CASE REPORT

Pancytopenia secondary to cytomegalovirus reactivation

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SUMMARY

A 64-year-old woman with a 1-year history of microscopic polyangiitis developed isolated pancytopenia secondary to cytomegalovirus (CMV) reactivation. The patient was originally admitted to the medical service for the management of a rapidly progressing 10 cm ulcer on her left lower extremity. Prior to admission, the patient had been on several immunosuppressive agents for the treatment of microscopic polyangiitis, including prednisone, azathioprine, cyclophosphamide and rituximab. Her hospital course was notable for pancytopenia and after a very thorough diagnostic work-up, the aetiology was found to be secondary to CMV reactivation. This was confirmed by blood analysis that revealed a highly elevated CMV level at 899 100 copies/mL by quantitative PCR. The patient was promptly treated with intravenous ganciclovir for a total course of 14 days before transitioning to an oral regimen. She had a pronounced response to the anti-CMV therapy with complete recovery of her white cell count, haemoglobin and platelet count to baseline.

BACKGROUND

Pancytopenia is a serious complication of cytomegalovirus (CMV) reactivation that requires a prompt treatment, especially in immunocompromised patients. However, it is often difficult to isolate CMV from other entities as the aetiology, particularly in patients with comorbid autoimmune disorders who are often exposed to immunosuppressive agents that either directly suppress the bone marrow or predispose them to infections that can lead to pancytopenia. CMV reactivation is also infrequently reported, especially among those with autoimmune disorders, even though mortality rates are higher in this patient population.¹ Moreover, the treatment of CMV viraemia is not inconsequential and requires a close surveillance because first-line anti-CMV agents such as ganciclovir can further cause myelosuppression. In this case, we present a patient with a 1-year history of microscopic polyangiitis exposed to multiple immunosuppressive agents who developed isolated pancytopenia in the setting of extraordinarily high levels of CMV viraemia.

CASE PRESENTATION

A 64-year-old woman with a history of microscopic polyangiitis presented to the emergency department with a progressing 10 cm ulcer on her left lower extremity. She developed the symptoms of systemic inflammatory response syndrome (SIRS) and was promptly started on broad spectrum

antibiotics vancomycin and meropenam, and was given intravenous fluids. The patient responded to the therapy, and was admitted to the medical service to receive further treatment.

Her history of microscopic polyangiitis began in 2012 when she noticed a sudden onset of muscular pain and purpuric lesions in her lower extremities. Laboratory investigation by the patient's rheumatologist revealed positive serologies for cytoplasmic antineutrophil cytoplasmic antibodies and myeloperoxidase autoantibodies. A diagnosis of microscopic polyangiitis was made based on the serological findings coupled with lower extremity purpuric lesions.

The patient's microscopic polyangiitis treatment history included a combination of prednisone 60 mg orally daily and cyclophosphamide 100 mg orally daily. However, she developed an infected leg ulcer and cyclophosphamide was discontinued. A new regimen of rituximab 375 mg intravenous weekly for 4 weeks, azathioprine 50 mg orally daily and prednisone 60 mg orally daily was initiated but azathioprine was subsequently discontinued due to leucopenia.

While being hospitalised for treatment of the ulcer, the patient was found to be neutropenic with a white cell count of 0.99×10^3 . Her absolute neutropenic count was 762. Her haemoglobin and platelet levels were also low at 10.3 and 98, respectively. A battery of blood work to investigate her pancytopenia that included ADAMTS13, haptoglobin, lactate dehydrogenase, indirect bilirubin, heparin platelet antibody, fibrinogen, partial thromboplastin time and international normalised ratio was unrevealing. The patient's peripheral blood smear confirmed pancytopenia without any abnormal cell morphologies. Given her immunocompromised state, a panel of viral quantitative PCR tests was performed that included Epstein-Barr virus (EBV), CMV and parvovirus B19. A day later, the CMV DNA quantitative PCR came back highly elevated at 899 100 copies/mL.

The extent of the patient's immunocompromised state can be illustrated by her B and T cell subset count: CD3 86 (normal range 841–2402); CD4 15 (355–1426); CD8 57 (255–1090), CD19 <1 (107–589) and natural killer cell 3 (71–477). This prompted an infectious disease consult, and a diagnosis of CMV reactivation as a consequence of her immunocompromised state was made.

TREATMENT

The patient was started on ganciclovir 5 mg/kg intravenous twice daily for a total course of 14 days

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for her CMV viraemia. She also received a 5-day course of daily filgrastim injections for her neutropenia. An ophthalmology evaluation showed no evidence of CMV retinitis. The patient also received a 70 g infusion of IVIG given her low γ -globulin levels. On completion of the 14 day course of intravenous ganciclovir, the patient was transitioned to a lifelong course of oral valganciclovir at 900 mg daily.

OUTCOME AND FOLLOW-UP

The patient had a dramatic response to the intravenous valganciclovir treatment with a complete recovery of her WCC, haemoglobin and platelet count. After 3 days of treatment, the CMV viraemia also improved with the CMV DNA quantitative PCR reduced to 41 540 copies/mL. Figure 1 depicts the patient's CMV viral load and complete blood counts while inpatient.

DISCUSSION

CMV is a herpes virus that commonly establishes asymptomatic latency in the majority of the population. Up to 76% of the general population has latent infection based on serological evidence. The prevalence increases with age, with more than 90% turning seropositive by age 60.^{2 3} Patients with primary CMV infection can be either asymptomatic or symptomatic. Those who are symptomatic typically present with mononucleosis syndrome, though other manifestations are also possible, including haemolytic anaemia, thrombocytopenia, liver function abnormalities, and less commonly, colitis, encephalitis and pneumonitis.^{3 4} Although patients with latent CMV develop IgG antibodies, seropositivity does not confer immunity, as all the patients are susceptible to infection by latent CMV or a new strain. The serological status of our patient was not known prior to her pancytopenia; however, we suspect that she would have had a positive IgG, given CMV's high prevalence among older populations. While reactivation in immunocompetent patients is rare, it is far more common in immunocompromised patients where cell-mediated immunity is depressed. For example, several studies have demonstrated that CMV reactivation is close to 100% in kidney and cardiac transplant populations.³

Though this discussion focuses on CMV, one may consider other viral aetiologies for pancytopenia. These viruses include hepatitis A–E, non-A–E hepatitis, parvovirus B19, HIV and EBV; the latter three are associated with immunocompromised states.⁵ EBV, similar to CMV, is a herpes virus that can establish

latency earlier in the patient's life and becomes reactivated after the immune response is suppressed.⁶

If left untreated, CMV reactivation can lead to serious complications such as oesophagitis, colitis, retinitis, pneumonitis or encephalitis within a few weeks.⁴

While CMV reactivation in transplant patient populations is well known, it is seldom reported in those with autoimmune diseases and mostly limited to case reports.^{7–9} As a result, the prevalence of CMV reactivation and its manifestations are largely undocumented.

There has only been one large-scale study of CMV reactivation in patients with rheumatic diseases, which identified 151 patients, 13 of whom had microscopic polyangiitis.¹ Almost all of these had been on corticosteroid therapy, and more than half had received pulse dose methylprednisolone. Fatal outcomes were reported in 44 patients, with those receiving pulse dose steroids at a higher risk of death. These data in conjunction with this case report highlight the importance for CMV reactivation in those undergoing immunosuppressive treatment for autoimmune disorders.

Learning points

- Viral aetiologies, such as cytomegalovirus (CMV) reactivation, should be considered in patients with autoimmune diseases who develop pancytopenia
- CMV reactivation in patients receiving the treatment for autoimmune diseases leads to a higher risk of death.
- As a first-line treatment for CMV reactivation, ganciclovir can suppress the bone marrow. While this is a significant adverse effect, the antiviral benefits are substantial and should be given to patients with pancytopenia secondary to CMV reactivation.

Contributors JRT and GXN cared for the patient, collected data, wrote initial drafts and proofread for final editing.

Competing interests None.

Patient consent Obtained.

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Figure 1 The patient's cytomegalovirus DNA levels by quantitative PCR, white cell count, platelet count and RBC count as a function of time while inpatient. The patient was started on intravenous ganciclovir on day 4 of her hospitalisation, which is shown at the top line.

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