



Concurrent Diffuse Large B-Cell Lymphoma and Epstein-Barr Virus-Associated Smooth Muscle Tumour in the Small Bowel of an HIV-Positive Adult—a Case Report and Review of the Literature

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Introduction

Epstein-Barr virus (EBV) has been causally linked to immunosuppression-associated smooth muscle tumours (SMT) as well as non-Hodgkin lymphomas. Concurrent diffuse large B cell lymphoma (DLBCL) and EBV-associated SMTs at different sites have been described in the setting of severe immune compromise [1–4]. We report a case of an adult with human immunodeficiency virus (HIV) who presented with concurrent diffuse large B cell lymphoma (DLBCL) and an EBV-associated SMT at the same site within the small intestine. The clinical presentation of ascites and a necrotic segment of small bowel was unusual and posed a clinical diagnostic challenge.

Case Report

A 31-year-old woman was admitted to hospital with a 3-day history of nausea, vomiting, diarrhoea and abdominal distension. The patient was HIV-positive, on anti-retroviral therapy, with a CD4 count of 22 cells/ μ L. The past medical history included pulmonary tuberculosis for which 6 months of treatment had been completed 2 years previously as well as a previous caesarean section. On admission, she was

tachycardic (heart rate 130 beats/minute) and hypotensive (blood pressure 107/57) with tachypnoea (respiratory rate of 26) and a fever (39.2 °C). Abdominal examination showed distension due to ascites but no peritonism. Biochemistry results revealed renal impairment (acute kidney injury, network grade I [5]) with a metabolic acidosis and raised infective markers (white cell count 20.63×10^9 /L and CRP 345 mg/L). Ascitic fluid biochemistry showed high protein 37 g/L, raised ADA 200.5 U/L and lactate dehydrogenase of 22,252 U/L. Abdominal ultrasound confirmed free fluid in the abdomen with distended and thick-walled bowel loops in the right upper quadrant and right iliac fossa. Abdominal CT scan with rectal contrast showed a dilated thick-walled terminal ileum with segmental pneumatosis suggestive of terminal ileum necrosis (Figs. 1 and 2). An emergency laparotomy was performed and confirmed the presence of 3 L of ascitic fluid with 30 cm of necrotic small bowel 20 cm proximal to the ileocecal junction.

Macroscopic examination of the resected segment of small bowel demonstrated a 20 × 20-mm well-circumscribed mass on the anti-mesenteric surface of the bowel as well as diffuse thickening of the bowel wall with an exudate on the serosal surface (Fig. 3). Microscopy of the mass lesion showed bland spindle cells which demonstrated positive immunohistochemical staining for smooth muscle actin and caldesmon thereby confirming a smooth muscle tumour (Fig. 4 and 5). In situ hybridization for the Epstein-Barr virus-encoded small RNAs (EBER) showed diffuse nuclear positivity in the smooth muscle tumour (Fig. 6).

The serosa along the entire length of the bowel contained a dense infiltrate of atypical large mononuclear cells which were confirmed on immunohistochemistry to be B lymphocytes

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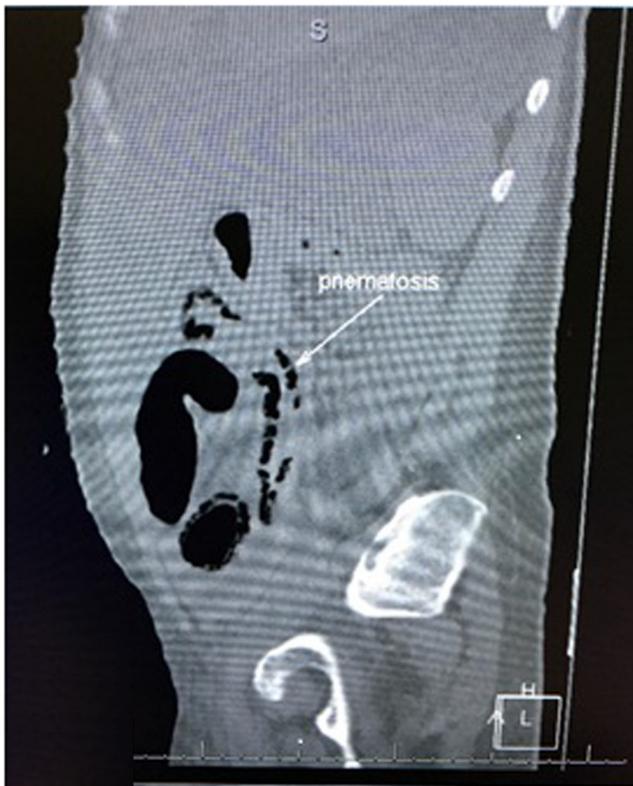


Fig. 1 Abdominal CT scan with rectal contrast, sagittal view, demonstrating pneumatosis intestinalis

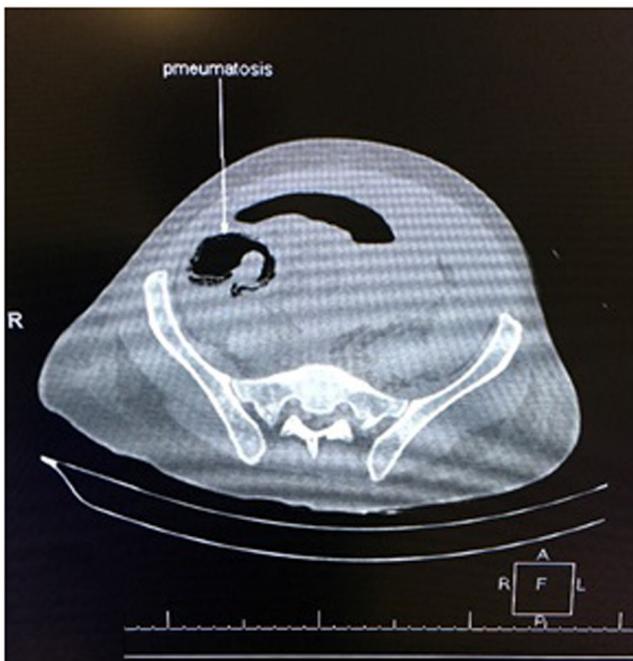


Fig. 2 Abdominal CT scan with rectal contrast, axial view, demonstrating pneumatosis intestinalis



Fig. 3 Macroscopic specimen showing the smooth muscle tumour in the mesentery of the bowel wall. The lesion is well circumscribed with a white whorled cut surface

(Figs. 7, 8, 9, 10). Further immunohistochemistry confirmed a diffuse large B cell lymphoma with activated B cell immunophenotype (CD10-negative, MUM1-positive, BCL-6-positive). The proliferative index using Ki-67 was high (90%) and BCL-2 was positive. In situ hybridization for EBV was negative in the lymphoma.

Discussion

Epstein-Barr virus (human herpesvirus 4) is a double-stranded DNA virus of the gamma subfamily of herpes viruses. It causes infectious mononucleosis, a self-limiting illness, and has been causally linked to several human malignancies such as nasopharyngeal carcinoma, Burkitt's lymphoma, gastric carcinoma, post-transplant lymphoproliferative disease, acquired immunodeficiency syndrome (AIDS)-associated non-Hodgkin lymphoma and Hodgkin lymphoma [6].

In 1995, a causal link was established between EBV infection and immunosuppression-associated smooth muscle tumours (SMTs) in two papers published simultaneously [7, 8]. EBV-associated SMTs have been described in human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and organ transplant recipients as well as congenital immunodeficiency syndromes [7, 9]. This causal role is demonstrated by EBV-associated SMT cells having high numbers of EBV copies as opposed to tumour cells of leiomyosarcomas in non-immunosuppressed individuals and adjacent normal tissue [10].

Since this link was made, multiple case reports have been published and two comprehensive literature reviews have

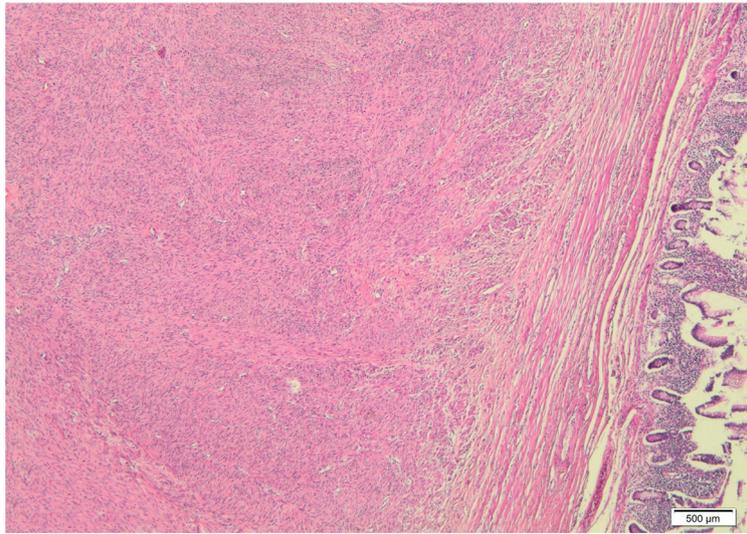


Fig. 4 The SMT shows fascicles of bland spindled cells with smooth muscle morphology, $\times 2$ objective, H&E

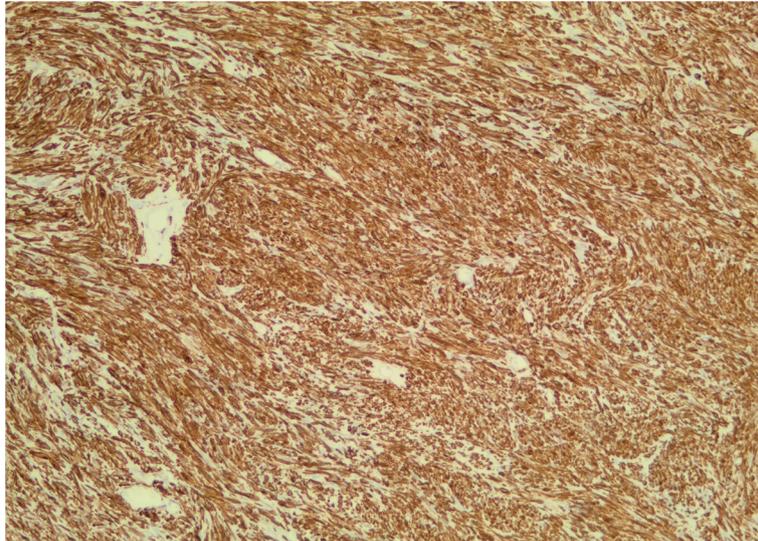


Fig. 5 Caldesmon immunohistochemical stain of the SMT showing diffuse positivity

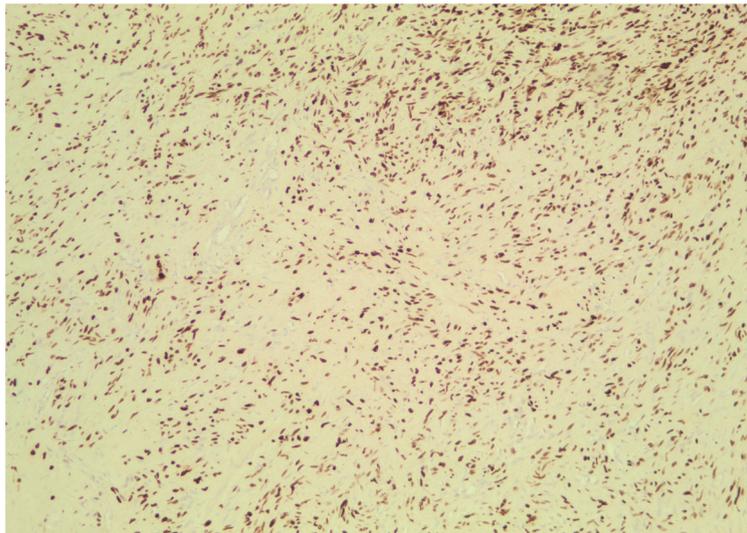
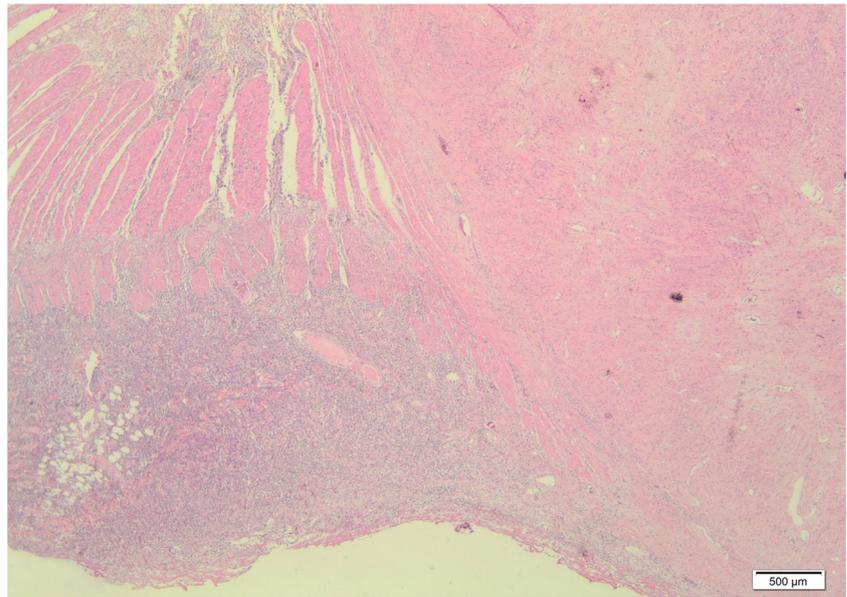


Fig. 6 EBER-ISH of the SMT showing diffuse nuclear positivity

Fig. 7 The SMT comprising fascicles of bland spindled cells is depicted on the right. The DLBCL comprising an infiltrate of atypical large cells in the serosa is depicted on the left, $\times 2$ objective, haematoxylin and eosin (H&E)



highlighted certain characteristic features of these tumours. This includes young age of onset in HIV/AIDS, predilection for unusual sites (liver, spleen, gastrointestinal tract, lung, thyroid, dura and soft tissue), the high rate of multiple tumours at presentation, the presence of intralesional T lymphocytes and the indolent yet unpredictable behaviour of these tumours [1, 11]. The mean CD4 count of HIV-positive patients with EBV-SMT's in one series was 60 cells/ μ L [11].

A review of the English literature for cases of EBV-associated SMTs occurring with lymphoma was

performed using the following databases: Worldcat, Worldcat.org, ScienceDirect, MEDLINE, ArchiveGrid, ArticleFirst, ERIC and SA ePublications Journal Collection. Cited references in previously published articles that were not recovered with this search were also included.

Four published case reports of patients with both DLBCL and EBV-associated SMTs in the setting of immune compromise have been published [1–4]. Of these four cases, three occurred in females and the mean age at

Fig. 8 The SMT is depicted on the right superiorly and the DLBCL on the left inferiorly, $\times 2$ objective, H&E

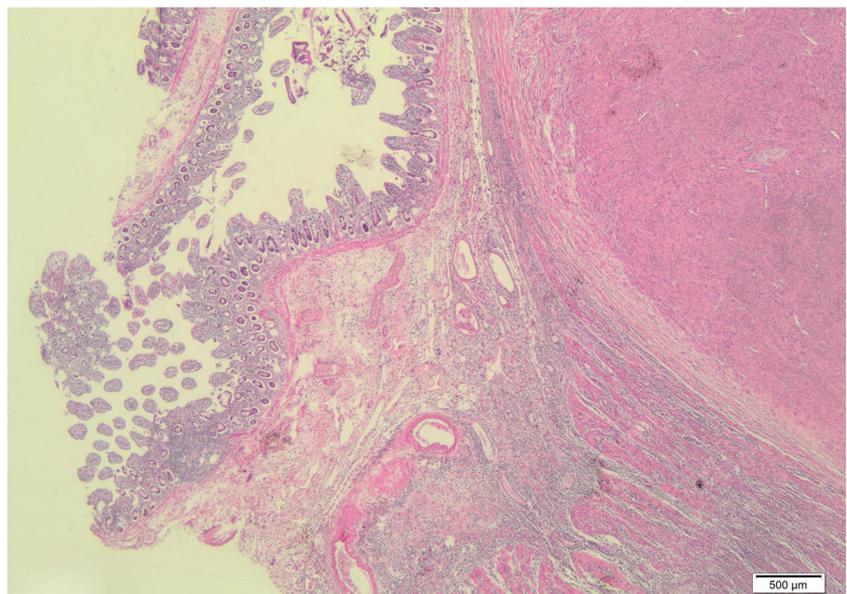
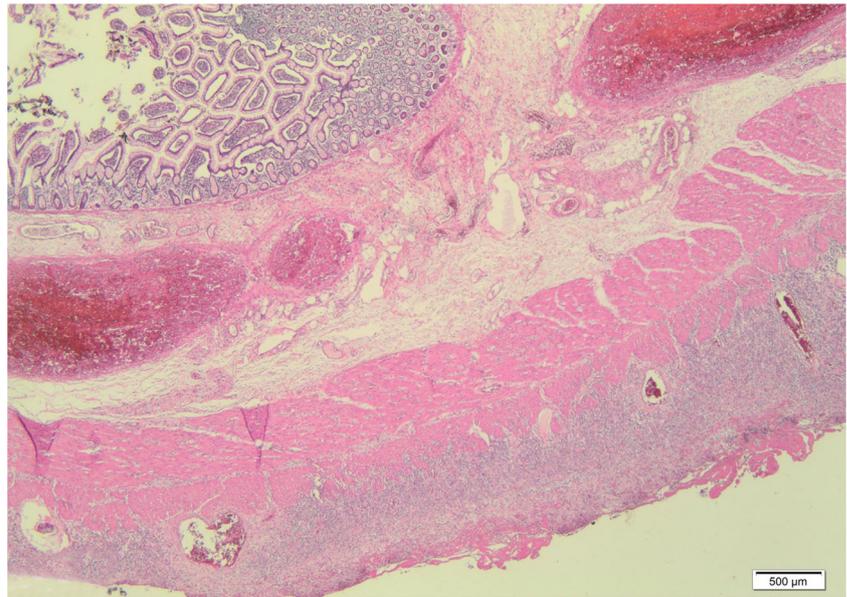


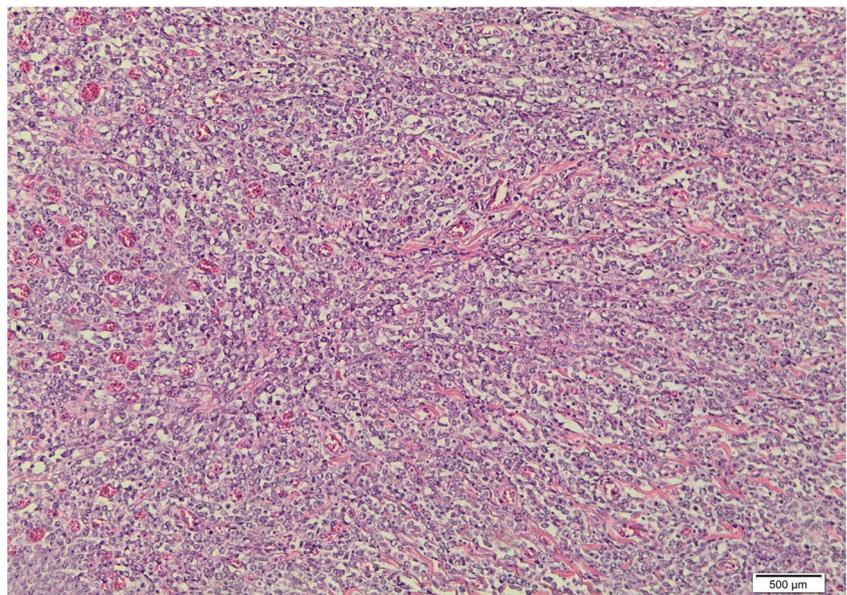
Fig. 9 The lymphoma within the serosal tissue of the bowel wall shows large atypical discohesive cells arranged in sheets, $\times 2$ objective, H&E



onset was 22 years. The cause of immune suppression in these cases included common variable immunodeficiency (CVID), HIV (CD4 count of 9 cells/ μ L) and post-transplant immunosuppressive therapy. In two of the cases, the site of the SMT was the liver, one occurred bilaterally in the adrenal glands and one occurred as multiple tumours in the transverse and right colon. The site of the DLBCL included the nasal cavity, soft tissue, intracranial, pelvic and cecal. In only one of the four cases, an HIV-positive patient, the tumours occurred concurrently. In all four cases, both tumours were positive for EBV using EBER-in situ hybridization (ISH).

We report the case of an HIV-positive adult with concurrent DLBCL and EBV-associated SMT at the same site within the small bowel. In keeping with the findings in the literature, this patient was severely immunosuppressed. Previous case reports of concurrent DLBCL and EBV-SMT have not been described to occur at the same site. In contrast to our case, these previous reports have shown positivity for EBV by EBER-ISH in both tumours. The clinical presentation in this case with ascites and a necrotic segment of bowel is unusual and posed a diagnostic challenge to the treating physicians. To our knowledge, this is the only published case of concurrent EBV-associated SMT and DLBCL at the same site.

Fig. 10 Sheets of large discohesive atypical cells are seen within the serosa. Immunohistochemistry confirmed this to be a DLBCL, $\times 10$ objective, H&E



Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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