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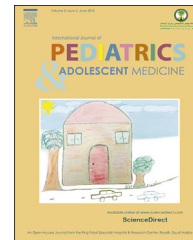


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## CASE REPORT

# Successful treatment of severe gastrointestinal manifestations of Henoch–Schonlein Purpura and factor XIII deficiency using cryoprecipitate transfusion



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Cryoprecipitate

**Abstract** Henoch–Schonlein Purpura (HSP) might present with severe gastrointestinal (GI) involvement. Herein, we report 3 cases of HSP with severe GI manifestations in the form of hematemesis, melena, pancreatitis, and erosive gastritis. Different treatment modalities were not successful. Low factor XIII levels were found in all patients and Cryoprecipitate transfusion resulted in significant immediate clinical improvement.

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## 1. Introduction

Henoch–Schönlein Purpura (HSP), a non-granulomatous, immunoglobulin A-mediated small vessels vasculitis. It is the most common vasculitis in pediatric age group with an incidence of 20 per 100,000 in children less than 17 years of age with a peak incidence of 70 per 100,000 in children between the ages of 4 and 6 years [1–5]. It presents with a tetrad of palpable purpura, arthritis or arthralgia,

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abdominal pain, and renal disease. Gastrointestinal (GI) manifestations may vary from solely colicky abdominal pain in about one-half of patients to GI bleeding in approximately 20–30 percent of patients [2,3]. However, rarely GI complications including acute pancreatitis and bowel perforation may occur [1]. A previous study by Prenzel have reported an association between severe HSP and factor XIII deficiency [5].

In this study, we report 3 cases of HSP with severe GI manifestations in the form of melena, hematemesis, acute pancreatitis, and erosive gastritis. All were unresponsive to corticosteroids. Low levels of factor XIII were found in all patients. Fortunately, they showed dramatic response to Cryoprecipitate transfusion.

## 2. Case 1

An 11-year-old girl, previously healthy, admitted with history of skin rash, abdominal pain, and vomiting for 12 days. The skin rash started at the lower extremities then progressed gradually to the buttocks area, upper extremities and face. The abdominal pain was periumbilical, colicky in nature, severe, and associated with vomiting. The vomiting had been associated with streaks of blood. She was admitted initially to a local hospital where she was treated conservatively, but she had worsening symptoms with significant abdominal distension and severe pain. She was referred to our hospital for further workup and management.

Physical examination upon arrival revealed ill-looking girl, in pain, conscious, oriented, and well hydrated. Her vitals were stable. She had purpuric rash over the face in a malar distribution (Fig. 1), upper and lower extremities with ulcerated lesions over both elbows and malleoli (Figs. 2–4). She had a distended abdomen with generalized tenderness, more in the epigastric and umbilical regions. Other examinations were unremarkable.

Laboratory data revealed: high white blood cell count at  $22 \times 10^9/L$  (normal 5–15) with predominant neutrophils (79%), low hemoglobin 10.4 mg/dl (normal 11–14), high platelet count  $358 \times 10^9/L$  (normal 140–350), normal erythrocyte sedimentation rate (ESR) at 2 mm/hr, high C-reactive protein (CRP) at 39.8 mg/L (normal > 3), normal renal functions and electrolytes, high amylase at 275 U/L (normal range 3–110), high lipase at 584 IU/L (normal range 0–60), and normal complements levels. Antinuclear antibodies, anti-SSB, anti-SSA, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), occult blood in stool and urinalysis were negative.



Figure 1 Purpuric rash in a malar distribution.



Figure 2 Purpuric rash over upper and lower extremities.



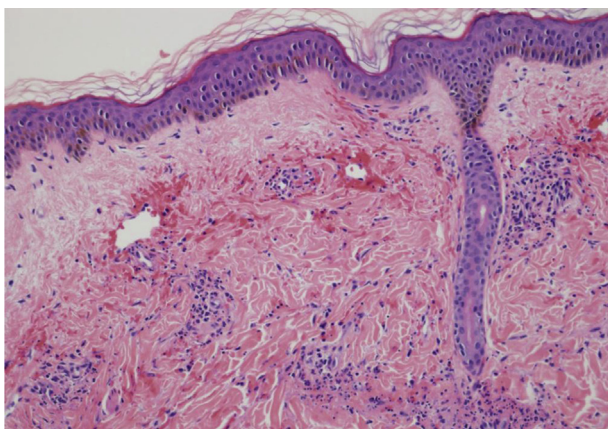
Figure 3 Purpuric rash over upper and lower extremities.

Abdominal radiograph showed evidence of paralytic ileus with multiple air-fluid levels suggestive of intestinal obstruction. Abdominal ultrasound reported moderate, free intraperitoneal fluid with inability to visualize the pancreas due to marked bowel gas shadowing. Abdominal computerized tomography (CT) showed diffuse swollen edematous pancreas, which confirmed the diagnosis of pancreatitis.

She was started on daily intravenous (IV) methylprednisolone pulse (30 mg/kg/dose) for 3 days without significant improvement. She was kept NPO (null per oral), on nasogastric tube (NGT) suctioning and analgesia. Skin biopsy showed leukocytoclastic vasculitis with IgA deposition confirming the diagnosis of HSP (Fig. 5). A week later, she developed melena; hence, upper endoscopy was performed and showed evidence of severe erosive gastritis with normal esophagus and duodenum. Therefore, NGT suctioning was continued and IV omeprazole and total parental nutrition (TPN) were started. IV methylprednisolone and IV immunoglobulin (IVIG) were administered, but it was without any significant improvement. Assay of Factor XIII showed low level at 0.3 IU/ml (normal range 0.7–1.2 IU/ml). Subsequently, Cryoprecipitate transfusion (60 ml equivalent to 3 units) was given 2 weeks after admission (on



Figure 4 Purpuric rash over upper and lower extremities.



**Figure 5** Leukocytoclastic vasculitis with IgA deposition.

day 11 after methylprednisolone and IVIG treatment), and the patient had dramatic improvement; her abdominal pain subsided and the rash lessened. The transfusion was well tolerated with adverse occurrences. Her oral intake improved and TPN was stopped. She became asymptomatic and was discharged in a stable condition.

### 3. Case II

A 3-year-old previously healthy girl presented one month prior to her admission with purpuric rash which started on her feet then progressed proximally to involve lower limbs, upper limbs, trunk, buttocks, and face. Simultaneously, she complained from mild abdominal pain, so she was diagnosed as HSP. Two days later, she had severe abdominal pain followed by vomiting, hematemesis, and melena. Methylprednisolone pulse (30 mg/kg/day) was given for 3 days followed by oral prednisolone 1 mg/kg/day for 8 days with partial improvement. She was then referred to our hospital for further management.

Upon arrival to our hospital, she had recurrent abdominal pain, vomiting, and rash reappeared on face, ears, trunk, lower, and upper extremities. However, there was no more hematemesis or melena. Investigations revealed normal complete blood counts, ESR, CRP, renal, and hepatic profiles. Urinalysis was negative for blood or protein. Abdominal radiograph showed fecal loading up to the cecum. Ultrasound abdomen was normal. Skin biopsy was consistent with leukocytoclastic vasculitis, and immunofluorescence was positive for fibrinogen in blood vessels, but it was negative for complements C3, C1q, immunoglobulin G, A, and M. Factor XIII assay showed low level at 0.39 IU/ml so Cryoprecipitate transfusion (40 ml equivalent to 2 units) was given (on day 16 after methylprednisolone treatment) with marked improvement of abdominal pain, vomiting, and rash. There were no complications encountered during or after transfusion.

### 4. Case III

A previously healthy 4-year-old boy presented 3 weeks prior to admission with periumbilical abdominal pain. It was intermittent, colicky, severe enough to interfere with daily

activities, and associated with vomiting. On the same day, he developed purpuric skin rash on lower limbs and buttocks. He was admitted twice due to recurrent abdominal pain and treated conservatively in the local hospital. In the third admission, he received steroid 15 mg/kg/day intravenously followed by maintenance on 1 mg/kg/day in divided doses with no significant response. Subsequently, he was referred to our hospital for further management.

Examinations showed a well-looking boy, normotensive, has scattered purpuric rash mainly over both elbows with fewer lesions on upper and lower extremities. His initial abdominal examination was reassuring, but he continued to have bouts of colicky severe abdominal pain associated with vomiting. His workup showed leukocytosis at  $16.75 \times 10^9/L$  with 82% neutrophils but normal hemoglobin, platelets, and inflammatory markers. Coagulation profile, lipase level, renal function, and hepatic profile were within normal ranges. Stool was positive for occult blood on more than one occasion. Abdominal X-ray showed moderate fecal loading, and abdominal ultrasonography showed normal viscera apart from fatty liver with no organomegaly and stool distended large bowel compatible with constipation. On the 4th day of admission, he developed a severe attack of abdominal pain associated with recurrent vomiting, hematemesis, and melena. An urgent ultrasound ruled out the presence of intestinal intussusception, and it only showed distended large bowel. Repeated CBC showed leukocytosis up to  $26.75 \times 10^9/L$  with 67% neutrophils, elevated CRP at 15.7 mg/L and normal ESR at 3 mm/Hr. Methylprednisolone pulse (10 mg/kg/day) was given for 2 days after the GI bleeding with no major effect. Factor XIII level was low at 0.58 IU/ml. Cryoprecipitate transfusion (60 ml equivalent to 3 units) was given 4 days after methylprednisolone pulses which shortly resulted in a significant improvement. However, the patient required a repeat transfusion of 3 extra units after which his symptoms completely resolved with no transfusion complications.

### 5. Discussion

HSP is the most common childhood vasculitis which has usually self-limited course with excellent prognosis. Purpura occurs in all cases, joint pains and arthritis in 80%, and abdominal pain in 62%. Some include gastrointestinal hemorrhage as a fourth criterion; this occurs in 33% of cases, sometimes, but not necessarily always, due to intussusception [6]. Severe clinical manifestations, including gastrointestinal, can be seen either at presentation or during the disease course. Intestinal bleeding and obstruction or intussusceptions can complicate the disease course [6]. Acute Pancreatitis was reported in a 3-year-old girl who presented with abdominal pain then developed characteristic rash of HSP at the fifth day of clinical onset [7]. A correlation between reduced plasma factor XIII activity, and the severity of multiple organ disorders, especially abdominal symptoms, has been shown in pediatric HSP in previous case studies [8].

In our series, we report 3 children with typical HSP but severe GI manifestations including severe abdominal pain, hematemesis, melena in all patients, in addition to pancreatitis, and erosive gastritis in the first patient. High

dose steroid pulses or oral prednisone as well as IVIG in the first patient did not help in alleviating the symptoms. All the three patients had low levels of factor XIII during their presentation then dramatic improvement within few hours following Cryoprecipitate transfusion which contain factor XIII.

Factor XIII (FXIII) is the last enzyme in the clotting cascade. Its main function is to convert the loose fibrin polymer into a firm, highly organized, cross-linked structure with increased tensile strength, firmly anchored to the site of the wound and possessing an in-built resistance to fibrinolysis. In factor XIII deficiency, standard clotting tests are normal, as the clotting end point is not affected by the absence of factor XIII [9]. All our patients had normal basic coagulation profile including PT, PTT, and INR despite significant hemorrhagic gastrointestinal symptoms.

Acquired factor XIII deficiency, when the level drops to 20–70% [10], remains a doubtful entity. Low plasma levels of factor XIII activity have been reported in some conditions like inflammatory bowel disease, systemic lupus erythematosus, and rheumatoid arthritis which are characterized by the presence of autoantibodies [11–13]. Whether the low factor XIII levels contribute to hemorrhagic complications in these diseases remains to be proven. Factor XIII deficiency might result into life-threatening bleeding. Massive intracerebral hemorrhage [14] and compartment syndrome of the forearm due to hemorrhage [15] were reported in two children with HSP and severe deficiency of factor XIII. Treatment of patients bleeding from the small bowel in HSP and from the large bowel in ulcerative colitis with factor XIII concentrate has been reported to be effective in controlling the bleeding [16]. The benefits of such therapy remain unconfirmed and factor XIII therapy in these circumstances cannot be recommended until more scientific evidence emerges in support of such an approach, and the possible mechanisms of factor XIII action in these situations elucidated.

In our reported cases, the first patient has the lowest level of factor XIII (0.3 IU/ml) and the most severe purpuric rash and gastrointestinal manifestations in form of acute pancreatitis and erosive gastritis, in addition to severe abdominal pain, hematemesis, and melena which were seen in the two other patients.

All our patients showed remarkable improvement of their gastrointestinal symptoms shortly after the transfusion of Cryoprecipitate. The amount transfused was one unit per 10 kg of body weight as per the blood products transfusion guidelines of our blood bank. Cryoprecipitate contains fibrinogen, factor VIII, von Willbrand factor, factor XIII, and fibonectin. Factor XIII substitution therapy using a fibrinogen preparation containing abundant factor XIII with an antiplasmin agent resulted in improvement of severe gastrointestinal hemorrhage in 13 out of 17 HSP affected children [17]. As well, other studies showed that administration of factor XIII in a group of moderate HSP showed remarkable improvement of joint symptoms and renal dysfunction in addition to gastrointestinal symptoms [18]. It is worth mentioning that all our patients had no significant renal or articular involvement despite the severe GI symptoms and widespread purpura.

Prenzel et al supported the hypothesis that factor XIII activity correlates well with the severity of abdominal

symptoms. There was no improvement after treatment with prednisone and symptoms resolved after factor XIII concentrate administration. Matayoshi et al showed that there was no correlation between factor XIII activities and the distribution of purpura, which in turn, was not correlated with the severity of organ disorders in adult patients [19]. Few studies have reported a correlation between the severity of HSP and factor XIII deficiency. Hogendorf et al showed improvement of factor XIII and symptoms resolution in 2 affected children without any intervention [20]. A case series of 3 children with HSP and isolated gastrointestinal symptoms described a reduction in factor XIII activity prior to the development of skin rash without the need for substitution treatment [21].

There is no literature differentiating the pathophysiological effects of cryoprecipitate, and it remains unclear if cryoprecipitate modify the inflammatory or thrombotic processes in such disease or similar vasculitic or inflammatory diseases.

Our study main limitation is the small number of patients, and the retrospective study type. Standardization of such therapy regarding treatment regimen and dosage needs to be tested in larger prospective studies.

In conclusion, Severe HSP manifestations particularly those related to GI symptoms like life-threatening GI bleeding might be associated with an acquired factor XIII deficiency. Factor XIII assay should be routinely measured in any patient with severe HSP since the replacement treatment of such temporarily deficient factor is curative. Cryoprecipitate should be an excellent alternative if factor XIII concentrate is not available.

## Conflict of interest

The authors declare that they have no conflict of interest related to this study.

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