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CASE REPORT

Varicella zoster meningitis complicating combined anti-tumor necrosis factor and corticosteroid therapy in Crohn's disease

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Abstract

Opportunistic viral infections are a well-recognized complication of anti-tumor necrosis factor (TNF) therapy for inflammatory bowel disease (IBD). Cases of severe or atypical varicella zoster virus infection, both primary and latent reactivation, have been described in association with immunosuppression of Crohn's disease (CD) patients. However, central nervous system varicella zoster virus infections have been rarely described, and there are no previous reports of varicella zoster virus meningitis associated with anti-TNF therapy among the CD population. Here, we present the case of a 40-year-old male with severe ileocecal-CD who developed a reactivation of dermatomal herpes zoster after treatment with prednisone and adalimumab. The reactivation presented as debilitating varicella zoster virus meningitis, which was not completely resolved despite aggressive antiviral therapy with prolonged intravenous acyclovir and subsequent oral valacyclovir. This is the first reported case of opportunistic central nervous system varicella zoster infection complicating anti-TNF therapy in the CD population. This paper also reviews the literature on varicella zoster virus infections of immunosuppressed IBD patients and the importance of vaccination prior to initiation of anti-TNF therapy.

Key words: Varicella zoster virus; Meningitis; Crohn's disease; Adalimumab; Infliximab; corticosteroids; Anti-tumor necrosis factor

Core tip: Opportunistic viral infections can complicate anti-tumor necrosis factor (TNF) therapy for inflammatory bowel disease (IBD). Central nervous system varicella zoster virus (VZV) infections associated with the use of anti-TNF therapy have not been previously described in Crohn's disease patients. We present the first reported case of VZV meningitis in a 40-year-old male with Crohn's disease who developed reactivation dermatomal herpes zoster and VZV meningitis after treatment with adalimumab and prednisone. Despite aggressive antiviral therapy, he had significant morbidity, highlighting the risk of opportunistic viral infections in this population and the importance of vaccination before anti-TNF therapy.

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INTRODUCTION

Biologic therapies which target tumor necrosis factor-α (TNF-α), including infliximab, adalimumab, and certolizumab pegol, are increasingly common in the management of inflammatory bowel disease (IBD); however, their use is associated with opportunistic infections[1,2]. For Crohn's disease (CD) patients, infection risk is further

increased by combination treatment with immunosuppressants such as corticosteroids, methotrexate, azathioprine, or 6-mercaptopurine (6-MP)[3,4].

As with the other herpes viruses, varicella zoster virus (VZV) infection risk is high for IBD patients[5,6]. VZV, an alpha-herpes virus, causes a primary infection (varicella/chickenpox), but the virus can also be reactivated from a latent state in which it sequesters in the dorsal root ganglia (herpes zoster/shingles)[7]. Evidence from the rheumatologic literature suggests an association between VZV and TNF inhibitors. Indeed, a large prospective cohort of 3266 rheumatoid arthritis patients on anti-TNF therapy found an adjusted hazard ratio for VZV of 1.82 (95%CI: 1.05-3.15), and these VZV cases were often severe enough to necessitate hospitalization[8].

While cutaneous VZV is common, neurological VZV is rare; presentations include cerebellar ataxia, myelitis, radiculitis, Ramsay-Hunt syndrome, and meningitis or encephalitis[9]. VZV meningitis in association with anti-TNF therapy for Crohn's disease has not previously been reported. Here, we present the case of a 40-year-old male with CD who developed debilitating VZV meningitis while being treated with adalimumab and prednisone. The literature on VZV among anti-TNF immunosuppressed CD patients and on pre-treatment vaccination is reviewed in the Discussion which follows.

CASE REPORT

A 40-year-old male presented to hospital with a four day history of increasing headaches. He had been diagnosed with medically refractory ileocecal CD in 2006. Initial treatment with azathioprine had to be discontinued because of acute pancreatitis. In 2007, he underwent an ileal resection and hemicolectomy; however, the disease recurred at the anastomosis by 2008. Despite treatment with post-operative mesalamine, disease activity persisted, and he began taking oral prednisone at 20 mg/d in September 2008. The disease became steroid-refractory, and infliximab 400 mg IV q8 weekly was started in 2009. With initiation of infliximab, the patient was able to wean off prednisone for a period of 8 mo. However, after one year, an allergic reaction to infliximab prompted a switch to adalimumab 40 mg SC q2 weekly at 25 mo prior to presentation. About 6 mo after the initiation of adalimumab, the patient experienced a disease flare and was restarted on prednisone. He experienced difficulties with weaning from the prednisone and was taking 15 mg *po* daily on presentation.

Four days prior to presentation, the patient developed insidious onset but constant bifrontal, progressively worsening headaches with photophobia. While the patient was experiencing unmeasured fever and generalized malaise, there was no history of neck pain, focal neurological deficits, seizures, or confusion. He had no recent infectious contacts or travel history. Though he had a history of childhood chickenpox, he had experienced no recent reactivation and he had not received a herpes zoster vaccination.

Two days prior to presentation, the patient developed increasing left upper quadrant abdominal pain, radiating to his back. The initial examination revealed voluntary guarding but no rash. Shortly after admission, the patient developed a vesicular maculopapular rash in the left T7 dermatome corresponding to the area of pain.

A detailed neurological examination demonstrated no focal motor or sensory deficits. Cranial nerve testing results were normal. Fundoscopy did not reveal papilledema. There was no nuchal rigidity; both Brudzinski's and Kernig's signs were negative, but jolt accentuation was positive.

Diagnostic investigations revealed an elevated white blood cell count of 14×10^9/L. Computer tomography of the head was unremarkable. Lumbar puncture was performed: the cerebrospinal fluid (CSF) revealed an elevated protein level [0.76 g/L, (normal range 0.15-0.45 g/L)], normal glucose [3.1 mmol/L, (normal range 2.2-4.4 mmol/L)], and a marked lymphocytic pleocytosis (391×10^6 WBCs with 98% lymphocytes). CSF polymerase chain reaction was subsequently positive for VZV. After consultation with the Infectious Disease specialist, we prescribed treatment for VZV meningitis: one month of intravenous acyclovir (10 mg/kg q8 h). Adalimumab was discontinued but, given the patient's severe CD, prednisone, 20 mg/d, was started. The patient has been unable to taper off this dose of prednisone.

Unfortunately, the patient's post-discharge course has been difficult. He continued to experience debilitating residual symptoms of post-meningitis syndrome, including intermittent headaches and cognitive slowing, and was unable to return to work 3 mo post-discharge. Given his ongoing symptoms and continuing immunosuppression, he was treated with an additional course of suppressive valacyclovir 1000 mg *po* daily for 3 mo.

DISCUSSION

Although VZV reactivation in response to anti-TNF therapy has been described in the literature, central nervous system involvement is rare. This is the first reported case of VZV meningitis in a CD patient taking adalimumab, and it highlights the risk of atypical and severe VZV infection among immunosuppressed patients. As the long-term sequelae of central nervous system VZV can be debilitating, even with early detection and antiviral therapy, preventative strategies including vaccination are very important for this population.

VZV infection risk for IBD patients is high; a review of six global trials of adalimumab (CHARM, CARE, CLASSIC, GAIN, CHOICE, M04-729) involving 3160 CD patients found 46 cases of VZV, six of which required hospitalization[10]. Furthermore, severe disseminated and fatal VZV infections have been experienced by IBD patients on immunosuppression with steroids, thiopurines and anti-TNF therapy[11-14]. In one case, VZV caused fatal hepatic failure and disseminated intravascular

coagulation shortly after infliximab initiation[15]. As in the currently reported case, the VZV infection risk attributable to anti-TNF agents is confounded by combination immunosuppression with prednisone and adalimumab. Evidence from the prospective TREAT registry suggests corticosteroids are an especially strong independent risk factor for serious infection (OR = 2.21, 95%CI: 1.46-3.34)[3] and VZV reactivation among IBD patients taking corticosteroids is well-described. Marehbian *et al*[16] retrospectively evaluated 22310 CD patients and reported a zoster hazard ratio of 3.11 (95%CI: 1.57-6.17) if patients were on corticosteroids. The risk was even higher among patients on combination immunosuppression therapy. Similar findings have been corroborated by other authors[17]. For instance, Cullen *et al*[18] recently reviewed nine cases of primary VZV related to anti-TNF therapy for CD patients. As in the current case, all were taking concomitant immunosuppressive or corticosteroid therapy. Cases of severe disseminated VZV have been reported among IBD patients on steroid therapy alone[11,12], while central nervous system VZV has been primarily described for immunosuppressive conditions such as HIV/AIDS or malignancies. Nonetheless, steroid therapy is recognized as a risk factor[7,19], with several case reports describing varicella encephalitis or meningitis associated with corticosteroids in other patient populations[20-22]. In our case report, the clinical picture is complex; likely both adalimumab and prednisone contributed to this patient's increased susceptibility to VZV meningitis.

In the CD population, only two previous cases of central nervous system VZV infection have been reported. Cullen *et al*[18] described a case of meningoradiculitis in a 49-year-old male taking 6-MP; despite three weeks of acyclovir and discontinuation of 6-MP, his neurological deficits persisted. Salmon-Ceron *et al*[23] also identified one case of radiculitis in a CD patient on adalimumab in the large French RATIO registry documenting > 50000 patient-years of anti-TNF exposure; additional details were not provided. No cases of VZV meningitis or encephalitis in CD patients on anti-TNF therapy have been reported until now, but at least two cases have been identified in the rheumatology literature. One case is of a 38-year-old female with psoriatic arthritis treated with one year of adalimumab who developed VZV encephalitis that resolved with acyclovir[24]. The other case of was of a patient on methotrexate and adalimumab; treatment details were not reported[25].

Currently, there is no evidence on which to base a decision as to whether anti-TNF therapy should be restarted after VZV infection. Some authors have suggested that, in cases of mild, confined zoster, biologics can be restarted after complete lesion resolution[8,26]. However, discontinuation has been advocated in cases of severe or disseminated VZV[27]. Discontinuation, however, poses a therapeutic dilemma for IBD patients when step-up management strategies have been employed and biologic agents initiated only after failure of other immunosuppressants. In these cases, few options exist for non-steroid maintenance therapy. In our case, adalimumab was discontinued but prednisone could not be further tapered off despite the possibility of its contributing to his VZV infection. In contrast, some experts have advocated for the use of steroid therapy as an anti-inflammatory in the management of central nervous system VZV infections[19]. Future management strategies in this setting may include consideration for granulocyte-macrophage colony-stimulating factor (sargramostim), but this is not yet an approved indication in our jurisdiction and would be accessible only through investigational trial.

Given both the likelihood of VZV infection and the seriousness of its potential sequelae, it seems obvious that CD patients should be vaccinated prior to initiation of steroid, immunosuppressive, or anti-TNF therapy. The varicella vaccine (VARIVAX®, PROQUAD®, Merck and Co., Inc)[28] and the herpes zoster vaccine (ZOSTAVAX®, Merck and Co., Inc)[29] are effective in reducing the incidence of VZV. Strong evidence from the Shingles Prevention Study Group, which evaluated > 38000 patients, demonstrated reduced herpes zoster incidence for vaccination (VZV dropped from 11.1 in the placebo group to 5.4 cases per 1000 person-years in vaccine treated patients)[30], and the vaccine was safe and generally well-tolerated[31]. However, this particular study excluded immunocompromised patients due to the risk of iatrogenic infection from the live, attenuated virus in the vaccine. For IBD patients without a history of chickenpox, shingles, or previous vaccination, the 2009 European Crohn's and Colitis Organization guidelines, which are based on expert consensus opinion, recommend routine immunization with VZV vaccine at least three weeks prior to the onset of immunomodulation[32]. Nonetheless, routine immunization is not universal in clinical practice. Survey-based evidence suggests that < 50% of susceptible patients actually receive immunization[33]. At a minimum, the physician should discuss VZV prevention, including immunization, with the patient, and serology should be performed to confirm immunity if there is no documented history of past varicella infection[32].

Even among IBD patients who have been previously vaccinated, evidence that post-vaccination immunity wanes over time argues for providing a second "catch-up" dose to adult patients. A retrospective review of 1080 breakthrough varicella cases found the annual rate increased from 1.6 (95%CI: 1.2-2.0) cases per 1000 person-years within 1 year of vaccination to 58.2 (95%CI: 36.0-94.0) cases per 1000 person-years 9 years post-vaccination[34]. Evidence in the pediatric literature also suggests that a two-dose vaccination regimen significantly decreases the risk of varicella infection[35]. Thus, immunosuppressed IBD patients, who are at higher risk for VZV infection, would benefit from a second vaccination in adulthood.

Vaccination timing presents another challenge in the case of IBD. Patients on other immunosuppressants or those started on rescue anti-TNF may not previously have had immunity evaluations, and the vaccine is con-

traindicated for patients already on immunosuppression therapy. This difficulty emphasizes the need for assessment of immunity at the time of CD diagnosis. In other patient populations, temporary 2-4 wk immunosuppression withdrawal to allow safe vaccination has been advocated[36]. However, such a temporary withdrawal of treatment is not usually feasible in the case of patients at risk of CD relapse. For susceptible CD patients already on anti-TNF agents, there may not be an ideal strategy for VZV prevention.

In conclusion, this paper presents the first reported case of VZV meningitis occurring opportunistically in association with adalimumab and corticosteroid therapy for CD. This case highlights this population's risk of severe, atypical opportunistic infections, the need for early recognition of VZV and aggressive management with antiviral therapy, and the potential confounders of this clinical picture, especially concomitant immunosuppression.

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