CASE REPORT

Acute EBV masquerading as peripheral T-cell lymphoma

Xiao-Yin Zhang,¹ Graham P Collins,¹ Elizabeth Soilleux,² Toby Andrew Eyre¹¹Department of Haematology, Oxford University Hospitals NHS Trust, Oxford, UK²Department of Cellular Pathology, Oxford University Hospitals NHS Trust, Oxford, UK**Correspondence to**
Dr Toby Andrew Eyre,
toby.eyre@ouh.nhs.uk

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SUMMARY

Histological features of Epstein-Barr virus (EBV) can rarely mimic lymphoma. A 25-year-old presented with a spontaneous splenic rupture following a short illness. Histopathology assessment of the splenic and marrow tissue was highly suggestive of peripheral T-cell lymphoma not-otherwise-specified (PTCL-NOS). T-cell receptor (TCR) PCR clonality studies revealed a monoclonal T-cell population expressing for both TCR β and γ , strongly suggestive of a T-cell clonal disease. EBV IgM was positive and IgG negative. EBV PCR was positive (7.02×10^4 /mL). Despite the strong suggestion of PTCL-NOS from histopathology and clonality studies, the decision was made to observe the patient and not start multiagent chemotherapy. The patient remained well, with no signs of PTCL and subsequently seroconverted to IgG+ EBV. We highlight the potential pitfall of acute EBV masquerading as PTCL and show the critical role of the multidisciplinary integration of histopathological, serology, molecular and clinical features to avoid misdiagnosis.

BACKGROUND

Epstein-Barr virus (EBV) is a ubiquitous DNA virus of the herpesvirus family. It infects over 90% of the world's population and persists lifelong. Primary infection is usually asymptomatic, but can cause infectious mononucleosis (IM), particularly in adolescents and young adults, and is characterised by fever, pharyngitis and generalised lymphadenopathy. In addition, it is associated with a number of haematological malignancies, most commonly of B-cell origin. Depending on the immunological response and status of the individual, EBV infection can cause a spectrum of diseases, from the benign to malignant. In the majority of cases, acute IM is diagnosed on the basis of clinical presentation and laboratory findings, including the presence of the classical blood appearance of basophilic, atypical T-cell lymphocytes and apoptotic B cells. The diagnosis is confirmed by EBV serology or the monospot test. Atypical presentations may need histological assessment to exclude lymphoma. Histological features of acute EBV infection can mimic lymphoma, leading to misdiagnosis and inappropriate treatment. We describe a striking case of acute EBV infection masquerading as peripheral T-cell lymphoma not-otherwise-specified (PTCL-NOS).

CASE PRESENTATION

A 25-year-old man presented with acute onset left upper quadrant pain following a 2-week history of

fatigue and cervical lymphadenopathy. At presentation, his haemoglobin was 12.4 g/dL, platelets 184×10^9 /L, white cell count 15.9×10^9 /L (neutrophils 7.2×10^9 /L, lymphocytes 7.3×10^9 /L) with atypical mononuclear, reactive-looking lymphocytes seen on the peripheral blood smear. His alanine transaminase at presentation was raised at 84 IU/L. A CT scan of the abdomen and pelvis showed a markedly enlarged, heterogeneous spleen with an associated subcapsular haematoma, and large volume (>3 L) haemoperitoneum consistent with spontaneous splenic rupture (figure 1). He underwent an emergency, uncomplicated open splenectomy.

INVESTIGATIONS

Histopathology assessment of the splenic tissue was highly suggestive of PTCL-NOS. The red pulp showed extensive diffuse infiltration by CD2+, CD3+, CD8+, TIA-1+, CD5-, CD7-, CD56-, ALK1-, CD30- and TdT- small T cells (figure 2). In situ hybridisation for EBV-encoded RNA was negative. The MIB-1 proliferation index was 25%. The differential diagnoses of PTCL-NOS, hepatosplenic T-cell lymphoma, T-prolymphocytic leukaemia and T-cell large granular lymphocytic leukaemia, were considered.

A bone marrow trephine performed subsequently was also highly suspicious of PTCL-NOS. There was a nodular (para-trabecular and intertrabecular) and interstitial infiltrate of T lymphocytes, which expressed CD3, CD2, CD5, CD7, CD8 and TIA-1. A minor population of interspersed CD4+ lymphocytes was also seen. The infiltrating T cells accounted for 10% of the marrow cellularity. Cytogenetics were normal. T-cell receptor (TCR) PCR clonality studies were performed on bone marrow and splenic tissue. Both revealed a monoclonal T-cell population expressing TCR β as well as for TCR γ , strongly suggestive of a T-cell clonal disease (figure 2).

Serology for EBV viral-capsid antigen (VCA) IgM was positive, but EBV VCA and Epstein-Barr nuclear antigen (EBNA) IgG were initially negative. EBV PCR was positive at 7.02×10^4 /mL. The clinical presentation and EBV serological findings were felt to contradict the histological description and TCR clonality studies from both splenic and marrow tissue.

DIFFERENTIAL DIAGNOSIS

Despite the strong suggestion of PTCL-NOS from histopathology and T-cell clonality studies, the decision was made to observe the patient and not start

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Figure 1 Coronal (A) and sagittal (B) sections of the CT of the abdomen-pelvis showing splenic rupture and capsular haematoma.

multiagent chemotherapy. The patient was followed up regularly and remained clinically well, with no B symptoms and neither lymphadenopathy nor organomegaly on examination. A repeat CT scan of the neck/chest/abdomen/pelvis 9 months from initial presentation showed stable, minimal lymphadenopathy.

OUTCOME AND FOLLOW-UP

Unusually for an acute EBV infection, the patient only became EBV VCA IgG and EBNA IgG positive over 12 months after initial presentation. In view of this slow seroconversion, a number of causes of possible immunodeficiency were excluded. Total serum immunoglobulins, CD27 expression and the OX40 assay for CD4-positive T-cell response to EBV were all within their respective normal ranges. Immunophenotypic SAP/XIAP

(X linked inhibitor of apoptosis) expression was normal, excluding X-linked lymphoproliferative disease (XLP) 1 and 2. Sequence analysis of the 17 exons and intron/exon boundaries of the interleukin-2-inducible T-cell kinase (ITK) gene also did not detect an abnormal mutation. The patient remained under follow-up for over 12 months from his initial presentation, with no evidence of lymphoma, and was therefore discharged from haematology follow-up. He remains well 18 months from presentation to the present day.

DISCUSSION

First described in 1941,¹ spontaneous splenic rupture is a rare but well-described clinical presentation of acute EBV, occurring in approximately 0.5–1% of cases. While acute EBV infection

Figure 2 (A–H) Histological appearance of spleen ((A) H&E stain), with corresponding immunohistochemical staining (B–H) using the immunoperoxidase method, which labels positive cells brown, with a haematoxylin (blue) nuclear counterstain. The immunostains demonstrate the infiltrating small lymphocytes to be CD3+, CD4–, CD8+, CD5+, CD7+, CD56–, with a Mib1 proliferation index of 25%. These histological features would strongly favour a CD8+ T-cell lymphoma and are not characteristic of benign infiltrates. T-cell receptor clonality study traces for tubes bB (I) and bC (J), indicating mono-clonality in the TCRβ locus. The top trace in each panel is the polyclonal control, and the two below are the results of PCR reactions using 200 and 50 ng templates, respectively, for each multiplexed PCR tube. A dominant 263 nucleotide Vb-Jb2 amplicon gives a clonal peak in tube bB (I), while a dominant 192 nucleotide Db-Jb2 amplicon gives a clonal peak in tube bC (J).

mimicking B-cell lymphoma has been described,^{2–4} very few cases have been reported where PTCL was suspected on histopathological assessment.^{5–9} He *et al*⁹ reported acute EBV infection associated with adeno-tonsillar enlargement, where the nasopharyngeal biopsy showed diffuse infiltration of atypical predominantly CD3+ T cells, and foci of immunoblast-like cells with cytological atypia and brisk mitosis. Tamura *et al*⁶ described a case of self-limiting EBV-associated enteropathy, where colonic biopsy showed atypical lymphocytic infiltrate (CD3+, CD8+, CD4–, CD30–, CD56–) of the lamina propria. PCR for the TCR γ gene did not detect any clonal populations in the biopsy specimen. To the best of our knowledge, only a single other reported case was found where the suspicion of PTCL was supported by both histology and T-cell clonality studies.⁷ A tonsillar biopsy showed an expanded T-zone of diffuse, monomorphous lymphocytes, over 90% of which expressed pan-T markers on immunophenotyping. Southern blot analysis demonstrated clonal rearrangement of the TCR gene.

EBV infection induces the proliferation of CD8+ cytotoxic T cells targeted against EBV-infected B cells. In IM patients, expansion of T cells displaying oligoclonal, monoclonal and polyclonal TCR repertoires is typically identified.^{10–11} Wang *et al*¹² reported two cases of IM where TCR clonality studies identified a transient clonal T-cell population. As our case highlights, this is likely to represent PCR amplification of one of the dominant clonotypes, rather than a *bona fide* monoclonal T-cell disease. Although EBV primarily infects B cells, infection of T cells can rarely occur and was recently demonstrated *in vitro*.¹³ An emerging picture is that EBV infection is associated with a continuous spectrum of T-cell proliferative disorders, ranging from the benign to the malignant. These include IM, EBV-associated T-cell/natural killer (NK)-cell lymphoproliferative disorders of childhood and in young adults, and subtypes of PTCL (angioimmunoblastic lymphoma, extranodal NK-cell/T-cell lymphoma, nasal type).¹² This adds a further layer of

complexity in correctly diagnosing cases such as this described case. Our case highlights the potential pitfall of how acute EBV infection can masquerade as PTCL, both on histology and T-cell clonality study. Our case highlights the critical role of the multi-disciplinary integration of histopathological, serology, molecular and clinical features of this patient's presentation to avoid misdiagnosis and inappropriate treatment.

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Contributors X-YZ and TAE collected the clinical data and wrote the manuscript. All the authors critically reviewed the manuscript. ES and GPC were involved in diagnostic interpretation, production of the images, critical analysis of the data, and the conception and design of the manuscript, and managed the patient.

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Learning points

- ▶ Acute Epstein-Barr virus (EBV) infection can masquerade as peripheral T-cell lymphoma when histopathological tissue is examined.
- ▶ Acute EBV can result in a monoclonal T-cell population expressing by T-cell receptor clonality studies, which can be strongly suggestive of a T-cell clonal disease.
- ▶ Multidisciplinary integration of histopathological, serology, molecular and clinical features of this patient's presentation was critical to avoid misdiagnosis.

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