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CASE REPORT

Epstein-Barr virus-associated smooth muscle tumours in a patient with an immuno-osseous dysplasia

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Introduction

Epstein-Barr virus (EBV)-related soft-tissue tumours are a rare occurrence in patients with a primary immunodeficiency. Here we present a case of multiple synchronous EBV-driven leiomyomata in a child with a T-cell immunodeficiency associated with short-limbed dwarfism, and review the literature.

Case report

A term female baby born via a normal delivery to consanguinous parents, presented with a lower respiratory tract infection in the neonatal period. At this time the patient was noted to have a low white cell count associated with short limbs. Immunological investigation revealed lymphopenia and markedly reduced lymphocyte proliferation in keeping with a T-cell immunodeficiency. This episode of lower respiratory tract infection responded well to antibiotic therapy and the patient remained well until 15 months of age. At 15 months of age the patient developed jaundice and was noted to have haemoglobin of 3.0 g/dl, which was treated with transfusion. Laboratory indices revealed an autoimmune haemolytic anaemia. This caused repeated anaemic episodes, requiring blood transfusions on multiple occasions. In an attempt to control the autoimmune haemolytic anaemia, therapy in the form of cyclosporin A and steroids were commenced. The autoimmune haemolytic anaemia was controlled on this regimen until the age of 3 years when it was noted that the patient was developing increasing abdominal distension and breathlessness.

Plain film radiography of the limbs was performed to investigate the nature of her limb shortening, which demonstrated generalized osteopenia, delayed bone age and symmetrical limb shortening. The metaphyses were noted to be flared, with under modelled, wide diaphyses and wide ribs. In the hands ivory and cone-shaped epiphyses were seen. These features were consistent with an immuno-osseous dysplasia, most likely to be metaphyseal chondrodysplasia McKusick type (Figs. 1 and 2).

An abdominal ultrasound was performed which showed hepatomegaly, with multiple well-defined reduced reflectivity focal lesions throughout both liver lobes, which were hypovascular on colour Doppler. No biliary dilatation was seen and the remaining abdominal viscera had a normal ultrasound appearance. Owing to her breathlessness a chest radiograph was performed which revealed a right lower zone soft-tissue density. Computed tomography (CT) of the thorax was then performed, demonstrating multiple soft-tissue density masses within the lungs. Percutaneous biopsy of both a chest lesion and a liver lesion was performed, revealing the lesions to be leiomyomata. The tumours were demonstrated to be positive for EBV using in-situ hybridization (Figs. 3–5).

This case presents a grave dilemma for future management. The optimal treatment for the congenital immunodeficiency and auto-immune haemolytic anaemia is ablation of the native bone marrow, followed by bone marrow transplant. The danger of this treatment strategy in this patient is the risk of unchecked proliferation of further smooth muscle tumours, which could become overwhelming. In patients with solitary EBV-associated leiomyomata, surgical excision is a viable option. In this patient with mutiple EBV-driven leiomyomata this is not a treatment option. Currently the patient is not receiving treatment for the tumours, and they are not rapidly progressing.

Discussion

This patient with an immuno-osseous dysplasia was found to have multiple EBV-associated smooth muscle tumours in both the liver and the lungs. The main differential diagnoses to be considered in terms of multiple hepatic lesions in an immunocompromised child are infection, such as *Candida* species and, in the setting of a post-transplant patient, post-transplant lymphoproliferative disease (PTLD). Multiple haemangiomas in children have a wide range of imaging features and may demonstrate increased or decreased reflectivity in comparison with the remaining hepatic tissue,

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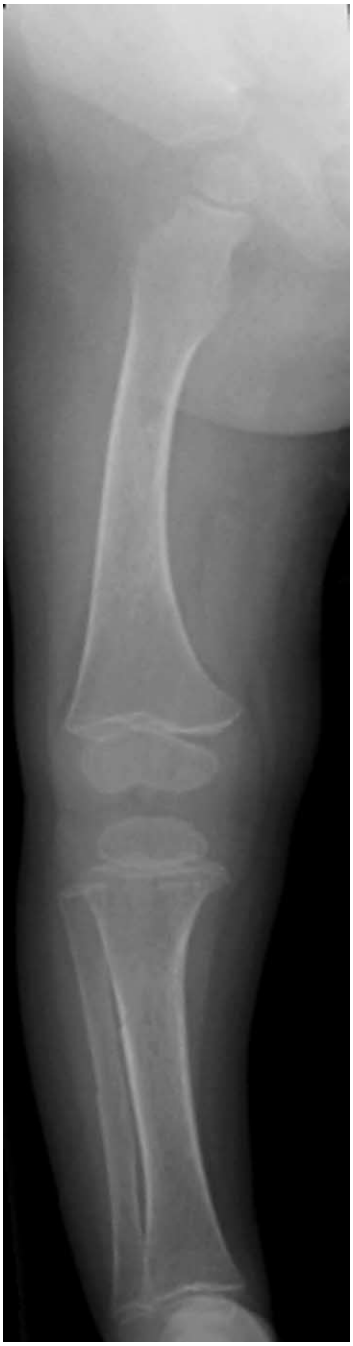

Figure 1 Anteroposterior radiograph of the right leg demonstrating flared metaphyses, associated with wide diaphyses.

making haemangiomas a further differential diagnosis.

Hepatic candidiasis is almost exclusively seen in immunocompromised patients and may present as a fever unresponsive to anti-microbial therapy, right upper quadrant pain and a raised alkaline phosphatase. On imaging studies hepatic candidiasis is seen as multiple, small reduced reflectivity, or reduced attenuation, masses with a central area of lower

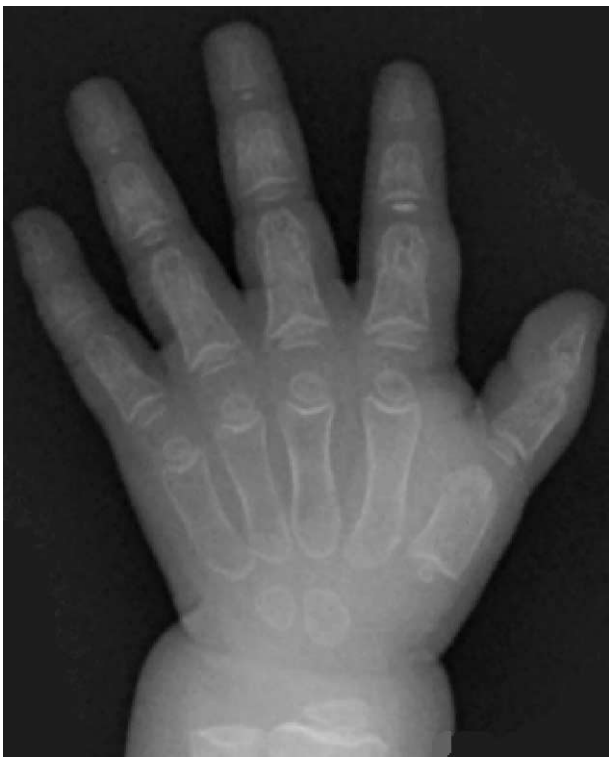

Figure 2 Anteroposterior radiograph of the left hand demonstrating ivory and cone epiphyses.

echogenicity or attenuation. PTLD is seen after both solid organ and bone marrow transplantation. Pathologically this is manifest as a spectrum from mild lymphoid hyperplasia to malignant lymphoma, with a predilection for extra-nodal sites. On imaging studies PTLD may be seen as a well-defined

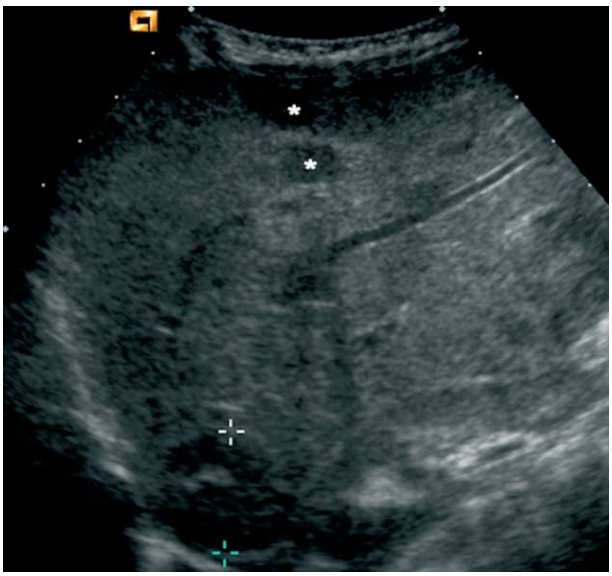

Figure 3 Ultrasound longitudinal section through the right lobe of the liver demonstrating a low reflectivity lesion between callipers and two further lesions indicated by asterisks.

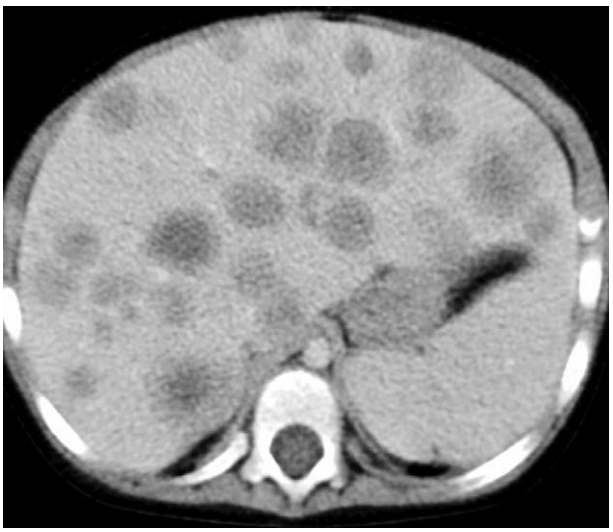

Figure 4 Axial CT section through the upper abdomen after intravenous contrast medium administration. Multiple low attenuation lesions are seen throughout the liver.

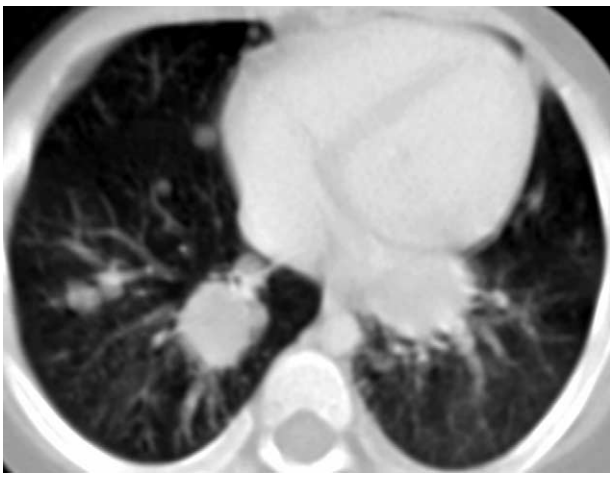

Figure 5 Axial CT section through the thorax (lung window settings) demonstrating multiple soft-tissue nodules throughout the right lung.

hepatic mass or as well-circumscribed chest nodules. PTLD may be multifocal.

EBV is thought to infect approximately 95% of individuals by early adulthood.[1] The majority of infections are sub-clinical, others producing infectious mononucleosis clinically. After primary infection the virus enters a latent stage and can reactivate at any time. A wide range of clinical entities is associated with EBV infection, classically including Burkitts lymphoma and nasopharyngeal carcinoma. The association of EBV with smooth muscle tumours has been well recognized since the 1980s,[2] and smooth muscle tumours are the second most prevalent solid neoplasm in the paediatric acquired immunodeficiency syndrome (AIDS) population, the most prevalent being non-Hodgkin's lymphoma.[3] EBV-associated smooth muscle tumours can be either benign (leiomyoma) or malignant (leiomyosarcoma) depending on the degree of mitotic activity[4] and other factors including cellular atypia and necrosis.

In addition to patients with AIDS, EBV-associated smooth muscle tumours have been well documented after organ transplantation.[4–6] In one series of paediatric post-transplant malignancies, lymphoma was found to account for 50% of the total, followed by skin malignancy (20%).[7] This series found non-Kaposi's sarcoma (including leiomyosarcomata) to account for 3% of the total.

EBV-associated smooth muscle tumours are seen in patients with a wide variety of organ transplants including liver, heart, lung and renal. The most commonly associated organ transplant is liver, with the liver also being the most commonly affected organ (both native and transplant). In the paediatric post-transplant population smooth muscle tumours are multifocal, more frequent, occur earlier in the disease, and are more likely to involve the abdominal viscera than those occurring in adult patients after transplant.[4]

It is well recognized that there is an increased risk of malignant tumours in patients with congenital immunodeficiency;[8] however, the number of cases of EBV-associated smooth muscle tumours in patients with congenital immunodeficiency is small. Cases have been reported in the literature of EBV-associated smooth muscle tumours in ataxia telangiectasia; a chromosomal breakage disorder with impaired DNA repair mechanisms and a degree of immunodeficiency,[1] and an EBV-associated leiomyosarcoma of the thyroid in a child with a congenital T-cell immunodeficiency.[9]

This patient had features of metaphyseal chondrodysplasia McKusick type, one of a spectrum of immuno-osseous dysplasias. McKusick-type metaphyseal chondrodysplasia is inherited in an autosomal recessive fashion, with incomplete penetrance. Incidence is highest amongst the Amish population of North America (1.5:1000 live births) and in Finland (1:23,000 live births). Clinically McKusick presents as short-limbed dwarfism associated with immunological defects. The most common immunological defect is a generalized immunodeficiency, seen in 90%; however B-cell and T-cell deficiencies have also been described. To our knowledge there has been no previous reports of EBV-associated smooth muscle tumours in the setting of an immuno-osseous dysplasia, and although uncommon, EBV-associated smooth muscle tumours should be considered in the

differential diagnosis of multifocal hepatic lesions in immunocompromised patients.

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