

# Gastrointestinal bleeding as an initial manifestation in asymptomatic multiple myeloma: A case report and review of the literature

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**Abstract.** Multiple myeloma (MM) is an uncommon type of malignant hematological neoplasm which, besides primarily involving the bone marrow, has a potent tendency to involve other organs and to present with various clinical manifestations. Involvement of the gastrointestinal (GI) system, particularly presenting with GI hemorrhage, in the course of MM is extremely rare. In the present study, we report a case of a middle-aged male who initially demonstrated GI bleeding and was finally diagnosed with MM. Further laboratory examinations, including analysis of globulin in the blood, bone marrow aspiration and radiogram, supported this diagnosis. This case may promote the possible involvement of plasma cell myeloma in the differential diagnosis of patients with unexplained and refractory GI bleeding. In this study we also present a thorough review of the literature with regard to the association between MM and GI hemorrhage.

## Introduction

Gastrointestinal (GI) bleeding usually originates from peptic ulcers, acute gastric mucosal lesions, esophageal varices second to hepatic cirrhosis and primary digestive system neoplasms. However, some potent asymptomatic diseases of the blood system manifesting as GI hemorrhage may be clinically ignored. The incidence of gastrointestinal bleeding has been reported as 10-30% of patients with neoplastic diseases of the hematopoietic organ (1). The pathogenesis of gastrointestinal bleeding in these diseases is usually multifactorial and may be caused by direct malignant hematopoietic cell infiltrations, mucosal changes ensuing from bone marrow suppression,

immunodeficiency states, infections due to various organisms, or preceding peptic ulcers (1).

Multiple myeloma (MM), also known as plasma cell myeloma, is a malignant hematological neoplasm, characterized by clonal proliferation of plasma cells in the bone marrow and associated with the overproduction of structurally homogeneous immunoglobulins. Anemia, renal failure, skeletal destruction, recurrent infections and hypercalcemia are the most common features of the disease. New diagnostic criteria of MM require the presence of at least 10% plasma cells on examination of the bone marrow (or biopsy of tissue with monoclonal plasma cells), monoclonal protein in the serum or urine, and evidence of end-organ damage (2). Clinicopathological studies demonstrated that clinically apparent extraosseous manifestations were present in less than 5% of patients with MM. Liver, spleen and lymph nodes were the most frequent sites of occurrence in approximately two-thirds of these patients, while central nervous system, kidney, skin, pleura, lung, testes, pancreas, thyroid, adrenal glands and omental involvement had also been revealed (3). Involvement of the GI system, particularly demonstrating with GI hemorrhage, in the course of MM is extremely rare.

In this report we describe a case which was finally diagnosed as MM, but was initially manifested as gastrointestinal hemorrhage. We also present a thorough review of the literature with regard to the association between MM and GI bleeding. The study was approved by the Ethics Committee of Taizhou People's Hospital, Jiangsu, China. Written informed consent was obtained from the patient.

## Case report

A 47-year-old male was admitted to the Taizhou People's Hospital (Jiangsu, China) with a two year history of recurrent hematochezia. Two days prior to admission, the patient's symptoms deteriorated with three times the normal blood stool passage. The patient also felt dizzy and experienced palpitations. In April and July 2012, the patient experienced two instances of hematochezia, and at that time, ulcers were identified in the stomach and duodenum through a gastroscopy. Meanwhile, colorectal polyps were identified through a colonoscopy and gastrointestinal barium imaging revealed a normal small intestine. Following acid suppression therapy, the

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patient's stool recovered to normal, and surgery was conducted five years ago to treat the intestinal obstruction.

Upon physical examination, the positive signs included the anemic appearance and a surgical scar on the left side of the abdomen.

At the initial examination, laboratory results were as follows: red blood cells,  $1.87 \times 10^{12}/l$  ( $4-5.5 \times 10^{12}/l$ ); hemoglobin, 102 g/l (120-160 g/l); white blood cells,  $5.35 \times 10^9/l$  ( $4-10 \times 10^9/l$ ); platelets,  $242 \times 10^9/l$  ( $100-300 \times 10^9/l$ ); and erythrocyte sedimentation rate (ESR), 125 mm/h (10-20 mm/h). Biochemical examination revealed the following results: total serum protein, 123.1 g/l (66-87 g/l); albumin, 25.6 g/l (35-54 g/l); globulin, 97.5 g/l (20-40 g/l); IgG, 82.4 g/l (8-17 g/l); IgA, 0.23 g/l (0.7-4.0 g/l); and IgM, 0.34 g/l (0.4-2.3 g/l). Lactate dehydrogenase (LDH), electrolytes, glucose, fat and renal function tests were all normal, and the Bence-Jones protein was not detected in the patient's urine.

In the bone marrow aspirate, 20% plasma cells were identified (Fig. 1). A plain radiogram, shown in Fig. 2, revealed that multiple lytic lesions were present in the skull, while diffuse osteoporosis was present in the ilium, pubis and sciatic and degeneration was present in the thoracic and lumbar vertebra. Furthermore, the capsule endoscopy revealed edema in the gastric mucosa and an ulcer in the duodenum. A gastroscopy and colonoscopy identified no active hemorrhage in the digestive tract. Thus, according to the diagnostic criteria, this patient was finally diagnosed as MM, IgG type, grade III.

Following diagnosis, the patient received systemic chemotherapy with mephalan, prednisone and oral thalidomide, and acquired partial remission. Following 6 months of therapy, bone marrow aspiration revealed that the number of plasma cells was less than 5%, and globulin and IgG decreased to 64 g/l and 53 g/l, respectively. To date, no GI bleeding has occurred.

## Discussion

MM is the second most prevalent hematological malignancy, representing 2% of all cancer mortalities (4). Although usually restricted to the bone marrow, extramedullary involvement of this disease can occur in up to 20% of cases. The most common extramedullary site is the upper respiratory tract, including the oropharynx, nasopharynx, nasal cavities, sinuses and larynx (2,5). Cases of MM with GI features are uncommon. Some clinical manifestations have identified nausea, vomiting and colic in 20% of cases, but hematemesis and melena, in contrast to bleeding from the nose and gums, are rare. The marked infrequency of GI hemorrhage in MM may easily lead the clinician to make an erroneous diagnosis of common peptic ulcer or gastric neoplasm, carcinoma or lymphoma. To the best of our knowledge, only a few cases corresponding to GI bleeding in MM have previously been published.

GI bleeding has been identified in 10-30% of patients with neoplastic diseases of the hematopoietic organ, including MM. Talamo *et al* (6) identified 24 patients with involvement of the GI system documented in a database of 2,584 patients with MM of which only two cases presented with GI hemorrhage. Through reviewing the limited literatures associated with GI hemorrhage in MM patients, we speculate that the potent pathogenesis of GI bleeding in MM through several pathways including direct plasma cell infiltrations in the form of

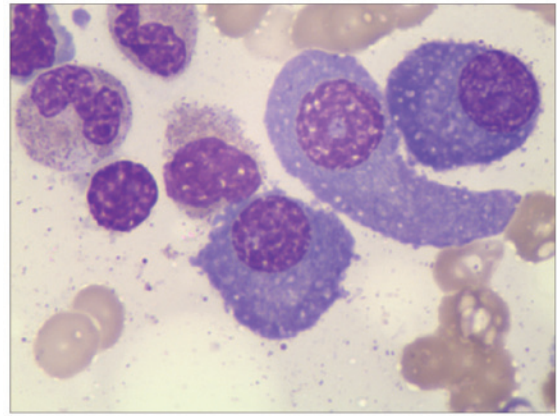


Figure 1. H&E staining of bone marrow biopsy section showing clusters of abnormal malignant-appearing plasma cells (magnification, x100). H&E, hematoxylin & eosin.



Figure 2. Multiple osteolytic bone lesions in the skull.

plasmacytomas, amyloid infiltration of the gut wall resulting in increased capillary fragility, platelet or coagulation abnormalities, and preceding peptic ulcers may sometimes be secondary to treatment with anti-inflammatory medications and corticosteroids.

Daram *et al* (7) reported a case of a 53-year-old female diagnosed with MM in 2005. The patient presented with acute upper GI bleeding in the form of hematemesis, and underwent chemotherapy and stem cell transplantation. An emergent esophagogastroduodenoscopy identified a multilobulated, submucosal mass on the proximal corpus along the greater curvature, and a small erosion on the lateral wall of the second portion of duodenum. Further biopsies revealed dense submucosal infiltrates of highly atypical plasmacytic cells in the stomach and duodenum. Additionally, Vicuña Arregui *et al* (8) and Suvannasankha *et al* (9) previously demonstrated that plasmacytomas were present in cases with MM. Amyloid was identified in other studies, which revealed another etiology of GI bleeding in MM patients. Chang *et al* (10) revealed a case of MM presenting with episodes of coffee-ground vomitus or

massive hematochezia. A tissue biopsy taken at the irregular mucosa beside the protruding vessels in the duodenum, confirmed the diagnosis of GI amyloidosis. Alvares *et al* (11) also reported the case of a 45-year-old female who presented with hematemesis. Further endoscopy identified nodular lesions and ulcers in the gastric antrum, and histology of the lesions confirmed the diagnosis of amyloidosis. Maza *et al* (12) reported an uncommon case of rectal bleeding and anemia with polypoid lesions and ulcerations in the colon, as the presenting symptom of amyloidosis and light chain MM. All of these cases mentioned above demonstrated the absence of systemic symptoms of amyloidosis, and non-specific endoscopic findings may make diagnosis difficult. Therefore, we recommend that a diagnosis of amyloidosis-induced GI bleeding should be considered in patients with MM with an obscure hemorrhage. Abnormal hemostasis, specifically the imbalance in function of all major components of the coagulation cascade, may increase the risk of bleeding in patients with MM. DiMinno *et al* (13) suggest that bleeding occurring in dysproteinemia may be the result of a specific interaction of monoclonal paraproteins with platelets. Saif *et al* (14) considered that patients with MM may develop bleeding diathesis secondary to a variety of mechanisms. One such mechanism is direct inhibition of fibrin monomer aggregation due to the paraprotein, resulting in prolongation of the thrombin and reptilase time.

Finally, the most common etiology may be peptic ulcer, which is usually secondary to treatment with anti-inflammatory medications and corticosteroids. In 2006, Dawson *et al* (15) reported a case of a 60-year-old female with MM relapse. The patient presented with hematemesis and melena following salvage chemotherapy with dexamethasone, cyclophosphamide, etoposide and cisplatin, and rescue therapy with single-agent bortezomib. However, in contrast to the cases mentioned above, in the present study, the patient manifested with recurrent GI hemorrhage. The only positive signature was the duodenal ulcer and focus mucosal lesion in a small bowel, without evidence of plasma cell infiltration or amyloidosis, following tissue biopsy. Furthermore, no fatigue, bone pain or recurrent infections were observed, while hyperproteinemia and reversal of the albumin/globulin ratio was identified during the period of present medical history, which fulfilled the criteria for asymptomatic myeloma (16). Additionally, prior to the patient's hematochezia, no non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids were administered and no abnormal hemostasis was identified in laboratory examinations. Thus, primary GI hemorrhage probably attributed to duodenal ulcers and mucosal erosion complicated with MM could explain this case. Following systemic chemotherapy with mephalan and prednisone complying with administration of antacid therapy, the patient acquired partial remission and no recurrence of GI hemorrhage was observed. As a result, since no evidence of related end-organ damage was present,

atypical myeloma should be paid more attention during our clinical diagnosis and treatment process.

In conclusion, MM is a systemic disease which may be rarely presented with GI involvement. It should be kept in mind that recurrent GI bleeding is difficult to explain through complete GI work-up using endoscopy, CT-scanning or MRI; thus, it may be related to certain hematopoietic neoplasms, particularly the asymptomatic myeloma involvement, and these patients should be examined further. Furthermore, early diagnosis of this disease has advantages of identifying preceding peptic ulcers and other lesions in the GI tract, as well as providing prophylactic steps to the GI mucosa, which is vulnerable to hemorrhage and further chemotherapy.

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