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Case Report

Refractory idiopathic thrombocytopenic purpura associated with an extended-spectrum beta-lactamase-positive *Escherichia coli* infection leads to continuous gastrointestinal hemorrhage: a case report

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Abstract: Idiopathic thrombocytopenic purpura (ITP) is an autoimmune hematologic disorder characterized by a low platelet count and bleeding. In approximately one-third of cases, acute ITP develops into chronic refractory ITP. Many biological factors may contribute to the development of refractory ITP. *Helicobacter pylori* infections have recently emerged as an important cause of refractory ITP. However, the relationship between ESBL-positive *Escherichia coli* infection and ITP has not yet been reported. Here, we present a very rare case of refractory ITP with ESBL-positive *E. coli* infection in which the patient died of hemorrhagic shock due to continuous bleeding of the lower digestive tract. Mucocutaneous hemorrhage is a primary and common symptom of ITP; however, severe hemorrhage of the gastrointestinal tract is rare, and continuous lower gastrointestinal bleeding is even rarer. This paper reports the diagnosis and treatment of a rare case of ITP associated with ESBL-positive *E. coli* infection. The report aimed to emphasize the importance of the findings and identify the biological factors that influence the prognosis of refractory ITP patients.

Keywords: Refractory idiopathic thrombocytopenic purpura, hemorrhagic shock, autoimmunity, ESBL-positive *Escherichia coli*

Introduction

Idiopathic thrombocytopenic purpura (ITP), also known as immune thrombocytopenic purpura, is a very common hematologic disorder characterized by the presence of anti-platelet antibodies in a patient's serum. The incidence of ITP, which is benign in most cases, is reported as approximately 5 per 100,000 children [1]. However, it may become life-threatening in some patients. ITP is associated with mortality and morbidity because of the increased risk of primary intracranial, soft tissue, or mucosal bleeding secondary to trauma. Conventional treatments such as corticosteroid administration and splenectomy help restore the platelet count to normal or "safe" levels in more than 70% of ITP patients. However, some patients (approximately 30%) who respond poorly to conventional ITP treatments or require prolonged and continuous medications are considered to have refractory ITP [2]. Many biological factors, especially chronic and persistent viral infections, have been found to be significantly associated with refractory ITP. Some bacteria are also capable of causing chronic and persistent infections and the relationship between bacteria and refractory ITP has become an important concern [3].

Autoantibody-mediated acceleration of peripheral platelet destruction is the central event in the pathophysiology of refractory ITP and immune reactions are often triggered by biological factors. To address the importance of the etiological diagnosis and treatment of refractory ITP, we present a very rare case of refractory ITP accompanied by ESBL-positive *Escherichia*

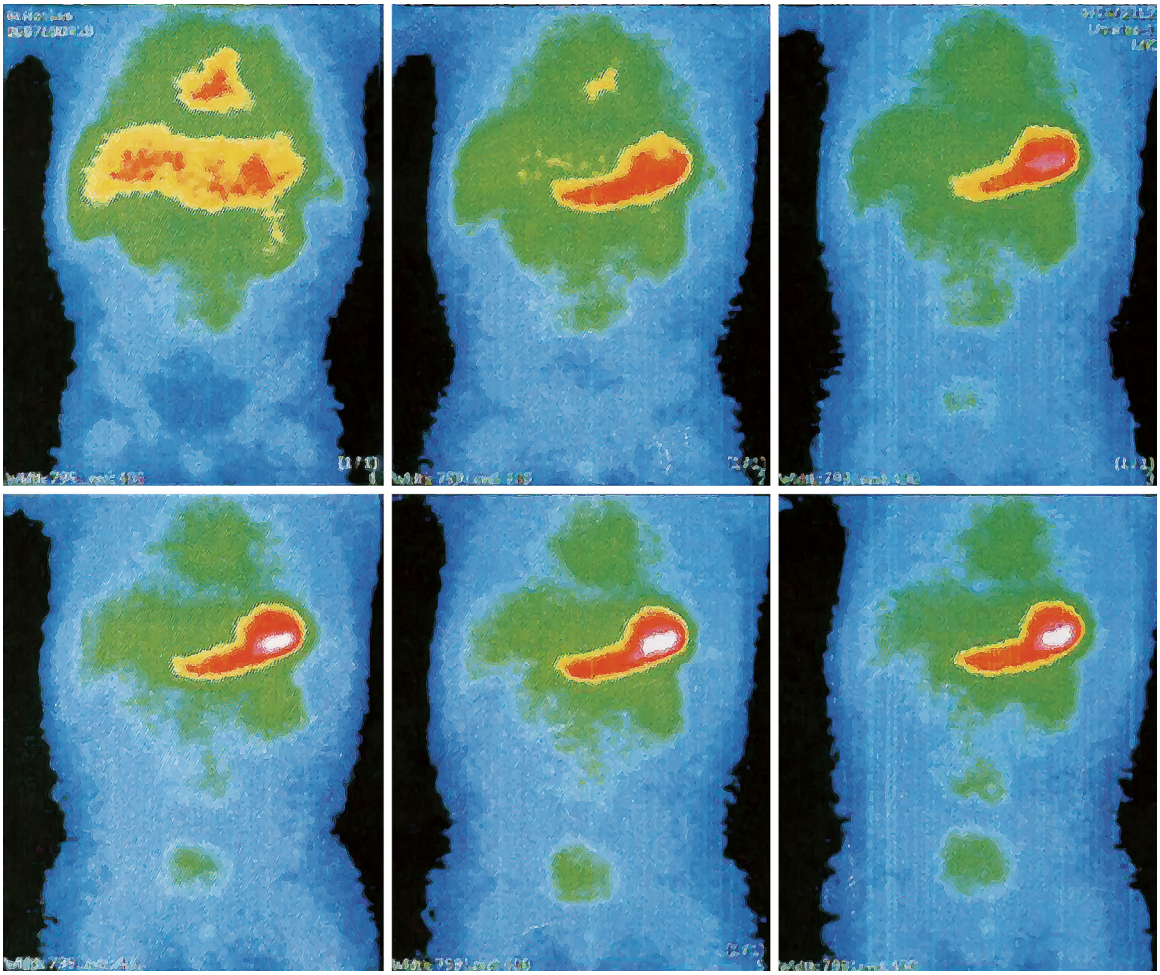

Figure 1. SPECT scan of the Meckel's diverticulum. SPECT images, which were taken continuously at the rate of 1 Zheng per minute after intravenous injection of 99mTc04, displayed abnormal radioactive uptake in the middle abdominal region.

coli infection in which the patient died from hemorrhagic shock due to continuous bleeding of the lower digestive tract.

Case report

In April 2012, a 2-year-old boy was admitted to the emergency department of the West China Second University Hospital due to sudden pale appearance. He had a history of recurrent ITP, with the most recent episode in January 2012. After he was diagnosed with ITP, *Helicobacter pylori* eradication therapy was initiated and the patient was treated with corticosteroids, intravenous immunoglobulin (IVIg), recombinant human thrombopoietin and recombinant human interleukin-11. The patient achieved remission after the treatment. However, ITP relapse occurred 2 months later and treatment using corticosteroids, interferon and platelet infusions was initiated, after which the patient achieved remission again. One day before this admission to the hospital, the patient experienced another episode of ITP relapse. The patient looked pale and had scattered petechiae on his neck. His platelet count was 3×10^3/μL, but he did not present with fever, vomiting, or bloody stools. No active bleeding, lymphadenopathy or hepatosplenomegaly was observed. His blood profile was as follows: white blood cell count, 11,000/μL (neutrophil, 82%; lymphocyte, 16%; and monocyte, 2%); platelet count, 4,000/μL; and C-reactive protein, 4.0 mg/dL. Corticosteroids, recombinant human thrombopoietin, IVIg, and hemopexin were administered to treat the ITP and cefathiamidine was given to prevent infection. However, the platelet count remained relatively unchanged between 1 and

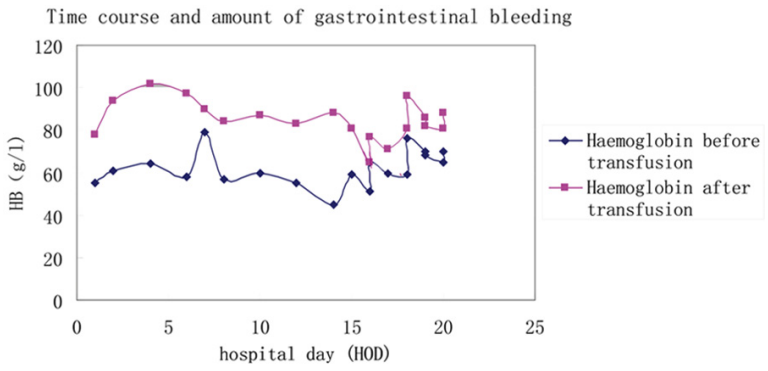

Figure 2. Time course and amount of gastrointestinal bleeding. The amount of gastrointestinal bleeding was scored based on the level of hemoglobin (g/L). For the first half of the month, our patient required 1.5 units of packed red blood cells every other day. The increased gastrointestinal bleeding also increased the volume of transfusion to 1.5 units of packed red blood cells every day, and even twice that amount every day towards the end.

7×10^3/μL and the patient developed hematemesis and started passing bloody stools 2 days after admission. Superactive hemostatic drugs, such as somatostatin and prothrombin complex concentrate, did not stop the continuous bloody stools. Transfusions of leukoreduced red blood cell suspensions, fresh blood plasma, and platelets were administered almost every other day to keep him alive. We conducted viral infection tests, autoantibody tests, bone marrow examination and biopsy, liver and kidney function tests, a disseminated intravascular coagulation test, and a urinary tract ultrasound examination, but did not find any evidence of hemolysis or any other diseases. It was assumed that the presence of active bleeding or a tumor in his digestive tract may be the cause, so a single-photon emission computed tomography (SPECT) scan of Meckel's diverticulum was performed. The SPECT scan revealed abnormal radioactive uptake in the patient's middle abdominal region (**Figure 1**). He was then transferred to the pediatric operating room where he underwent laparoscopy and laparotomy. The procedures revealed a hematocele from the distal jejunum to the ascending colon, but no active bleeding or lumps were observed. However, the levels of a few inflammatory cytokines (procalcitonin, serum amyloid protein, and interleukin-6) were significantly elevated. A blood culture was performed, which showed infection resistance with cefmetazole sodium. Eventually, the child required blood transfusions twice a day to keep him alive (**Figure 2**). One day after the operation, he died of hemorrhagic shock because the blood transfusion was discontinued on his family's request. The postmortem blood culture was positive for ESBL-positive *E. coli*.

Discussion

Refractory ITP is a rare condition in children, but it is associated with high morbidity and mortality in some cases [4]. This case is of special interest because severe and continuous hemorrhage of the gastrointestinal tract is rare. Moreover, the available therapeutic drugs are ineffective against refractory ITP. In addition, the association between ESBL-positive *E. coli* infection and ITP has not been reported.

Patients who fail to respond to first-line treatments or require unacceptably high doses of steroids to maintain a "safe" platelet count are considered to have refractory ITP [5]. Thrombopoietin can be used to successfully treat refractory ITP and a splenectomy currently has limited indications [6]. Our patient received IVIg and thrombopoietin. However, there was no change in the platelet count. Therefore, we assumed that certain unique factors may affect treatment outcomes.

Harrington *et al*. [7] were the first to highlight the role of immunity in platelet destruction among ITP patients. ITP may occur in isolation (primary) or in association with other disorders (secondary). Secondary causes include autoimmune diseases (in particular, antiphospholipid antibody syndrome), infections, and certain drugs. Most ITP cases are self-limiting and require no treatment because in most cases, antiplatelet antibody production is triggered by viral infection [8]. Many biological factors, such as viral [9, 10] and *H. pylori* infections [11], are significantly associated with the development of refractory ITP. *H. pylori* eradication therapy may result in the improvement of thrombocytopenia through mechanisms independent of H. pylori, including immune modulation or the removal of other commensal bacteria [12]. In support of these hypotheses, a recent meta-analysis demonstrated an increase in platelet count following eradication therapy in some ITP

patients regardless of the treatment outcomes [13].

Evidently, ITP and most chronic inflammatory and autoimmune disorders have complex immunopathological and clinical heterogeneities. *E. coli* is a common intestinal commensal bacterial species. In this case, we detected ESBL-positive *E. coli* only in the third blood culture, along with elevated levels of certain inflammatory cytokines. It was believed that the ESBL-positive *E. coli* infection in this patient may be linked to the development of refractory ITP because the bacteria were not detected in the previous 2 blood cultures. Moreover, the gastrointestinal bleeding was not severe. It was hypothesized that continuous gastrointestinal bleeding caused the endogenous intestinal infection, which led to an exacerbated immune function disorder. If this is true, then do ESBL-positive *E. coli* and *H. pylori* have similar mechanisms of action? We cannot provide an answer to this question now. However, an appropriate treatment modality should be considered for patients with refractory ITP who are at risk of developing continuous bleeding. Further studies should be conducted to determine whether the examination and eradication of ESBL-positive *E. coli* infections should be pursued in patients with ITP. An improved understanding of the pathogenesis of this condition and the availability of newer therapies with different mechanisms of action will lead to better management of these patients.

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Disclosure of conflict of interest

None.

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