Refractory Duodenal Bleeding Ulcers Successfully Treated with Factor XIII Transfusion

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Abstract:
A 67-year-old woman with a history of autoimmune hepatitis was admitted for fever, acute hepatic dysfunction, and acute kidney injury. She was diagnosed with multiple duodenal ulcers. Despite the administration of proton pump inhibitor and red blood cells, her black stool and anemia progressed, and she was therefore transferred to our hospital. Despite hemostatic treatments, she continued to bleed. On the 21st day of admission, an endoscopic examination showed the oozing of blood from the duodenal mucosa. A low factor XIII (FXIII) activity level was detected, and she was administered FXIII concentrate. The bleeding stopped and she was thereafter discharged.

Key words: coagulation factor XIII, duodenal ulcers, anemia, factor XIII deficiency

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Introduction

Coagulation factor XIII (FXIII) is known to stabilize fibrin during the final stage of the coagulation cascade and it is involved in wound healing (1-5). Acquired FXIII deficiency is caused due to its decreased production (owing to liver disorders) and excessive consumption (e.g., during injury, major surgery, and disseminated intravascular coagulation).

General coagulation screening tests are unable to detect the presence of acquired FXIII deficiency. The diagnosis of acquired FXIII deficiency is possible only by estimating the FXIII activity levels (6). Therefore, it is important to consider the possibility of an acquired FXIII deficiency as an underlying cause for bleeding tendency and delayed healing of wounds of unknown cause.

We herein report the case of a patient with refractory duodenal ulcer bleeding that was successfully treated with FXIII therapy after a diagnosis of acquired FXIII deficiency was made.

Case Report

A 67-year-old woman with a history of autoimmune hepatitis was admitted to a local hospital due to fever, acute liver dysfunction, and acute kidney injury. Her liver dysfunction showed a tendency to improve after conservative treatment. However, on the 5th day of admission, she had black stools and demonstrated a progression of anemia. Upper gastrointestinal endoscopy showed multiple duodenal ulcers. Despite the administration of proton pump inhibitors and red blood cell transfusion, her anemia did not improve. It progressed to acute renal failure. Therefore, on the 11th day of admission, she was transferred to our hospital.

Since no signs of mucosal atrophy were observed on esophagogastroduodenoscopy, the possibility of Helicobacter pylori infection was ruled out. She was not taking any non-steroidal anti-inflammatory drugs or steroids.

We conducted various laboratory tests, which revealed the following: hemoglobin, 7.5 g/dL (normal range, 11.3-15.2 g/dL); serum urea nitrogen, 133 mg/dL (normal range, 8.0-22.0 mg/dL); serum creatinine, 6.9 mg/dL (normal range, 0.31-1.10 mg/dL); total bilirubin, 3.0 mg/dL (normal range, 0.3-1.2 mg/dL); aspartate aminotransferase, 47 IU/L (normal

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The test results showed previous cytomegalovirus infection. Therefore, we performed several screening tests (Table 1). We suspected various diseases that may cause liver dysfunction but no signs of any active cytomegalovirus infection.

Regarding low IgM, the patient had no history of immunodeficiency, and although there was a possibility that autoimmune conditions were involved, no evidence thereof was found. Additionally, we suspected a FXIII deficiency as an underlying factor that might have delayed wound healing and caused oozing of blood from the gastrointestinal mucosa. Therefore, we estimated the FXIII activity levels, which were low (47%) on the 21st day of admission. The patient was therefore administered FXIII concentrate (Table 2). No bleeding was observed thereafter, and the patient was discharged from our hospital on the 37th day of admission. The patient provided her written informed consent for the publication of this report.

**Discussion**

In this report, we describe the case of a patient with refractory duodenal ulcers related to acquired FXIII deficiency that were successfully treated with FXIII concentrate transfusion. To the best of our knowledge, no case of refractory duodenal ulcers related to FXIII deficiency has so far been previously reported.

FXIII stabilizes fibrin clots, has an antifibrinolytic effect, and is also involved in wound healing. Patients with acquired FXIII deficiency do not have increased clotting time or thrombocytopenia. Therefore, general examinations cannot detect the acquired FXIII deficiency. Normal FXIII activity levels have been reported to be 70% or higher, whereas plasma FXIII levels of 5-30% have been found to be sufficient to prevent natural bleeding (7). However, the incidence of postoperative bleeding has been reported to be significantly higher in patients with FXIII levels of less than 60%, and these patients require postoperative hemostasis (8, 9).

In the present case, bleeding from duodenal ulcers, along with reduced production of FXIII due to acute liver disor-
Figure 2. (A) Upper gastrointestinal endoscopy at the time of admission showed shallow map-like ulcers extending from the duodenal bulb to the second portion of the duodenum. Therefore, cauterization was performed on the anal side. (B) On the 2nd day of admission to our hospital, homeostasis after endovascular treatment of duodenal ulcers was maintained. (C) During the second endoscopy at 2 days after admission in our hospital, bleeding from duodenal ulcers of the anterior wall of the duodenal bulb was observed. (D) At 3 days after admission to our hospital, rebleeding from the same site as in (C) was observed. Therefore, hemostasis was performed by clipping the site. (E) At 9 days after admission to our hospital, the ulcers were covered with a regenerated epithelium. However, after aspiration of the normal duodenal mucous membrane, oozing of blood was observed as shown in (F). (G) At 10 days after admission to our hospital, no bleeding from ulcers was observed, but oozing from the duodenal mucous membrane was observed as shown in (H). Seven days after the end of FXIII concentrate administration, the ulcers shrank, and the healing progressed as the ulcer bed became covered with the regenerated epithelium (I).

Figure 3. Clinical course. FXIII: coagulation factor XIII, FFP: fresh frozen plasma, FIB: fibrinogen, Hb: hemoglobin, PLT: platelets, RBC: red blood cells
Table 1. Pertinent Laboratory Investigations at the Time of Presentation to the Hospital.

| Test                                | Values     | Reference range          |
|-------------------------------------|------------|--------------------------|
| Gastrin                             | 130 pg/mL  | 42-150 pg/mL             |
| TSH                                 | 0.97 μIU/mL| 0.35-4.94 μIU/mL         |
| FT3                                 | 1.58 pg/mL | 1.71-3.71 pg/mL          |
| FT4                                 | 0.58 ng/dL | 0.70-1.48 ng/dL          |
| IgG-CMV Ab                          | 68.6       | <2.0                     |
| IgM-CMV Ab                          | 0.80       | <0.80                    |
| CMV pp65 antigen test               | 0/50,000   | 0/50,000                 |
| vWF activity                        | 131 %      | 60-170 %                 |
| ANA titer                           | 1:20       | <1:40                    |
| Anti-smooth muscle antibody         | Negative   | Negative                 |
| PR3-ANCA                            | 10 U/mL    | <10 U/mL                 |
| MPO-ANCA                            | 10 U/mL    | <20 U/mL                 |
| Anti-smith antibody                 | 4 U/mL     | <7 U/mL                  |
| Anti-ss DNA antibody IgG            | 5 AU/mL    | <25 AU/mL                |
| Anti-ss DNA antibody IgM            | 15 U/mL    | <15 U/mL                 |
| IgG                                 | 1,838 mg/dL| 870-1,700 mg/dL          |
| IgA                                 | 109 mg/dL  | 110-410 mg/dL            |
| IgM                                 | 30 mg/dL   | 46-260 mg/dL             |

Ab: antibody, ANA: anti-nuclear antibody, ANCA: antineutrophil cytoplasmic antibody, CMV: cytomegalovirus, FT3: triiodothyronine, FT4: thyroxine, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, MPO: myeloperoxidase, PR3: proteinase 3, ss: single-stranded, TSH: thyroid stimulating hormone, vWF: von Willebrand factor

Table 2. FXIII Activity Level.

| FXIII activity level before FXIII concentrate transfusion | 47% (normal range, 70-140%) |
| FXIII activity level after 2 days of FXIII concentrate transfusion | 125% (normal range, 70-140%) |

FXIII: coagulation factor XIII

...ders, might have led to a significant decrease in the FXIII level. The FXIII activity level were estimated on the 21st day of admission after frequent fresh frozen plasma transfusion. Therefore, it may be presumed that the FXIII activity levels at the time of admission might have even been lower.

The most highly suspected cause of liver dysfunction and duodenal ulcers is a cytomegalovirus infection. However, there were no findings indicating its reactivation. The findings for the relapse of autoimmune hepatitis were also negative. Additionally, there were no diagnoses of lupus nephritis or vasculitis as the cause of renal damage. Hepatic injury was alleviated without treatment and its cause remained unknown. From the process of exacerbation and improvement of renal disorder, it was likely that this was a case of pre-renal acute kidney injury due to bleeding.

Autoimmune FXIII deficiency is one of the underlying causes of acquired FXIII deficiency. However, the current case had no history of bleeding, and the increase in FXIII activity levels persisted for more than a year after FXIII therapy without any bleeding tendency. Therefore, the possibility of FXIII deficiency due to autoantibody production was extremely low. In addition, it has been suggested thatFXIII deficiency leads to the delayed healing of wounds and that FXIII therapy reduces the duration of wound healing (3, 10, 11).

Our observations suggest that, besides routine blood tests, the FXIII activity level should be determined in patients with bleeding due to an unknown cause, delayed wound healing, and repeated bleeding. In cases of patients with FXIII deficiency, the early administration of FXIII concentrate may improve the symptoms of bleeding and may also enhance the wound healing process. However, to date, there is no consensus on the FXIII activity level that leads to bleeding tendencies and a delay in wound healing in acquired FXIII deficiency. Future research is warranted to elucidate the optimal FXIII activity level to prevent bleeding tendencies and enhance the wound healing process.

Conclusion

Our observations suggest that FXIII deficiency could be an underlying reason for refractory gastrointestinal bleeding. However, FXIII deficiency cannot be diagnosed unless its activity level is measured. Therefore, a FXIII deficiency may go undetected. In cases that present with continued bleeding...
but without any abnormality in regular coagulation tests, FXIII deficiency may be an underlying cause, and it should therefore be included in the differential diagnosis. Hence, the FXIII activity levels should be determined during the course of treatment.

The authors state that they have no Conflict of Interest (COI).

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