CASE REPORT

Severe thrombocytopenia and recurrent epistaxis associated with primary Epstein-Barr virus infection

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SUMMARY

Infectious mononucleosis, caused by the Epstein-Barr virus (EBV), generally follows a benign, yet protracted course, with the majority of symptoms being systemic somatic symptoms. Rarely, the clinical picture can be complicated by more acute severe haematological sequelae of the disease, requiring hospitalisation and causing diagnostic uncertainty, particularly when distinguishing between a viral illness and a lymphoproliferative disorder. We describe the case of a young male patient who presented with headache, recurrent epistaxis and severe thrombocytopenia.

BACKGROUND

Epstein-Barr virus (EBV), or human herpesvirus 4 (HHV-4), is the virus most commonly associated with classic infectious mononucleosis (a mononucleosis-like syndrome can also be caused by cytomegalovirus (CMV)). It is also an oncogenic virus, and is associated with malignancies such as Burkitt's lymphoma and nasopharyngeal carcinoma.¹

In the majority of cases, the disease is characterised by minor symptoms such as fatigue, fever, lymphadenopathy and sore throat lasting from weeks to months in some patients. In a small number of individuals, however, a variety of moderate to severe haematological, neurological, hepatic, respiratory and psychological complications can arise.² The diagnosis is often made clinically, together with a positive rapid heterophile antibody test (monospot); although immunofluorescence assays of the IgM and IgG antibodies against the viral capsid antigen (VCA) of EBV or amplification of EBV DNA via quantitative real-time PCR (qPCR) are useful if the clinical picture is uncertain.¹

CASE PRESENTATION

A 27-year-old Caucasian man presented with a severe generalised headache, photophobia, diplopia and four episodes of epistaxis over the previous week. He had also been suffering from fever and drenching night sweats. He had recently returned from Spain where he claimed to have fallen from a first floor balcony and hit his head. On examination, he appeared pale and clammy, had a fever of 39°C and a heart rate of 112 bpm. He had multiple palpable lymph nodes in both submandibular regions along with bilateral inguinal lymphadenopathy but there was no evidence of rashes or purpura. Cardiovascular, abdominal and neurological examinations were unremarkable.

INVESTIGATIONS

His initial laboratory investigations were as follows: haemoglobin 160 g/L, white cell count (WCC) $5.5 \times 10^9/L$ (neutrophils $1.8 \times 10^9/L$, lymphocytes $2.6 \times 10^9/L$ with atypical lymphocytes—likely lymphoid blasts) and platelets $56 \times 10^9/L$. Prothrombin time was 14 s and activated partial thromboplastin time 61.6 s. Serology for EBV (VCA IgM), CMV, herpes simplex virus, varicella-zoster virus and HIV were negative. His renal and liver function tests were initially normal, although ferritin was markedly raised at 19 500 ng/mL and lactate dehydrogenase was 912 U/L. He underwent urgent head CT to rule out intracerebral haemorrhage, but this was unremarkable and lumbar puncture (LP) had to be postponed due to his low platelet count, which dropped to $23 \times 10^9/L$ soon after admission (haemoglobin at this point remained steady at 161 g/L, WCC $5.2 \times 10^9/L$). He was started on empirical treatment for meningoencephalitis with intravenous cefuroxime and acyclovir.

The patient continued to spike fevers of 39–40°C and his liver function became moderately deranged, with an alanine transaminase of 400 U/L and alkaline phosphatase of 214 U/L. After receiving a platelet transfusion, an LP was performed (bringing his platelet count to $105 \times 10^9/L$), which showed normal glucose, lactate and protein with no evidence of xanthochromia. Cerebrospinal fluid white and red cell counts were $0.4 \times 10^6/L$ and $0.2 \times 10^6/L$, respectively. By now, his neutrophil count had dropped to $1 \times 10^9/L$ (lymphocytes $3.1 \times 10^9/L$) and C reactive protein (CRP) was 216 mg/L, therefore he was started on piperacillin and tazobactam to cover for neutropenic sepsis.

At this point, a lymphoproliferative disorder was high on the list of primary differential diagnoses, and an ultrasound of the cervical lymph nodes was performed, showing multiple enlarged nodes with loss of the central fatty hilum and no internal vasculature, in keeping with a diagnosis of lymphoma. The patient subsequently underwent submandibular lymph node biopsy. His symptoms and laboratory results had improved sufficiently around this time (WCC $6.5 \times 10^9/L$, neutrophils $2.5 \times 10^9/L$, lymphocytes $3.2 \times 10^9/L$, platelets $311 \times 10^9/L$) for him to be discharged with a plan to follow him up in the haematology clinic with the histopathology results.

OUTCOME AND FOLLOW-UP

When the patient returned to clinic, the news was excellent. His symptoms had almost completely resolved, with some residual fatigue but no episodes of headache or epistaxis since his original

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hospital admission. The lymph node tissue had demonstrated changes consistent with EBV infection and a blood sample that had been sent to an external laboratory for qualitative real-time EBV PCR (and so the result was delayed by a week) had come back positive. His full blood count had also remained normal.

DISCUSSION

This case was initially notable due to the confounding nature of the patient's presenting symptoms. The history of head trauma followed by headache and photophobia required investigation for intracerebral haemorrhage, as well as meningoencephalitis. The clinical history presented something of a red herring, in fact.

There are, however, some more important points that can be inferred generally to patients presenting similarly in the future. The most significant aspect of this case was that the patient presented with a severe thrombocytopenia with haemorrhagic sequelae (recurrent spontaneous epistaxis). Although a mild deficiency in platelet count occurs in 25–30% of EBV cases, the more severe form is incredibly rare.² We carried out a PubMed search looking at precisely this correlation, finding 31 cases of EBV associated with severe haemorrhagic and/or life-threatening thrombocytopenia dating back to 1990.^{3–28} Cases involving immunocompromised patients, such as those with primary immunodeficiency syndromes, HIV and on immunosuppressive therapy were not included.

Eleven cases described an EBV-driven immune thrombocytopenia, with or without purpura, and most of these demonstrated antibodies targeting glycoproteins IIb-IIIa or Ib-IX. Another three cases described a disorder known as haemophagocytic lymphocytosis, whereby activation of EBV infected T cells and macrophages leads to pancytopenia, liver dysfunction and a coagulopathy. Two of the cases suffered from an EBV-induced haemolytic uraemic syndrome. The more severe sequelae suffered by some of these patients ranged from acute renal failure, to spontaneous intracerebral and peritoneal haemorrhage, with the majority of life-threatening cases being treated with corticosteroids, intravenous immunoglobulin (IVIG) or other immunosuppressive agents such as cyclosporin.

Although there is no single unifying process that can describe severe thrombocytopenia in EBV, it would appear that there is a spectrum of autoimmune responses against the virus that often feature one or more antibodies directed against platelet membrane glycoproteins. This is supported by serological evidence, as well as BioMedical Admissions Test (BMAT) analysis almost always demonstrating evidence of peripheral platelet consumption. The fact that only 40% of these patients have demonstrable antiplatelet antibodies has also led some proponents to advocate splenic sequestration secondary to hypersplenism as a significant contributor, although many patients also have normal-sized spleens on ultrasound.² There is subsequently a belief that EBV present in the bone marrow may impair platelet generation and function.²⁹

Another important feature of this episode was how severe cases of EBV can mimic lymphoma considerably. The clinical picture of drenching night sweats, lymphadenopathy, bicytopenia and lymphoma-like appearances of nodes on ultrasound predisposed the patient to a prolonged hospital stay and subjected him to a series of unnecessarily invasive procedures, causing a great deal of distress to him and his family. The process was evidently not helped by a false-negative EIA to the EBV antigen, a test that has been shown to have 98% sensitivity for detection of the virus.³⁰ Some commentators believe that testing for EBV VCA IgM or VCA IgG in the absence of EBV nuclear antigen

(EBNA) is not solely reliable for a diagnosis and that PCR is a necessary confirmatory test.³¹ This serves as an important reminder to promptly order a viral PCR if there is any lingering suspicion of EBV, as this could spare the patient further invasive investigations.

Learning points

- ▶ Epstein-Barr Virus (EBV) can be associated with severe, and sometimes life-threatening, thrombocytopenia.
- ▶ Always consider EBV in those presenting with symptoms and laboratory findings consistent with a lymphoproliferative disorder.
- ▶ PCR for EBV DNA should always be requested for patients with negative serology for whom clinical suspicion remains.

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