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Case report

Disseminated varicella-zoster virus infection with abdominal pain possibly caused by pirfenidone: A case report

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ABSTRACT

We report a case of chronic hypersensitivity pneumonitis treated with pirfenidone in a 76-year-old woman who complained of acute-onset abdominal pain and rashes. The patient was diagnosed with disseminated varicella-zoster virus (VZV) infection, and pirfenidone was discontinued. Her condition improved in one month. Pirfenidone may induce disseminated VZV infection.

1. Introduction

Varicella-zoster virus (VZV) is a double-stranded linear DNA virus that belongs to *Herpesviridae* and causes two types of infection: primary VZV infection (varicella or chickenpox) and endogenous reactivation (herpes zoster or shingles) [1]. Varicella and chickenpox are common in children and are usually self-limited. However, immunocompromised hosts, especially patients with acute leukemia receiving steroids, chemotherapy, or bone marrow transplantation, are at risk for severe varicella disease with dissemination and pneumonia or neurologic complications [2]. During the primary varicella infection phase, viruses establish latency in neurons within the regional ganglia [3]. Cell-mediated immunity plays an important role in suppressing VZV reactivation; immunocompromised patients, such as HIV-infected individuals or transplant recipients, have an increased risk for dissemination and complications [4]. Reactivation of latent VZV infection, herpes zoster, or shingles is typically mild and localized to unilateral skin, but in patients with disseminated type of reactivation, visceral organ involvement is often noted and can be life-threatening [5]. Cases with disseminated VZV infection with severe abdominal pain have been reported previously [6]. In some cases, disseminated herpes zoster is suspected because patients have an apparent history of varicella during their childhood [7,8]. Visceral VZV infection often precedes eruptions, and thus, the diagnosis is extremely difficult. However, in most previous case reports, distinguishing between disseminated varicella and disseminated herpes zoster was difficult because serological tests, such as those assessing VZV IgM and IgG levels, lack accuracy and require expert interpretations.

Here, we report the first known case of disseminated VZV infection complicated by severe abdominal pain, which was treated successfully by acyclovir. We examined the distinction between disseminated varicella and disseminated herpes zoster and concluded that pirfenidone could cause a cell-mediated immunodeficiency.

2. Case report

A 76-year-old woman visited our clinic with complaints of nausea, vomiting, abdominal pain, and rash. The patient was previously diagnosed with chronic hypersensitivity pneumonia, and treatment with pirfenidone, an antifibrotic agent, was started at 600 mg/day, 5 months before admission. Three months before admission, the dose of pirfenidone was increased from 600 mg/day to 1200 mg/day. She developed nausea 2 months before admission, which progressed to vomiting and abdominal epigastric postprandial crampy pain 6 days before admission. Two days before admission, she developed vesicular eruption on her face, which spread to her trunk and extremities. She denied experiencing headache or fever and had no urinary symptoms. She had well-controlled diabetes mellitus with HbA1c of 7%, which was being treated with a dipeptidyl peptidase-4 inhibitor. She had not received immunization for VZV and had no apparent history of varicella during her childhood. She also had no contact with VZV-infected individuals.

She was alert and oriented at the time of presentation. Her blood pressure, pulse rate, respiratory rate, oxygen saturation, and body temperature were 147/83 mmHg, 82 beats/minutes, 14 breathes/minute, 95% at ambient air, and 37.3 °C, respectively. Purpuric papules typical of VZV infection were present all over her body, and severe

Abbreviations: VZV, varicella-zoster virus

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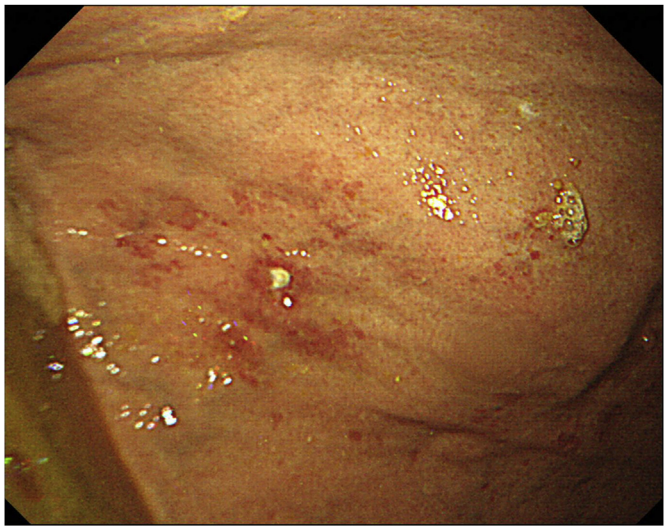

Fig. 1. Gastroduodenoscopy showing multiple mild erosions contrary to the patient's complaint.

epigastric tenderness without rebound tenderness were noted on physical examination. Laboratory findings revealed the following: mild inflammation and slightly elevated liver enzyme levels; white blood cell count, 5200/μL with 80.2% neutrophils; aspartate transaminase, 105 U/L; alanine transaminase, 102 U/L; total-bilirubin, 0.6 mg/dL; amylase 55 U/L; and C-reactive protein, 2.89 mg/dL.

On admission, we discontinued pirfenidone. Upon physical examination by dermatologists, a diagnosis of disseminated VZV was made, and contact and airborne precautions were initiated. Abdominal contrast-enhanced computed tomography scan revealed only mild inflammation of the ascending and transverse colon. Gastroduodenoscopy showed unspecific multiple erosions with unrevealing biopsy (Fig. 1). The patient was intravenously administered 10 mg/kg acyclovir every 8 hours for 7 days. She was allowed nothing through her mouth; treatment with 20 mg/day intravenous omeprazole was started. Tests for VZV IgM were negative, but those for VZV IgG were positive. VZV DNA was detected using real-time PCR in specimens obtained from skin lesions. Tests for HIV antibody and HTLV-1 were negative, and CD4 count was normal. On hospital day 10, she resumed food intake. On hospital day 12, all vesicular rashes developed crusting, and contact and airborne precautions were discontinued. Her postprandial abdominal pain gradually resolved over a month, and she was discharged on hospital day 34.

Informed consent was obtained from the patient for the publication of this case report.

3. Discussion

The clinical course of this patient provided two important clinical suggestions. First, pirfenidone could be a risk factor for disseminated VZV infection. Second, disseminated VZV infection could be complicated by severe abdominal pain.

Disseminated VZV infection could be induced by immunodeficiency due to pirfenidone. In Japan, the varicella vaccine was introduced in 2014, and most adults, like our patient, were not immunized. VZV is highly contagious, and most cases of varicella occur in children. According to surveillance data in Japan, almost all adults aged > 70 years have positive VZV IgG test results [9]. Varicella or chickenpox can be severe in adults. Our patient did not have an apparent history of varicella, so there is a possibility that she had contacted the disseminated primary infection from an immunocompetent patient. However, because the proportion of VZV IgG-positive adults is extremely high in Japan, regardless of the low inoculation rate of vaccination, it is natural to conclude that her disseminated VZV infection was disseminated herpes zoster. In addition, in this patient, the interval between the appearance of symptoms and serological testing was short, so the negative VZV IgM and positive VZV IgG test results were atypical for the primary infection. In most immunocompetent patients, herpes zoster or shingles is localized to one dermatome. Cutaneous or visceral dissemination usually occurs in immunocompromised hosts such as HIV-infected patients and transplant recipients [4]. Pirfenidone inhibits profibrotic synthesis and inflammatory mediators; thus, it may have influenced cell-mediated immunity targeted at VZV [10]. To date, there are no reports of immunodeficiency caused by pirfenidone. The etiology of induction of disseminated VZV infection is unknown. It is possible that administering pirfenidone to patients with chronic hypersensitivity pneumonitis is a risk for disseminated VZV. In this case, fibrosis caused by chronic hypersensitivity pneumonitis progressed, and pirfenidone was administered exceptionally without administering steroids or other immunosuppressants. Considering the lack of other factors for immunodeficiency in this patient, we concluded that the VZV infection could be disseminated herpes zoster due to cell-mediated immunodeficiency by pirfenidone.

Second, severe abdominal pain could be complicated by disseminated VZV infection. The etiology of abdominal pain in this case was not elucidated. In a previous case report, VZV reactivation at the dorsal root ganglia was thought to be an etiology [11]. In another case, a patient with disseminated VZV infection had severe abdominal pain with hemorrhagic spots on the liver and upper gastrointestinal tract [12]. However, in most cases, causes of abdominal pain could not be clearly determined. In our case, abdominal computed tomography and gastroduodenoscopy revealed little abnormality, contrary to the patient's complaints. Etiology remains unknown, but considering her clinical manifestations, her abdominal pain was thought to be caused by disseminated VZV infection.

In conclusion, physicians must be aware that treatment with pirfenidone could be a risk for disseminated VZV infection, and if patients present with severe abdominal pain, disseminated VZV infection as a differential diagnosis should be considered.

Declarations of interest

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