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Case Report

A case of IgG multiple myeloma with initial presentation with treatment refractory spontaneous intramuscular bleeding – a clinical conundrum with diagnostic and therapeutic challenges

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Introduction

Multiple myeloma, the second most common haematological malignancy, is due to the clonal proliferation of plasma cells associated with excess monoclonal paraprotein secretion. It is diagnosed by demonstrating at least 10% of plasma cells in the bone marrow or the presence of extramedullary plasmacytoma, along with at least one of the following myeloma-defining events: anaemia, renal insufficiency or increased blood calcium and bone lesions. In addition, clonal bone marrow plasma cells of at least 60% and an abnormal serum-free light chain (FLC) ratio are independently diagnostic for multiple myeloma [1].

This case report presents the clinical course of a 59-year-old woman with difficult-to-control bleeding manifestations, eventually diagnosed with IgG-Kappa multiple myeloma. The report highlights the diagnostic dilemmas, treatment challenges and additional medical complications encountered in the management of this patient, shedding light on the complexities of managing bleeding in the context of multiple myeloma.

Case Report

A 59-year-old, postmenopausal woman with no significant past medical or family history was admitted to the general medical ward with a spontaneous onset, painful, progressively enlarging swelling on her right thigh, accompanied by a bruise on the overlying skin of 4 days duration. She had spontaneous episodic gum bleeding, fatigue, lethargy lasting for 2 weeks, and weight loss with anorexia for 2 months. However, she

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denied having a fever, other bleeding manifestations or abnormal bowel or urinary habits. On examination, the patient had a BMI of 18 kg/m² and normal vital signs. She exhibited severe conjunctival pallor but no lymphadenopathy or organomegaly. Palpation of the anterior aspect of the right thigh revealed a tender, firm, non-fluctuant lump measuring 15 x 20 cm. The rest of the physical examination was unremarkable. Table 1 summarizes the investigations performed. Rotational thromboelastometry indicated prolonged clotting time due to clotting factor abnormality with normal clot stability and no features of hyperfibrinolysis. The results of mixing studies are provided in Table 2. Screening for inhibitors upon incubation was negative. However, assays of levels of individual clotting factors or von Willebrand factor were not available at the facility.

Table 1. Investigations performed during presentation

Investigation (unit)	Patient's value	Normal range
Total white cell count (/uL)	6,200	4,000 – 10,000
Haemoglobin level (g/dL)	5.6	11.0 – 16.0
Mean corpuscular volume (fL)	93.5	80.0 – 94.0
Mean corpuscular haemoglobin (pg)	28.7	27.0 – 34.0
Platelet count (x10^3/uL)	667	150 – 450
Reticulocyte index (%)	5.34	0.3 – 3.0
LDH (U/L)	453	135 – 225
Serum iron (umol/L)	8.31	5.5 – 32.4
Transferrin saturation (%)	5	20 – 50
Prothrombin Time (sec)	103.3	11.0 – 13.0
International Normalized Ratio	>10.0	0.9 – 1.1
Activate Partial Thromboplastin Time (sec)	154.9	21 – 35
Bleeding time (min)	9	2 – 8
Clotting time (min)	13	2 – 8
Thrombin time (sec)	15.1	11.0 – 16.0
Plasma fibrinogen (mg/dL) by Clauss method	264	220 – 496
Erythrocyte sedimentation rate (mm/h)	99	<30
C-reactive protein (g/dL)	2.6	< 6.0
Serum albumin (g/dL)	4.8	3.5 – 5.3
Serum globulin (g/dL)	5.2	2.0 – 3.3
Serum creatinine (umol/L)	38.12	45.0 – 84.0
Serum potassium (mmol/L)	3.8	3.5 – 5.0
Serum sodium (mmol/L)	132	135 – 145
Serum ionized calcium (mmol/L)	2.7	2.1 – 2.5
Urine protein Creatinine ratio (mg of Protein/g of creatinine)	1225	<150

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Table 2. Results of mixing studies

50:50 mixing of patient's plasma with	Prothrombin time (control – 12.9 seconds)	Activated Partial Thromboplastin Time (control – 34.2 seconds)
Control plasma	14.1	33.5
Factor VIII deficient plasma	-	35.3
Factor IX deficient plasma	-	56.3

An ultrasound of the thigh, revealed a 9.7 x 11 x 7.4 cm haematoma in the upper anteromedial aspect of the right thigh with possible communication with the right superficial artery. There was a positive urine Bence Jones protein and a monoclonal protein level of 33g/L with an IgG kappa monoclonal band on serum protein immunofixation (Figure1).

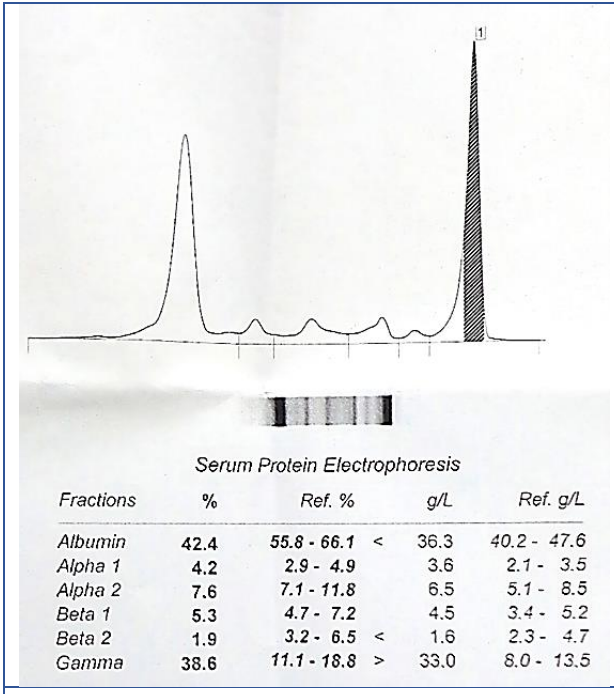

Figure 1: Serum protein electrophoresis report

Lateral radiograph of the skull showed a few lytic lesions (Figure 2). Blood picture revealed moderate rouleaux formation and many plasma cells (Figure 3).

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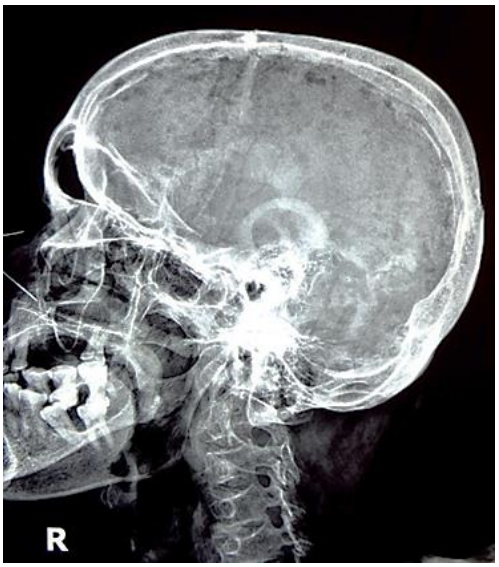

Figure 2: Lytic lesions on skull radiograph

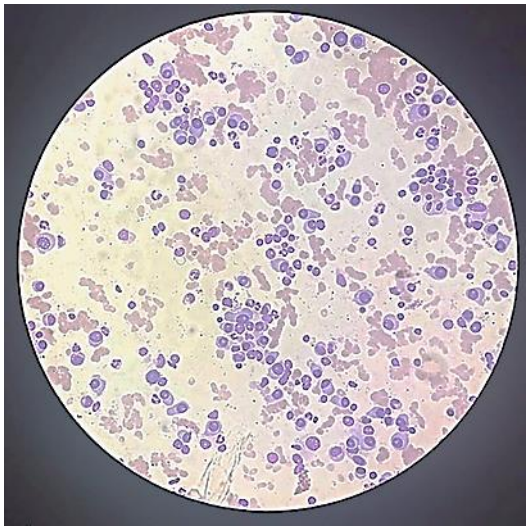

Figure 3: Blood picture revealed moderated rouleaux formation of red cells and numerous plasma cells

Bone marrow aspiration revealed 60% marrow infiltration with plasmablasts, binucleated and trinucleated plasma cells, suppressed erythropoiesis, intact granulopoiesis and megakaryopoiesis and depleted iron stores. Immunohistochemical staining of bone marrow trephine biopsy confirmed the diagnosis of multiple myeloma with more than 70% infiltration with CD138-positive myeloma cells. Tests for anti-nuclear factor, CA 125, AFP, CEA, and antibodies against Hepatitis B and Hepatitis C were negative. Congo red staining of bone marrow and fat aspirate were negative ruling out amyloidosis.

A diagnosis of IgG-Kappa myeloma associated with acquired clotting factor deficiency, hypercalcemia and anaemia was made. She was seen by the specialist haematology team. Her bleeding manifestations and prolongation of INR and APTT remained refractory to a massive transfusion protocol with packed red blood cells, platelets, coagulation factor replacement, vitamin K, folic acid therapy, tranexamic acid and administration of 4-factor prothrombin complex concentrate (4F-PCC). Bleeding and deranged coagulation profile stabilized temporarily up to 2 days with fresh frozen plasma (FFP).

The patient was offered chemotherapy cycles containing bortezemib, thalidomide and dexamethasone. Despite receiving multiple cycles of therapy, bleeding manifestations persisted and complete resolution of the INR and APTT was not observed. Due to her high risk of major bleeding, she was advised on fall prevention measures. Her subsequent prolonged hospital stay was complicated by glucocorticoid or hypercalcemia precipitated pancreatitis and pseudocyst, chemotherapy-induced neutropenic sepsis and myocardial infarction with new-onset left bundle branch block. She succumbed to severe COVID-19 infection, 9 months after initial presentation, while on multiple myeloma specific treatment.

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Discussion

The patient presented with non-traumatic, progressively enlarging, thigh haematoma, gum bleeding, fatigue and constitutional symptoms, raising concerns of an underlying systemic pathology. Laboratory findings revealed iron deficiency anaemia, reactive thrombocytosis and abnormal coagulation parameters including prolonged PT and APTT indicating a clotting factor deficiency. Importantly, the mixing studies and lack of inhibitors suggested that the clotting abnormalities were not due to the presence of circulating antibodies against clotting factors. Amyloidosis was also ruled out. The normal thrombin time and rotational thromboelastographic findings make dysfibrinogenaemia unlikely. Normal bleeding time makes platelet dysfunction unlikely. The findings pointed towards reduced synthesis or consumption of clotting factors, as the possible mechanism underlying her bleeding.

Bone marrow aspiration and trephine biopsy confirmed the diagnosis of multiple myeloma. The elevated IgG-Kappa monoclonal protein levels and the presence of Bence Jones protein in the urine further supported the diagnosis. Additionally, the patient exhibited hypercalcemia, lytic bone lesions and proteinuria, which are known complications of multiple myeloma.

Common presentations of multiple myeloma include hypercalcemia (13%), renal failure (20%-40%), anaemia (70%), lytic bone lesions (80%), weight loss (24%) and recurrent infections [2]. Bleeding diathesis occurs in less than 15% of patients with multiple myeloma. Bleeding complications are more likely with IgM (36%) and IgA (33%) paraproteins than with IgG (13%) [3]. Increased risk of bleeding is associated with higher concentrations of serum immunoglobins, higher serum viscosity and prolonged bleeding time but not with low platelet counts, prolonged prothrombin time, prolonged activated partial thromboplastin time or prolonged thrombin time [3]. It is postulated that multiple pathogenic mechanisms including thrombocytopenia from bone marrow failure, paraprotein-induced thrombosthaenia, reduced platelet survival, damage to vascular endothelium, dysfibrinogenaemia causing inhibition of fibrin polymerization, presence of monoclonal thrombin inhibitor, circulating heparin-like anticoagulant, acquired clotting factor deficiencies, acquired Von Willebrand syndrome, AL-amyloidosis related vascular damage and AL-amyloidosis related factor X deficiency, acquired fibrinolysis due to excess plasminogen activator and increased heparin-like circulating anticoagulants contribute to the bleeding these patients. [4]. Bleeding manifestations in multiple myeloma contribute to significant morbidity and mortality and are frequently related to disease progression, therapy related toxicity, infections, renal insufficiency and invasive procedures, rather than to the monoclonal paraprotein itself [8].

The management of bleeding problems in plasma cell dyscrasias is poorly covered in the literature. Protamine sulfate in the presence of an acquired heparin-like anticoagulant, arginine, vasopressin and platelet factor 4 are some of the treatment regimens that can be employed for the symptomatic management of bleeding [9]. In refractory cases, splenectomy, intravenous immunoglobulin, plasma exchange and extracorporeal immune absorption have been tried [2]. Despite treatment with clotting factor

replacement therapies such as FFP and 4F-PCC and attempted control of underlying disease with chemotherapy, our patient's bleeding manifestations persisted, and complete resolution of the coagulopathies was not achieved. We also faced challenges in diagnosing the exact clotting factor or factors deficient in this patient. This limitation hindered the ability to precisely tailor factor replacement therapies and indicates that access to specialized laboratory resources can lead to precise diagnosis, risk stratification, tailored treatment plans and, ultimately, to improved patient outcomes.

Conclusion

This case report highlights the diagnostic challenges, treatment complexities, and additional medical complications encountered in a patient with difficult-to-control bleeding manifestations, ultimately attributed to IgG-Kappa multiple myeloma. The difficulties in identifying the specific clotting factor deficiency due to the lack of facilities for individual factor level assessments underscore the need for improved diagnostic resources in managing acquired clotting factor deficiencies.

The case also emphasizes the importance of a multidisciplinary approach, to optimize patient care and address the complexities associated with multiple myeloma and bleeding tendencies. Further research is warranted to enhance our understanding of the underlying mechanisms and develop targeted therapeutic strategies to improve the management of bleeding complications in patients with multiple myeloma.

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