 DOI:10.19056/ijmdsjssmes/2017/v6i2/149915

Case Report

Amyloidosis presenting as severe bleeding diathesis

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Received: 19-02-2017
Revised: 27-02-2017
Accepted: 01-03-2017

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ABSTRACT

Bleeding is one of the rare presentations of Amyloidosis. The mechanism behind spontaneous or peri- interventional bleeding in patients of amyloidosis is complex and involves multiple co-existing factors like coagulation factor deficiency, abnormal synthesis of coagulation factors due to advanced liver dysfunction, acquired Von Willebrand disease, platelet dysfunction, amyloid angiopathy and other unknown mechanisms. We present a case of middle aged female, presenting with spontaneous retroperitoneal haemorrhage, on further investigations was found to have systemic amyloidosis and secondary severe factor X deficiency (2.7 % of normal by one stage factor assay method). Factor X deficiency (both inherited and acquired) is known to present with the most severe bleeding phenotype. The management option for such acute spontaneous haemorrhage is limited and mostly supportive in nature. Definitive treatment is directed towards the primary pathology and requires chemotherapy and hematopoietic stem cell transplantation.

Key Words: *Amyloidosis, bleeding, factor X deficiency, platelet dysfunction*

Introduction

Amyloidosis is a heterogeneous disorder presenting with a myriad of symptoms. Almost a third of patients (15% -41%) of amyloidosis present with bleeding symptoms during the course of disease. [1,2] This bleeding can be either an associated finding in a known case of amyloidosis or rarely, be the presenting feature in some patients. [3] Also, the severity of bleeding is variable ranging from minor skin bleeds, peri-interventional bleeds to fatal bleedings like cerebral haemorrhage, Gastrointestinal bleeding, retroperitoneal bleeding etc. [1] In patients where the cause of bleeding is a diagnostic dilemma, finding the primary pathology is of paramount importance as the management is mostly directed towards the primary pathology.

The pathomechanisms of abnormal bleeding in patients with systemic amyloidosis are complex and are dependent on the type of amyloidosis and extent of different organ involvement. [4] The most common cause for bleeding in systemic amyloidosis is found to be acquired coagulation factor deficiencies for e.g factor X deficiency, factor V deficiency, factor II deficiency, factor VII deficiency and rarely combined factor deficiencies of two or more factors. [4] These acquired factor deficiencies in patients of amyloidosis can be partly explained by adsorption of coagulation factors by amyloid fibrils and partly by their reduced synthesis due to secondary liver dysfunction which is common in these patients. [5] Other proposed mechanisms for bleeding in amyloidosis are abnormal fibrin polymerization, hyperfibrinolysis, platelet dysfunction caused by amyloid fibrils, amyloid deposition in micro vessels (amyloid angiopathy) and haemostatic abnormality secondary to renal

dysfunction. [4] Often these mechanisms operate simultaneously and it is difficult to pin point the exact cause of bleeding. The management of such patients involves supportive treatment in acute setting and specific chemotherapy for the underlying pathology. [5] Such cases pose great diagnostic difficulties and a lot of time and efforts may be lost in unnecessary investigations or treatment.

Case Report

Mrs X, a 48 yrs old female, presented to the emergency department with complaints of sudden onset of pain in lower abdomen. The pain was severe, continuous and not associated with fever, vomiting, loose motions, bleeding per rectum or any urinary symptoms. Patient gave history of generalized weakness and fatigue for past few months and noticeable weight loss (5 kg in 3 months). She had two grown up children born by caesarean section. Old medical documents revealed history of splenectomy 9 months earlier for a sudden onset hematoma. On examination, the patient was in distress due to pain, however was conscious and oriented. Vitals showed hypotension (80/50mmHg), tachycardia (124 bpm) and pallor. She was afebrile and had no icterus, cyanosis or lymaphadenopathy. Abdominal examination showed tender abdomen and a soft fluctuating mass in suprapubic region. Also, liver was palpable 5 cm below costal margin.

Investigation showed Hb of 35 g/L, WBC count of 13,800/cmm, platelet count 284000/cmm, Prothrombin time (PT) was prolonged at 20 sec (control 11-14 sec) and INR - 2.37. Abdominal CT scan showed hepatomegaly (liver span -23 cm) and large retroperitoneal hematoma (11x8x6.5 cm) in midline. The patient was taken up for emergency exploratory laparotomy with packed red cells and FFP support. The retroperitoneal hematoma was evacuated; however the surgeons could not find cause for the bleeding. Before closing the abdomen, a liver biopsy was taken to look for cause of hepatomegaly. The patient made an uneventful recovery postoperatively. However, her coagulation profile remained deranged (PT-21 sec, APTT – 42sec).

The liver biopsy on histopathology showed, focal deposition of acellular amorphous eosinophillic material between hepatocytes which was confirmed to be amyloid. Further evaluation revealed high Alkaline phosphatase (Bilirubin – 1.2mg/dl, AST/ ALT- 35/42 IU/L, ALP – 420 IU/L), normal renal function tests & serum electrolytes. A monoclonal spike was detected on serum protein electrophoresis in gamma region (1.4 gm/dl) and skewed Free light chain levels (kappa / lambda ratio of 9.09, kappa –259.23 mg/l lambda- 28.49mg/l). 2- D echocardiography revealed cardiomegaly with normal LV function and normal ejection fraction. Bone marrow examination revealed a normocellular marrow with mild prominence of mature plasma cells (10%) and deposition of acellular amorphous eosinophillic material extracellularly as well as in the blood vessels wall. (Fig. 1,2,3) Congo Red staining on bone marrow biopsy showed apple green birefringence; thereby confirming the presence of amyloid.

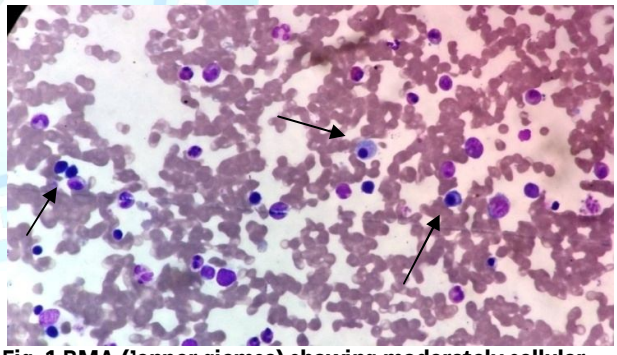

Fig. 1 BMA (Jenner giemsa) showing moderately cellular Bone marrow and mild prominence of plasma cells (10%)

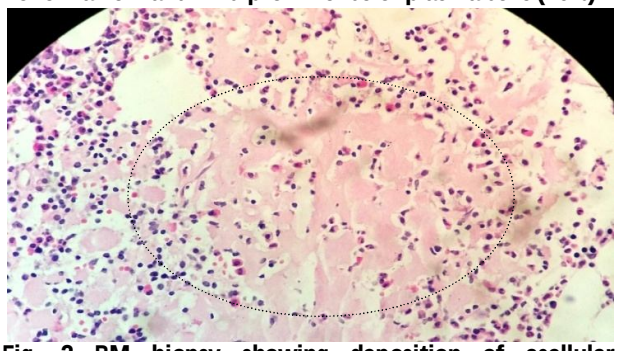

Fig. 2 BM biopsy showing deposition of acellular eosinophillic material which showed apple green birefringence under polarized light (Amyloid deposition)

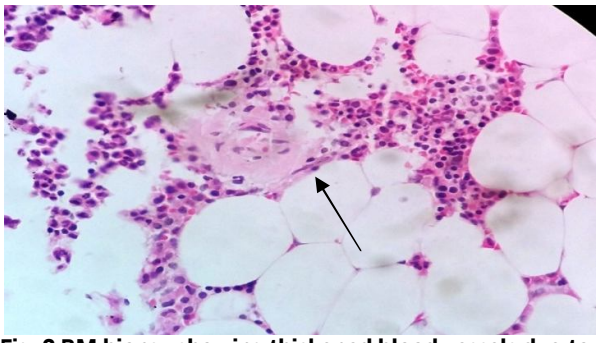

Fig. 3 BM biopsy showing thickened blood vessels due to deposition of amyloid in cell wall

Coagulation workup done during evaluation showed prolonged Prothrombin time and activated prothrombin time (PT-25 sec, APTT 45 sec, Thrombin Time-19 sec, fibrinogen – 340 mg/dl). On mixing with normal plasma, both PT and APTT were corrected thereby indicating towards a coagulation factor deficiency. Factor level assays were done for common pathway factors using one stage factor assay method with factor X and factor V deficient plasma. The tests revealed a normal factor V level (90% of the normal) and severely reduced Factor X levels (2.7% of the normal). Inhibitor assay done for factor X inhibitor was negative for presence of inhibitors. A final diagnosis of primary amyloidosis with bleeding diathesis due to factor X deficiency was made. The patient is currently under our OPD follow up and had not had any bleeding events thereafter. The plan is to give supportive care (FFP) during bleeding episodes and start her on chemotherapy for amyloidosis after complete work up.

Discussion

Potentially fatal bleeding can be present in almost 20% cases of primary amyloidosis and it can involve virtually any organ. [1] Isolated factor X deficiency has been found to be the most common cause and has been reported to occur in 8.7% to 14% of patients. [6] This was shown in a large series of 95 patients by Griepp et al in 1986. [6] Factor X deficiency is described to occur mainly via the adsorption of factor X to amyloid fibrils however presence of acquired inhibitors has also been reported. [7] Coagulogram in present case showed prolongation of both PT and APTT with normal TT and tests for inhibitor was negative. Severity of bleeding usually correlates well with the severity of factor deficiency. [5] More than half of the patients have moderate deficiency (25-50%) however, those who have severe deficiency (<25%) present with severe bleeding complications requiring FFP (fresh frozen plasma) transfusions. [5] The risk increases manifold if the patient requires any invasive procedure or organ biopsies for confirmation of diagnosis. [1,2,5] The present case showed severe factor X deficiency at 2.7% of normal levels.

Till date, the data regarding the treatment of bleeding due to factor deficiency in primary amyloidosis is sparse. Replacement with prothrombin complex concentrates and fresh frozen plasma may not be yielding as the factor X in these products gets adsorbed onto the amyloid and, thus, be removed from the circulation quickly. [7] Recombinant factor VIIa and plasma exchange have been reported to be successful however their use has not been validated till now. [7] Resolution of hemostatic abnormality has been described by many investigators post splenectomy which helps by removing a considerable burden of amyloid. [8] Spontaneous remission with no specific active therapy has also been described in literature. [9] As a more aggressive approach, high-dose chemotherapy followed by autologous stem-cell transplantation usually have the best response rate of up to 60% as described by Chouffeni et al and thus offer advantages regarding long term outcome or survival. [5] However, the significant morbidity and mortality associated with this modality of treatment leaves patient selection a matter of debate, especially in patients with multiple vital organ involvement.

In conclusion, advances in therapy necessitate early histological diagnosis of amyloid diseases. To prevent bleeding complications either during the diagnostic workup or in the course of the disease, exact classification of an underlying haemostatic disorder is mandatory.

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Cite this article as: Tripathi P, Pati HP, Tyagi S, Mahapatra M, Ahuja A, Saxena R. Amyloidosis presenting as severe bleeding diathesis. Int J Med and Dent Sci 2017;6(2):1535-1538.

Source of Support: Nil
Conflict of Interest: No