**CASE REPORT**

**Cytomegalovirus duodenitis in immunocompetent patients: what else should we look for?**

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**SUMMARY**

Cytomegalovirus (CMV) infection is a well-recognised complication of immunodeficiency, although the burden of CMV disease in immunocompetent adults is still unknown. We present the case of a 54-year-old male patient admitted due to severe diarrhoea, epigastric pain and fever. Initial diagnostic workup revealed pericardial and pleural effusion, enlarged abdominal lymph nodes and mild elevation of liver enzymes. CMV serology was IgM positive, and upper endoscopy revealed proximal enteritis. Histology and immunohistochemistry of duodenal samples confirmed CMV disease. An extensive investigation of possible immunodeficiency was conducted with positron emission tomography (PET) scan revealing an abnormal hypermetabolic pulmonary nodule. The patient underwent a right superior lobectomy which, on analysis, confirmed an atypical bronchopulmonary carcinoid tumour. We report this case to reinforce the importance of considering CMV infection as a differential diagnosis in apparent immunocompetent patients and to emphasise the importance of looking for any condition that may cause any degree of immune dysfunction.

**BACKGROUND**

Cytomegalovirus (CMV) infection is a well-recognised complication of immunodeficiency and an important cause of morbidity and mortality. It has been receiving increasing attention as a potential pathogen in the apparent immunocompetent population, mostly in critically ill patients with sepsis.1 2 After primary infection, CMV becomes latent and can later be reactivated by immunosuppression or inflammation.3

While CMV infection in immunocompetent hosts is generally asymptomatic or presenting as a mild mononucleosis-like syndrome, in certain circumstances this β-herpesvirus is capable of producing a systemic life-threatening disease due to a wide-range of tissue tropism.1 4 5 The gastrointestinal (GI) tract is usually the primary site of involvement by the CMV infection, primarily colitis.1

Therefore, we believe that it shall be regarded as a possible aetiology of persistent diarrhoea in immunocompetent hosts but, at the same time, once the diagnosis of CMV infection has been established, an extensive investigation of immunodeficiency states shall be pursued. This case illustrates perfectly this point of view.

**CASE PRESENTATION**

A 54-year-old man presented with a 3-week history of severe aseptic diarrhoea, asthenia, anorexia and 10% of total body weight. In the week before, he developed an intense epigastric pain, fever and night sweats. There was no nausea, vomiting, blood in stools or other relevant symptoms. He referred a recent high-risk sexual behaviour and denied sick contacts at work or home and any history of travelling. He also denied the use of laxatives or any new drugs or supplements, as well as any known malabsorption disease or alimentary intolerance. Of his medical history, the patient referred previous intravenous drug and alcohol abuse until the age of 30 years, chronic hepatitis C infection diagnosed at the age of 29 years and a history of current smoking since the age of 13 years (30 pack-years). At the moment, he drinks alcohol sporadically (25 g/week).

On admission, the patient appeared sick and looked dehydrated and pale. Physical examination was unremarkable, except for mild epigastric tenderness on abdominal palpation, with no signs of peritonitis or any palpable mass.

**INVESTIGATIONS**

Initial blood tests showed leucocytosis (13.3×109/μL) with lymphocytosis and mild thrombocytopenia (118×109/μL). The serum biochemical profile revealed increased liver-associated enzymes: serum aspartate aminotransferase of 100 U/L (normal value 12–78 U/L) and serum alanine aminotransferase 102 U/L (normal value 15–37 U/L). His serum bilirubin, prothrombin time and albumin were normal along with renal function and urinalysis. Markers of inflammation such as erythrocyte sedimentation rate and C-reactive protein were normal. Abdominal ultrasonography was also normal. Blood cultures, stool cultures, stool ova and parasite tests yielded no pathogens.

Following admission, he also developed dyspnoea, hypoxic respiratory failure and continued to have diarrhoea and temperature spikes ranging from 100 to 102°F, mostly at night. Immediate chest X-ray revealed a fibrotic basal parenchyma and a small right pleural effusion.

Considering the data described, serology tests were requested. CMV was positive with an IgM titre of 2.72 IU/mL (normal range 0–0.89) and IgG titre of 2.52 IU/mL (normal range 0–0.9). Serology also revealed previous hepatitis B virus infection with seroconversion and confirmed hepatitis C chronic infection (Genotype 1a; RNA: 610344 IU/L). *Rickettsia conorii* and *Coxiella burnetii* tests all came back negative. HIV viral load was negative. Besides, autoimmunity diseases were also excluded.

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Upper gastrointestinal endoscopy (UGE) revealed extensive ulcers with necrotic centre and yellowish plaques through the observed duodenal mucosa, suggestive of infectious enteritis (figure 1). Histology and immunohistochemistry study of duodenal samples identified cytomegalic inclusion in endothelial cells, which confirmed CMV disease (figure 2). Colonoscopy was normal. CMV retinitis was excluded.

The hypothesis of an immunodeficiency state was studied. Immunoglobulin count was normal, despite slightly low levels of complement. The hypothesis of an occult tumour was also considered. A contrast-enhanced thoracoabdominopelvic CT revealed important subpleural apical emphysema and a non-specific nodule of 9 mm in diameter at the right superior pulmonary lobe associated with mediastinal ganglia, a mild right pleural and pericardial effusion, multiple enlarged retroperitoneal lymph nodes and also moderate hepatomegaly with increased portal calibre. Transient elastography excluded liver fibrosis (stiffness 5.9 kPa).

$^{18}$F-FDG positron emission tomography (PET) scan revealed high metabolic activity in the pulmonary lesion and in the thoracic and abdominal lymph nodes (figure 3). Bronchofibroscopy was normal and bronchoalveolar lavage was negative for neoplastic cells and *Mycobacterium tuberculosis*.

**TREATMENT**

Initially, the patient received intravenous ganciclovir (5 mg/kg every 12 hours) for 1 week and completed the treatment outside the hospital with oral valganciclovir (900 mg twice daily for 1 week and 900 mg once daily for another 2 weeks). This therapy led to a remarkable improvement of the clinical and analytical status (including normalisation of platelet count and liver enzymes),
Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

which allowed him to quickly resume his professional activity, although complete recovery was delayed for 2 months.

OUTCOME AND FOLLOW-UP
A 2-month follow-up PET scan was performed and showed persistence of hypermetabolic activity in the pulmonary nodule, although lymph nodes caption was absent. Guided transthoracic aspiration biopsy was not successful. The patient underwent a right superior lobectomy by video-assisted thoracoscopy. Histology analysis revealed an atypical bronchopulmonary carcinoid tumour (WHO classification), moderately differentiated, with a tumour, node, metastases staging grade of pT1aN0 (figure 4).

A 6-month follow-up UGE was normal and thoracoabdominopelvic CT only revealed the subpleural apical emphysema previously reported. Neuroendocrine tumour markers (neuron-specific enolase and chromogranin A) were negative. The patient was also treated with ledipasvir and sofosbuvir (90/400 mg, once daily for 8 weeks) for hepatitis C virus (HCV) and achieved a sustained virological response. He remains asymptomatic.

DISCUSSION
The burden of CMV disease in immunocompetent adults is still unknown. Invasive disease is rare in these patients and usually caused by reactivation of CMV infection. Although GI tract is the primary site of involvement in this population, CMV duodenitis has been rarely described, even in immunosuppressed patients. Clinical or pathological features of CMV infection in the duodenum have been seldom reported. Endoscopic images of CMV infection in the upper GI tract are generally non-specific, ranging from oedematous mucosa, ulcers to pseudotumour formations.

We would like to emphasise that CMV infection was from the beginning our best hypothesis due to the persistent diarrhoea, elevation of liver enzymes, thrombocytopenia, pleural and pericardial effusion and recent risky sexual behaviour. The improvement of clinical status with ganciclovir reinforces our premise and excludes carcinoid syndrome, an important differential diagnosis in this patient. Moreover, normalisation of platelet count and liver parenchyma with this treatment most likely excludes HCV involvement.

While treatment with ganciclovir is recommended in immunocompromised patients, its role in severe CMV infection in immunocompetent individuals is controversial, as it is mostly a self-limited disease. In this population, the alleged benefit should be considered against the potential toxicity of therapy. In this case, the patient was highly symptomatic; hence, we

Figure 3  Non-specific nodule of 9 mm in diameter at the right superior pulmonary lobe in CT image (left), revealing hypermetabolic activity in PET scan (right).

Figure 4  High-power magnification H&E stained slide of neoplasm with organoid nesting arrangement. The tumour cells have a moderate amount of cytoplasm and finely granular nuclear chromatin (left). Immunohistochemistry with synaptophysin showing strong staining of the cytoplasm (right).
opted for treatment with full clinical recovery. The quick patient recovery made us shorten the induction period for 1 week and discharge the patient earlier than expected.

This increasing recognition of CMV infection in immunocompetent patients is intriguing and some scepticism remains in considering CMV as a pathogen in this population. It should be enhanced that the mostly used definition of immunodeficiency only includes patients with a severe impairment of the immune system, such as HIV-infected patients, chemotherapy and transplant recipients. There are apparent ‘immunocompetent’ patients reported with comorbidities that predispose to some degree of immune dysfunction (diabetes mellitus, renal failure, cirrhosis, inflammatory bowel disease, etc). This partial immune impairment may represent a neglected risk factor for CMV disease.

On the other hand, even when severe impairment of the immune system is known, CMV infection has a low incidence, which highlights other possible reasons to CMV infection other than immunosuppression. It has been suggested that viral load is directly proportional to the ability to reactivate virus from latency with a septic stimulus. Moreover, location of the reactivation stimulus influences the ability to reactivate virus.

CMV infection has been associated with carcinoid tumours, although this is generally related to paraneoplastic syndromes, such as Ectopic Cushing syndrome. This was excluded by lack of clinical signs and normal plasma cortisol and adrenocorticotropic hormone. It is questionable if this small and limited bronchopulmonary lesion is capable of predisposing to an acquired immunodeficiency state. Hepatitis C chronic infection is known to induce a persistent state of inflammation and has been linked to numerous diseases with immune dysfunction, even without liver fibrosis.

Undoubtedly, a multifactorial mediated pathway must contribute to CMV reactivation in an individual. In this case report, hepatitis C chronic infection, atypical bronchopulmonary carcinoid tumour, tabagism and age may have contributed, along with uncharacterised features inherent to the host and virus.

We report this case to reinforce the importance of considering CMV infection as a differential diagnosis in apparent ‘immunocompetent’ patients and to emphasise the importance of looking for a cause of low degree of immune dysfunction.

Contributors DC performed the literature search and wrote the paper. DF performed the endoscopy. AF performed the histological analyses. ASC contributed to the management of the patient and supervised the writing of the paper. All authors read and approved the final manuscript.

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**Learning points**

- Cytomegalovirus (CMV) duodenitis generally presents with a non-specific broad of endoscopy images, even in immunocompetent patients.
- CMV infection must be considered as a differential diagnosis regardless of the patient’s immune status.
- When CMV disease is diagnosed in apparent ‘immunocompetent’ patients, it is relevant to look for a cause of immune dysfunction.

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