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CAN YOU DIAGNOSE IMMUNE THROMBOCYTOPENIA IN MYELOMA? A CASE OF THROMBOCYTOPENIA IN A PATIENT WITH MULTIPLE MYELOMA

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ABSTRACT

Multiple myeloma (MM) is the second most common haematological malignancy, the diagnosis of which has doubled in recent years. Immune thrombocytopenia consists of isolated thrombocytopenia secondary to antibody mediated peripheral platelet destruction. In most cases, there is no identifiable cause (primary immune thrombocytopenia). Its association with multiple myeloma is rare. Early recognition of this association is essential for raising awareness among clinicians, allowing for a rapid differential diagnosis and therapeutic optimization, reducing side effects and improving prognosis. Thus, we present a clinical case of concomitant immune thrombocytopenia and MM, whose initial presentation was thrombocytopenia. This clinical case is the first case among thirteen described in the literature in which chemotherapy was the initial treatment for both pathologies, as seen in this review.

KEYWORDS

Multiple myeloma, immune thrombocytopenia, differential diagnosis, association, chemotherapy

LEARNING POINTS

- Multiple myeloma is the second most common haematological malignancy and is associated with a broad group of pathologies, including, in some cases, autoimmune manifestations. Thrombocytopenia in multiple myeloma is common due to therapy or bone marrow plasmacytosis, but the association of immune thrombocytopenia with multiple myeloma is rare.
- Raising clinicians' awareness of the association of multiple myeloma with immune thrombocytopenia is essential for a rapid differential diagnosis. This can alter therapeutic possibilities and consequent patient prognoses.

INTRODUCTION

Multiple myeloma (MM) is a plasma cell disorder characterized by monoclonal proliferation of plasma cells, and it is the second most common haematological malignancy (10-15%), with an estimated incidence in Europe of 4.5-6/100,000 inhabitants per year[1]. The diagnosis of this pathology has almost doubled in recent years; however, despite the significant improvement in patient survival,

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only 10 to 15% achieve the expected survival compared to the general population[1,2]. Its classic presentation is called hypercalcemia, renal failure, anaemia and lytic bone lesions (CRAB)[1,3-10]. Rarely, MM can also be asymptomatic. To establish the diagnosis of MM, more than 10% clonal bone marrow plasma cells or histopathological confirmation of plasmacytoma (bone or extramedullary) and at least one multiple myeloma-defining event are required[1,10].

The risk factors for developing MM are advanced age, family history, male sex, environmental factors such as exposure to chemical substances or ionizing radiation, as well as a history of autoimmune diseases. However, despite the higher risk of developing MM described in patients with autoimmune diseases[11], the diagnosis of immune thrombocytopenia (ITP) is rarely documented simultaneously with MM in the literature, as in the majority of cases thrombocytopenia in MM is due to therapy myelotoxicity or bone marrow plasmacytosis[12-16].

CASE DESCRIPTION

A 62-year-old man was referred for new onset isolated thrombocytopenia (platelets 52 x10^9/l). He described a single episode of self-limited epistaxis due to more intense exertion in the past weeks. No other blood losses, recent travels or contact with animals. The physical examination was unremarkable. An etiological study of thrombocytopenia was carried out, excluding toxic, infectious causes (including human immunodeficiency virus, hepatitis C and *Helicobacter pylori*), metabolic causes (thyroid function, vitamin deficiencies) or autoimmune and liver diseases, as well as pseudothrombocytopenia *(Table 1)*. Peripheral blood smear showed only occasional giant platelets. Serum protein electrophoresis and immunofixation were positive for monoclonal IgG lambda, with IgG 6249 mg/dl (700-1600 mg/dl) and associated immunoparesis and lambda/kappa free light chain ratio of 70.61 (1.53-3.29) *(Table 1)*. The whole-body skeletal survey revealed lytic lesions on the skull and distal portion of the right lower limb *(Fig. 1)*. The bone marrow assessment revealed 23% medullary plasmacytosis, which, together with the bone lesions, was compatible with symptomatic MM and an indication for starting treatment. It also showed an increased megakaryocytic proliferation, comparable with peripheral platelet destruction, as seen in immune thrombocytopenia. Immune thrombocytopenia specific treatment was not initiated because the patient did not meet any criteria, namely active bleeding episodes or platelet count <20-30 x10^9/l[14-16]. The patient was referred to the haematology department and started induction treatment for multiple myeloma with bortezomib, lenalidomide and dexamethasone (RVd) with normalization of the platelet count and medullary megakaryopoiesis, during the first cycle, which remained stable throughout induction treatment.

DISCUSSION

We have reported a rare case of immune thrombocytopenia diagnosed simultaneously with multiple myeloma. ITP is defined as an isolated thrombocytopenia with a platelet count <100 ×10^9/l, without anaemia or leukopenia and without another apparent cause of thrombocytopenia. It is caused by antibody mediated peripheral platelet destruction, mostly in the spleen. No single test exists that confirms the diagnosis and therefore ITP is a diagnosis of exclusion[15]. However, secondary causes of immune thrombocytopenia are well documented, such as connective tissue disorders or certain haematological malignancies. Severe thrombocytopenia at the time of MM diagnosis is unusual, with <10% of patients having a platelet count <100 ×10^9/l. Platelet counts <20 ×10^9/l are very unusual and thrombocytopenia as the sole abnormal hemogram abnormality in patients with MM is exceedingly rare[1]. The patient's peripheral blood smear showed giant platelets, which is rare in thrombocytopenia secondary to bone marrow plasmacytosis but common in ITP as they represent immature platelets released into the blood stream by an increased megakaryopoiesis, in an attempt to compensate for the peripheral platelet destruction. The

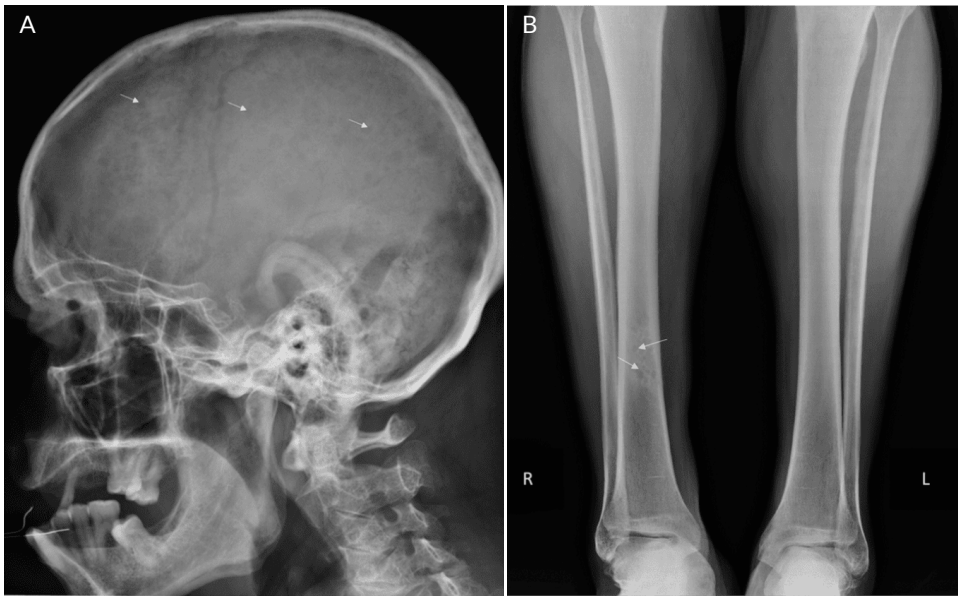


Figure 1. Lytic lesions on A) the skull and on B) the distal portion of the right lower limb revealed on whole-body skeletal survey.

Test	Results	Reference range
White blood cells (x10^{3}µl)	8.5	4-10
Neutrophils (x10^{3}µl)	4.5	1.8-8
Haemoglobin (g/dl)	13.5	13-17.7
Platelets (x10^3/µl)	**52**	150-500
Peripheral blood smear	**No platelet aggregates. Presence of some giant platelets.** Otherwise, unremarkable.	
PA anti–GPIIb-IIIa autoantibodies	Negative	
ESR (mm)	**71**	<10
Creatinine (mg/dl)	0.85	0.67-1.18
Ionized calcium (mmol/l)	1.16	1.15-1.3
Total proteins (g/l)	**104**	66-83
Albumin (g/l)	**32**	35-52
Bilirubin (mmol/l)	15.1	5-21
ALT (U/l)	25	3-34
GGTP (U/l)	12	<38
TSH (µUI/ml)	2.75	0.38-5.33
Vitamin B12 (ng/ml)	257	180-914
Folate (ng/ml)	5.6	>2.3
CRP (mg/l)	3.5	<5
Hepatitis B virus serology	Negative	
Hepatitis C virus serology	Negative	
HIV serology	Negative	
H. pylori breath test	Negative	
ANA	Negative	Positive ≥160
C3 (mg/dl)	134	90-180
C4 (mg/dl)	30	10-40
Serum protein electrophoresis and immunofixation	**Monoclonal IgG lambda (46.5 g/l)**	
IgG (mg/dl)	**6249**	7000-1600
IgA (mg/dl)	**20**	70-400
IgM (mg/dl)	**19**	40-230
Kappa free light chain (mg/dl)	**114**	629-1350
Lambda free light chain (mg/dl)	**8050**	313-723
Evolved free light chain ratio	**70.61**	1.53-3.29
Bone marrow smear	**23% plasma cells**, otherwise unremarkable	
Trephine bone marrow biopsy	**12% plasma cells and increased megakaryocytic proliferation**	

Abbreviations: MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; RDW, red cell distribution width; PA, platelet-associated; ESR, erythrocyte sedimentation rate; ALT, alanine transaminase; AST, aspartate transferase; GGTP, gamma-glutamyl transpeptidase; TSH, thyroid-stimulating hormone; CRP, C-reactive protein; HIV, human immunodeficiency virus; ANA, antinuclear antibody test; C3, Complement C3; C4, Complement C4; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M.

Table 1. Results of extensive blood tests was performed for the differential diagnosis. Abnormal results are shown in bold.

finding of an increased megakaryocytic proliferation in the bone marrow trephine biopsy supports the assumption of an increased peripheral platelet destruction as the main cause for the patient's isolated thrombocytopenia, as seen in ITP. As mentioned above, in most cases, thrombocytopenia in the setting of MM is due to medullary infiltration by plasma cells or therapy-related myelosuppression, both impairing normal haematopoiesis and, as such, patients present with cytopenias, most commonly anaemia. The bone marrow trephine biopsy usually shows reduced megakaryocytic proliferation, which, consequently, causes impaired platelet production[1-3,6-9,13].

Both these finding led us to conclude that the patient had a simultaneous diagnosis of MM and (possibly secondary) immune thrombocytopenia. We can even hypothesize that the monoclonal IgG produced by the malignant plasma cell clone could somehow be involved in the antibody mediated peripheral platelet destruction. Furthermore, the negative result in the assay for antibodies to specific platelet glycoproteins does not rule out immune thrombocytopenia,

Reference	Age/Sex	M protein type (diagnosis)	M protein (g/l)	Hb (g/dl)	Platelet count (x10^9/l)	BM plasma cells (%)	Immune thrombocytopenia diagnosis timing	Immune thrombocytopenia management	Immune thrombocytopenia response to treatment (x10^9/l)
Sarfraz et al.[3]	60 y/M	IgG/lambda	0.8	5.9	1	30	At MM diagnosis	MM directed therapy	171
Jain et al.[4]	57 y/F	IgA/kappa	N/A	11.0	29	20	At MM diagnosis	Prednisone	29
Verdirame et al.[5]	67 y/F	IgG/lambda	2.4; 3.4	N/A	10	25	After MM treatment	Prednisone and splenectomy	219
Verdirame et al.[5]	55 y/M	IgG/kappa	3.4	N/A	69	12	During MM treatment	Prednisone and splenectomy	652
Gupta et al.[7]	49 y/M	IgG/lambda	4.0	5.9	21	20	At MM diagnosis	IVIg and MM directed therapy	100
Gupta et al.[7]	36 y/M	IgG/kappa	11.9	N/A	5	N/A	Before MM diagnosis	MM directed therapy and IVIg, prednisone and splenectomy	80
Gupta et al.[7]	45 y/F	IgG/lambda	6.1	N/A	20	N/A	Before MM diagnosis	Prednisone, IVIg and splenectomy	N/A
Falco et al.[8]	45 y/M	IgG/kappa	1.8	12.5	97	10	After MM treatment	Prednisone, IVIg, thalidomide	250
Faller et al.[12]	66 y/M	IgA/kappa	10	N/A	<10	20	After MM treatment	IVIg	171
Faller et al.[12]	41 y/F	IgG/kappa	12.5	N/A	<10	18	After MM treatment	IVIg and dexamethasone	177
Tabata et al.[17]	78 y/M	IgG/kappa	4.18	11.3	17	N/A	At MM diagnosis	MM directed therapy	21
Yao et al.[9]	61 y/M	IgG/kappa	60.5	N/A	27	9	Before MM diagnosis	Prednisolone and IVIg	100
Siniscalchi et al.[13]	67 y/F	IgG/kappa	26	10	3	30	At MM diagnosis	Prednisone, IVIg, Rituximab	100

Abbreviations: y, years; F, female; M, male; N/A, not applicable; Hb, haemoglobin; IVIg, intravenous immunoglobulin; BM, bone marrow; MM, multiple myeloma.

Table 2. Cases of immune thrombocytopenia purpura with MM described in the literature to date excluding the current case.

as said assays have high specificity but low sensitivity, and thus, are not routinely recommended in the latest guidelines. There are few similar cases in the literature. Tabata et al. presented the case of a patient with MM complicated by thrombocytopenia[17]. The patient was treated with melphalan and prednisolone (MP), which were suspended due to severe neutropenia, leading to MM progression[17] as well as progressive worsening thrombocytopenia due to an increase of antibodies associated with platelets despite the number of preserved megakaryocytes in bone marrow assessment[4].

The literature contains twelve cases of immune thrombocytopenia associated with MM *(Table 2)*. Verdirame et al. presented one case where thrombocytopenia developed after the treatment of MM with MP and Jain et al. another case where it developed during treatment with MP[4-5]. The authors believe it was an immune thrombocytopenia concomitant with MM and not a thrombocytopenia secondary to chemotherapy since the patient's bone marrow study showed megakaryocytic proliferation, even at the end of treatment with melphalan, a drug associated with high rates of myelosuppression. In the cases presented by Jain et al., it was impossible to exclude all known causes of thrombocytopenia since the patients were undergoing chemotherapy[4]. However, as they underwent several consecutive cycles of chemotherapy without recurrence of thrombocytopenia, the diagnosis of presumed ITP was made[4]. Jain A et al. also reported a similar case of immune thrombocytopenia associated with indolent MM that responded to corticosteroid therapy, the recommended first line therapy for ITP, normalizing the platelet count[4], without starting MM directed therapy.

Gupta et al. described three cases with clinical manifestations of immune thrombocytopenia in patients diagnosed with MM[7]. Thrombocytopenia was the primary presentation in two of those cases with MM being subsequently diagnosed[7]. This clinical course is similar to that observed in immune thrombocytopenia secondary to lymphoproliferative diseases. In all three cases, the secondary causes of thrombocytopenia were excluded, and the diagnosis was presumed ITP[7].

Despite several cases described, the underlying aetiology of ITP concomitant with or preceding the diagnosis of MM remains unknown. It is believed that it can be related to inflammatory processes and chronic stimulation of immune responses, potentiating clonal proliferation and consequent development of dyscrasias of the plasma cells[2,11]. Sarfraz et al., among other authors, point out that is important to include ITP in the differential diagnosis of patients with MM whose first manifestation is isolated severe thrombocytopenia (20-30 x10^9/l) because although the majority of cases of immune thrombocytopenia that need immediate treatment respond well to corticosteroid therapy or intravenous immunoglobulins, there are others refractory these therapies that require the control of the underlying disease[3,7,9,11-13,17].

Our rare case of MM and concomitant immune thrombocytopenia treated with antineoplastic therapy

should raise awareness to the complex and little understood relation between these two clinical entities. As mentioned above, in our case, immune thrombocytopenia directed treatment was not initiated because the patient did not meet any criteria[14-16], avoiding possible complications. Awareness of the high efficacy of chemotherapy regimens in the treatment of MM and MM related immune thrombocytopenia is essential for therapeutic optimization, to avoid inappropriate treatment and to improve prognosis.

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