abstract

We report on an 18-year-old man with common variable immunodeficiency presenting with abdominal pain and vomiting due to gastric ulcers caused by reactivation of varicella-zoster virus (VZV). Endoscopy revealed multiple ulcers in the gastric antrum. Fever and rash developed the next day. Skin biopsy showed multinucleated cells with intranuclear inclusions highly suggestive of VZV infection, and high-dose intravenous acyclovir was started. VZV was detected on direct immunofluorescence from skin biopsy and polymerase chain reaction from endoscopic biopsy. His course was complicated by encephalopathy, pancreatitis, hepatitis, renal impairment, and hyponatremia. After 3 weeks of antiviral therapy, he gradually improved. Skin lesions cleared within a week. He remained well on follow-up 1 year later. Disseminated zoster presenting as gastric ulcers in the absence of the classic rash is unusual but has been reported in immunosuppressed patients with a history of bone marrow and stem cell transplant. We report this rare presentation in a patient with common variable immunodeficiency and highlight the importance of considering zoster as a cause for severe abdominal pain and of seeking endoscopic diagnosis to facilitate early therapy and reduced mortality risk.
Varicella-zoster virus (VZV) infection is a challenging diagnosis to establish in the absence of skin manifestations. VZV remains a source of serious morbidity and mortality in immunosuppressed patients and carries up to a 50% mortality risk in this group. Patients at greatest risk are stem cell transplant recipients, with varicella reactivation observed in 30% to 60%. Additionally, the greatest risk are stem cell transplant patients with history of congenital varicella infection, solid organ transplant, comorbid skin or lung disease, and congenital or acquired T-cell immunodeficiency (including lymphoid and myeloid malignancy and those receiving immunosuppression or high-dose systemic corticosteroids) are also at risk for severe infection. The majority of reactivation presents as localized zoster; however, a significant minority presents with disseminated disease. Clinically important zoster syndromes presenting without a classic skin rash include trigeminal zoster with keratitis, Ramsay-Hunt syndrome, encephalitis, and visceral (intra-abdominal) zoster. Intraabdominal reactivation of zoster with few or no skin lesions is associated with delayed diagnosis and subsequently high mortality. Abdominal pain is often the presenting feature and can appear up to 3 weeks before the characteristic rash. The next day, he developed fever, lethargy, and a diffuse macular pruritic rash, sparsely distributed on trunk and upper extremities, that did not correspond to dermatomal distributions. Small vesicles later appeared within the erythematous lesions. Skin biopsy showed multinucleated cells with intranuclear inclusions highly suggestive of VZV infection, and high-dose intravenous acyclovir was started. Disseminated zoster was confirmed by direct immunofluorescence staining for VZV from the skin specimen as well as polymerase chain reaction detection of VZV from the gastric mucosa. Herpetic inclusion bodies were found in the gastric mucosa (Fig 1B).

**CASE REPORT**

An 18-year-old man with CVID and Evans syndrome (autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura) presented with cramping upper abdominal pain and nonbilious emesis lasting 1 week with no evidence of fever, rash, cough, or changes in bowel movements. He reported no aggravating or relieving factors to his pain. He denied recent use of nonsteroidal antiinflammatory drugs, corticosteroids, or alcohol. Past medical history was pertinent for childhood varicella, Evans syndrome, and CVID treated with intravenous immunoglobulin therapy (597 mg/kg per month). Physical examination revealed a severely tender epigastrium. Initial laboratory studies showed a mildly elevated sedimentation rate (14 mm/h) and bilirubin (2.0 mg/dL) with normal complete blood cell count, comprehensive metabolic panel, and lipase, and a negative Monospot. Abdominal computerized tomography scan showed splenomegaly, enlarged retroperitoneal lymph nodes, and bibasilar pulmonary infiltrates. Abdominal ultrasound showed gallbladder sludge. Upper gastrointestinal endoscopy was performed and showed multiple ulcers in the gastric antrum (Fig 1A). The results of a rapid urease test for *Helicobacter pylori* were negative.

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Syndrome of inappropriate antidiuretic hormone hypersecretion responded to intravenous vasopressin receptor antagonist therapy. Persistent pancreatitis resulted in prolonged parenteral nutrition. After 3 weeks of intravenous acyclovir and aggressive supportive care, the patient gradually recovered. Skin lesions cleared within a week. He was discharged and remained well on follow-up 1 year later.

**IMMUNOLOGIC EVALUATION**

The patient had been treated for idiopathic thrombocytopenic purpura since 5 years of age. After an episode of autoimmune hemolytic anemia, he was diagnosed with Evans syndrome. Serum immunoglobulin levels were obtained on multiple occasions over a 6-month period. Serum IgG and IgA levels were persistently decreased 253 to 491 mg/dL and 9 to 28 mg/dL (Table 1). Serum IgM level was near-normal initially, then remained progressively elevated, 65 to 1664 mg/dL. Antibody titers to vaccine antigens were decreased to nondetectable. CD19+ B cells were decreased 12 to 55 cells/mm³ (normal, 110–920 cells/mm³), and CD27+ memory and CD27+IgD—switched B cells were 0%. He remained persistently lymphopenic. Although the percentages of CD3+, CD4+, and CD8+ T cells were normal, the absolute numbers of CD3+ and CD4+ T cells were mildly decreased 12 to 55 cells/mm³ (normal, 110–920 cells/mm³).
decreased. T-cell function was measured after recovery from varicella infection. As seen in Table 1, lymphoproliferative responses to mitogen and antigen stimulations were decreased. Natural killer cell cytotoxicity was normal. Expression of CD40L on stimulated T cells was slightly decreased at initial evaluation, but subsequently normal, 81% (normal, 79%–96%; performed by Cincinnati Children’s Immunology Laboratory). Expression of CD40 on CD19% B cells was slightly decreased, 4.3% (control, 11.6%; performed by Pediatric Immunology Laboratory, Saint Louis University); however, total CD40 expression was normal, 48%. Gene sequencing for CD40L (CD154) and CD40 were normal (Correlagen Laboratories). Evaluation for autoimmune lymphoproliferative syndrome revealed normal percentages of CD3+CD4−CD8−TCRαβ+ double-negative cells. CVID is associated with Evans syndrome and was diagnosed in this patient after the development of Evans syndrome based upon the hypogammaglobulinemia, B-cell and T-cell defects, and exclusion of other causes of immunodeficiency.

**DISCUSSION**

VZV is a Herpesviridae DNA virus that remains latent within sensory nerve ganglia after infection. During reactivation, the virus replicates within the sensory ganglia and then travels along the nerves to the skin, evading immune recognition and producing the typical unilateral dermatomal rash. The trigeminal and thoracic ganglia are the most common sites of latency. Clinical and experimental observations suggest the human enteric nervous system is also a well-defined site for VZV latency. VZV infection has been implicated in gastrointestinal disorders, including severe abdominal pain preceding fatal varicella and acute colonic pseudoobstruction. Gershon and colleagues have demonstrated VZV latency in enteric tissues of nearly all asymptomatic children with a history of previous vaccination or VZV infection. Additional mouse and guinea pig experiments have supported routes of viremia, infected lymphocyte transmission, and direct spread from enteric neurons as mechanisms for potential gastrointestinal VZV infection. Varicella-zoster reactivation is a common complication in the T-cell immunodeficiency caused by HIV and AIDS, even in the era of highly active antiretroviral therapy. Clinically relevant VZV infections in HIV and AIDS patients involve the skin and central nervous system, whereas gastrointestinal involvement is rare. Several studies examined HIV and AIDS patients with significant abdominal pain and found an overall low incidence of ulcers and no reported cases of VZV infection in the gastrointestinal tract upon endoscopic evaluation.

Myeloablative therapy in bone marrow and stem cell transplantation seems to predispose patients uniquely to gastritis caused by VZV. Myeloablative conditioning achieves global immune suppression for the purpose of successful engraftment. Mucositis is a universal side effect of conditioning regimens. Whether an insult to gastric mucosal barrier function in addition to global immune dysfunction increases vulnerability to disseminated VZV is unknown. Some patients with CVID have associated T-cell defects. Our patient falls...
within a subgroup of patients with CVID who have lymphopenia and decreased CD4+ T cells. Furthermore, our patient had decreased T-cell function as assessed by in vitro lymphoproliferative responses to mitogen and antigen stimulations. In addition, some CVID patients may have decreased interleukin-2 synthesis. The pattern of immunodeficiency with decreased serum IgG and IgA levels with normal to elevated IgM levels, profound antibody deficiency, and decreased T-cell function, as seen in our patient, can also be found in hyper-IgM syndrome (HIGM). Mutations of CD40L (CD154) and CD40 are responsible for X-linked HIGM and autosomal recessive HIGM. CD40L expression on T cells was normal, and CD40 expression on B cells, although decreased, was present. Results of gene analyses of CD40L and CD40 were normal in our patient, excluding HIGM as a cause for his immunodeficiency.

Diagnostic considerations for abdominal pain in CVID include granulomatous enterocolitis, intestinal lymphoid hyperplasia, sprue-like disease, atrophic gastritis, and infection by *Giardia* and *H pylori*. Increased incidence of symptomatic *H pylori* infection and difficulties eradicating *H pylori* are well described in CVID patients.

Distinguishing VZV from other causes of abdominal pain is paramount, because the institution of early treatment reduces mortality risk, especially in immunocompromised patients. Serologic diagnosis is not timely nor clinically useful, because diagnosis is retrospective at best, after comparing acute and convalescent sera. Serology may also be unreliable in patients with immunodeficiency. Scholl and colleagues demonstrated negative varicella serology in a stem cell transplant patient with gastric ulcers caused by VZV confirmed by endoscopic tissue biopsy. Endoscopy has an established role in evaluating immunodeficient patients with HIV for the possibility of opportunistic infections like cytomegalovirus.

We support early endoscopy in evaluating upper abdominal pain in patients with CVID as demonstrated by this case.

**CONCLUSIONS**

Initial presentation of VZV with gastric ulcers is rare and has not been reported in patients with CVID. Early endoscopic diagnosis facilitates appropriate therapy and reduced mortality. This report demonstrates the importance of considering VZV as a cause for severe abdominal pain in patients with CVID.

**REFERENCES**


**Gastric Ulcers Due to Varicella-Zoster Reactivation**  
Ki Lee Milligan, Ajay Kumar Jain, Jeremy S. Garrett and Alan P. Knutsen  
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