Thrombotic complications in multiple myeloma: a report of three cases and review of the literature

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Abstract The risk of venous thromboembolism (VTE) increases in the presence of plasma cell dyscrasias. Monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) share an intrinsic increased risk of VTE. Treatment with thalidomide and lenalidomide further increases the incidence of VTE in certain MM patient subsets. The pathogenesis remains unclear, but probably involves several factors such as activation of procoagulant factors, acquired activated protein C resistance, and inflammation. In addition to general risk factors for VTE, such as older age, immobility, surgery, and inherited thrombophilia, there are some MM-specific and treatment-related factors that contribute to the increased risk. The risk for VTE is high under treatment with thalidomide or lenalidomide in combination with dexamethasone or multi-agent chemotherapy. We report 3 cases of MM with VTE with review of the literature. This review highlights the risk factors for VTE in MM and general, disease-specific and treatment-related mechanisms for thrombosis.

Keywords Plasma cell dyscrasia · Multiple myeloma · Monoclonal gammopathy of unknown significance · Venous thromboembolism

Introduction

MM can be associated with hemostatic abnormalities, more often bleeding than thrombosis. The association with

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thrombosis is unclear because of coexisting factors such as old age and immobility, which confound the interpretation of available data; however, the risk of thrombosis may be increased in MM patients [1, 2]. Monoclonal proteins have been shown to be responsible for the development of lupus anticoagulants [3, 4], acquired protein S deficiency [5, 6], acquired activated protein C resistance [7], and inhibition of tissue plasminogen activator [8]. Venous thrombotic complications are more common than generally appreciated in MGUS and MM, but the underlying pathogenesis remains unclear and the risk cannot be predicted with currently available laboratory tests. Successive clinical trials have confirmed dramatic improvements in survival for MM patients treated with thalidomide and lenolidomide. Unfortunately, this success has been accompanied by high rates of VTE, and insufficient progress has been made toward determining the most appropriate prophylactic strategy for deep vein thrombosis (DVT). We report the clinical and laboratory features of 3 MM patients with thrombosis.

Cases

Case 1

A 48-year-old man suffering from headache and loss of consciousness was admitted to the neurology department 6 years ago. He was diagnosed with dural sinus vein thrombosis. Screening tests for hypercoagulability were normal. The laboratory parameters were normal except M-protein:1.4 g/dl consistent with monoclonal gammopathy of undetermined significance (MGUS). Oral anticoagulant (warfarin sodium) for 6 months was given. Four months after the cessation of warfarin sodium, the patient

presented with deep venous thrombosis (DVT) of the left lower leg. The laboratory results were as follows: hemoglobin 11.9 g/dl, hematocrit 34%, total leukocytes 6000/mm^3, neutrophils 2230/mm^3 and platelets 228000/mm^3, erythrocyte sedimentation rate 120 mm/h, LDH 264 U/L, calcium 9.1 mg/dl and albumin 3.6 g/dl. Serum protein electrophoresis revealed monoclonal paraprotein (M protein:4.56 g/dl) with IgG-kappa type monoclonal paraproteinemia on serum immunofixation electrophoresis. Pelvic plain film showed lytic bone lesions on the left acetabulum and left side of inferior pubic ramus. The bone marrow was normocelular with patchy interstitial plasma cell infiltration. Serum beta-2 microglobulin level was 2.37 mg/l (normal, 0–2.5 mg/l). The diagnosis was multiple myeloma (MM) of IgG-kappa type (Durie-Salmon Stage IIIA, ISS Stage I). VAD protocol (vincristine 0.4 mg/day and adriamycine 9 mg/m^2/day on days 1–4, oral dexamethasone 40 mg/day on days 1–4, 9–12 and 17–20) was initiated as remission induction therapy with monthly intravenous bisphosphonate, zoledronate 4 mg. The patient was retreated with oral anticoagulant for 6 months. After 6 VAD courses, partial response was attained with serum monoclonal band reduced to 50% of the basal level (4.56–2.26 g/dl). Zoledronate was stopped after 3 years due to osteonecrosis of the jaw. After 4 years, M-protein was 2.64 g/dl. Six courses of bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11 plus dexamethasone 40 mg/day on days 1, 2, 4, 5, 8, 9, 11, 12 and cyclophosphamide 750 mg/m^2/day intravenous infusion on days 1 and 3 was given. After 6 courses, M-protein was 0.24 g/dl, evaluated as very good partial response (VGPR). Subsequently, dexamethasone 40 mg/day on days 1–4 per month was given as maintenance therapy. Three months later, G-CSF (10 µg/kg/day) was used for mobilization of autologous peripheral stem cells with a yield of CD34-positive cells of 5×10^6/kg. Autologous peripheral blood stem cell transplantation (PBSCT) with high dose melphalan (200 mg/m^2) as the conditioning regimen was performed in the presence of VGPR status. The patient is still under follow-up in our hematology department.

Case 2

A 48-year-old man was examined for bilateral paralysis of the lower extremities 1 year ago. On dorsolumbar magnetic resonance, there was spinal cord compression by a 65×30 mm solitary thoracic extradural mass at the level of D9 vertebrae. The excisional biopsy of the mass lesion was consistent with plasma cell myeloma of kappa light chain. The laboratory results showed the following: hemoglobin 9.8 g/dl, hematocrit 27%, total leukocyte 6000/mm^3, neutrophil 2500/mm^3 and platelets 381000/mm^3, erythrocyte sedimentation rate 55 mm/h, LDH 337 U/l, creatinine

0.8 mg/dl, calcium 9.9 mg/dl, albumin 3.5 g/dl. On serum protein electrophoresis, M protein was 1.33 g/dl and IgG-kappa type monoclonal paraproteinemia was present on serum immunofixation electrophoresis. Serum beta-2 microglobulin level was 2.5 mg/l. 10% of the cells obtained on bone marrow aspirate were plasma cells and the biopsy revealed CD38 (+) interstitial plasma cell infiltration. The diagnosis was MM of IgG-kappa type (Durie-Salmon Stage IIA, ISS Stage I). Palliative radiotherapy was given to the area of the mass lesion on thoracic vertebrae. Subsequent remission induction therapy was initiated as dexamethasone 40 mg/day on days 1–4, 9–12 and 17–20 with monthly intravenous zoledronate. Two months later, lytic lesions on the left side of femur and both humerus appeared on plain films. Because of progressive disease status, thalidomide 200 mg/day, low-dose dexamethasone and low-dose aspirin for thrombo-prophylaxis were given. On the first month of this regimen, DVT of the left lower leg developed. Thalidomide was cessated and oral anticoagulation was started. The new treatment regimen was six courses of bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11 plus dexamethasone 40 mg/day on days 1, 2, 4, 5, 8, 9, 11, 12 and cyclophosphamide 750 mg/m^2 intravenous infusion on days 1 and 3. Following six courses, radiotherapy was performed to lesions on D12-S2 vertebrae, right and left humerus. Also, cervical (C6) corpectomy with subsequent radiotherapy was applied. After 1 month, radiological findings showed a 4 cm plasmocytoma in the left asetabulum and bilateral avascular necrosis of the femoral heads. Lenalidomide 25 mg on days 1–21 in a 28 day cycle and oral dexamethasone 40 mg/day on days 1–4, 9–12 and 17–20 were started. At the end of the first cycle, DVT of the right lower leg occurred despite oral anticoagulant treatment. Radiotherapy was applied to the left hip. One month later, the patient was admitted to the orthopedics department with multiple abcesses in the right scapular region, left gluteal region, right humerus and multiple plasmocytomas in costae. Fracture of the left 8th costa was detected. Cultures from the debridement of the right humerus abcess revealed metisiline sensitive *Staphylococcus auerus*. Vancomycin and gentamycine were started. After 3 months, the laboratory results were as follows: hemoglobin 5.7 g/dl, hematocrit 17%, total leukocytes 650/mm^3, neutrophils 430/mm^3 and platelets 99000/mm^3, erythrocyte sedimentation rate 120 mm/h, LDH 348 U/l, calcium 8.56 mg/dl. Serum protein electrophoresis revealed M protein of 0.9 g/dl. Cells on bone marrow aspirate were all plasma cells, some of which were atypical and multilobular. Because of progressive disease, he received cyclophosphamide 400 mg/m^2 on days 1–4, etoposid 40 mg/m^2 on days 1–4, methylprednisolone 1 g/m^2 on days 1–3. The patient is still under follow-up in our hematology department with progressive disease status.

Case 3

A 51-year-old man was admitted to the outpatient clinic with left leg swelling three years ago. Venous thrombosis of the left saphena parva was detected. Laboratory parameters were normal except for M-protein:1.2 g/dl. The patient was diagnosed with MGUS and received oral anticoagulant for 6 months. After 8 months, the following laboratory results were obtained: hemoglobin 7.3 g/dl, hematocrit 21%, erythrocyte sedimentation rate 91 mm/h, LDH 257 U/l, calcium 10.5 mg/dl. Serum beta-2 micro-globulin level was 2.4 mg/l. IgG-lambda type monoclonal paraproteinemia was detected in serum immunofixation electrophoresis. Quantitative IgG level was 12 g/dl. The patient was admitted to our hospital with MM of IgG-lambda type (Durie-Salmon Stage IIIA, ISS Stage I). VAD protocole (vincristine 0.4 mg/day and adriamycine 9 mg/m^2/day on days 1–4, oral dexamethasone 40 mg/day on days 1–4, 9–12 and 17–20) was initiated for remission induction. No response was obtained after four courses and hepatotoxicity developed. The treatment was switched to bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11, dexamethasone 40 mg days on days 1, 2, 4, 5, 8, 9, 11, 12 and cyclo-phosphamide 750 mg/m^2 intravenous infusion on days 1 and 3. After 6 courses, the laboratory results were as fol-lows:hemoglobin 13.9 g/dl, hematocrit 40.5%, LDH 527 U/l, calcium 9.1 mg/dl. Serum protein electrophoresis revealed no monoclonal paraprotein. IgG-lambda type monoclonal paraproteinemia was present on serum immu-nofixation electrophoresis. Quantitative IgG level reduced to 4 g/dl. VGPR was achieved. Autologous PBSCT was performed with high dose melphalan (200 mg/m^2) as the conditioning regimen. After 11 months, due to relapse, thalidomide 200 mg/day and low-dose dexamethasone and low-dose aspirin for thrombo-prophylaxis. After 2 months of therapy, right upper extremity venous thromboembolism occurred. Screening for thrombophilic factors revealed lupus anticogulant positivity. Oral anticoagulant therapy was started. Thalidomide was switched to a combination of dexamethasone and cyclophosphamide. One month later, cyclophosphamide was stopped because of cytopenia. Yet on the following month due to disease progression, the treatment regimen was planned as bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11, dexamethasone 40 mg on days 1, 2, 4, 5, 8, 9, 11, 12 and cyclophosphamide 750 mg/m^2 intrave-nous infusion on days 1 and 3. After three courses septic shock due to *Escherichia coli* bacteremia complicated by acute renal failure developed. At that time, laboratory results were as follows hemoglobin 8.9 g/dl, hematocrit 26%, total leukocytes 4140/mm^3, neutrophils 1820/mm^3 and platelets 14000/mm^3, erythrocyte sedimentation rate 120 mm/h, LDH 544 U/l, calcium 8 mg/dl, creati-nine 1.8 mg/dl. Serum protein electrophoresis revealed

monoclonal paraprotein (M protein: 3.9 g/dl). Currently, he is at progressive disease status and being treated with broad-spectrum antibiotics for septicemia.

Discussion

MM poses an increased risk for venous thrombosis, espe-cially when treated with immunomodulatory drugs (IMiDs), thalidomide and lenalidomide, in combination with dexamethasone and/or chemotherapy. The risk of VTE has also been explored in MGUS, with some, [9, 10] but not all, [11] studies observing an increased risk. In one large study of more than 4 million veterans in the United States, Kristinsson et al. [12] identified 2374 MGUS cases, 31 of which developed DVT with crude incidence, 3.1 per 1000 person–years [13]. Compared with non-MGUS cases, this translated to a statistically significant threefold increased risk of DVT for MGUS patients. The underlying mechanisms for the hypercoagulable state are not com-pletely understood. Two of our patients had first been admitted to our hospital with dural sinus vein thrombosis and venous thrombosis of the left saphena parva, respec-tively and was subsequently diagnosed with MGUS.

Kristinsson et al. [12] reported that IgG/IgA (but not IgM) MGUS patients were at increased risk of venous thrombosis, suggesting that there might be a biological difference between IgG/IgA and IgM MGUS with regard to the risk of thromboembolism. Our two patients, diagnosed as IgG-kappa type and IgG-lambda type MGUS trans-formed to MM, 10 and 8 months after the diagnosis of MGUS, respectively. This observation supports the studies suggesting that the increased risk for VTE in MM is present prior to the onset of MM, possibly resulting from ongoing clonal plasma cell activities [12, 13]. One of these patients, who had presented with dural vein sinus throm-bosis at the time of MGUS, suffered from DVT at the time of transformation to MM. DVT in this newly diagnosed MM patient, is probably due to high tumor burdens. This has to be studied in a large prospective study.

MM is an independent risk factor for VTE, and treat-ment with the IMiDs, thalidomide and/or lenalidomide further increases the risk, particularly in newly diagnosed patients and when combined with dexamethasone or che-motherapy [14]. There is also evidence that the higher the dexamethasone dose, the higher is the risk of VTE. Patients with MM often have additional transient risk factors for VTE, such as infections, immobilization due to skeletal pain and during hospitalization, erythropoietin treatment and indwelling central venous catheter. Thalidomide and its analog lenalidomide have various mechanisms of action, including immunomodulatory, anti-angiogenic, and anti-inflammatory effects, as well as an effect on the bone

marrow microenvironment. The exact mechanisms for the underlying thrombogenic effects of these agents are not known. There is evidence that these IMiDs enhance the expression of tissue factor and vascular endothelial growth factor, down-regulate thrombospondin, and cause cytokine-mediated, activated protein C resistance [15, 16]. Thalidomide has been shown to increase the levels of von Willebrand factor and factor VIII [17]. Thalidomide also regulates the level of the prothrombotic factor, COX-2 [18]. Furthermore, there is evidence for an effect on the endothelial cells, possibly via tumor necrosis factor in patients treated with thalidomide and lenalidomide [19].

The risk of VTE is increased beyond that observed in relapsed/refractory patients when thalidomide is used in combination with dexamethasone, alkylating agents, as part of a three-agent therapy, and with doxorubicin. In most studies, the highest risk was observed during the first few months of therapy; however, VTE still occurs after several months of therapy [20].

In our second case, DVT of the left lower leg occurred 1 month after thalidomide and low-dose dexamethasone despite low-dose aspirin for thrombo-prophylaxis. At that time, the only recognised risk factor for this patient was progressive disease status. One month after lenalidomide and high-dose dexamethasone treatment, the same patient developed DVT of the right lower leg despite oral anticoagulation. At the time of second thrombotic attack, the following risk factors were identified: progressive disease status, previous VTE, high-dose dexamethasone and surgery (cervical corpectomy) within 2 months.

The therapeutic use of thalidomide in MM is often complicated by VTE. The results of the retrospective study by Talamo et al. suggest that MM patients suffering from thromboembolic complications with thalidomide have a frequent concomitant underlying thrombophilic state [21]. In our third patient, who developed right upper extremity VTE on the third month of thalidomide and low-dose dexamethasone therapy despite low-dose aspirin thrombo-prophylaxis, screening for thrombophilic factors showed lupus anticoagulant (LA) positivity. The other individual risk factor was previous VTE.

The results of Talamo et al. indicate that MM patients undergoing VTE during treatment may harbor multiple concomitant factors increasing their thrombotic risk. Although work-up for thrombophilia is not routinely recommended in MM patients treated with thalidomide, this study suggests that laboratory screening could identify patients at higher VTE risk, thus enabling physicians to better target such high-risk individuals [21].

Potential hypercoaguable mechanisms unique to MM include cytokine-mediated (predominantly IL-6) interactions between malignant plasma cells, bone marrow stromal cells, and endothelial cells, and paraprotein effects on fibrin polymerization and resistance to fibrinolysis [22]. Rarely, paraproteins exhibit specific (anti-protein S and anti-protein C) and nonspecific (lupus anticoagulant) prothrombotic properties [4, 23, 24]. Intact Ig paraproteins have been reported to possess LA activity. Zahida Yasin was the first to report a similar activity for light-chain paraproteins, resulting in clinically evident thrombosis. Light chain paraproteins could serve as useful models for further study of the mechanisms of activity of acquired LA inhibitors [4]. In our third case, we believe that lambda light chain possessed acquired LA activity and resulted in second VTE attack.

In summary, the pathogenesis of thromboembolic disease in haematological malignancies is complex and multifactorial: tumour cell-derived procoagulant, fibrinolytic or proteolytic factors and inflammatory cytokines affect clotting activation, and chemotherapy and anti-angiogenic drugs increase thrombotic risk in patients with MM.

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