CASE REPORT

Massive splenomegaly due to concurrent primary Epstein-Barr virus and cytomegalovirus infection in a patient on adalimumab

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SUMMARY

A 32-year-old man who was receiving adalimumab for seronegative rheumatoid arthritis presented with a 4-week history of fever, night sweats, fatigue, myalgias and diarrhoea. On examination, he had obvious splenomegaly but no lymphadenopathy or pharyngitis. Full blood count revealed mild neutropenia and significant lymphocytosis, with a blood film showing atypical lymphocytes. Liver function tests were mildly deranged with a mixed hepatitic and obstructive pattern. Ultrasound confirmed massive splenomegaly with a span of 21 cm in the long axis. Serological tests confirmed the presence of both primary Epstein-Barr virus and cytomegalovirus infections. The patient had his adalimumab withheld, was treated with supportive measures and improved over a period of 8 weeks. He remained well 5 months after the onset of illness with complete normalisation of blood count and a resolution of the splenomegaly.

BACKGROUND

Epstein-Barr virus (EBV) and cytomegalovirus (CMV) belong to the herpesviridae family of viruses. Primary EBV infection peaks in adolescent years in developed countries and most cases are asymptomatic. Symptomatic infections usually present as infectious mononucleosis (IM) with a triad of fever, pharyngitis and lymphadenopathy.¹ The diagnosis of primary EBV infection in adults requires a high index of suspicion as adults rarely present with classical IM.² Primary CMV infection can mimic IM or present as a non-specific febrile illness associated with gastrointestinal symptoms.³ Both diseases are associated with splenomegaly; however, the splenomegaly is usually mild.^{3,4} We discuss the atypical presentation of primary EBV and CMV infection in an adult receiving anti-tumour necrosis factor (TNF) therapy resulting in massive splenomegaly and hypothesise the mechanisms leading to the massive splenomegaly.

CASE PRESENTATION

Our patient was a 32-year-old man who presented with a 4-week history of systemic illness. The patient's initial symptoms were fevers, drenching night sweats and myalgias. Two weeks into the illness, he developed gastrointestinal symptoms with large volume diarrhoea. There was associated nausea but no vomiting.

The diarrhoea worsened and he presented to hospital. At this time, he was having six bowel actions a day. He also complained of ongoing night sweats, myalgias and fatigue. He did not have symptoms of coryza, dysuria, penile discharge, rash or recent loss of weight.

The patient's medical history was significant for seronegative rheumatoid arthritis diagnosed 3 years ago. He had been treated with methotrexate 25 mg weekly (with folic acid) since diagnosis and had also been commenced on fortnightly adalimumab 40 mg injections 2 years ago. The last dose of adalimumab was 12 days prior to the onset of his systemic symptoms and the most recent dose of adalimumab had been withheld due to concern that the patient's symptoms may have represented an adverse reaction. However, this did not result in any improvement of the patient's symptoms. His only other medical problem was stable bipolar disease that was being managed with lithium 500 mg two times a day and sertraline 100 mg daily.

The patient was born in Australia and had not travelled recently. He did not have any sick contacts or contact with young children. There was no history of intravenous drug usage, hazardous occupational or animal exposure. He was in a stable relationship with his long-term male partner. HIV testing 12 months prior had been negative. He was a non-smoker and drank up to 10 standard drinks a week.

On examination, the patient had vital signs within the normal limits and was afebrile. He was diaphoretic with clothes drenched in sweat. The oropharynx had no obvious erythema or tonsillar enlargement. Examination of the cardiovascular and respiratory system was unremarkable with no murmurs or crackles heard. Splenomegaly was present 6 cm below the costal margin. There was no associated hepatomegaly or lymphadenopathy. Examination of the joints revealed mildly tender metacarpophalangeal joints bilaterally with no evidence of active tenosynovitis. There was a palpable rheumatoid nodule on the patient's right elbow.

INVESTIGATIONS

A full blood count revealed a mild neutropenia of $1.6 \times 10^9/L$, a lymphocytosis of $6.3 \times 10^9/L$ and a blood film showing reactive lymphocytes. Inflammatory markers were normal with a C reactive

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Table 1 Relevant haematological and biochemical markers in the weeks since onset of illness

	Week 4	Week 14	Normal range
Neutrophils	1.6	4.9	2.0–7.5×10 ⁹ /L
Lymphocytes	6.3	2.5	1.0–4.0×10 ⁹ /L
ALT	358	27	5–40 U/L
AST	177	6	10–40 U/L
GGT	427	59	5–50 U/L
ALP	183	68	35–110 U/L
Bilirubin	8	9	4–20 µmol/L
Albumin	33	44	36–47 g/L
ESR	3	5	1–10 mm/hour
CRP	4	–	<5 mg/L

ALP, Alkaline Phosphatase; ALT, Alanine Transaminase; AST, Aspartate Transaminase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GGT, Gamma Glutamyl Transferase.

protein of 4 mg/L and erythrocyte sedimentation rate of 3 mm/hour. The liver function was deranged in a mixed hepatitic and obstructive picture: Alanine Transaminase (ALT) 358 U/L, Aspartate Transaminase (AST) 177 U/L, Gamma Glutamyl Transferase (GGT) 427 U/L, Alkaline Phosphatase (ALP) 183 U/L and bilirubin 8 µmol/L (see table 1). An abdominal ultrasound did not reveal any hepatic or biliary pathology but confirmed the presence of splenomegaly, measuring 21 cm in the long axis. Initial cultures of blood, urine and stool were negative and chest X-ray did not suggest infection in the lungs. CT scanning of the chest, abdomen and pelvis confirmed the presence of splenomegaly (see figure 1) but did not reveal a source of infection and did not identify any lymphadenopathy. The patient was negative for rheumatoid factor and other autoantibodies. Serological tests for hepatitis A, B and C did not indicate previous or current infection and repeat HIV testing was negative. Interestingly, serological testing for EBV and CMV was suggestive of primary infection for both, given the rise and then fall of IgM antibodies and the progressive rise in IgG antibodies towards both viruses. In addition, the development of antibodies to Epstein-Barr nuclear antigen was also suggestive of recent EBV infection (see table 2). Monospot testing for heterophile antibodies was negative.

DIFFERENTIAL DIAGNOSIS

Given the massive splenomegaly and deranged liver function tests, a myeloproliferative or lymphoproliferative disorder was considered. However, apart from a mild neutropenia and lymphocytosis, the remainder of our patient's cell lines were

Figure 1 Coronal slice of CT abdomen demonstrating massive splenomegaly.

Table 2 EBV and CMV antibodies and titres in the weeks since onset of illness

	Week 4 (initial serology)	Week 5	Week 14 (convalescent serology)
EBV-VCA IgM (titre)	Equivocal (20.4)	Detected (128)	Equivocal (17.3)
EBV-VCA IgG (titre)	Detected (153)	Detected (202)	Detected (553)
EBV-NA IgG	Negative	Equivocal	Detected
CMV IgM (titre)	Detected (12.2)	Detected (20.4)	Detected (5.0)
CMV IgG (titre)	Low level (27)	Low level (27)	Detected (116.3)

CMV, cytomegalovirus; EBV, Epstein-Barr virus; VCA, viral capsid antigen; NA, nuclear antigen.

normal and the diagnosis of a haematological disorder was thought to be unlikely. Viral infections such as EBV and CMV infections were considered as well, although the presence of massive splenomegaly with these infections is unusual.^{3 4} A metabolic disease such as Gaucher disease was also considered, but again this was unlikely given the age of onset and resolution of symptoms without specific treatment. Finally, a differential unique to this patient is that of Felty's syndrome. This consists of the triad of rheumatoid arthritis, neutropenia and splenomegaly, although Felty's syndrome usually occurs in patients with seropositive rheumatoid arthritis with long-standing, uncontrolled disease activity. Additionally, in Felty's syndrome the neutropenia is more marked and the splenomegaly less severe.⁵

TREATMENT

The patient was kept off his adalimumab and methotrexate and received supportive treatment with intravenous fluids, antipyretics and antidiarrhoeal medications. He continued to improve symptomatically and his liver function tests also improved throughout his hospital admission. He was discharged after a 5-day hospital stay with the presumed diagnosis of concurrent primary EBV and CMV infection.

OUTCOME AND FOLLOW-UP

The patient was reviewed in outpatients 2 weeks postdischarge from hospital. He reported ongoing symptomatic improvement and repeat full blood count and liver function tests were normal. A repeat abdominal ultrasound 5 months after the initial illness showed ongoing splenomegaly; however, the spleen had now receded from its original size of 21 cm in long axis to 16 cm. The patient remained off methotrexate and adalimumab as his rheumatoid arthritis was judged to be quiescent based on clinical assessment and inflammatory parameters.

DISCUSSION

EBV and CMV are members of the herpesviridae family of viruses and are also known as human herpes virus 4 and human herpes virus 5, respectively.⁶ The seropositivity for both these viruses is up to 90% in adults with seroprevalence increasing with age and inversely correlated to socioeconomic status. Both viruses require close contact for transmission with EBV most commonly transmitted via salivary secretions and CMV most commonly transmitted from the upper respiratory tract.¹⁷

IM is a clinical manifestation of EBV infection and generally consists of the triad of fever, pharyngitis and cervical lymphadenopathy. Not all EBV infections manifest as IM; some people present with milder forms of the disease with fever and pharyngitis only and some patients may be asymptomatic.⁴ IM is rarely seen above the age of 30 years, as was the case with our patient

Figure 2 Proposed mechanism for massive splenomegaly in this patient. CMV, cytomegalovirus; EBV, Epstein-Barr virus.

who also did not have any pharyngitis or cervical lymphadenopathy.² Primary CMV infection can manifest in a variety of ways; however, the most common presentation in immunocompetent hosts is with a mononucleosis-type syndrome or a systemic illness associated with gastrointestinal symptoms.¹⁷

Both CMV and EBV infections are associated with splenomegaly.^{3,4} There are varying definitions as to what constitutes splenomegaly and what constitutes massive splenomegaly. The presence of a palpable spleen in itself may be considered diagnostic of splenomegaly.⁷ More objective definitions for splenomegaly include a length of more than 13 cm on ultrasound scanning or a wet weight of greater than 250 g at excision.^{8,9} Massive splenomegaly is defined as a spleen that crosses the midline or extends into the left lower quadrant of the abdomen, greater than 18 cm in length on radiographic evaluation or more than 1500 g wet weight.^{8,10}

Based on the length criteria, our patient had massive splenomegaly. In a study of more than 2000 patients with splenomegaly in a developed country, the most common causes for massive splenomegaly were haematological disorders (myelofibrosis or chronic myeloid leukaemia), infectious diseases (malaria, syphilis) and other diseases such as chronic liver disease and collagen storage diseases.⁸ In that case series spanning almost 50 years, there was only one patient with IM who had massive splenomegaly. There were no cases of CMV infections associated with massive splenomegaly in that cohort.⁸

The diagnosis of primary EBV and CMV infection was made on the basis of serological testing (see table 2). Initial testing for heterophile antibodies using the monospot test was negative. Approximately 10% of patients with the classical IM syndrome

do not test positive for heterophile antibodies.¹ Other serological tests available for the diagnosis of EBV infection include testing of IgM and IgG antibodies against EBV viral capsid antigen (EBV-VCA) and IgG antibodies against EBV nuclear antigen (EBV-NA). A rise in the titre of EBV-VCA IgM antibodies in the early phase of the illness and significant rise in the EBV-VCA IgG antibodies in the convalescent phase of the illness is consistent with the diagnosis of primary EBV infection. Furthermore, IgG antibodies against the EBV-NA being negative at the onset of the illness and becoming positive in the convalescent phase, as occurred in our patient, supports the diagnosis of primary EBV infection.^{11,12} Likewise, a rise in the CMV-specific IgG titre in the convalescent phase of the illness confirms the diagnosis of primary CMV infection. The patient did not have a significant IgM antibody response towards CMV. This is unusual given that IgM antibodies appear 2 weeks into the course of the infection and may persist for up to 9 months.¹³ We postulate that this could be due to the patient's immunosuppressive medications.

The question remains about how important adalimumab was in causing this unexpectedly severe manifestation of EBV and CMV infection. Patients with rheumatoid arthritis are known to have impaired immune response to EBV with higher EBV viral load, excess antibodies to EBV antigens and higher risk of EBV associated lymphoproliferative disease.¹⁴ The effect of anti-TNF therapy alone on the risk and severity of EBV-associated disease is uncertain because patients are often on other immunomodulatory drugs. There have been case reports of EBV-associated lymphoproliferative disorders and fulminant hepatitis in patients receiving anti-TNF therapy.^{15,16} Most of these cases occur with infliximab therapy.¹⁷ However, limited cohort studies in patients receiving anti-TNF therapy for rheumatoid arthritis and inflammatory bowel disease have demonstrated that anti-TNF therapy does not increase the risk of EBV-associated diseases.^{14,18} Of note, severe manifestations of CMV infection including disseminated multiorgan disease, retinitis and colitis have been reported in patients treated with anti-TNF agents.^{19–21} Again it is difficult to attribute these complications solely to anti-TNF therapy because the patients were also on other immunosuppressive medications. Similar to anti-TNF therapy, the exact link between EBV infection in patients with rheumatoid arthritis receiving methotrexate has not been fully elucidated. Although there have been case reports of severe manifestations of EBV infection in patients with rheumatoid arthritis receiving methotrexate, the exact contribution of methotrexate to the risk of infection is not known.²²

The unique points of this case are the concurrence of primary EBV and CMV infection and the presence of massive splenomegaly in a patient receiving anti-TNF therapy. Massive splenomegaly in association with EBV infection is usually due to an underlying secondary pathology such as Gaucher disease or haemophagocytic lymphohistiocytosis (HLH).^{23,24} A bone marrow aspirate would have definitively ruled out the above diagnoses; however, this was felt to be an unnecessarily invasive procedure, especially since the patient was symptom free and the laboratory parameters had normalised. Rheumatoid arthritis can give rise to massive splenomegaly in the context of Felty's syndrome; however, this syndrome usually occurs in patients who are seropositive for rheumatoid factor and who have severe, erosive disease (unlike our patient).^{8,25} There are no case reports to date of massive splenomegaly due to concurrent primary EBV and CMV infection in an adult patient with well-controlled rheumatoid arthritis.

The possible mechanisms for splenomegaly in the patient include excess macrophage activation similar to the pathogenesis of EBV-driven HLH or splenomegaly secondary to a

lymphoproliferative disorder.^{15 26} We feel these scenarios are unlikely given that the patient did not meet diagnostic criteria and there was complete resolution of the splenomegaly with supportive therapy only.²⁷

The most likely mechanism of splenomegaly in this setting is due to chronic antigenic stimulation, akin to the mechanism of splenomegaly in tropical splenomegaly syndrome.²⁸ Tropical splenomegaly syndrome, also known, as hyperactive malarial splenomegaly is a consequence of chronic antigenic stimulation usually due to malarial infection combined with a decrease in function of T-regulatory lymphocytes. The result is overstimulation of antibody production and deposition of antibody–antigen complexes in the spleen causing massive splenomegaly and hypersplenism.^{28 29}

We postulate that adalimumab therapy played a significant role in the manifestation of massive splenomegaly, in part due to the chronic antigen stimulation hypothesis. It is known that patients with autoimmune diseases such as rheumatoid arthritis have decreased T-regulatory cell function resulting in the production of autoantibodies. Adalimumab and other TNF- α receptor antibodies cause an upregulation of T-regulatory cells.³⁰ We hypothesise that cessation of adalimumab in the acute phase of this patient's illness caused a decrease in T-regulatory cell numbers or function. This coupled with concurrent EBV and CMV primary infection, resulted in unregulated antibody production and deposition of excess antigen–antibody complex in the spleen causing massive splenomegaly (figure 2).

Learning points

- Primary Epstein-Barr virus (EBV) infection can result in clinical presentations not resembling infectious mononucleosis, particularly in older adults.
- Heterophile antibody testing can be negative in up to 10% of primary EBV infections.
- Concurrent primary EBV and cytomegalovirus (CMV) infection in adults is rare.
- Massive splenomegaly can occur with primary EBV and CMV infection; however, an underlying haematological or glycogen storage disorder needs to be considered.

Contributors BRR and AF were responsible for providing medical care to the patient during his hospital stay at Cabrini Hospital, Malvern. The idea for the case report was courtesy of AF and BRR. BRR takes responsibility for the clinical details of the case. A brief literature search was conducted by DJ and BRR and the case was identified as unusual. The initial content was authored by BRR, and BRR was responsible for a conducting a detailed literature review on the subject matter. The interpretation of the serological was testing was done with the aid of DJ and PC. PC was responsible for editing most of the manuscript with contributions from DJ and AF. The final version of the manuscript was approved by all four authors.

Competing interests None declared.

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