Seronegative visceral Varicella Zoster infection – a not so benign skin infection

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ABSTRACT

Varicella zoster virus (VZV) infection is usually a self-limiting cutaneous childhood disease typically occurring due to impaired cell-mediated immunity. One manifestation of VZV is a visceral infection accounting for less than 15% of all VZV infections. We describe a severe case of visceral varicella infection several months following an autologous stem cell transplant for a high-grade B-cell lymphoma. The patient initially presented with abdominal pain accompanied by severe hepatitis which preceded the cutaneous manifestation. Initial serological testing was negative due to significant hypogammaglobulinemia following previous chemotherapy. However, the diagnosis was confirmed on VZV DNA PCR analysis of the vesicles. The patient developed further visceral complications including encephalopathy, gastritis, hiccups, colonic pseudo-obstruction, normocytic anaemia and thrombocytopenia. The infection responded well to intravenous acyclovir and intravenous immunoglobulin therapy. This is the first reported case report of seronegative VZV infection with an extensive visceral involvement likely caused by the underlying immunoglobulin deficiencies.

Keywords: Varicella Zoster, Stem cell transplant, Hypogammaglobulinemia, Haematology
Introduction
Primary varicella zoster infection is a common self-limiting childhood disease. It has a high prevalence with approximately 90% of the population aged over 20 years being serologically positive. Visceral VZV infection is uncommon and rarely manifests in immunocompetent states. It more commonly affects immunocompromised individuals and is associated with high rates of long-term complications and death. To date, there have been no reported case of serologically negative visceral VZV infection. We report the first of such case with multiple disseminated disease sites. This seronegative phenotype may be a significant cause for the extensive visceral involvement.

Case
A 64-year-old male presented in February 2017 with a two-day history of abdominal pain. The patient was in complete metabolic remission from a high-grade B-cell lymphoma which was previously treated with chemotherapy and autologous stem-cell transplant (SCT).

Day 3 of his admission, his pain improved but he developed a new predominantly cholestatic liver function (LFT) derangement. Biliary obstruction was excluded on magnetic resonance cholangiopancreatography. Day 6 of his admission, he developed fevers, encephalopathy with a generalised maculopapular rash suspicious for VZV infection and was commenced on intravenous acyclovir. Both his IgM and IgG VZV antibody levels were negative. However, he was noted to have severe hypogammaglobinemia with IgG 1.4g/L. His IgM and IgG levels were similarly reduced compared to his initial post chemotherapy levels. Consequently, he was prescribed a single dose of 0.5g/kg of intravenous immunoglobulin during week 2 of his admission. His VZV infection was confirmed through PCR analysis of a skin biopsy.

During this time, he also developed persistent hiccups with worsening abdominal pain and distension. An abdominal X-ray and CT revealed colonic pseudo-obstruction (Fig 1). He required intravenous neostigmine for bowel decompression after poorly tolerating a rectal tube. Prochlorperazine had minimal success in controlling his hiccups; which eventually self-resolved.

Figure 1 – Abdominal X-Ray consistent with pseudo-obstruction
During this second week of his admission, he also developed a worsening normocytic anaemia and thrombocytopenia. His haemoglobin and platelet count nadired at 69g/L and 36x10^6/L, respectively. He received two units of packed cell transfusion. A gastroscopy performed on day 10 demonstrated three small gastric erosions with no stigmata of recent bleeding. He was discharged two weeks later after resolution of his fevers and improvement in his full blood count and LFT.

Discussion

Visceral VZV infection is uncommon, accounting for 15% of all VZV presentations. However it is the most common viral infection after autologous SCT with an incidence of 14-28% in the first year. Known visceral manifestations as evident in this case include abdominal pain, hiccups, hepatitis which can precede vesicular rash eruption, colonic pseudo-obstruction, normocytic anaemia, thrombocytopenia, and gastric ulceration.

VZV infection typically occurs due to impaired cell mediated immunity rather than defects within the humoral immunity. Allogeneic SCTs have been postulated to be associated with more cell-mediated immune dysfunction compared with autologous SCTs. This is because of the higher rates of VZV infection seen in patients post allogeneic SCT. Other immunocompromised states with associated increased risk of visceral VZV infection include solid organ transplant recipients, patients on long-term immunosuppression therapy and individuals with immunodeficiency disorders either congenital or acquired.

Whilst cellular immunity leads to viral reactivation, humoral mediated circulating antibodies appear to prevent dissemination of the VZV infection. Hypogammaglobulinemia has been reported in cases of varicella induced hepatitis and has been implicated as a potential dominant cause for visceral involvement. Hypogammaglobulinemia with reduced IgA, IgM, and IgG immunoglobulin levels have previously been reported after rituximab administration in patients with haematological malignancies. The overall low levels of immunoglobulin demonstrated in this patient would account for the observed negative VZV serological testing and potentially for the severity of the disease.

Given the severity of the disease, it is unsurprising that the mortality rate associated with visceral VZV infection has been reported to be as high as 50%. The cause of death is typically from respiratory failure due to pneumonitis, but can also occur due to hepatitis, and encephalitis. Despite the extensive visceral manifestations, our patient recovered from his infection.

Conclusion

Visceral VZV infection has a potential for multisystem involvement with high morbidity and mortality amongst immunocompromised individuals. It is unsurprising that this infection is often misdiagnosed in the early stages. This reported experience highlights the importance of maintaining a high index of clinical suspicion for atypical presentation of VZV infection particularly in the setting of immunosuppression.

Conflict of Interest

No Conflict of Interest.

Funding Statement

No external funding was provided.

Ethical Approval

No ethical approval from the local hospital board was required for publication of this case report.

Consent

The patient provided written consent for this article to be submitted for publication.

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