Annals of Clinical Case Reports

Case Report
Published: 13 Jul, 2022

A Rare Cause of Post-Polypectomy Bleeding: Primary Hyperfibrinolysis

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Abstract

Delayed Post-Polypectomy Bleeding (DPPB) is an uncommon but serious adverse event. Some factors have been reported to be closely related to DPPB, including cardiovascular disease, hypertension, polyp size, and polyp location. Risk factors for DPPB have been widely investigated, but primary hyper fibrinolysis was overlooked. Here we reported a routine Endoscopic Mucosal Resection (EMR) that resulted in long hospitalization and increased expenses. This report provides some clinical information and treatment options for some similar cases.

Keywords: Polypectomy; Delayed bleeding; Hyperfibrinolysis; Fg; Hg

Introduction

DPPB is defined as bleeding that occurs between the end of the procedure and 30 days after polypectomy [1]. Previous studies have shown that DPPB occurs in 0.3% ~ 0.6% of polypectomies [2-4]. However, in a prospective study including only patients who underwent polypectomy with EMR, the incidence of DPPB was as high as 3.4% [5]. Most of the risk factors for DPPB are currently considered to be related to the patient, the polyp, and the surgeries [5-7]. The case we reported is a patient with unexpected and recurrent hemorrhage caused by primary hyperfibrinolysis after polypectomy. There is no standardized management of DPPB. We aimed to investigate the diagnostic process and therapy of unexpected DPPB.

Case Presentation

A 64-year-old female underwent endoscopic colon polypectomy in our department on July 30th, 2018, with normal preoperative blood routine test, hepatic and renal function and coagulation function. Her medical history includes tubal tuberculosis in her youth, which has been cured, and she denied any history of chronic illnesses such as liver disease, hypertension or diabetes. The polyp was located at the junction of the rectum and sigmoid colon, about 1.5 cm × 1.2 cm, and no pedicle on the base. It was removed by standard Endoscopic Mucosal Resection (EMR) and then the wound was clamped with two hemostatic clips and no bleeding was observed (Figure 1A, 1B). After 24 h of postoperative observation, the patient was discharged without abdominal pain or hematochezia. At noon on the day, the patient presented with bloody stools, dark red and approximately 50 ml, and again in the evening, and came to our emergency department. According to emergent colonoscopy, 'The EMR wound was located 15 cm above the anal verge, two metal clips were *in situ*, and a small amount of oozing blood was seen on the surface and edge of the wound (Figure 1C, 1D), so another 3 hemostasia clips were placed'. She was readmitted to the gastroenterology department after emergent endoscopic treatment. Nutritional and hemostasis support were given promptly, including Suling (Hemocoagulase Agkistrodon for Injection) and Tranexamic Acid (TXA), and the Hemoglobin (Hb, 133 g/L) and Platelet (Plt) were normal on readmission. However, bleeding recurred with an obvious drop of Hb to 107 g/L. The re-examination showed that Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) were within the normal range, while Fibrinogen (Fg) was significantly reduced to only 0.3 g/L. The urgent supplementation of the thrombin complex was performed and then the bloody stools stopped. But 2~3 days later, the bloody stools reappeared and the Fg was lower than 1.0 g/L again.

The effect of human fibrinogen only lasted a short period. With the decrease in Fg, the bloody stools recurred every 3 days or so (Figure 2). Further examinations of coagulation factor activity were normal, including protein C activity, protein S activity, antithrombin III activity, lupus

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Received Date: *26 May 2022*
Accepted Date: *07 Jul 2022*
Published Date: *13 Jul 2022*

Citation:
Wen C-C, Zhu C, Tang W-X, Wang Y, Wu D-Q, Zhao Y, et al. A Rare Cause of Post-Polypectomy Bleeding: Primary Hyperfibrinolysis. Ann Clin Case Rep. 2022; 7: 2256.

ISSN: 2474-1655

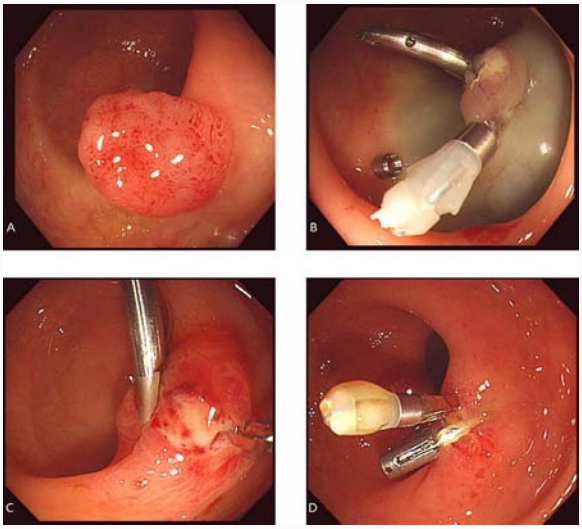

Figure 1: Endoscopic features. (A) Gross morphological features of the polyp. (B) No bleeding was seen at the wound after the polypectomy. (C) A small amount of oozing blood was seen on the surface and edge of the wound at emergent endoscopy. (D) No bleeding was observed after emergency endoscopic treatment.

anticoagulant, and three items of DIC (Thrombin Time (TT), 3P test, and plasminogen activity determination). With the specialists of Hematology, Blood Transfusion, and Pharmacy, we finally considered that the bleeding was caused by primary hyperfibrinolysis and developed a replacement therapy of cryoprecipitate and human fibrinogen to maintain Fg level at 1.0 g/L ~ 2.0 g/L. *Via* a series of treatments, the hematochezia stopped and the patient was finally discharged after about 30-day hospitalization.

Discussion

It was a routine planned EMR procedure for this patient. The polyp was not very large and no bleeding occurred intraoperatively or 24 h postoperatively. There were no abnormalities in preoperative blood routine and coagulation function and the patient had no history of liver diseases, hypertension, diabetes, or hematologic diseases, and no history of taking special drugs, such as aspirin, Clopidogrel, Ibuprofen or Indomethacin (NSAIDs). It was obvious that the patient had a low risk of bleeding complications. But her recurrent hematochezia happened and treatment lasted for nearly a month after the polypectomy, therefore the cause of her bleeding and treatment are worthy of concern and discussion. DPPB is thought to be due to the sloughing of the eschar of the cautery-induced ulcer that exposes and injures the underlying vessel [8]. We observed that the occurrence of her hematochezia was accompanied by an obvious decrease in Fg (0.29 g/L ~ 1.01 g/L). Hypofibrinogenemia is diagnosed when the fibrinogen level drops below 1.5 g/L ~ 2 g/L (2.0 g/L ~ 4.0 g/L in the healthy non-pregnant adults) [9], and fibrinogen replacement therapy should be implemented [10]. When fibrinogen is less than 1.0 g /L, the patients may show signs of bleeding, severe visceral hemorrhage, and there is a high risk of death [11].

Hyperfibrinolysis is a state of increased clot resolution. From a clinical point of view, it has been classified into two forms: Primary (qualitative or quantitative abnormalities of proteins directly involved in the fibrinolytic process) and secondary (conditions of imbalanced excessive activation of the otherwise normal fibrinolytic system) [12]. Primary hyperfibrinolysis is not associated with a hypercoagulable or prothrombotic state [12]. The combined detection of fibrin degradation products and D-dimer can help to identify primary hyperfibrinolysis or secondary hyperfibrinolysis. Primary hyperfibrinolysis is divided into inherited, such as α2-plasmin inhibitor deficiency, PAI-1 deficiency, Quebec platelet syndrome, and acquired primary hyperfibrinolysis, such as chronic liver disease, acute promyelocytic leukemia, severe trauma, and post-partum hemorrhage, tumor, etc. [13].

In our case, repeated examination of the Plt, PT, and APTT was within the normal range, DIC-related indexes were normal, and there were no clinical symptoms of DIC, so secondary hyperfibrinolysis could be ruled out. Chronic liver disease was also excluded based on her medical history and related examinations. No evidence of malignant tumors was found based on imaging and tumor markers performed during hospitalization. Therefore, her recurrent bleeding

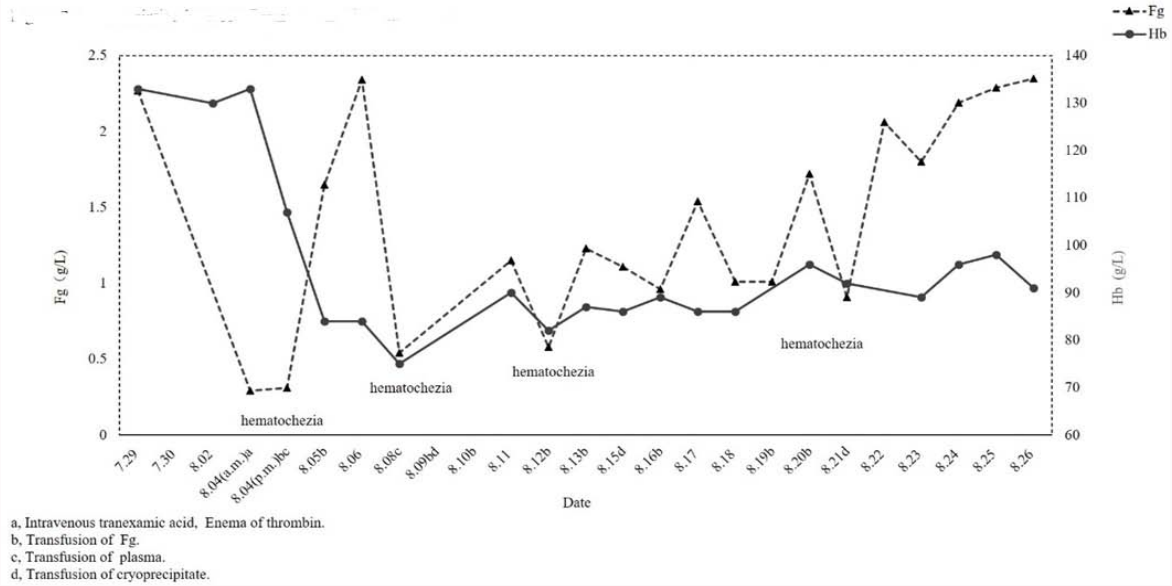

Figure 2: The association between fibrinogen and hematochezia.

after the polypectomy was due to rare primary hyperfibrinolysis, and the specific cause for acquired primary hyperfibrinolysis is not clear.

Coagulation and fibrinolysis systems are highly regulated and interrelated mechanisms to ensure balanced hemostasis. Fibrinogen is converted into fibrin monomer during coagulation, and then a stable fibrin polymer is formed, which eventually binds to Plt and erythrocytes to provide structural integrity for the growing thrombus [14]. Fibrinolysis is readily considered as two consecutive steps: (i) The generation of plasmin by plasminogen activators, and (ii) The digestion of fibrin by plasmin [12]. The central event of hyperfibrinolysis is the generation of plasmin in the blood circulatory system. The presence of high activity of the plasmin causes a pathological degradation of fibrin and fibrinogen, which further leads to rapid clot breakdown with consequent bleeding. The hemostatic capacity of a patient depends on the stability in the processes of formation and degradation of a blood clot. The clot strength increases linearly with the concentration of fibrinogen. Low fibrinogen concentrations form weaker clots that are more susceptible to lysis [15]. There may be a mechanism that prevents the patient from forming stable fibrin polymers on the wound surface, where Fg is continuously consumed and the bleeding cannot effectively stop. In this case, the pathology of the polyp was villous adenoma with mild to moderate atypical hyperplasia of glandular epithelium. Besides, the complexity of rectal blood supply and the variability of blood vessels are likely to be the underlying factors. Plasminogen Activator (PA) mainly comes from the uterus, adrenal, lymph node, prostate, thyroid and so on. This case suggests that hyperfibrinolysis can also occur in non-PA-enriched intestines, which is rare indeed. Primary hyperfibrinolysis is often caused by primary diseases or inducing factors, mainly treated with antifibrinolytics and supplementation of fibrinogen and cryoprecipitate. Antifibrinolytics should be applied before fibrinogen is administered whenever hyperfibrinolysis is suspected [16]. Tranexamic Acid (TXA) has been commonly used in the clinic for its better hemostasis effect and low risk of complications.

Conclusion

This case highlights the importance of a close monitoring coagulation function in the clinical diagnosis and therapy of unexpected DPPB. Once hyperfibrinolysis is considered, Multi-Disciplinary Teams (MDT) working is of great significance for the diagnosis and treatment.

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