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CASE REPORT

Isolated coagulopathy without classic CRAB symptoms as the initial manifestation of multiple myeloma: A case report

Ya Zhang, Fang Xu, Jing-Jing Wen, Lin Shi, Qiao-Lin Zhou

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Abstract

BACKGROUND

Multiple myeloma patients usually present with CRAB symptoms (hypercalcemia, renal disease, anemia and bone diseases) as initial manifestations. Bleeding symptoms are less common, most of which result from thrombocytopenia or infiltration of plasmacytoma. Relatively, coagulopathy is not so common, especially isolated coagulopathy without CRAB manifestations, which is very rare. Herein, we report a 54-year old female who was hospitalized for intermittent and recurrent mild oral mucosal hemorrhage without other bleeding symptoms for almost one month or typical myeloma features.

CASE SUMMARY

Two months before admission, the patient underwent implantation of a permanent pacemaker due to sick sinus syndrome. Prothrombin time and activated partial thromboplastin time were significantly prolonged. Factor X deficiency was demonstrated to account for the coagulation dysfunction. An M protein peak was shown by serum protein electrophoresis. 26.11% of abnormal plasma cells were detected in bone marrow by flow cytometry, expressing CD38, CD138, CD56 and intracellular immunoglobulin Kappa light chain. Bone marrow biopsy also proved the presence of abnormal plasma cells, but Congo red stain was negative. The patient was finally diagnosed with multiple myeloma IgA-κ type. A literature review indicated that factor X deficiency was highly related to amyloidosis. Before bleeding signs, the patient had cardiac arrhythmia, enlargement of the heart, and progressive heart failure; thus, cardiac amyloidosis was suspected.

CONCLUSION

Bleeding related to coagulation dysfunction is uncommon in multiple myeloma, especially as the initial manifestation. Amyloidosis is a well-recognized cause of isolated acquired factor X deficiency.

Key Words: Multiple myeloma; Coagulation function; Hemorrhage; Factor X; Deficiency; Case report

Core Tip: Coagulopathy resulting from isolated acquired factorX deficiency is uncommon in myeloma. Typical symptoms in multiple myeloma include hypercalcemia, renal disease, anemia and bone diseases (CRAB). Factor X deficiency could herald the CRAB symptoms, and was reported to be closely related to amyloidosis. Secondary amyloidosis could be reasonably suspected if factor X deficiency is verified in myeloma patient.

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INTRODUCTION

Multiple myeloma is one of the most common hematological malignancies. Usually myeloma patients initially present with CRAB symptoms (hypercalcemia, renal disease, anemia and bone diseases). As reported, bleeding occurs in almost 7% of *de novo* myeloma patients[1], often combined with CRAB symptoms. Thrombocytopenia and infiltration of plasmacytoma account for most bleeding events. Coagulopathy is not common, especially isolated coagulopathy without CRAB manifestations, which is very rare. Herein, we report a multiple myeloma patient presenting with recurrent bleeding of oral mucosa and coagulopathy as initial manifestations without typical myeloma features.

CASE PRESENTATION

Chief complaints

A 54-year old female was hospitalized for intermittent and recurrent mild oral mucosal hemorrhage without other bleeding symptoms for almost one month.

History of present illness

Initially, the patient presented no weakness, oliguria, edema, bone pain, *etc*. Drug abuse, and contact with rodenticide and other toxic agents was denied. Coagulation function was assessed two weeks before admission during her first visit to the Hematology Outpatient Department. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were significantly prolonged, and were 20.7 s and 41 s, respectively. Fibrinogen was 1.79 g/L and thrombin time was normal. D dimer and fibrin degradation products were higher than the normal level, and were 6.2 mg/L and 2.29 mg/L, respectively. Considering the prolongation of both PT and APTT, vitamin K1 was administered at 40 to 80 mg/d. Bleeding seemed to initially improve slightly but recurred and became more obvious and frequent. PT and APTT were still longer than normal. The patient also had a cough and expectoration. She was admitted for further investigation and diagnosis.

History of past illness

Past history indicated that the patient was a hepatitis B virus carrier. Two months before admission, she underwent implantation of a permanent pacemaker due to sick sinus syndrome in another hospital. Before and after the operation, routine blood tests and laboratory examinations were normal, and PT was 15.7 s. The patient denied taking any other drugs except atorvastatin calcium after discharge.

Personal and family history

The patient denied having personal and family history.

Physical examination

On admission, several oral blood blisters and spontaneous gingival bleeding were noted. No petechiae, ecchymoses or purpura were observed on the skin. Some wet rales were heard on both sides of the lungs. The heart boundary was enlarged. No splenomegaly, hepatomegaly or masses were found in the abdomen.

Laboratory examinations

Laboratory examinations showed that the level of factor II, factor VIII and factor IX were normal, but factor X level was 9.8%. PT delay could be corrected once fresh frozen plasma was used. Routine blood tests revealed normal white blood cell (WBC) count, hemoglobin of 10.7 g/L and platelets of 90 × 10^9/L. Brain natriuretic peptide was 5966 ng/L (normal range < 125 ng/L). Immunoglobulin (Ig)A level was 17.6 g/L, significantly higher than normal (range 1.0-4.2 g/L), while IgG, IgE, and IgM were lower than the normal level. β2 microglobulin was 4.836 mg/L (normal range 0.9-2.0 mg/L). Blood immunofixation electrophoresis verified the existence of monoclonal immunoglobulin, which was IgA-κ type. An M protein peak was shown by serum protein electrophoresis. M protein was 11.26 g/L. Liver function indicated a mild to moderate increase in liver enzymes, including alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase and alkaline phosphatase. Renal function tests showed that creatinine was 67 μmol/L, uric acid was 366.5 μmol/L, and the glomerular filtration rate was 45.9 mL/min.

Imaging examinations

A low dose computed tomography (CT) scan of the whole body did not find any obvious osteolytic lesions. A CT scan and color Doppler ultrasound both indicated enlargement of the heart, especially both atria. Moderate tricuspid regurgitation, mild mitral regurgitation, widened pulmonary artery diameter, mild pulmonary hypertension, a slightly thicker ventricular septum, and mild pericardial effusion were also noted.

Further diagnostic work-up

26.11% of plasma cells were detected in bone marrow by flow cytometry, expressing CD38, CD138, CD56 and intracellular immunoglobulin Kappa light chain. The expression of CD38 and CD138 indicated that the abnormal cells were originated from plasma cells. Restricted expression of intracellular immunoglobulin Kappa light chain suggested they were clonal plasma cells. CD56 expression further proved that they were abnormal and neoplastic plasma cells. Bone marrow biopsy also proved the existence of abnormal plasma cells, but Congo red stain was negative.

FINAL DIAGNOSIS

Multiple myeloma (IgA-κ type); acquired factor X deficiency; And sick sinus syndrome.

TREATMENT

The patient started the first cycle of chemotherapy including bortezomib (1.3 mg/m^2, weekly) and dexamethasone (20 mg, weekly) as soon as the myeloma diagnosis was established.

OUTCOME AND FOLLOW-UP

Unfortunately, the patient died of heart failure during the first cycle of chemotherapy in the third week.

DISCUSSION

Multiple myeloma is usually characterized by CRAB symptoms. Bleeding is relatively uncommon in myeloma patients. As reported in a retrospective study[1], the incidence of hemorrhage is 7% in myeloma patients. Men appear to be more affected than women[2-6], most of whom are middle-aged and elderly patients (Table 1). In terms of bleeding sites, not only skin and mucos[1-4,7] but also deep vital organs[8-12] including the gastrointestinal tract, respiratory tract, brain, *etc* can be involved. Hemorrhagic symptoms can also manifest spontaneously or postoperatively[13-14], occur in isolated sites or multiple sites. With regard to Ig type, a literature review indicated that myeloma patients with IgA type were inclined to bleed[9-10,12,15]. This patient was also IgA-κ type.

The causes of bleeding in myeloma patients are mainly related to thrombocytopenia, hematopoietic failure due to infiltration of plasma cells or hyperviscosity syndrome. Patients rarely present with bleeding symptoms or coagulopathy alone. Our patient initially only presented with recurrent bleeding of oral mucosa and abnormal coagulation function. Factor X deficiency accounted for her coagulopathy. As the disease progressed, immunoglobulinemia, mild anemia, pneumonia, and heart failure were noted. The diagnosis of IgA-κ type multiple myeloma was finally confirmed by bone marrow tests and immunofixation electrophoresis.

Table 1 Summary of clinical features in patients with multiple myeloma with bleeding symptoms

Ref.	Number of bleeding cases/total cases	Gender (*n*)	Median/average age (yr)	Types of M protein (%)	Amyloidosis (*n*)	Bleeding sites	APTT	PT	TT	FIB	Involved coagulation factors (*n*)
Kyle[1], China, 2014	3	Male (3)	57	NS	Yes	Skin; Mucous	Prolonged	Prolonged	Prolonged	N	XX
Zou *et al* [2], China, 2002	44636	Male (9); Female (7)	68.9 (average)	IgG (87.5); IgA (6.25); IgD (6.25)	NS	Skin; Nasal mucosa; Gingiva	NS	NS	NS	NS	I, VII, X, Fbg
Zeng *et al* [3], China, 2013	44772	Male (16); Female (14)	60 ± 10 (average)	IgG (90); IgA (6.7);IgD (3.3)	NS	Skin; Nasal mucosa; Gingiva (7)	NS	NS	NS	NS	II, VIII
Xie *et al*[4], China, 2002	12/358	Male (208); Female (150)	55 (median)	NS	NS	Skin; Nasal mucosa; Gingiva (12)	NS	NS	NS	NS	NS
Zhuang *et al*[5], China, 2004	20/218	Male (136); Female (82)	57 (average)	IgG (45.3); IgA (18.4); IgD (11.7); IgM (0.6%); κ (11.2); λ (9.5); No secretion (2.2); bi-clone (1.1)	Yes (18)	NS	NS	NS	NS	NS	NS
Zhang *et al* [6], China, 2005	30/148	Male (98); Female (50)	58 (average)	Heavy chain types; IgG (44.7); IgA (22.0); IgM (2); No secretion (31.7); Light chain types; κ (47.7%); λ (52.3%)	NS	Nasal mucosa (17); Gingiva (7); Melena (6); Hematuria, fundus hemorrhage, gingiva	NS	NS	NS	NS	NS
Sari *et al* [13], Japan, 2008	1	Female	43	IgG	NS	Post operation of ovarian cyst	Prolonged	NS	NS	NS	VIII
Dicke *et al* [14], China, 2016	1	Male	63	IgG	NS	Post operation of orthodontics	Prolonged	NS	NS	1.8g/l	vWF:Ac
Hobbs *et al* [8], USA, 2019	1	Male	59	NS	NS	Gastrointestinal tract	Prolonged	prolonged	NS	NS	X
Kawashima *et al*[9], Japan, 2018	1	Male	52	IgA	NS	Thigh muscle, hematuria	Prolonged	N	NS	NS	VIII, vWF
Furube *et al* [10], Japan, 2018	1	Male	77	IgA	NS	lung	Prolonged	prolonged	NS	NS	NS
Richard *et*	1	Female	67	IgA	NS	Melena	Prolonged	N	N	NS	VIII, vWF

al[15], USA, 1990											
Li *et al*[7], England, 1977	1	Male	49	NS	Yes	Mucosa	Prolonged	Prolonged	Prolonged	low	X
Sun *et al* [11], USA, 2001	18/368	Male (221); Female (147)	58	NS	Yes	Gastrointestinal tract, hematuria, skin, spleen, abdomen	Prolonged	NS	NS	NS	X(32)
Zhang *et al* [12], USA, 2018	1	Male	48	IgA	NS	intracranial	NS	NS	NS	NS	NS

NS: No significance; N: Normal; κ: Kappa; λ: Lambda; APTT: Activated partial thromboplastin time; PT: Prothrombin time; TT: Thrombin time; FIB Fibrinogen.

The main mechanism of coagulation dysfunction in myeloma is believed to involve excessive immunoglobulins which affect coagulation factors, platelets, or fibrinogen, forming protein complexes. These complexes further lead to secondary deficiency of coagulation factors and hemorrhagic symptoms [7,11-12]. Factor II, VII, VIII, X, XI, XII, von W X gen deficiency have been reported in myeloma patients [2-3,16]. As reported, isolated acquired FX deficiency mostly occurs in amyloidosis, and is not so common in myeloma[16-18] (Table 1). In the largest clinical study on acquired Factor X deficiency and amyloidosis, of 368 consecutive patients with systemic light chain amyloidosis, 32 patients (8.7%) had factor X levels lower than 50% of the normal level. Eighteen of these patients (56%) had bleeding complications, which were more frequent and severe in the 12 patients who had factor X levels lower than 25% of the normal level[18]. Earlier studies indicated that the incidence of factor X deficiency in patients with amyloidosis was 6.3% to 14%[19]. With the exception of amyloidosis, isolated acquired factor X deficiency has seldom been reported in other diseases[20]. In this case, we failed to prove the existence of secondary amyloidosis. Before bleeding signs, the patient had cardiac arrhythmia, enlargement of the heart, and progressive heart failure; thus, cardiac amyloidosis was highly suspected. However, this was not proved as a cardiac muscle biopsy was difficult to obtain. Whether isolated acquired factor X deficiency can predict amyloidosis is worth further study.

CONCLUSION

Bleeding related to coagulation dysfunction is uncommon in multiple myeloma, especially as the initial manifestation. However, coagulopathy may still be the main complaint in myeloma patients. Many coagulation factors and coagulation inhibitors could be involved in myeloma including factor X. Amyloidosis is a well-recognized cause of isolated acquired factor X deficiency. Whether isolated acquired factor X deficiency can predict the presence of amyloidosis requires further investigation.

FOOTNOTES

Author contributions: Zhang Y and Fang Xu F contributed equally to this work; Zhang Y and Xu F designed the study; Zhang Y and Wen JJ collected the data; Zhang Y and Xu F analyzed the data; Zhang Y, Xu F, and Wen JJ interpreted the data; Zhang Y, Xu F, Wen JJ and Shi L prepared the manuscript; Shi L and Zhou QL searched and reviewed the literature.

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