Case report

Acquired factor X deficiency in a patient with multiple myeloma: a rare case highlighting the significance of comprehensive evaluation and the need for antimyeloma therapy for bleeding diathesis

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SUMMARY

Factor X deficiency is a rare bleeding disorder that can be associated with life-threatening bleeding events. Factor X deficiency can either be inherited or acquired. Acquired cases of factor X deficiency can be seen in patients with plasma cell dyscrasias as well as amyloidosis. Coagulopathy, with clinically relevant bleeding events, although rare, is not an unusual phenomenon for patients with systemic amyloidosis. However, clinically relevant bleeding in patients with symptomatic multiple myeloma, without associated amyloidosis, has not been reported in literature before. We present a rare case of multiple myeloma without concomitant amyloidosis that presented with life-threatening bleeding from acquired deficiency of factor X and responded remarkably to treatment for underlying multiple myeloma. This case not only highlights the diagnostic workup required in patients with factor X deficiency but also provides the principles of management of acquired coagulopathy in plasma cell dyscrasias.

BACKGROUND

Multiple myeloma and amyloidosis are two of the most common haematological malignancies. Presentation for these haematological malignancies can be highly varied due to localised and/or systemic involvement. Coagulopathy, although rare, is not entirely unusual in patients with systemic amyloidosis. Diagnostic workup for bleeding diathesis requires careful evaluation of the coagulation profile as well as testing for plasma cell dyscrasias and amyloidosis. Provided a good control of the underlying disorder is achieved, factor X coagulopathy can be treated with reasonable efficacy, avoiding life-threatening bleeding complications.

CASE PRESENTATION

A 59-year-old African-American man with no prior history of coagulopathy presented to the hospital with melena of 1-month duration. Melena was associated with fatigue and pain in the right upper thigh and knee. Physical examination revealed a 6 cm palpable mass in his right-upper leg. The patient denied the use of any anticoagulant or antiplatelet agents. He denied any social history of alcohol abuse or family history of bleeding disorders.

INVESTIGATIONS

Initial laboratory studies revealed a creatinine level of 3.13 g/dL, haemoglobin of 60 g/L, platelets of 106 000/μL, serum calcium 9.3 mg/dL, albumin 3.5 g/dL and beta-2 microglobulin 8.5 g/dL. Coagulation studies revealed prothrombin time (PT) of 45 s, partial thromboplastin time (PTT) of 40 s and an international normalised ratio (INR) of 3.3. Mixing studies revealed normalisation of both PT and PTT with normal plasma, consistent with coagulation factor deficiency. Direct measurement of factor X activity by functional quantitative chromogenic assay was <2%, where activity <10% [0.1 international units/mL] is considered as factor X deficiency. CT scan of the right-lower extremity revealed a 6.6 cm soft tissue density within the distal right femur marrow space; however, lytic lesions were absent on comprehensive skeletal survey. Serum protein electrophoresis showed no monoclonal protein, but the serum kappa light chains were elevated at 470 mg/dL, lambda light chains at 2.7 mg/dL and serum kappa/lambda-free light chain ratio elevated at 175. The 24-hour urine collection revealed 80 mg/24 hours of proteinuria with no kappa or lambda light chains or Bence Jones proteins detected in urine. Bone marrow biopsy revealed a hypercellular marrow (70% cellularity) with multilineage haematopoiesis and maturation and an abnormal population of CD138+ plasma cells identified by flow cytometry analysis. Plasma cells comprised 80%–90% of the total marrow cellularity by CD138 immunohistochemistry with no morphological evidence of overt dysplasia seen. Karyotype was normal male 46 XY. FISH analysis was consistent with standard risk cytogenetics ie, negative for deletion 13 q, t(4;14), t(14;16), t(14;20) or gain of 1 q. Congo red staining of the bone marrow specimen did not reveal the presence of amyloidosis. This was followed by an abdominal fat pad biopsy which failed to reveal evidence of amyloidosis.

DIFFERENTIAL DIAGNOSIS

The results of coagulation profile and mixing study were consistent with factor X deficiency. With no previous personal or family history of bleeding disorders, this was considered an acquired factor X deficiency and factor X assay confirmed the

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diagnosis. Liver dysfunction was considered one of the underlying etiologies for acquired factor X deficiency, but liver enzymes were normal. Workup for plasma cell dyscrasias was consistent with multiple myeloma. As factor X deficiency is typically seen in patients with concomitant multiple myeloma and amyloidosis, a comprehensive workup, including bone marrow Congo red staining and fat pad biopsy, was conducted to exclude the presence of amyloidosis. Based on the entire workup, the final diagnosis was made as symptomatic multiple myeloma International Staging System stage III with acquired factor X deficiency.

TREATMENT

While undergoing evaluation for coagulopathy and active gastrointestinal (GI) bleeding, the patient was aggressively resuscitated with 3 units of packed red blood cells, 4 units of fresh frozen plasma and a one-time dose of 2500 units (25 units/kg) of prothrombin complex concentrate. For source control, he underwent emergent esophagogastroduodenoscopy which revealed bleeding gastric and duodenal ulcers which were clipped. For factor X deficiency, he received factor X concentrates (Coagadex) at 25 units/kg every 24 hours. Once bleeding was controlled, factor X was infused two times weekly for prophylaxis at 25 units/kg keeping factor X through activity >50% (5 international units/mL). Once the resolution of melena and stabilisation of haemoglobin were achieved, the patient was started on a combination chemotherapy of lenalidomide, bortezomib and dexamethasone every 3 weeks for four cycles, resulting in very good partial response based on the reduction of serum free light chain burden and bone marrow plasma cell percentage. Subsequent stem cell mobilisation with filgrastim and plerixafor yielded (adequate) 7.2×10^6 CD34+ cells/kg. The patient eventually underwent myeloablative conditioning with melphalan at 200 mg/m^2 , followed by infusion of 3×10^6 CD34+ cells/kg of haematopoietic stem cells.

OUTCOME AND FOLLOW-UP

By day 40 post the postautologous stem cell transplant, the patient's coagulation profile (PT/PTT/INR) and factor X activity had normalised (70%–140%) and he achieved complete independence from factor X infusions.

Post-transplant evaluation on day 90 was consistent with ongoing very good partial response based on serum free light chains and bone marrow plasma cell percentage. He was started on maintenance lenalidomide and continues to enjoy good response to antimyeloma therapy and independence from factor X infusions (figure 1).

DISCUSSION

Multiple myeloma is characterised by the proliferation of malignant clones of plasma cell origin with excess production of monoclonal immunoglobulins. Patients may present with one or more of the features included in the CRAB criteria (hypercalcaemia, renal disease, anaemia and bone disease). The criteria proposed by the International Myeloma Working Group is used to diagnose and differentiate multiple myeloma from other plasma cell dyscrasias.¹ Laboratory workup includes complete blood count and comprehensive metabolic panel to evaluate for the presence of anaemia (haemoglobin $\leq 120 \text{ g/L}$), renal failure (creatinine $\geq 2 \text{ mg/dL}$) and elevated protein or hypercalcaemia ($\geq 11 \text{ mg/dL}$). Serum and urine protein electrophoresis help identify spike in M-protein, whereas the immunofixation study confirms the presence and type of protein. Kappa/lambda serum free light chain ratio may be abnormal (<0.26 or >1.65) with involved/uninvolved serum free light chain ratio of >100 considered as myeloma defining event. In the presence of one or more of the CRAB features, a bone marrow biopsy showing $\geq 10\%$ clonal plasma cells is necessary to establish diagnosis of symptomatic multiple myeloma. However, more than 60% involvement of the bone marrow with atypical plasma cells is considered a myeloma defining event.² Imaging studies including skeletal survey, positron emission tomography -CT and/or whole/limited body MRI help identify the presence of skeleton-related events ie, lytic bony lesion, compression fractures and cord compression.³

If a patient is a candidate for intensive treatment, including autologous stem cell transplant, induction therapy using a three-drug regimen (bortezomib, lenalidomide, dexamethasone) as used on our patient, is preferred over a two-drug regimen. This is followed by consolidation with high-dose

Figure 1 Improvement in the coagulation profile in response to antimyeloma therapy.

chemotherapy and rescue with infusion of autologous haematopoietic stem cells. Post-transplant maintenance with lenalidomide or bortezomib improves both, progression-free survival and overall survival. For transplant in eligible patients, induction therapy with a similar triplet or doublet chemotherapeutic regimen is continued until a stable disease response is achieved, followed by maintenance therapy until disease progression.³

Factor X deficiency is a rare disorder with an associated incidence of 1 in a million in the general population.⁴ Patients typically present with bleeding into joints, mucosal surfaces, brain and gastrointestinal tract. Factor X deficiency can be an inherited or acquired disorder. Association of factor X deficiency with systemic amyloid light-chain (AL) amyloidosis is reported in 6.3% to 14% of the cases. Although not entirely unusual, isolated factor X deficiency (without other concomitant factor deficiencies) is rarely acquired from haematological conditions other than amyloidosis and has only been reported in 34 patients with non-amyloid haematological disorders per study published in 2012.⁵ Some of the potential causes of acquired factor X deficiency include vitamin K deficiency, anticoagulant therapy, liver disease, drugs (eg, phenytoin), upper respiratory tract viral infection and malignancy (eg, chronic myelomonocytic leukaemia, primary or secondary hepatic malignancy).⁶ There are several mechanisms that explain the underlying pathophysiology including the formation of complexes between paraproteins and factor X with subsequent sequestration by the reticuloendothelial system,⁷ IgG4-mediated interruption of factor X activation (specific factor X inhibitor)⁸ and adsorption of coagulation factors by amyloid fibrils (seen in patients with concomitant amyloidosis). Diagnosis is suspected when both PT and PTT are elevated with normal bleeding time. Correction of PT and PTT on mixing with normal plasma differentiates factor X deficiency from the presence of inhibitors (eg, seen in lupus anticoagulant, specific factor antibody). Factor X activity <10% is associated with significant life-threatening bleeding events.

Once diagnosis has been established, human coagulation factor X is the recommended treatment as it replenishes only the required component and has no side effects that are associated with fresh frozen plasma (allergic reactions, transfusion-related acute lung injury) and prothrombin complex concentrate (hypercoagulable complications such as disseminated intravascular coagulation and venous thromboembolism).⁹ Vitamin K administration is considered in those with suspected deficiency or severe liver dysfunction. For cases secondary to amyloidosis, splenectomy by virtue of limiting reticuloendothelial sequestration has shown promising results, giving complete and long-lasting correction of factor X deficiency.¹⁰ For life-threatening bleeding, emergent control of source of bleeding (eg, clipping of GI bleed, nasal packing for epistaxis) is strongly recommended. Given the significantly increased risk of bleeding, factor X activity should be maintained above 10% using human coagulation factor X, fresh frozen plasma, prothrombin complex concentrates and/or vitamin K as needed.¹¹ Once adequate control of bleeding has been achieved, factor X concentrates should be infused two times weekly keeping Factor X trough activity above 50%.⁹ For patients with underlying plasma cell dyscrasias, definitive therapy in the form of induction chemotherapy, followed by consolidation with high dose therapy–autologous stem cell transplant has the strongest likelihood of achieving long-term improvement in factor X levels and independence from factor infusions. Based on a retrospective analysis, 32 out of 368 patients with

AL amyloidosis had factor X activity <50%, with bleeding events seen in 56% of the patients. 10 out of the 32 patients received high dose melphalan followed by autologous stem cell transplant. For the seven out of 10 patients that survived 1 year post-transplant, six showed adequate haematological response (four complete response, two partial response) and were free of factor X deficiency. Only one patient was labelled as non-responder.¹¹ Hence, high dose melphalan followed by autologous stem cell transplant can be potentially curative for factor X deficiency.

Learning points

- ▶ Consider acquired coagulopathy in patients with multiple myeloma and/or amyloidosis who present with bleeding. Coagulation profile (prothrombin time/partial thromboplastin time/international normalised ratio, mixing studies and factor levels should be tested to determine specific factor deficiency).
- ▶ Conversely, in a patient with known or new-onset coagulopathy, underlying multiple myeloma and/or amyloidosis should be considered in the differential diagnoses and laboratory investigations including complete blood count, comprehensive metabolic panel, serum protein electrophoresis with immune fixation and serum free light chains should be part of the necessary workup.
- ▶ Acquired factor X deficiency is rarely seen in multiple myeloma with absence of concomitant amyloidosis. Presence of amyloidosis can have serious prognostic and therapeutic implications. Hence, comprehensive evaluation for underlying amyloidosis with Congo red staining of the bone marrow and a fat pad biopsy should be considered in patients presenting with bleeding diathesis and multiple myeloma.
- ▶ Treatment for underlying plasma cell dyscrasia, including high dose therapy with melphalan and autologous hematopoietic stem cell transplantation, may be required for definitive treatment of coagulation factor X deficiency and to achieve independence from factor replacement.

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