CASE REPORT

Severe perianal shingles during azathioprine and budesonide treatment for Crohn's disease—preventable with zoster vaccine?

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SUMMARY

Patients with inflammatory bowel disease (IBD), particularly those on immunosuppressive medications, suffer a high incidence of, and worse clinical outcomes relating to, herpes zoster (HZ) reactivation. We report on the presentation and management of a patient with Crohn's disease who developed severe perianal HZ after starting azathioprine and oral budesonide treatment. The zoster vaccine may prevent such zoster reactivation in patients with IBD. The zoster vaccine is effective in decreasing the risk of HZ in older adults but its role in younger adults and those with IBD has not been tested prospectively. A review of the potential risks and benefits of this live vaccine in patients with IBD and an approach to further determining its role in this patient population is discussed.

BACKGROUND

Herpes zoster (HZ) infection is an increasing problem in immunosuppressed patients with inflammatory bowel disease (IBD) and can have a severe clinical course. We report on an unusual case of severe perianal HZ after azathioprine and budesonide therapy in a patient with Crohn's disease and discuss the potential benefits and risks of the zoster vaccine to prevent HZ in patients with IBD.

CASE PRESENTATION

A 40-year-old man presented with worsening right iliac fossa pain and six loose bowel motions per day for 3 months on a background of a 4-year history of similar but less severe intermittent symptoms. Colonoscopy demonstrated moderate terminal ileitis with numerous ileal ulcers but normal colonic mucosa. MRI enterography demonstrated a 25 cm length of thickened terminal ileum with associated mucosal enhancement on the dynamic post gadolinium imaging consistent with active inflammation (figure 1). Ileal histology confirmed active ileitis. There were no risk factors for tuberculosis (TB) and a QuantiFERON-TB Gold test was negative indicating no evidence of latent TB. A diagnosis of likely moderately active ileal Crohn's disease was made and the patient was initiated on oral budesonide 9 mg daily. The patient did not clinically respond to budesonide over the next 8 weeks. Further therapeutic options were then discussed with the patient, including switching to oral prednisolone to induce clinical remission, surgical resection of the inflamed ileal segment and

azathioprine therapy, which was recommended to improve the likelihood of long-term maintenance of clinical remission. The patient preferred to continue with budesonide while initiating azathioprine, rather than switch to oral prednisolone, with a plan to change budesonide to prednisolone in 2 weeks if his symptoms had not improved. An opportunistic infections screen was undertaken as per European Crohn's and Colitis Organisation (ECCO) guidelines, prior to initiation of azathioprine therapy.¹ Despite a positive clinical history of childhood chickenpox, his varicella zoster virus (VZV) IgG antibody was negative. Given his clinically active Crohn's disease, a decision was made to start azathioprine, initially at 100 mg daily (normal thiopurine methyltransferase level), rather than consider two doses of standard varicella vaccination to prevent the possibility of primary varicella, which would delay azathioprine initiation by at least 7 weeks. Two weeks after starting azathioprine, the patient developed severe lethargy, a maculopapular rash over his arms and an extremely painful ulcerating vesicular rash on the left internal buttock/perianal region (figure 2) in the S4 dermatome. Initially, there was some concern that this may have been a manifestation of perianal Crohn's disease but viral PCR from the perianal vesicular rash was positive for VZV and repeat VZV IgG serology was now positive. A diagnosis of left S4 dermatome HZ

Figure 1 MRI enterography demonstrating a 25 cm length of thickened terminal ileum with associated mucosal enhancement on the dynamic postgadolinium imaging consistent with active inflammation (arrow).

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Figure 2 Healing vesicular rash in left S4 dermatome secondary to herpes zoster.

infection with systemic manifestations was made. The microbiologist's advice was sought and a course of oral famciclovir 500 mg 8 hourly for 10 days was given and azathioprine ceased. The patient remained unwell for some weeks with severe lethargy, perianal pain and weight loss of 10 kg, and was unable to work for 6 weeks. The rash healed with some scarring by 2 months and there was no postherpetic neuralgia at follow-up. Six months later, he suffered worsening right iliac fossa pain, diarrhoea and a raised serum C reactive protein (72 mg/L) secondary to his ileal Crohn's disease which was refractory to further budesonide therapy. Further management options including surgery, oral prednisolone and alternative immunosuppression were considered, with the knowledge that further immunosuppression might lead to further reactivation of HZ. Ultimately, the patient opted for treatment with adalimumab with standard induction therapy followed by 40 mg fortnightly to which he had an excellent clinical response and no further HZ reactivation at 1 year follow-up.

DISCUSSION

HZ affects ~30% of the population in their lifetime.² Patients with IBD, particularly those on immunosuppressive medications are at risk of life-threatening primary varicella infection and have a higher prevalence of, and more severe outcomes relating to, HZ.³⁻⁴ In a recent review of 32 published cases of patients with IBD who suffered zoster reactivation, 25 were on a thiopurine (azathioprine or 6-mercaptopurine) and five of these developed central nervous system involvement.³ The varicella vaccine can prevent primary varicella infection but its role in the prevention of HZ is less clear.⁵⁻⁸ HZ can be prevented using the zoster vaccine in older adults but its role in younger adults, patients with IBD or immunosuppression has not been prospectively examined.²⁻⁵ The varicella and zoster vaccines are live vaccines which raises concern about their use in the setting of immunosuppression. Although ECCO guidelines exist for the role of varicella vaccination to prevent primary varicella, ECCO makes no clear recommendations regarding the use of zoster vaccine to prevent secondary zoster infection.¹ Our patient had a history of chickenpox but his initial VZV serology was negative, consistent with data from two previous studies which found a significant minority (10% and 7%, respectively) of patients with IBD who reported a history of chickenpox had negative VZV serology.⁹⁻¹⁰ The appropriateness of vaccination with the varicella or indeed the zoster vaccine in this patient group remains unclear. Unfortunately our patient developed a severe reactivation of HZ on immunomodulation with

azathioprine. Could this have been prevented with zoster vaccination?

In a large randomised placebo-controlled trial of adults over the age of 60, the zoster vaccine was associated with a 51% decrease in the incidence of HZ and a decrease in the incidence and severity of postherpetic neuralgia.⁵ A subsequent retrospective study demonstrated that patients with IBD over the age of 60 exposed to antitumour necrosis factor (TNF) therapy within 42 days of vaccination also had a lower risk of HZ at 2 years (HR 0.61) without evidence of active varicella after the live zoster vaccine despite being immunosuppressed.¹¹ The minimum potency of the zoster vaccine is at least 14 times that of the varicella vaccine.² Preliminary studies found that this greater potency was necessary to elicit an adequate T cell response to VZV for the prevention of HZ.⁵ The zoster vaccine is given as a single dose, with a recommended 4-week wait after dosing prior to the initiation of immunomodulation.⁵ Interestingly, current Centers for Disease Control and Prevention guidelines recommend that the zoster vaccine is safe for use with standard IBD doses of azathioprine, 6-mercaptopurine and methotrexate but that its safety during anti-TNF and other immunomodulatory use is unknown.² However, safety and efficacy concerns in the IBD population remain and whether the zoster vaccine can be given to patients previously immunised with the varicella vaccine remains uncertain.²

In order to further advance our understanding of this issue and perhaps influence ECCO guidelines, a prospective randomised trial investigating the role of the zoster vaccine in patients with IBD prior to immunomodulation could be considered. A sample size calculation for such a study can be performed based on the annual incidence of HZ in patients with IBD reported as 734/1000⁴ and a possible decrease of HZ incidence of 51% based on the study in adults >60 years.⁵ Using these data, 2472 newly diagnosed patients with IBD who would subsequently require immunomodulation, would need to be enrolled (1236 receiving the vaccine and 1236 receiving a placebo prior to immunomodulation) in order to detect a potential decrease of HZ incidence over 5 years follow-up by 51% from 3.7% to 1.84% with a power of 80% and an α value of 0.05. Clearly, conducting a study of this magnitude would require a large, multicentre collaborative approach but may lead to better

Learning points

- ▶ Herpes zoster infections in patients with inflammatory bowel disease (IBD) exposed to immunosuppressive medications can be life-threatening and may warrant the cessation of immunosuppressive medications and initiation of antiviral therapy.
- ▶ Reactivation of herpes zoster may occur in any unilateral dermatomal distribution including but rarely the perianal region.
- ▶ Varicella serology is not always a reliable indicator of previous varicella zoster virus exposure particularly in patients with IBD.
- ▶ The zoster vaccine, which decreases the risk of zoster infection and postherpetic neuralgia in adults over 60 years, may be beneficial for patients with IBD but a large prospective study is required to determine its safety and efficacy in this setting.

outcomes for patients with IBD who are increasingly being exposed to the risks of immunosuppression.

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