Lee. They reported on 3 cases after liver transplantation, which affected children from 2 to 7 years of age. However, EBV-SMT has also been reported after other organ transplantations (heart, lung, kidney, bone transplantations). In our case, EBV-SMT appeared after kidney transplantation.

The liver seems to be the organ most frequently affected by EBV-SMT, as described in 17 of 36 cases.^{6,21} We found 8 other cases of EBV-SMT that targeted the respiratory tract or lungs in children, mostly affecting females (n=6) (Table 1).

In 8 cases, > 1 EBV-SMT is present, either in different organs or in the same organ.^{6,21} In our case, it is important to note that there were multiple tumors affecting both lungs, but the liver was spared as confirmed by ultrasound.

We found 4 descriptions of leiomyosarcoma which is a malignant form of smooth muscle tumor.²¹ In our case, no sign of malignancy was found on biopsy.

The time interval between the transplant and the diagnosis of EBV-SMT ranges from 12 months to 8 years. In our case, EBV-SMT was diagnosed 4 years after transplantation.

The symptoms of EBV-SMT depend on the localization of the tumors. Recurrent respiratory infections and wheezing occurred in our case because of obstruction of the airways by tumor tissue.

The biologic signs of EBV-SMT are scarce. In posttransplant lymphoproliferative diseases, the EBV viral load is a well-known marker.²⁵ Concerning EBV-SMT, EBV viral load is not a universal marker at the time of the diagnosis but is frequent.²¹ In our case, we noted that EBV viral load was negative until 6 months after transplant, reached a peak at the time of EBV-SMT and decreased afterwards.

The most frequently described treatments include surgery and reduction of immunosuppressive treatment. The tumorigenesis of EBV-SMT remains unclear. An activation of the Akt/mammalian target of rapamycin signaling has been described in literature.²⁶ This may explain the effectiveness of sirolimus, a mammalian target of rapamycin inhibitor.²⁴ The reduction of immunosuppressive treatment is used hoping that it will restore T-cell function and its ability to react against EBV.

In more severe cases, some children received chemotherapy or radiotherapy.^{6,21} Chemotherapy seems to show little benefit on EBV-SMT and has well-known side effects. Different chemotherapy treatments have been tried including vincristine, dactinomycin, cyclophosphamide, cisplatin, etoposide. A successful treatment has also been described with rituximab.⁵

Given the scarcity of EBV-SMT in posttransplant children, drawing inspiration from the management from EBV-SMT in human immunodeficiency virus infected children would have been useful. But the management of these children is still case-by-case.²⁷

Even in adults, posttransplant EBV-SMT is an uncommon entity. The most frequent treatments include surgical resection, reduction of immunosuppressive treatment and chemotherapy for the most severe cases.²⁸

Eleven deaths were reported among the 36 pediatric cases.^{6,21} The length of follow-up is variable. The longest known follow-up is 12 years.²¹ But most of the found articles described the management and not the follow-up.

In our case, reduction of immunotherapy and removal of the tumors seemed effective. One year after the lobectomy, the bronchoscopy did not show any relapse.

CONCLUSIONS

EBV-SMT of the airways are rare during childhood with only 36 pediatric cases described in the literature, typically affecting immunosuppressed patients. We describe an additional case of a young boy with multiple bronchial EBV-SMT after renal transplant, who was successfully treated by reduction of immunosuppression and surgical removal of the tumors.

Given the scarcity of the disease, no guidelines exist for the treatment of EBV-SMT. Pursuing the reporting of these cases is therefore crucial.

From our review of literature, we can summarize the usual practice. First as for any tumor, a histopathologic confirmation is necessary as well as the anatomical distribution. Second, reduction of immunosuppression is commonly done given the nature of the tumors. Indeed, EBV is known as a major pathogen for posttransplant patients. The immunosuppressive balance is capital to avoid the emergence of viral pathogens for these patients without compromising the transplant. Last, additional surgery is performed in most cases.

In conclusion, EBV-SMT is a rare diagnosis that must be mastered by those that look after posttransplant patients.

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