Multiple Epstein-Barr Virus–associated Smooth Muscle Sarcomas of the Gut in a Child Treated for Acute Lymphoblastic Leukemia

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Summary: A 7-year-old boy with a history of low-risk acute lymphoblastic leukemia developed multiple intussusceptions shortly after the end of maintenance therapy. Explorative laparotomy showed > 10 polyps in the small intestine. Histologic examination revealed intestinal smooth muscle sarcomas associated with Epstein-Barr virus. The patient recovered well after partial cuneiform resection of the largest polyps and treatment with sirolimus. This case report indicates that these tumors may arise even after moderate transient immunosuppression and that association with acute lymphoblastic leukemia is possible although rarely described. We discuss the potential benefit of the mTor/Akt signal inhibitors as treatment for these tumors.

Key Words: smooth muscle tumor, immunodeficiency, acute lymphoblastic leukemia treatment complications, secondary neoplasm, Epstein-Barr virus

(*J Pediatr Hematol Oncol* 2018;00:000–000)

Epstein-Barr virus-smooth muscle tumors (EBV-SMT) are rare and present typically in immunocompromised patients. Most EBV-SMTs cases are reported in adults. Nevertheless, SMTs appear to be the second most frequent neoplasm arising in children with acquired human immunodeficiency virus.[1,2] According to the literature, these tumors typically show a smooth muscle phenotype of spindle-shaped cells with immunohistochemical staining positive for actin. Presence of EBV involvement using in situ hybridization for Epstein-Barr encoding region (EBER) confirmed the diagnosis of EBV-SMT in all reports.[3] Complete surgical resection represents the main therapeutic approach, in particular in progressive tumors. Reduction of immunosuppressant dose in organ transplant patients or improvement of the immune status is also crucial in disease control. Finally, sirolimus could be a potential alternative treatment of EBV-SMT.

Received for publication July 31, 2017; accepted February 28, 2018.
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CASE DESCRIPTION

A 4.5-year-old boy was referred for fever and asthenia. Clinical examination revealed multiple adenopathies, without hepatomegaly and blood count showed pancytopenia. Bone marrow examination confirmed the diagnosis of B-precursor acute lymphoblastic leukemia (ALL). There were no unfavorable prognostic factors and he was treated according to the French ALL protocol for low-risk patients (Fralle 2000 A group). Complete remission was achieved after induction therapy. The first 20 months of treatment were unremarkable except for a short febrile episode, 14 months into treatment, with positive EBV serology (immunoglobulin [Ig] M). Of note, EBV antibodies were negative at diagnosis of ALL and 1 month after the febrile episode (IgM and virus capside antigen IgG).

Towards the end of maintenance treatment, he began to complain of abdominal pain. Abdominal ultrasound showed 2 ileal reducible intussusceptions with spontaneous resolution and the presence of an intraluminal polyp (10 mm) in the left iliac fossa. His chemotherapy regimen ended after 33 months but the symptoms of chronic abdominal pain increased while his general condition worsened. Repeat ultrasound showed persistence of 2 intussusceptions. As 1 intussusception was no longer reducible, laparotomy was performed. An ileal volvulus, starting from an irreducible intussusception of a large intestinal polyp and a second intussusception, also associated with a polyp but easily reducible, were found. More than 10 polyps were detected along the small intestine but were not resected to avoid extensive small bowel resection. One week later, a second laparotomy was necessary because of symptom recurrence with relapse ileo-ileal invagination. Reduction of an intussusception was achieved and a cuneiform resection of 9 polyps along the small bowel was performed. Several smaller polyps were not removed.

Histologic examination of the polyps was consistent with sarcoma and excluded Gardner syndrome and Peutz-Jeghers disease. The tumor cells were arranged in interlacing bundles and had elongated nuclei with numerous mitotic figures (Ki67 index: proliferation > 90%) (Figs. 1A, B). Immunohistochemical stains were positive for smooth muscle actin, locally positive for caldesmon and negative for desmin. Epstein-Barr encoding region in situ hybridization was positive, indicating that tumor cells were massively infected by EBV and leading to the diagnosis of EBV-SMT (Fig. 2). Presence of necrotic foci was noted in some lesions. The immune status of the patient was normal at that time (serum IgA, IgM, IgG levels; T and B lymphocyte count within the normal range; CD4:CD8 ratio of 1, 5) (Table 1). EBV serology revealed positive virus capside antigen IgG measured at 28 U/mL (Negatif < 20 U/mL). Real-time quantitative polymerase chain reaction (PCR) for EBV (Taqman) in blood lymphocytes after the second look surgery showed a positive viral load of 685 EBV copies/μg of DNA. One month later, the viral load increased to 1301 EBV copies/μg of DNA. A positron emission tomography-computed tomography scan revealed multiple active lesions in the small bowel with a maximal SUV between 2.73 and 3.49. Treatment with sirolimus was initiated (2 mg/m^2/d) and maintained for 7 months. The abdominal symptoms subsided while the EBV load decreased progressively and completely disappeared after

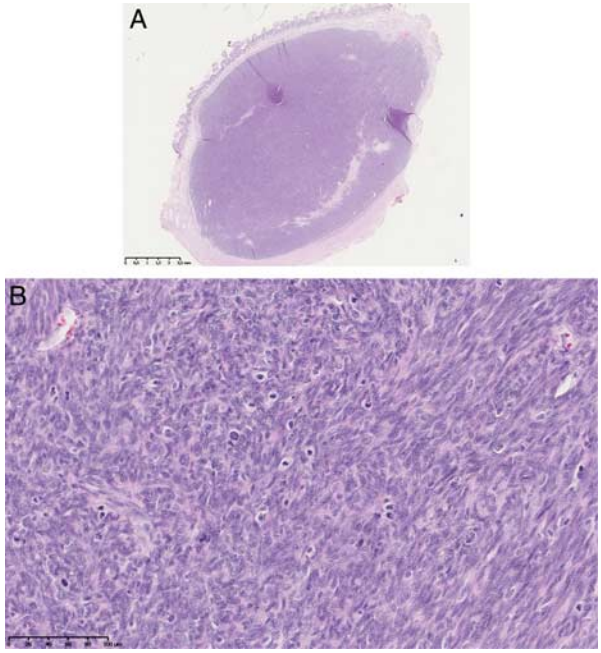

FIGURE 1. A and B, Intestinal nodules and polyps characterized by a proliferation of spindle cells showing focally a muscular differentiation (low magnification [A] and high magnification [B]). full color online

2 months, it stays negative 30 months after the end of treatment. Two and a half years after the surgeries, the child remains in very good general condition, without abdominal symptoms and in complete remission.

DISCUSSION

EBV-SMTs are rare and typically manifest in immunosuppressed patients such as acquired immunodeficiency syndrome patients, patients with primary immunodeficiency syndromes or after organ transplantation.[4–7] Most cases are truly multifocal. The presence of several tumor clones from different locations supports the hypothesis that the multifocal disease is the result of multiple independent primary lesions rather than metastasis.[2] The association between immune status of the patients and EBV-SMTs suggest that immunosuppression is a predisposing factor in the development of these lesions. However, although mechanisms

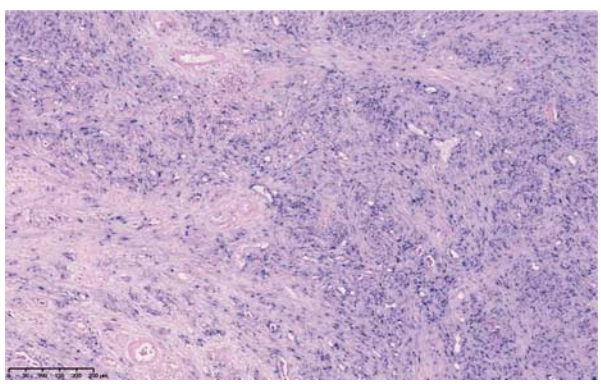

FIGURE 2. Epstein-Barr encoding region in situ hybridization detected large numbers of copies in nuclei of tumor infected cells. full color online

TABLE 1. Ig Levels, Lymphocyte Count for Our Patient and Laboratory References

	Patient	Normal Range	Units
IgA	1.61	0.45-2.5	g/L
IgM	0.66	0.5-2	g/L
IgG	6.3	6.5-14.5	g/L
IgG2	83	63-350	mg/dL
IgG3	71	17-88	mg/dL
IgG4	4.78	100-121.00	mg/dL
Lymphocytes	3370	880-5000	/µL
CD16+ CD56+	340		/µL
CD3	2730	1578-3608	/µL
CD4	1516	821-1887	/µL
CD8	1011	564-1252	/µL
CD4-CD8 TCR α/β	84	33-115	/µL
CD4-CD8 TCR γ/δ	103	73-409	/µL
CD19	246	256-851	/µL
CD27-IgD+	90.0%		
CD27+	4%		

Ig indicates immunoglobulin; TCR, T Cell Receptor.

such as an altered immune surveillance system or an increased susceptibility for viral infections have been suggested, the relationship between immunodeficiency and tumor development is not clearly established.[4]

We have previously described a case of SMT in a child treated for high-risk ALL including autologous stem cell transplantation, but the appearance of multiple intestinal SMTs after treatment for low-risk ALL has been reported before.[7] In this case, EBV IgM positivity was noted 1 year before the onset of abdominal symptoms. We suspect that our patient presented a subclinical EBV primo-infection which was not cleared due to chemotherapy-related immunosuppression. When the intestinal polyps became symptomatic, the EBV PCR in blood was positive despite the presence of anti-EBV IgG.

Histologically, most reported cases showed mild nuclear atypia and low mitotic activity. Unusually, our patient's lesions had a high mitotic index. In addition, the histopathologic features are poorly predictive of outcome in EBV-SMTs. Immunosuppression-associated complications appear to be more relevant than histopathologic features in these types of SMTs.[3,8]

SMTs are most often confined to 1 organ, but can be multifocal, as in this case.[8] The gut is a location described in EBV human immunodeficiency virus-SMT but also in EBV posttransplantation SMTs.

Therapeutic strategies mainly depend on tumor localization but also the etiology of the immunodeficiency.[8] The mainstay of treatment includes complete surgical resection and the reduction of immunosuppressant dose. There is currently no EBV-targeted therapy for EBV-induced SMT. Recent studies have suggested the use of EBV-specific immunotherapy, mTor inhibitors, and demethylating agents as possible therapeutic options for EBV-SMTs.[3,9,10] The mTor pathway plays a role in regulating cell growth and proliferation and its deregulation is associated with various human cancers. It has been hypothesized that the mTOR pathway is implicated in EBV-SMT.[11] Successful treatment of EBV-SMTs using sirolimus has been described, and confirmed in our patient.[12,13] The mTor/Akt signal inhibitor has been shown to be tolerated in kidney transplant patients with SMT but it is not clear if sirolimus alone was responsible for the stable disease status in these cases.[14] To date, there is no clear evidence that sirolimus

is more efficacious than reducing immunosuppression in patients receiving immunosuppressive therapy. In any case, there is no role for aggressive chemotherapy or irradiation.[14] In our patient, the immunosuppressive treatment (ALL maintenance treatment) was completed 2 months before the diagnosis of EBV-SMT. His poor general condition, the presence of multiple lesions and the increasing EBV viral PCR led us to treat him with sirolimus, which was well tolerated. We assume that sirolimus may not have been solely responsible for the clinical improvement of our patient. A few lesions showed necrosis before treatment, suggesting that some spontaneous involution of the tumors had occurred, possibly due to improving immune status after the end of chemotherapy. A more profound understanding of the physiopathogenesis of EBV-SMTs is warranted to define new treatment options and further improve prognosis.

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