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CHALLENGES IN DIAGNOSING POST-SPLENECTOMY CYTOMEGALOVIRUS MONONUCLEOSIS

Kim Abbegail Tan Aldecoa[1,2], Rahul Pidikiti[1,2], Jaisal Brar[1,2], Geetha Krishnamoorthy[1,2], Shamla Kalyan[3], Cecilia Cosma[1,2], Pritha Chitagi[1,2]

[1] Department of Internal Medicine, Trinity Health Oakland, Pontiac, USA
[2] Wayne State University, Detroit, USA
[3] Department of Infectious Diseases, Trinity Health Oakland, Pontiac, USA

Corresponding author: Kim Abbegail Tan Aldecoa **e-mail:** KimAbbegailTan.Aldecoa@trinity-health.org

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ABSTRACT

Cytomegalovirus (CMV) infection is often asymptomatic. However, in certain individuals, it can cause non-specific signs and symptoms that maybe hard to recognise. The condition may therefore be overlooked or misdiagnosed, leading to prolonged illness and serious sequelae. In this case report, we present a rare instance of CMV infection in an HIV-negative patient who had a remote history of splenectomy and was experiencing prolonged fever and markedly elevated white blood cell (WBC) count.

KEYWORDS

Cytomegalovirus, post-splenectomy, CMV mononucleosis

LEARNING POINTS

- The clinical presentation of CMV infection in a post-splenectomy patient can be intricate and deceptive, involving non-specific symptoms such as prolonged fever and a markedly elevated WBC count.
- The decision on treatment among individuals without apparent risk factors (such as AIDS, transplant, or cancers) led to in-depth deliberations and discussion.
- Post-splenectomy patients with CMV infection may exhibit prolonged illness, potentially leading to severe consequences if left untreated.

INTRODUCTION

Cytomegalovirus (CMV) can infect people of all ages[1], and studies show that about 83% of the global population has been exposed to the virus[2]. This percentage is even higher, at 86%, in women of childbearing age and blood or organ donors[2]. In most cases, people who are not immunocompromised do not experience any symptoms[1,3] because their immune system keeps the virus under control[2]. However, those who have

weakened immune systems, such as people living with HIV, transplant recipients and infants infected during pregnancy, are highly susceptible to the virus[1,4]. In such cases, CMV can replicate uncontrollably, leading to viremia, dissemination to multiple organs and end-organ diseases[2].

The spleen is responsible for clearing microorganisms and mounting antibody response[4,5], making it an important defence against blood-borne pathogens. While it is widely known that people who have undergone splenectomy are at a higher risk of infection from encapsulated bacteria and intraerythrocytic parasites, there is little evidence linking splenectomy to viral infections[5]. In this case, we present a rare instance of a CMV infection in an HIV-negative patient who had undergone splenectomy in the past.

CASE DESCRIPTION

A 21-year-old man who had a splenectomy following a gunshot injury at age 16, presented with a 3-week history of intermittent fever, intermittent abdominal pain, and diarrhoea. The patient reported a previous history of blood transfusion during splenectomy surgery, although he was unable to recall the exact number of units received. He denied IV drug use and admitted to five previous sexual partners. He was febrile on presentation (38.4°C). Physical examination was unremarkable except for the midline surgical abdominal scar; chest X-ray was consistent with left lower lobe pneumonia. Laboratory evaluation showed leukocytosis with an average of 30,000–68,000/µl (peak 81,000/µl) during the hospitalisation *(Table 1)*. Despite broad-spectrum antibiotics for 5 days, the patient continued to be febrile *(Table 2)*. Further laboratory work-up revealed: HIV test negative, CMV IgM 110 (N: <30), CMV 1gG 1.40 (N:<0.6), CMV DNA 68,265 units (N:<126). A hepatitis panel was negative. Given the presence of diarrhoea and pneumonia, a legionella urinary antigen test was also conducted, yielding a negative result. A computed tomography (CT) of the abdomen only showed post-surgical changes after the splenectomy. A peripheral smear showed absolute lymphocytosis *(Fig. 1)*. Due to persistent leukocytosis flow cytometry was ordered, which only showed marked T-cell expansion, suggestive of a viral infection. Infectious disease specialists were consulted. Broad-spectrum antibiotics were discontinued, and a decision was made to start CMV treatment with ganciclovir for 14 days on hospital day 9. Initiation of ganciclovir caused resolution of the fever within 48 hours of treatment. The patient was admitted for a total of 20 days.

DISCUSSION

CMV infection is a serious health concern that can affect people of all ages[1]. The virus can be transmitted through direct contact with infectious body fluids such as blood, saliva, urine, tears, semen, and breast milk. The infection can also be transmitted through sexual contact, blood transfusions and organ transplants[1]. CMV infection can occur as a primary infection (without prior infection), reinfection or reactivation[2,4]. The virus remains dormant in the host's

	Result	Normal range
White blood cell count	30–68×10^3/µl, peak 81×10^3/µl	5–10 ×10^3/µl
Haemoglobin	11.8–12.1 g/dl	13–18 g/dl
Platelets	301–622 /µl	150–450,000 /µl
HIV test	Negative	-
Hepatitis panel	Negative	-
CMV IgM	110 U/ml	<30 U/ml
CMV IgG	1.40 U/ml	<0.60 U/ml
CMV DNA	68,265 copies/ml	<126 copies/ml
Urine drug screen	Negative	-
Chest X-ray	Left lower lobe pneumonia	-
CT abdomen	Unremarkable	-
Flow cytometry	Marked T-cell expansion, suggestive of a viral infection	-

Table 1. Summary of important laboratory and imaging findings.

	Day 1	Day 3	Day 5	Day 7	Day 9*	Day 11	Day 13	Day 15	Day 17
White blood cell count (×10^3/µl)	40.4	53.1	55.8	61.7	56.7	77.6	39.4	29.6	23.4
Temperature (°C)	38.4	39	38.6	39	38.0	37.1	36.2	36.7	36.7

*Start of ganciclovir treatment

Table 2. Summary of patient's white blood cell count and temperature during hospital admission.

body and can reactivate from time to time[1], depending on the patient's immune status. Critically ill patients with AIDS, bone marrow transplants or haematological cancers are at higher risk of reactivation[4]. Previous studies with primary CMV infection and individuals who have undergone splenectomy noted a prevailing pattern of a history of blood transfusion in such cases[4,6]. Consistently, our patient who underwent splenectomy surgery also disclosed a history of blood transfusion.

The spleen is an important part of the immune system. It acts as a secondary lymphoid organ and is involved in both innate and adaptive immunity. In terms of innate immunity, phagocytic cells play a vital role in clearing infectious organisms by removing antibody and complement-coated microorganisms[5,7]. On the other hand, the spleen also plays a significant role in adaptive immunity, as mature B-cells are present in the germinal centres of secondary lymphoid organs. These B-cells help in processes such as proliferation, differentiation and antibody class switching[5,7]. Splenectomy can lead to various consequences, ranging from mild symptoms similar to flu to severe infections including fulminant sepsis, which can occur anywhere from a week to over 20 years after surgery[8]. A review of the literature reveals that post-splenectomy CMV infection can cause a particular clinicopathological syndrome, which is attributed to the compromised control of early viremia due to the absence of both splenic filtration and a robust IgM response[6]. It is noteworthy that some cases demonstrated a marked IgG response compensating for an inadequate IgM response[5]. Additionally, post-splenectomy, there is a significant impairment in the function of B-cells, and CD4+, CD8+ T cells. The bone marrow tries to compensate for the spleen's absence in the immune response, leading to a T-cell lymphoproliferative response to CMV infection[6].

CMV infection exhibits a broad spectrum of organ involvement. In a study conducted by Rafaidilis and colleagues among immunocompetent individuals, the most common organs affected include the gastrointestinal tract, the central nervous system, haematological, eyes, lungs, and arterial and venous systems[3]. Notably, the gastrointestinal tract is the most frequently reported site affected by CMV infection, giving rise to various conditions such as gastroenteritis, duodenitis, ileitis, colitis, proctitis or exacerbation of inflammatory bowel disease[3]. In the case of our patient, the presentation included a constellation of symptoms, particularly gastrointestinal manifestations such as abdominal pain and diarrhoea, along with non-specific symptoms such as prolonged fever and an elevated WBC count with T-cell lymphoproliferation on flow cytometry. Symptoms reported in other cases of CMV infection post-splenectomy include protracted high fever (89.7%) similar to our patient's case, followed by dyspnoea/respiratory distress (27.6%), malaise (20.7%), visual disturbances (10.3%), headache/sore throat/dry cough (6.9%), weight loss/night sweats (6.9%) and nausea/vomiting (6.9%)[4]. Most cases have also reported to have elevated WBC count with a mean of 30,000/µl and above, with lymphocytic predominance[4].

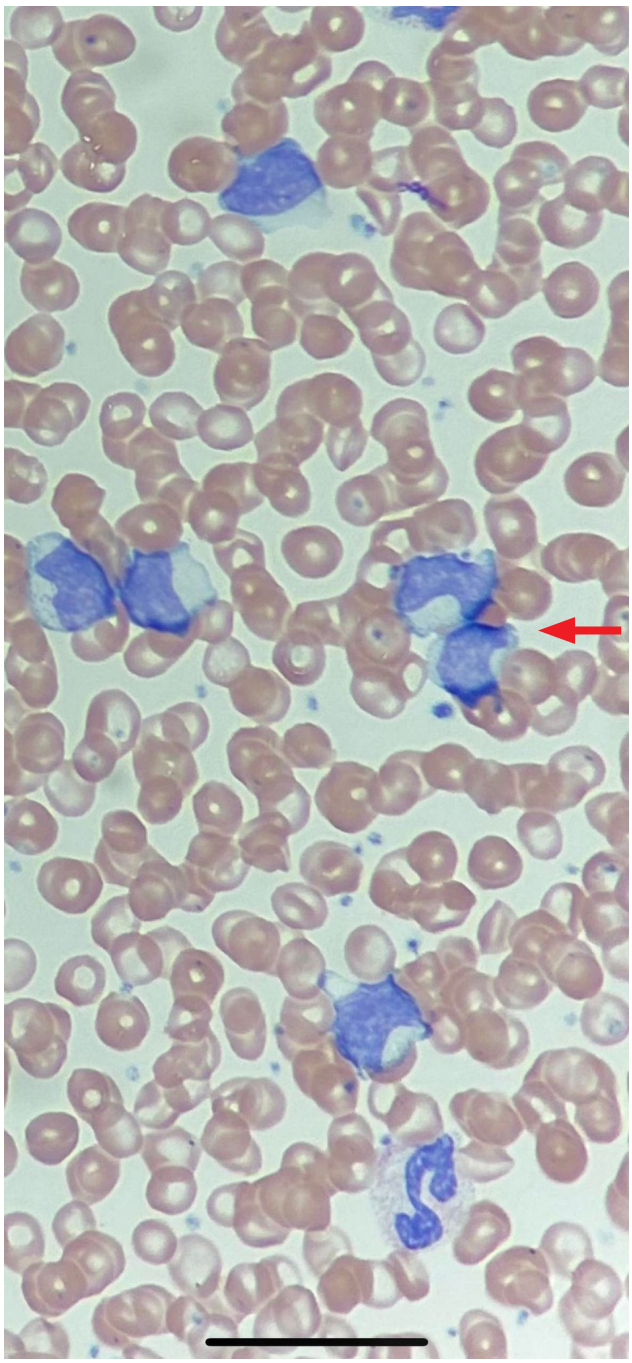

Figure 1. Peripheral smear showing atypical lymphocytes (red arrow).

In a meta-analysis regarding CMV diagnosis post-splenectomy, most cases were diagnosed based upon serology alone (33%), or in a combination with other methods (67%)[4]. Some studies have demonstrated that most patients have weakly positive or negative IgM (50%) and strong IgG (38%)[4]. However, histopathology demonstrating the CMV antigen and cytopathogenic changes in tissue specimens remains the reference standard for the diagnosis of tissue-invasive CMV disease[9], but this is not commonly done due to invasiveness of the procedure. Other methods for diagnosis include culture (highly specific but low sensitivity), reverse transcriptase-polymerase chain reaction (RT-PCR) for detection of CMV viremia, and immunofluorescent assays for the detection of CMV proteins (e.g. pp65)[4,9].

The criteria for specific antiviral therapy for CMV infection among immunocompetent individuals have yet to be established as most CMV infections in immunocompetent patients resolve with very few complications. While severe cases of CMV disease may prompt consideration of treatment options, including ganciclovir or valganciclovir, there is hesitancy in initiating therapy due to potential toxicities associated with these treatments[3]. Notably, both ganciclovir and valganciclovir may lead to bone marrow suppression, while valganciclovir is also linked to renal insufficiency[10]. Fortunately, our patient did not experience any toxicity following initiation of treatment. A literature review also indicates that, in many cases, broad-spectrum antibiotics were pre-emptively administered before the diagnosis of CMV infection. This pre-emptive approach was adopted in response to the patient's non-specific presentation, characterised by prolonged fever and leukocytosis/lymphocytosis[4], similar to our patient's case.

While symptomatic CMV infection among the immunocompetent typically follows a self-limiting course and is managed through observation, individuals can experience prolonged illness if the diagnosis is missed, and treatment is delayed. In our patient's case, the serologic evidence of CMV infection prompted extensive discussions about initiating treatment, given the potential associated toxicity. However, the persistence of fever and an escalating trend of leukocytosis ultimately justified the initiation of CMV infection treatment.

CONCLUSION

The clinical presentation of CMV infection in a post-splenectomy patient can be complicated and misleading, often leading to a delayed identification if not promptly recognised. Similarly, our patient's symptoms were non-specific, leading to a delayed diagnosis and an extended hospital stay. This was primarily attributable to challenges in promptly diagnosing CMV infection and the decision on treatment. Having a high index of suspicion for distinctive features is crucial after splenectomy. It is noteworthy that splenectomy not only associates with infections related to encapsulated bacterial organisms, but also poses a risk from serious viral infections.

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