

## CASE REPORT

# Cytomegalovirus-associated portal vein thrombosis in an immunocompetent patient: an underestimated complication

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## Abstract

We describe an immunocompetent adult with acute cytomegalovirus (CMV) infection complicated by extensive portal vein thrombosis. A literature review on the incidence, presentation, pathophysiology and management of CMV-associated thrombosis is included. Previously thought to be a rare complication, recent large case series and the present case reconfirm the increasing prevalence of CMV-associated thromboembolism in the immunocompetent adult.

## INTRODUCTION

Portal vein thrombosis typically occurs in patients with cirrhosis and/or prothrombotic disorders. It can be clinically silent or may present with abdominal pain, fever and other non-specific dyspeptic symptoms. Acute cytomegalovirus (CMV) infection has been reported to be associated with portal vein thrombosis in immunocompromised patients. We report a case of an immunocompetent adult with acute CMV infection complicated by extensive portal vein thrombosis.

## CASE REPORT

A previously fit and well 61-year-old man presented with a 3-week history of shortness of breath, night sweats and a cough productive of yellow sputum. In the previous 3 months, he had noted worsening fatigue, reduced appetite and weight loss of 20 kg. In the

week prior to his admission, he had completed a 5-day course of erythromycin without improvement to his symptoms. There was no significant past medical history or travel history. He had penicillin allergy and was not on any regular medications.

On admission, he had documented fever (38°C), tachycardia (111 bpm) and blood pressure of 103/70 mmHg as well as oxygen saturations of 94% on room air. Clinical examination revealed no systemic findings, and specifically no hepatosplenomegaly or lymphadenopathy. The chest radiograph showed no focal consolidation. Blood tests revealed a raised white cell count ( $22.4 \times 10^9/l$ ), with a predominant lymphocytosis ( $14.1 \times 10^9/l$ ), normal ESR (14 mm/h) and raised lactate dehydrogenase (1529 IU/l).

Liver function tests were normal. Screening for tuberculosis including three sputum samples for acid fast bacilli and the Mantoux test were negative.

A computed tomography scan of his chest, abdomen and pelvis demonstrated an extensive thrombus in the portal venous

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system, but was otherwise normal (Fig. 1). Expert radiologist opined that this was likely to be acute thrombus as it did not have features of chronicity such as cavernous portal transformation. Further investigations were undertaken to exclude an autoimmune, haematological or neoplastic cause for the portal vein thrombus. Tumour markers (CEA, CA19-9, AFP and  $\beta$ -hCG), anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies (ANCA), anti-cardiolipin antibodies, lupus anticoagulant and mitochondrial antibodies were negative. The prothrombin time, anti-thrombin III levels and protein C and protein S activity were normal, making hereditary thrombophilia unlikely. JAK 2 mutation was negative. Flow cytometry showed polyclonal expansion, but bone marrow aspirate revealed no abnormal infiltrates, suggesting that haematological malignancy was unlikely.

The lymphocytosis was marked but appeared to be reactive. Therefore, screening tests for organisms known to cause severe lymphocytosis were performed. Serological tests for HIV, hepatitis (A, B, C and E), toxoplasma and EBV were normal. However, CMV serology (VIDAS—enzyme-linked fluorescence assay) revealed high-titre IgM antibodies (0.94, reference range: <0.7 negative; >0.9 positive; 0.7–0.89 equivocal), negative IgG antibodies (3.2 AU/ml, reference range: <4 negative; >6 positive; 4–6 equivocal) and a low IgG avidity index (0.18, reference range: <0.2 low; >0.8 high; 0.2–0.8 equivocal), suggesting recent infection.

The patient was anti-coagulated with low-molecular-weight heparin and commenced on warfarin. The patient's symptoms gradually resolved without the need for anti-viral therapy. The patient was discharged, and at follow-up 3 weeks later the white cell and lymphocyte count had reverted to normal and he was feeling well. Warfarin therapy was discontinued after 6 months.

## DISCUSSION

Our patient had acute CMV infection as evidenced by the serological testing. He had normal liver function tests despite symptomatic acute CMV infection, which is unusual. Although the patient did not have any specific signs or symptoms of acute complete portal vein thrombosis such as abdominal pain, the CT findings were in keeping with a diagnosis of acute portal vein thrombosis.



**Figure 1:** Computed tomographic scan of the abdomen showing extensive portal vein thrombosis.

Thromboembolism following acute CMV infection is a well-described complication in immunocompromised patients, predominately in HIV-positive or post-transplant patients [1]. Latent CMV is a prevalent yet asymptomatic infection in immunocompetent adults (seroprevalence: 40–100% depending on the population) [2, 3]. Until recently, CMV-associated thrombosis was considered a rare complication in immunocompetent patients [2, 4]. However, a recent case-control study identified the incidence of thrombosis following acute CMV infection being as high as 6.4%, although the true incidence could be even higher as patients with acute CMV infection do not routinely undergo investigations to rule out thrombotic complications [5]. Similarly, Justo *et al.* [1] revealed a significant increase in the last decade citing 64 cases to date, with a mean age of 37.6 years (range: 2–83 years) with no gender predominance. The majority of patients had prothrombotic predispositions, most commonly, oral contraceptive use, anti-phospholipid syndrome or Factor V Leiden. The most prevalent complications were deep vein thrombosis/pulmonary embolism (29 cases), splanchnic vein thrombosis (24 cases) and splenic infarction (10 cases). Importantly, splanchnic vein thrombosis encompassing portal vein, superior mesenteric vein, inferior mesenteric vein and colic vein thrombosis were significantly more common in immunocompetent patients [1]. Our case emphasizes that thrombosis can complicate acute CMV infection in immunocompetent individuals who do not have other prothrombotic risks.

Several theories exist on the mechanism of CMV-associated thrombosis. The current most popular theory, which has been confirmed repeatedly *in vivo*, describes a transient CMV-induced production of anti-phospholipid antibodies [6, 7]. However, the levels of anti-phospholipid antibodies frequently only remain detectable in the acute phase of illness and disappear with resolution of infection.

The majority of cases identified in the literature were managed with anticoagulation using low-molecular-weight heparin and warfarin. Isolated cases have also received both systemic and local thrombolysis [4, 8]. The duration of warfarin therapy ranged from 20 days till 9 months [1]. The decision to stop anticoagulation was based on the resolution of thrombosis or the decrease of anti-phospholipid antibody levels [1, 6].

A recent meta-analysis revealed only 17.2% of immunocompetent patients who received anti-viral agents (ganciclovir and/or valganciclovir) compared with 51.5% in the immunocompromised group [1].

To conclude, thromboembolism is an underestimated but significant complication of acute CMV infection. This case emphasizes that this potentially serious complication can occur in immunocompetent individuals with no other prothrombotic risk factors.

## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES

1. Justo D, Finn T, Atzmony L, Guy N, Steinvil A. Thrombosis associated with acute cytomegalovirus infection: a meta-analysis. *Eur J Intern Med* 2011;22:195–9.
2. Abgueguen P, Delbos V, Ducancelle A, Jomaa S, Fanello S, Pichard E. Venous thrombosis in immunocompetent patients with acute cytomegalovirus infection: a complication that may be underestimated. *Clin Microbiol Infect* 2010;16:851–4.

3. Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988–1994. *Clin Infect Dis* 2006;**43**:1143–51.
4. Ofotokun I, Carlson C, Gitlin SD, Elta G, Singleton TP, Markovitz DM. Acute cytomegalovirus infection complicated by vascular thrombosis: a case report. *Clin Infect Dis* 2001;**32**:983–6.
5. Atzmony L, Halutz O, Avidor B, Finn T, Zimmerman O, Steinvil A, et al. Incidence of cytomegalovirus-associated thrombosis and its risk factors: a case-control study. *Thromb Res* 2010;**126**:e439–43.
6. Labarca JA, Rabagliati RM, Radrigan FJ, Rojas PP, Perez CM, Ferrés MV, et al. Antiphospholipid syndrome associated with cytomegalovirus infection: case report and review. *Clin Infect Dis* 1997;**24**:197–200.
7. Delbos V, Abgueguen P, Chennebault JM, Fanello S, Pichard E. Acute cytomegalovirus infection and venous thrombosis: role of antiphospholipid antibodies. *J Infect* 2007;**54**:e47–50.
8. Van Moerkercke W, Pauwelyn K, Brugman E, Verhamme M. Cytomegalovirus-associated superior mesenteric vein thrombosis treated with systemic and in-situ thrombolysis. *Eur J Gastroenterol Hepatol* 2009;**21**:587–92.