SHORT REPORT

Cytomegalovirus disease, haemophagocytic syndrome, immunosuppression in patients with IBD: ‘A cocktail best avoided, not stirred’

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Abstract

We report two cases of cytomegalovirus (CMV) viraemia resulting in severe pneumonitis and associated haemophagocytic syndrome manifesting in patients with inflammatory bowel disease, on stable doses of azathioprine in clinical remission. In both cases, azathioprine was withdrawn at time of hospital presentation and after delays in diagnosis; intravenous ganciclovir was then administered, with resultant rapid improvement of haematological and clinical parameters. Following recovery, immunomodulators were not recommenced given patient aversion and the theoretical risk of CMV reactivation, albeit the evidence for this approach is limited. CMV-related haemophagocytic syndrome and organ dysfunction, in the context of immunomodulator therapy in IBD are rare but life-threatening, and thus requires further investigation and discussion.

1. Introduction

Despite coverage in recent European consensus (ECCO) guidelines,1 the management of CMV infection in inflammatory bowel disease remains unclear, yet for the treating clinician the importance of increased awareness, early diagnosis and prompt intervention is demonstrated by these two recent cases below.

2. Patient 1

A 32-year-old mother of two was diagnosed with distal ulcerative colitis (UC, involving distal 30 cm of colon/rectum only) on colonoscopy in 2001 and received maintenance
therapy with azathioprine 100 mg daily and mesalazine enema thrice weekly with no significant disease flares for two years prior presentation. She was a non-smoker and had no other significant medical or family history.

She presented to hospital with a 7 day history of fevers, lethargy, myalgia and generalized headache. On admission she had a productive cough, right basal crepitations were noted and oxygen saturation was 86% on room air. Pneumonia was confirmed by chest x-ray showing bilateral consolidation with small bilateral pleural effusions. Azathioprine was ceased. Despite institution of appropriate intravenous antibiotic therapy for community-acquired and atypical pneumonia, she progressively deteriorated with respiratory distress and was transferred to the intensive care unit for 10 days post-admission.

Subsequently, the respiratory failure worsened necessitating intubation, mechanical ventilation and inotropic support. Given the likely immunosuppression, antimicrobial cover was augmented empirically to meropenem, ciprofloxacin, vancomycin, pentamidine (for Pneumocystis jiroveci), and voriconazole (for fungaemia) and alternative diagnoses were considered. Computerised tomography (CT) revealed bilateral mid-lower zone alveolar infiltrates, early consolidation and mild hepatosplenomegaly (Fig. 1). There was no evidence for toxic megacolon or proximal extension of distal colitis on abdominal imaging (colonoscopy was not performed during admission). Bronchoscopy however was performed in order to obtain bronchial washings.

Soon after, CMV IgM was positive and CMV was demonstrated by polymerase chain reaction (PCR) in both serum (quantitatively 294,000 copies/ml) and bronchial washings, establishing the diagnosis of CMV viraemia and pneumonitis. Intravenous ganciclovir (and subsequently also foscarnet given clinical severity) was commenced, along with hydrocortisone 400 mg/day. She remained persistently febrile, and developed a worsening pancytopenia (nadir on day 17), evidence for disseminated intravascular coagulopathy (DIC) and deranged liver function tests. Bone marrow aspirate/biopsy revealed a mildly hypercellular marrow with prominent haemophagocytosis (Fig. 2). Hence, CMV-associated haemophagocytic syndrome in context of azathioprine therapy for ulcerative colitis was established.

After 2 weeks of antiviral therapy, she became afebrile, with rapid resolution of her respiratory dysfunction and cytopenias, leading to discharge from intensive care after nearly 4 weeks with complete recovery thereafter. Five years later, she remains well (with normal cell counts) on combination of oral/rectal mesalazine maintenance therapy for distal colitis. Her treating clinicians have not restarted an immunomodulator due to fears of precipitating another reactivation of CMV viraemia and patient aversion.

3. Patient 2

A 22 year old mechanic, married with one child, had penetrating Crohn’s disease, resulting in a spontaneous sigmoid perforation and requiring local resection and colostomy 2 years after diagnosis. Post-operatively, he was placed on maintenance therapy with azathioprine 150 mg daily. He was a non-smoker with no other medical history.

Twelve months later, he presented to his local doctor with 2 weeks of fatigue, malaise, fevers and sore throat. He failed to respond to two courses of penicillin-based antibiotics and was admitted to hospital. He was noted to be febrile (39.0 °C) with tachycardia, bi-basal crepitations and bronchial breath sounds over the left lung base on auscultation. Despite intravenous antibiotics for atypical pneumonia, his fevers, dyspnoea and other symptoms persisted along with a rapidly progressive pancytopenia. Azathioprine was then ceased and antimicrobial cover was augmented to include tazobactam, azithromycin, co-trimoxazole and oseltamivir (Tamiflu®). CMV serology showed positive IgM but negative IgG antibodies. High resolution CT scan of the chest showed bilateral, patchy alveolar opacification, and CMV PCR of serum and bronchial washings were positive. A bone marrow aspirate/biopsy showed evidence for haemophagocytic syndrome (Fig. 2). Furthermore, liver function tests deteriorated and early disseminated intravascular coagulopathy (DIC) became apparent. Hence a diagnosis of CMV-associated haemophagocytic syndrome with pneumonitis and hepatitis was made. Intravenous ganciclovir was then commenced, with decrudescence of fevers within 72 h and complete symptomatic and biochemical resolution 5 days later.

Currently, at 16 month follow-up, he remains well and his Crohn’s colitis has remained in clinical remission on anti-MAP (Mycobacterium avium spp. paratuberculosis) therapy which was offered as a non-immunomodulator, non-trial based.
Bone marrow-derived cells. As opposed to the hereditary appropriate activation of macrophages which phagocytose haemophagocytic lymphohistiocytosis) characterized by in-haemophagocytic syndrome (HPS, or more precisely, these significant, albeit rare, complications.

IBD warrants an improved awareness and understanding of the setting of viraemia, septicaemia or malignancy, often as a form of HPS, reactive HPS (as in these cases) usually occurs in approximately 30%, early diagnosis is essential. The disorder, with a mortality reported in one IBD series of a milder prodromal phase before escalating to a fulminant potentially reversible and its evolution typically begins with observation.

First, it is known that T-lymphocyte-mediated transplantation, knowledge of IBD pathogenesis and clinical from assimilating the extensive literature on solid organ tor therapy, CMV infection and HPS is perhaps best derived on immunosuppression, CMV infection appears to predominate on immunosuppressive therapies for IBD.12

As opposed to the hereditary form of HPS, reactive HPS (as in these cases) usually occurs in the setting of viraemia, sepsis or malignancy, often as a ‘haematologic cofactor’ of MODS. Given reactive HPS is potentially reversible and its evolution typically begins with a milder prodromal phase before escalating to a fulminant disorder, with a mortality reported in one IBD series of approximately 30%, early diagnosis is essential. The cardinal features in early HPS of unexplained fevers, cytopenia(s) and a serum ferritin ≥ 1000 ng/ml necessitate a high degree of clinical suspicion and prompt blood film and bone marrow examination in at-risk patients, including those on immunosuppressive therapies for IBD.

Moreover, a provisional diagnosis of HPS should also prompt a search for the underlying precipitant. Notably in IBD patients on immunosuppression, CMV infection appears to predominate in this context. The pathophysiological basis for the apparent synergistic relationship among IBD, immunomodulator therapy, CMV infection and HPS is perhaps best derived from assimilating the extensive literature on solid organ transplantation, knowledge of IBD pathogenesis and clinical observation.

First, it is known that T-lymphocyte-mediated immune responses drive both IBD-related gut inflammation and control of CMV replication and reactivation. Secondly, the massive cytokine release from activated T-cells (plus their defective cell cycling regulation and decreased apoptosis in IBD perpetuates gut inflammation and also enhances recruitment of CMV-infected cells to the inflamed intestine. Hence in active IBD, the widely reported occurrence of intestinal CMV reactivation (predominantly as a ‘bystander’) is unsurprising. Thirdly, the inappropriate macrophage activation of HPS seems to require two or more precipitants, including infection, an underlying proinflammatory, defective cellular immunity disease (such as IBD), genetic mutation(s) in cell cytotoxicity pathways (including NK cells, cytotoxic T cells as seen in hereditary HPS and/or immunosuppression.

Furthermore, in transplant medicine, the risk of CMV reactivation appears commensurate with the degree of immunosuppression. However, not all immunosuppressants are created equal with regard to CMV. For instance, corticosteroids alone may not convey significant CMV risk but thiopurines in isolation apparently do, and corticosteroids combined with thiopurines or cyclosporine appear to act synergistically. In contrast, a comparatively low risk of CMV reactivation is reported with the mammalian target of rapamycin (mTOR) inhibitors such as sirolimus, and also possibly with anti-TNFα monotherapy (e.g. infliximab), as both mTOR and TNFα appear crucial to CMV replication within host cells.

Hence as illustrated by the cases presented, we recommend testing for plasma CMV PCR in IBD patients on immunomodulator therapy (especially thiopurines) who are present with 1) fever (otherwise unexplained) and nonspecific viral-type symptoms, particularly where concurrent hyperferritinaemia and/or cytopenia(s) consistent with HPS occurs. If CMV viraemia is confirmed, we advocate cessation of immunomodulators (at least temporarily) depending on clinical need. Ganciclovir (intravenous) or valganciclovir (oral) therapy may then be instituted, but only after balancing the mortality risk of CMV disease as in these two cases, against expensive over-use of antiviral therapy and its potential side effects, including myelosuppression, nephrotoxicity and male infertility.

Theoretically once clinical resolution and CMV PCR negativity are both achieved, immunosuppression may be resumed, though the risk of CMV reactivation is high. Alternative ‘lower-risk’ immunomodulators may be considered, such as mTOR or TNFα inhibitors if available. As the current cases highlight however, patient preferences are also paramount and non-immunomodulating agents such as aminosalicylates, antibiotics or experimental therapies may be chosen, albeit with potentially suboptimal IBD control.
In summary, these cases of CMV in IBD demonstrate that ‘prevention is better than cure’; early diagnosis of both CMV viraemia, and/or the potential concurrence of HPS, with earlier introduction of antiviral therapy where appropriate, are critical in minimizing patient morbidity but also to avoid the dilemma of whether, when and how (or not) to reintroduce immunomodulator therapy post-CMV reactivation. Otherwise, the clinician may be left precarious vacillating between the risks of CMV reactivation and IBD deterioration in what remains an evidence-free zone.

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