Unusual association of diseases/symptoms

Cytomegalovirus oesophagitis following treatment with fludarabine for refractory lymphoplasmacytic lymphoma

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Summary

A 64-year-old man with a 2-week history of fatigue and fever presented to the medical admissions unit. He had a background of lymphoplasmacytic lymphoma and had recently completed a course of fludarabine-based chemotherapy. CT of the abdomen demonstrated an increase in spleen size and it was thought that his fevers were most likely due to disease recurrence or high-grade transformation. A bone marrow trephine was organised, which showed no evidence of lymphoma and positron emission tomography-CT demonstrated an area of increased avidity at the gastro-oesophageal junction. An oesophagogastrroduodenoscopy was recommended, which revealed ulceration within the oesophagus and stomach. Biopsy of the lesions and immunohistochemistry confirmed a diagnosis of cytomegalovirus oesophagitis. He was treated with intravenous ganciclovir followed by oral valganciclovir for a total of 3 weeks. His fever resolved and he was discharged home approximately 8 weeks after he first presented.

BACKGROUND

Cytomegalovirus (CMV) oesophagitis is quite an unusual cause of fever, but is important to be aware of as a differential. This is especially true in patients who have received extensive chemotherapy treatments, or in patients who are immunocompromised for other reasons. This case brings together aspects of infectious diseases, haematology/oncology and gastroenterology.

CASE PRESENTATION

A 64-year-old man with a 2-week history of fatigue and fever presented to the medical admissions unit. He had been diagnosed with lymphoplasmacytic lymphoma with IgM paraprotein and had received six cycles of chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (RCHOP). He was refractory to RCHOP and hence was treated with five cycles of fludarabine, cyclophosphamide and rituximab (FC-R). A CT chest/abdomen/pelvis, following his last course of FC-R, reported a reduction in the disease with 'residual retroperitoneal and mesenteric soft tissue mass'. There was no other significant medical history. He had been on prophylaxis treatment consisting of fluconazole, aciclovir and co-trimoxazole. He lives with his wife, is a non-smoker and drinks minimal alcohol. Apart from being feverish, the clinical examination was unremarkable.

INVESTIGATIONS

The patient's complete blood count on admission showed haemoglobin 9.6 g/dl (13.0–17.0), white blood cells 3.1×10^9 per litre (3.7–11.1), neutrophils 2.4×10^9 per litre (1.7–7.5), lymphocytes 0.3×10^9 per litre (0.9–3.2) and platelet count 73×10^9 per litre (150–450). Serum urea, electrolytes and liver function tests were within normal limits and C-reactive protein was 20 mg/l (0–6.0). Urine dipstick was negative. Throat swab and stool samples

were sent for culture, but the results were negative. Blood cultures were negative and bloods were sent for CMV PCR. Epstein-Barr virus (EBV) and adenovirus PCR were negative. Chest x-ray was normal. Echocardiogram demonstrated normal valve structure and function with no obvious valvular vegetation. A CT chest/abdomen/pelvis reported no consolidation or ground glass opacification, no lung nodule or mass, no collapse, no pleural effusion and no pleural nodularity. Multiple mesenteric lymph nodes were noted to be marginally smaller when compared with a previous scan; however, the spleen size had increased from 11 to 14.5 cm.

The increased spleen size led to the consideration that his fevers were most likely due to disease recurrence or high-grade transformation. In order to investigate this

Figure 1 Positron emission tomography-CT scan: no evidence of high-grade transformation. A focal area of increased avidity at the gastro-oesophageal junction.

further, a bone marrow trephine and positron emission tomography (PET)-CT were organised to look for areas of active disease. Bone marrow trephine showed no evidence of lymphoma and PET-CT showed extensive, but not fluorodeoxyglucose avid, retroperitoneal and mesenteric lymphadenopathy, but no evidence of high-grade transformation. A focal area of increased avidity was noted at the gastro-oesophageal junction (figure 1) and an oesophagogastrroduodenoscopy was recommended to exclude a small carcinoma. This revealed ulceration within the oesophagus and stomach (figure 2). Biopsy of the lesions within the oesophagus showed squamous epithelium with ulceration and subepithelial inflammation (figure 3). Immunohistochemistry techniques using mouse monoclonal antibodies to CMV revealed inclusion bodies which were positively stained, thus confirming a diagnosis of CMV oesophagitis (figure 4). Quantitative CMV PCR was positive, with a viral load of 1.04×10^3 copies/ml when first detected, rising to a maximum of 1.15×10^4 copies/ml.

DIFFERENTIAL DIAGNOSIS

The main differential in this case was of lymphoma disease recurrence, or high-grade transformation, which was considered following an increase in spleen size demonstrated on CT. However, further investigations disproved this theory and highlighted the gastro-oesophageal junction as an area to focus on.

TREATMENT

The patient was started on intravenous ganciclovir, followed by oral valganciclovir for a total of 3 weeks.

OUTCOME AND FOLLOW-UP

Following a 3-week course of intravenous ganciclovir, followed by oral valganciclovir, the patient's clinical condition steadily improved. His fever resolved and he was able to first take home leave and was then discharged approximately 8 weeks after his initial presentation.

DISCUSSION

CMV is an opportunistic pathogen. It is a double-stranded DNA virus and a member of the Herpes viridae family.¹ At least 60% of the USA population are believed to have been exposed to CMV, with the majority of people infected with CMV remaining asymptomatic. Within immunocompetent symptomatic individuals it usually presents as a mononucleosis syndrome.

In immunocompromised patients CMV infection is most often associated with AIDS, solid-organ transplantation or

bone-marrow transplantation. It can present as fever of unknown origin, CMV retinitis, encephalitis and most commonly pneumonitis.² CMV infection has rarely been associated with Hodgkin's or non-Hodgkin's lymphoma and there have been few reported cases of CMV infection in the gastrointestinal tract.²⁻³ In some instances this has been believed to have caused small bowel perforation.³⁻⁵ Other cases have been described in patients receiving high-dose steroids, or other immunosuppressive medication, where CMV infection is believed to occur as a result of reactivation of latent virus in previously infected patients.⁶

In this case reactivation of CMV was believed to occur following treatment with an intensive fludarabine-based chemotherapy regime. Fludarabine is a purine analogue and a potent inhibitor of DNA repair.⁷ It has been demonstrated to be effective in the treatment of chronic lymphocytic leukaemia and low-grade non-Hodgkin's lymphoma.⁷ A major side effect of fludarabine is immunosuppression, particularly affecting T-lymphocytes and serious infections, including pneumocystis carinii and aspergillus pneumonia have been described.⁸⁻¹⁰

In the literature there are limited reports of CMV infection in patients who have been treated with fludarabine-based chemotherapy.⁶ A retrospective case series reviewed the epidemiology of CMV disease in patients treated for haematological malignancies with a range of chemotherapy agents. One patient developed CMV pneumonitis after treatment with FC-R.⁶ Another paper examined the impact of alemtuzab, an anti-CD52 monoclonal antibody, after initial treatment with fludarabine and found that 15% of patients developed CMV infections.¹¹ A surveillance programme for CMV and EBV infections in patients treated with fludarabine-cyclophosphamide combination did not detect any CMV infection in those patients treated with fludarabine and cyclophosphamide; however, during alemtuzab consolidation CMV was detected in the blood of nine patients (52%), of which four were symptomatic.¹²

This demonstrates that CMV infection following a fludarabine-based chemotherapy regime is not a common presentation, but that it becomes much more likely

Figure 2 Oesophagogastrroduodenoscopy demonstrating ulceration within the oesophagus.

Figure 3 Oesophagogastrroduodenoscopy biopsy: oesophageal squamous epithelium with ulceration and subepithelial inflammation.

Figure 4 High-power views of oesophagogastrroduodenoscopy biopsy showing inclusion body, with positive staining using immunohistochemistry with mouse monoclonal antibodies to cytomegalovirus.

when combined with alemtuzab. As more intensive chemotherapy regimens are increasingly used in the treatment of haematological disorders and for other malignancies, perhaps there will be an increase in the reactivation of latent viruses.

Learning points

- ▶ Clinicians should maintain a high index of suspicion of cytomegalovirus (CMV) infection, as well as other viruses, in postchemotherapy patients.
- ▶ Can also consider CMV infection as a differential in patients who have other conditions causing them to be immunocompromised.
- ▶ Treatment with strong antiviral medication is required to treat CMV infection.

Competing interests None.

Patient consent Obtained.

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