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Abnormal hemostasis screening tests leading to diagnosis of multiple myeloma

Abstract

Multiple myeloma (MM) is a rare malignancy, characterized by clonal proliferation of plasma cells, secreting monoclonal immunoglobulin. It is usually diagnosed based on histopathologic and immunophenotypic bone marrow examination. Abnormal results of screening coagulation tests, including prothrombin time, activated partial thromboplastin time and thrombin time, are commonly encountered in patients with plasma cell neoplasms. They do not, however, reflect bleeding tendency. We describe a 71-year-old patient who was accidentally diagnosed with multiple myeloma during coagulation diagnostics.

Keywords:

multiple myeloma, paraprotein, hemostasis screening test, thrombin time

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Multiple myeloma (MM) is a rare malignancy, characterized by clonal proliferation of plasma cells. Monoclonal immunoglobulin (paraprotein), secreted by plasmocytes, can cause plasma hyperviscosity and renal damage. Proliferation of plasma cells can lead to bone marrow suppression and cause hypercalcaemia. These features of MM give rise to different symptoms, such as bone pain from direct skeletal involvement, fatigue from anemia, or headache from hyperviscosity. The incidence of MM is estimated at 4.5-6/100 000 [1]. It mostly (90%) affects people above 50 years of age (median 70 years), more often men (M/W = 1.21) [2].

The diagnosis of MM requires detection of clonal plasma cells in histopathologic and immunophenotypic examination of bone marrow or in extramedullary plasmacytic tumor biopsy. Blood examination reveals increased total protein concentration and presence of monoclonal protein, as well as hypercalcaemia (in 30% of patients), increased uric acid concentration (50%), creatinine (35%), C-reactive protein, beta-2 microglobulin and lactate dehydrogenase. Erythrocyte sedimentation rate over 40 mm/1h is typical for MM (84%). Complete blood count (CBC) abnormalities include normocytic anemia (ca 70%), rouleaux-forming erythrocytes (50%), leukopenia and thrombocytopenia (20% and 5%, respectively) [1, 2].

It is known that plasma cell dyscrasias can be accompanied by both thrombotic and hemorrhagic events, including venous thrombosis, acquired von Willebrand syndrome and acquired hemophilia. Increased risk of venous thromboembolism in myeloma patients is associated with increased FVIII and von Willebrand factor activity [3, 4, 5], decreased protein S activity [3] and acquired resistance to activated protein C [6]. Bleeding occurs in approximately 15% of patients with IgG and more than 30% of patients with IgA and IgM monoclonal proteins [7, 8]. Coagulation defects that result in bleeding diathesis are caused by a variety of mechanisms, including coagulation factor deficiencies due to amyloid adsorption [9], production of paraproteins with inhibitory activity toward coagulation factors [10, 11], e.g. von Willebrand factor [12], circulating proteins with heparin-like activity [13], impaired fibrin monomer polymerization [14–17] or systemic fibrinolysis [18]. Abnormal screening coagulation test results, including prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT), are commonly encountered in patients with plasma cell neoplasms and are not typically associated with clinically significant bleeding [4, 5].

We describe a patient who was accidentally diagnosed with multiple myeloma during diagnostic work-up of screening coagulation tests prolongation. A 71-year-old patient diagnosed with renal tumor was referred to the hematologist due to abnormal results of pre-surgery screening tests: PT (1,25 INR, normal range: 0.85-1.15), APTT (42 s, normal range: 25.0-33.5) and TT (58 s, normal range: 14.0-21.0). Fibrinogen level, transaminase activities and CBC (complete blood count) were normal. No bleeding symptoms were present neither at presentation nor in the past. Teeth extractions were uncomplicated as well as cataract surgery, despite documented abnormalities in coagulation tests. The patient complained of no symptoms. He suffered from benign prostatic hyperplasia, treated with finasteride. He was also taking numerous herbs and dietary supplements at his own discretion: saw palmetto, vitamin E, vitamin C, magnesium, sodium bicarbonate, curcuma and olive oil with lemon.

Laboratory analysis confirmed previous findings: PT was 14 s (1.25 INR), APTT 42.5 s and TT 60.2 s with normal fibrinogen concentration assessed with both Clauss method (2.2 g/L, normal range: 1.8-3.5) and nephelometry (3.1 g/L, normal range: 1.8-3.5). Results of repeated tests, performed after 2 weeks wash-out from all over-the-counter preparations, were not different. Coagulation factors activity was normal [table I]. Batroxobin time (BT) and D-dimer were normal (18.9 s, normal range: 16.0-22.0 and < 0.17 mg/L, normal range: < 0.55, respectively). All coagulometric parameters were performed using Siemens kits with BCS XP analyzer (Siemens, Germany). Due to significant disproportion of TT and BT values dabigatran plasma concentration was measured with Innovance DTI Assay (Siemens, Germany) and yielded a positive result: 31 ng/ mL (near the lower limit of measuring range). The patient and his family denied dabigatran intake, therefore a false positive result was suspected. Further diagnostics included antiphospholipid antibodies and paraprotein assessment. Presence of lupus anticoagulant

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and IgG/IgM anticardiolipin antibodies was excluded. Total protein concentration was significantly increased (91.6 g/L, normal range: 66.0-87.0) and monoclonal beta-globulin was detected (43.2 g/L) (Fig. 1). Serum calcium concentration was increased to 2.73 mmol/L (normal range: 2.15-2.55). Serum immunofixation test showed kappa immunoglobulin G. Urine examination also revealed the presence of monoclonal light chains. Bone marrow histopathology showed diffuse (80%) infiltration of atypical plasma cells. Computed tomography detected multiple osteolytic lesions of the spine and flat bones, as well as fractures of L3 and L4 vertebrae. Analysis of chromosomes stained by the GTG and FISH stripes showed: 46, XY[20] nuc ish (IGH, TP53, D17Z10x2[200]. Multiple myeloma IgG kappa was diagnosed, ISS (International Staging System) stage II. After four VTD cycles (thalidomide, dexamethasone, bortezomib) the patient achieved partial remission of MM.

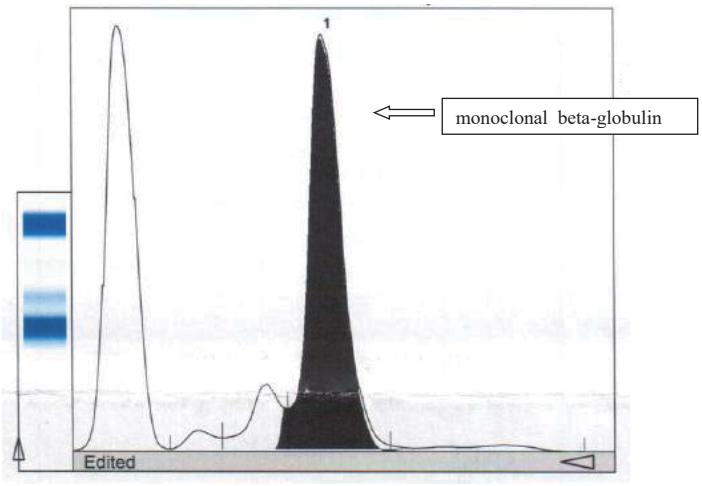
Discussion

Numerous studies addressed the issue of abnormal screening coagulation tests in asymptomatic patients with multiple myeloma and other plasma cell neoplasms. Post et al. [19] and Xin-yao [20] showed that the PT, but not APTT, was positively correlated with serum paraprotein level, regardless of the reagents and instrumentation used to assess clotting time. Huang et al. [21] and Pandey et al. [22] confirmed this finding and, more importantly, showed a strong correlation between TT prolongation and total light chain (not M protein) concentration. Prolonged TT most likely results from acquired dysfibrinogenemia, secondary to multiple myeloma. Fibrin polymerization induced by thrombin was impaired by paraprotein, interacting with γ-chain of the fibrinogen molecule [23]. Light chain paraprotein might have a stronger nonspecific binding effect to fibrinogen and can affect TT more likely than other immunoglobulin types. In most cases TT prolongation was accompanied by a prolonged PT, suggesting that TT is more sensitive to the presence of monoclonal protein than PT [22]. This hypothesis is in line with our observations. All three screening tests (PT, APTT, TT) were prolonged, but TT to the greatest extend (almost 3 times). We also measured BT that evaluates the same part of the coagulation process with the use of batroxobin instead of thrombin (batroxobin is a proteolytic snake venom enzyme, inducing coagulation by cleavage of fibrinopeptide A from fibrinogen). Disproportion between TT and BT is typical for dysfibrinogenemia, heparin therapy and also for the

Table I. Results of laboratory parameters measured before the diagnosis of multiple myeloma

Test	I visit	II visit	Reference range
PT (sec)	14.0	13.5	9.8-12.1
PT (INR)	1.30	1.20	0.85-1.15
APTT (sec)	42.5	40.0	25.0-33.5
TT (sec)	60.2	59.9	14.0-21.0
BT (sec)	18.9	18.7	16.0-22.0
Fibrinogen (Clauss method, g/L)	2.0	2.2	1.8-3.5
Fibrinogen (nephelometric method, g/L)		3.1	1.8-3.5
D-dimer (mg/L)		< 0.17	< 0.55
Factor II (%)	116.1		50-150
Factor V (%)	126.2		50-150
Factor VIII (%)	103.8		50-150
Factor IX (%)	122.8		50-150
Factor X (%)	94.2		50-150
Factor XI (%)	82.6		50-150
Factor XII (%)	58.0		50-150
GGTP (U/L)	11		8-61
Cholinesterase (U/L)	7622		5320-12920
LDH (U/l)		119	135-225
Lupus anticoagulant		negative	negative
Anticardiolipin antibodies IgG (GPL)		2.5	< 10
Anticardiolipin antibodies IgM (MPL)		1.3	< 20
Calcium (mmol/L)		2.73	2.15-2.55
Total protein (g/L)		91.6	66.0-87.0
Monoclonal protein (g/L)		43.2	0
Beta-2 microglobulin		2.23	1.09-2.53

Abbreviations: PT– prothrombin time; APTT – activated partial thromboplastin time; TT – thrombin time; BT– batroxobine time; GGTP – gamma-glutamyl transpeptidase; LDH – lactate dehydrogenase.



Fraction	Result (%)	Reference range (%)	Result (g/l)	Reference range (g/l)
Albumin	41.5 ↓	60.0-71.0	38.1	35.0-55.0
Alpha 1	2.1	1.4- 2.9	2.0	0.9- 2.1
Alpha 2	7.5	7.0-11.0	6.9	5.0- 7.9
Beta	46.9 ↑	8.0-13.0	43.2↑	5.7- 7.9
Gamma	2.0 ↓	9.0-16.0	1.9↓	6.5-11.5

Fig. 1. Electrophoresis of serum proteins

presence of paraprotein (no interaction with thrombin is detected). The same disproportion is visible during dabigatran therapy; this is why we decided to perform the dilute thrombin assay. Its abnormal result can be explained by a similar interference to that observed in the TT assay (the presence of paraprotein impaired thrombin induced fibrin polymerization).

We noticed a small disproportion in fibrinogen levels measured with two different methods (functional Clauss assay and nephelometric test), with both results remaining in the reference range (2.2 g/L and 3.1 g/L). It may likely reflect an acquire dysfibrinogenemia state, observed sometimes in patients with MM [23]. Richter et al. [24] suggest that light chain paraprotein is not prone to inhibit coagulation factors, accordingly this was not the reason of coagulation tests prolongation in our patient (all clotting factors activities remained normal).

It is worth emphasizing that the results of coagulation assays does not always reflect the real coagulation status in vivo. Coagulation disturbances, however, tend to increase with the progress of the disease [25].

Authors' contributions/ Wkład autorów

TI – performance of laboratory tests, data analysis, writing the manuscript.

JZ – clinical assessment of the patient, reviewing the manuscript.

AJ – clinical assessment of the patient, data analysis, reviewing the manuscript.

Conflict of interest/ Konflikt interesu

We declare no conflict of interest.

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Ethics/Etyka

The work descibed in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to biomedical journals.

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