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BRIEF REPORT

Ileocolic Intussusception as the Presenting Symptom of Primary Enteric Varicella-Zoster Virus Infection in a 7-Month-Old Infant

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Ileocolic intussusception is the invagination of ileum into the colon. In a subset of patients, the disease is caused by mesenteric lymphadenopathy in response to (viral) infection. We present a case of an ileocolic intussusception necessitating surgery in a 7-month-old immunocompetent infant with concurrent primary wild-type varicella-zoster virus (VZV) infection, in whom chickenpox rash developed 2 days after surgery. Detailed in situ analyses of resected intestine for specific cell type markers and VZV RNA demonstrated VZV-infected lymphocytes and neurons in the gut wall and in ganglion cells of the myenteric plexus.

Keywords. Intussusception; varicella-zoster virus; chickenpox; lymphocyte; enteric nervous system; ganglion.

Ileocolic intussusception, defined as the invagination of one part of the distal ileum into an immediately adjacent colon segment, is a potentially life-threatening condition that commonly affects children <3 years old [1]. Although in 75% of cases the cause of the invagination is not known, an anatomic leading point, such as enlarged lymph nodes, a polyp, or Meckel diverticulum is found in 25% of cases. Recent data advocate that virus infection, specifically adenovirus C and enterovirus B, can trigger intussusception by causing intestinal wall lymphadenopathy that may lead to peristaltic entrapment of enlarged lymph nodes and subsequent invagination [2].

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Varicella-zoster virus (VZV) is a ubiquitous human neurotropic alpha-herpesvirus. VZV infects >90% of individuals before adolescence in most temperate regions of world, except for countries that included varicella vaccination in their routine childhood vaccination schedule [3, 4]. During primary infection, VZV initially replicates in epithelial cells of the respiratory tract, before virus is disseminated by T cells to skin and ganglia to cause varicella (chickenpox) and establish lifelong latent infection of sensory neurons of dorsal root and cranial ganglia, as well as autonomic and enteric ganglia [4, 5]. Although in one-third of individuals VZV will be reactivated later in life, causing herpes zoster (shingles), it may also be reactivated from enteric ganglia, causing severe gastrointestinal disease such as gastric ulcers and Ogilvie syndrome [6, 7]. By contrast, it is unclear whether enteric VZV infection may have gastrointestinal consequences during primary infection. Here, we describe a patient who presented with an intussusception 2 days before chickenpox skin rash.

CASE REPORT

A 7-month-old boy was referred to our emergency department with a 1-day history of vomiting and bloody stools. At physical examination, we saw a dehydrated, pale, and lethargic infant with a tender abdominal mass in the left lower quadrant. Abdominal ultrasonography showed an ileocolic intussusception reaching into the rectum. Hydrostatic reduction of the intussusceptum was not successful. At laparotomy, an intussusception of the terminal ileum reaching the sigmoid was partly redressed, and the ischemic bowel was resected. On the second day after operation, the patient had a diffuse vesiculopapular rash over his entire body and a mild cough. The clinical diagnosis of varicella was confirmed by polymerase chain reaction detection of VZV DNA in skin lesion swab samples by (data not shown). The patient showed a complete recovery from intestinal disease and was discharged 5 days after operation. His parents confirmed that he had been in contact with other children with chickenpox in the daycare facility in the weeks before his illness.

METHODS

For histopathological studies, consecutive 4-µm-thick formalin-fixed paraffin-embedded tissue sections of the resected bowel specimens were processed for immunohistochemistry (IHC) and in situ hybridization (ISH) analysis. IHC was performed with an automated staining system (Ventana BenchMark ULTRA; Ventana Medical Systems) using a red chromogen. In brief, after deparaffinization and heat-induced antigen retrieval, tissue sections were incubated with mouse

monoclonal antibodies directed toward CD45 (Ventana) or synaptophysin (Ventana), for 1 hour at 36°C. A subsequent amplification step was followed by conventional hematoxylin counter stain, according to the manufacturer's instructions (Ventana). ISH was performed using RNAScope technology, according to the manufacturer's instructions (Advanced Cell Diagnostics). Briefly, deparaffinized tissue sections were incubated with probes against VZV gene 63, using the RNAscope 2.0 Kit Red (Advanced Cell Diagnostics) [8]. To localize VZV-infected inflammatory cells in situ, sequential CD45 IHC with a brown chromogen and VZV ISH with a red chromogen were performed according to the manufacturers' instructions.

RESULTS

To investigate the potential relationship between VZV infection and intussusception, resected intestine biopsies were processed as a formalin-fixed paraffin-embedded tissue block, and serial sections were cut and subjected to chromogenic IHC ISH analysis to determine the specific cell types infected with VZV. VZV-infected cells were readily detected by ISH in 8 of 10 intestine samples. VZV RNA was detected in myenteric ganglia and submucosal nerve fiber–like tissue (Figure 1). In addition, a majority of VZV-infected cells were CD45-positive lymphocytes, mostly present within the lamina propria and lymph nodes and to a lesser degree within the submucosa and muscularis propria (Figure 2). Although there was considerable recruitment of lymphocytes, we did not observe signs of immune-mediated abnormalities of the myenteric ganglia.

DISCUSSION

Abdominal diseases seem to be rare, but clinically important, complications of primary and recurrent infections with wild-type VZV [9–11]. Previously, gastrointestinal complications were observed in 8 of 2534 hospitalized patients with varicella, including 5 cases of appendicitis and 3 of decreased intestinal function [9].

Although gastrointestinal disease may arise from secondary bacterial infections, a more active role for the virus was recently suggested, based on the detection of VZV DNA in an inflamed appendix of an immunocompromised child with varicella [10]. The report extends these prior observations by describing a case of concurrent ileocolic intussusception and primary wild-type VZV infection with evidence of VZV localization in the gut, specifically in the enteric nervous system (ENS).

Latent VZV has been demonstrated in the human ENS. The route by which VZV infects ENS neurons may involve transaxonal spread from dorsal root ganglia neurons or viremic spread via VZV-infected T cells [12]. Detection of VZV-infected lymphocytes in the affected bowel of our patient—who presented with ileocolic intussusception at the peak of viremia (1–2 days before onset of rash)—supports T-cell–mediated transfer of virus to the gut during primary VZV infection. This observation is consistent with findings in the guinea pig model of enteric VZV infection [12] and our group's previous findings in a nonhuman primate model for VZV infection [8], wherein virus-infected T cells were present in gut-draining lymph nodes and adjacent to enteric neurons during primary infection. Histological examination of the resection bowel specimens from our patient, combined with the use of ISH to detect VZV RNA expression, showed that VZV could be independently localized within enteric ganglia, as well as in CD45-positive lymphocytes recruited to the lamina propria and submucosal and muscular layers.

Based on the tropism of VZV for T cells and (enteric) neurons, we hypothesize that the virus may cause intussusception through 2 probable, non–mutually exclusive, mechanisms. First, VZV infection of the gut could lead to enlarged lymph nodes through mobilization and recruitment of lymphocytes. These lymph nodes can subsequently be "trapped" in the peristaltic motions, hereby causing invagination into the adjacent bowel. Second, infection or inflammation caused by VZV

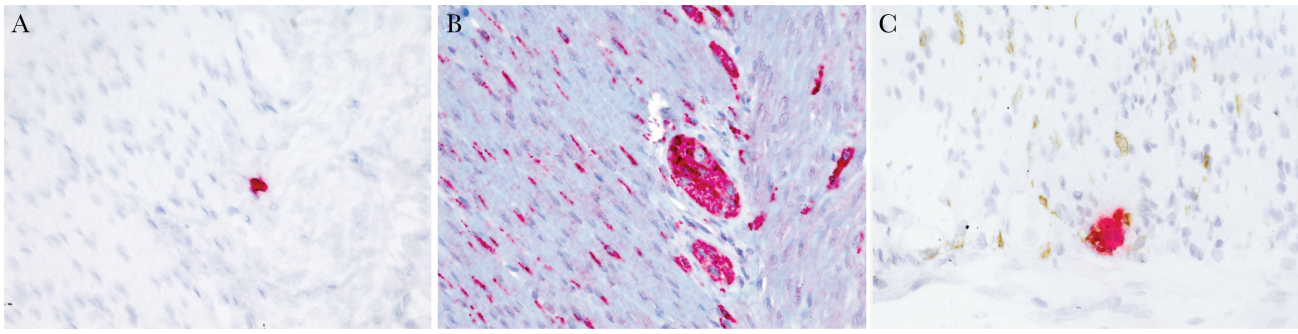

Figure 1. Varicella-zoster virus (VZV) RNA expression in ganglion cells. *A,* VZV RNA expression in ganglion cells of the myenteric plexus as confirmed by synaptophysin staining to detect neurons in the consecutive section (*B*) (original magnification ×400). *B,* Synapthophysin-positive ganglion cells and nerve fibers of the myenteric plexus (original magnification ×400). *C,* Double staining for VZV RNA (*red*) and CD45 (*brown*). VZV-infected lymphocytes (*brown and red* [double positive]) are closely associated with infected ganglion cells of the deep myenteric plexus (original magnification ×400). Except in *C,* all positive staining signals are in red.

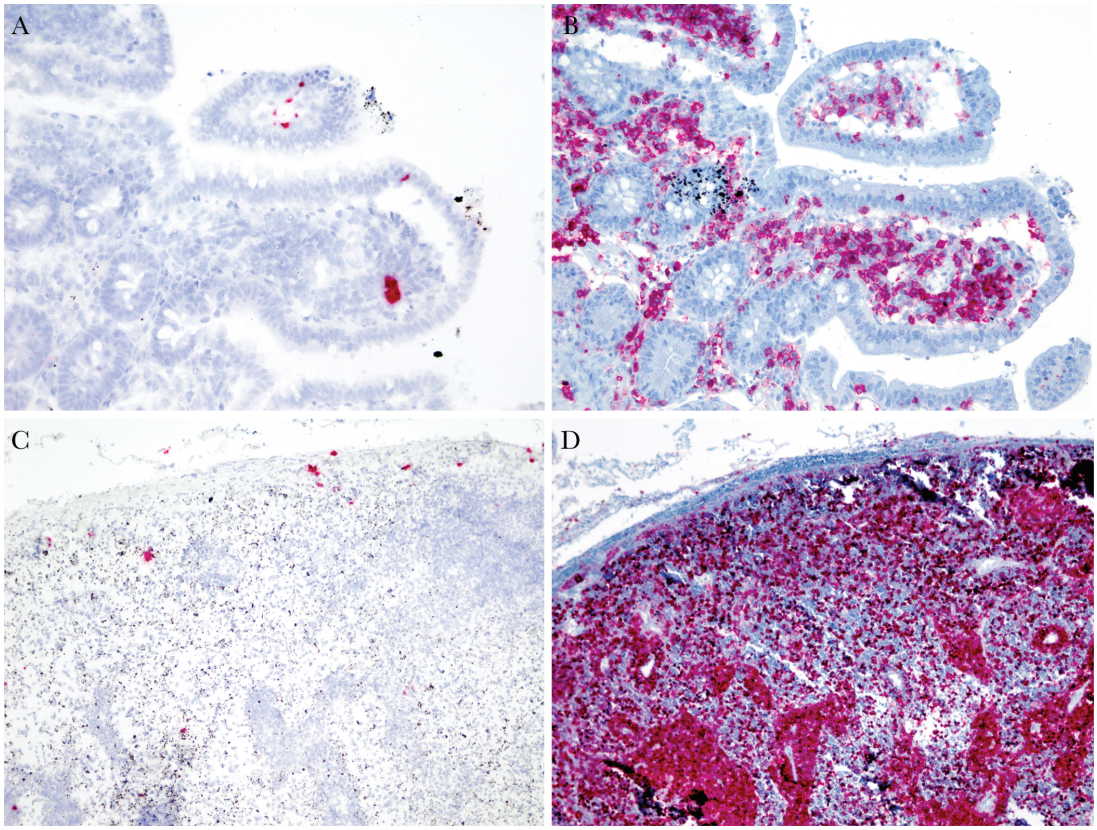

Figure 2. Varicella-zoster virus (VZV) RNA expression in lymphocytes. *A,* VZV RNA expression in lymphocytes of the lamina propria, as confirmed in consecutive sections by positive staining for CD45 (*B*) (original magnification ×200). *B,* CD45-positive lymphocytes (original magnification ×200). *C,* VZV RNA expression in lymphocytes of a mesenterial lymph node, as confirmed by CD45 staining in the consecutive section (*D*) (original magnification ×100). *D,* CD45 positive lymphocytes in the mesenterial lymph node (original magnification ×100). All positive staining signals are in red.

dissemination to the bowel may result in neuronal injury, resulting in ENS dysfunction with reduced or disharmonious peristalsis of the gut, triggering the telescoping of one part of the bowel into the other. Neuropathic ENS dysfunction is known to manifest as the key symptom in a variety of infectious and inflammatory diseases. The possible effect of inflammation of the bowel on ENS malfunction is illustrated by a number of diseases, such as viral infection, lymphocytic ganglionitis, and inflammatory bowel disease [13].

These conditions have been associated with enteric ganglionitis leading to chaotic and ineffective motility in the affected intestinal segment [14]. Moreover, the putative toxic effect of neurotropic viruses on enteric neurons has been demonstrated recently by White and colleagues [15] in a murine model. Those authors infected mice with West Nile virus (WNV) to determine the pathological characteristics of flavivirus-associated gastrointestinal motility. The data showed that WNV preferentially infects enteric neurons of the myenteric and submucosal plexus. Furthermore, WNV infection resulted in leukocyte infiltration of WNV-infected muscularis propria and myenteric ganglia, leading to cell death in enteric ganglion cells [15]. In our patient, we demonstrated infiltration of lymphocytes into the submucosal and myenteric plexus with no extensive transmural inflammation or major depletion or destruction of ganglia. Therefore, we hypothesize that a direct cytopathic effect of VZV on infected enteric neurons may play a role in ENS dysfunction. Future studies using immunodeficient animal models are required to further investigate this theory.

In summary, the current report describes a concurrent primary VZV infection of the ENS and adjacent lymphocytes in an immunocompetent child presenting with severe intussusception. Our findings illustrate the role of lymphocytes in VZV dissemination through the body, including the intestine, and add VZV as a potential cause of severe intussusception. Although gastrointestinal symptoms are rare in both primary and recurrent VZV infection, it is important to remain aware of the potentially severe complications of primary enteric infection or enteric reactivation of VZV in the gut.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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