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Case Report

Elevated Prothrombin Time: An unusual presentation of Monoclonal Gammopathy of Undermined Significance – A Case Report and literature review

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Abstract

Monoclonal Gammopathy of Undetermined Significance (MGUS) is one of the plasma cell dyscrasias. An isolated finding of a monoclonal para-protein in serum or urine is the hallmark finding in MGUS. Most often it is found incidentally during an unrelated medical evaluation and/ or investigation to find a cause for neuropathy, anaemia, rashes, vasculitis or elevated Erythrocyte Sedimentation Rate (ESR). This case report illustrates an evaluation of a patient with persistently elevated prothrombin time has eventually lead to a diagnosis of MGUS.

Key words

Monoclonal Gammopathy of Undetermined Significance (MGUS), Prothrombin time, haematuria

Introduction

There are two different types of MGUS: Non-IgM type, IgM type. Each type constitutes a distinctive intermediate premalignant stage and may progress to an overt lymphoproliferative disorder or a malignant plasma cell dyscrasia. [1]

Non-IgM Mgus is defined as the presence of the serum M-protein (IgG, IgA or rarely IgD) at a concentration of <30g/l with clonal bone marrow plasma cells <10% and absence of end organ damage such as hypercalcemia, renal insufficiency, anaemia and bone lesions, and amyloidosis attributable to the plasma cell proliferative disorder. IgM-MGUS is defined by a serum IgM paraprotein concentration <30g/l with bone marrow lymphoplasmacytic infiltration of <10% and no evidence of anaemia, constitutional symptoms, hyper viscosity, hepatosplenomegaly or other end organ damage that can be associated with underlying lymphoproliferative disorder.

Several Studies have reported an increase in the incidence of arterial and venous thrombosis in patients with MGUS. [2,3,4] Even though the mechanism is not still clearly understood, it is presumed that the prevailing clonal plasma cell activity may lead to an acquired hypercoagulable state.

It is stated in some studies that the isolated prolong Prothrombin Time is seen among patients with plasma cell dyscrasia, and it correlate with the significantly higher monoclonal protein level in patients with multiple myeloma than the patients with other plasma cell neoplasms. [5]

Case history

A 63-year-old gentleman with a history of type 2 Diabetes Mellitus, Hypertension and coronary heart disease of eight years' duration presented with symptomatic anaemia to the medical ward. During the initial admission he was noted to have macroscopic haematuria following urinary

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catheterization which did not settle with parenteral vitamin K which was given as his prothrombin time was prolonged. However, he was discharged from the surgical ward with a plan to be followed up at the urology clinic. As he had persistently prolonged prothrombin time without apparent any other bleeding manifestations even three weeks after the first admission, he underwent further evaluation to identify the cause. Investigations are summarized in table 1.

Table 1: Summary of Investigation Findings

Full Blood Count White cell count Hb MCV Platelet count	 $10.79*10^9$/l (4.00-11.00) 90g/l (12-16) 88.6fl(80-96) $124*10^9$/l (150-450)
Serum urea Serum sodium Serum potassium Serum creatinine	7.1mmol/l 138 mmol/l 3.6 mmol/l 150 µmol/l 126µmol/l
ESR	40mm/hr
Urine Protein Urine Bence Jones Protein	Nil Negative
Total protein Serum albumin Serum globulin	54g/dl 23g/dl 31g/dl
Prothrombin time INR APTT	22.4s 1.9 36.50s (28-40s)
Fasting blood sugar	93mg/dl
2D Echocardiogram	Ejection fraction 70% Left ventricular hypertrophy with diastolic dysfunction
Lower limb venous duplex	No evidence of deep vein thrombosis
Fundoscopy	No diabetic retinopathy
Sputum acid-fast bacilli	Negative in three samples
Rotational thrombo-elastometry (ROTEM)	No evidence of coagulopathy

His corrected serum calcium, serum phosphate and serum magnesium levels were normal. Additionally, his serum TSH, free T4, ferritin and uric acid levels were also within normal range while ASOT and Mantoux test were negative.

In view of his anaemia, the blood picture findings were in favour of anaemia of renal pathology with recent blood loss. The oesophagoduodenoscopy revealed reflux oesophagitis with antral gastritis. Findings of the Ultrasound scan of the abdomen were suggestive of prostatomegaly with bladder outflow obstruction causing bilateral hydronephrosis and hydroureter with normal renal cortical echgenicity. Additionally, his prostate specific antigen level was within normal range.

Serum protein electrophoresis yielded a monoclonal peak in IgA lambda region (Figure 1).

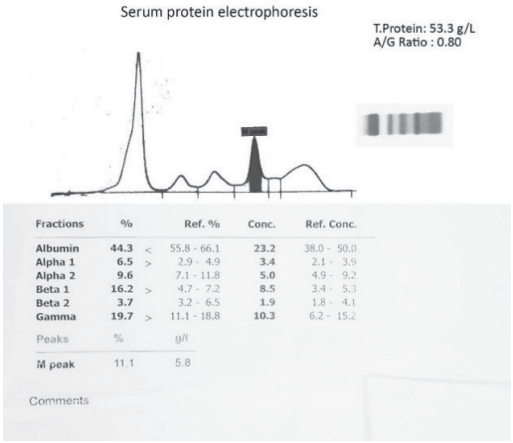


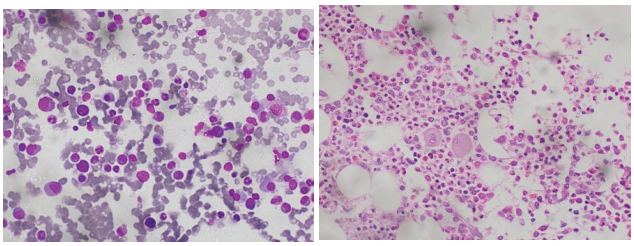
Figure 1: Serum Protein Electrophoresis

The skeletal survey findings were unremarkable with no evidence of lytic lesions or compression fracture of spine which prompted a bone marrow biopsy and the findings (Figure 2) were in favour of Monoclonal Gammopathy of Undetermined Significance with bone marrow plasma cells 7% M protein 5.8g/l. Additionally, Congo red staining revealed no evidence to suggest an amyloid deposition.

He was managed conservatively with supportive care and symptomatic treatment. As there is no

clear role for a specific pharmacological therapy, a routine review at monthly interval was planned by the haematology team. The result of the repeat serum protein electrophoresis is awaited.

Figure 2: Bone marrow picture



Discussion

This case report is based on a patient, who was not on an anticoagulation therapy however had bleeding manifestations with prolonged prothrombin time (PT) and normal activated partial thromboplastin time(APTT). The traditional list for this combination of prolonged PT with normal APTT include liver disease, vitamin K deficiency, vitamin K antagonist (warfarin) therapy, chronic low-grade disseminated intravascular coagulation and decreased or defective factor VII. In this patient, further evaluation confirmed the presence of monoclonal protein of IgA lambda with a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) which can rarely manifest with prolonged prothrombin time.

A patient with MGUS could present with an array of clinical symptoms and disorders. However, it is most often an incidental finding while evaluating for peripheral neuropathy, vasculitis, haemolytic anaemia, skin rashes, hypercalcaemia or elevated erythrocyte sedimentation rate. [6] The diagnosis necessitates bone marrow biopsy and exclusion of end organ damage related to lymphoplasmacytic proliferative disorders.

In this case, the abnormal finding was a prolongation of prothrombin time which usually associates with multiple myeloma out of the other monoclonal gammopathies. [5] However, there are few cases only described in the literature of MGUS where the initial presentation was prolongation of PT with bleeding manifestations.

There are several mechanisms that could lead to bleeding manifestations in patients with monoclonal gammopathies, namely, amyloid adsorption leading to factor deficiencies, M-proteins inhibiting the coagulation factors, impairment in polymerization of fibrin monomers and systemic fibrinolysis. [7] It is documented that the concentration of M-proteins in the plasma correlates with the extent of bleeding, suggesting M-protein is important in pathogenesis of the bleeding manifestations. [7] However, the haematological manifestations differ in individual patients and inappropriate therapeutic intervention may lead to unfavorable outcome.

Conclusion

The concentration of M-proteins in the plasma is known to correlate with the bleeding tendencies in patients with plasma cell disorders. However, it should be emphasized that even patients with a serum monoclonal immunoglobulin concentration of less than 30g/l can present with bleeding manifestations, compelling careful evaluation.

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