Indian J Hematol Blood Transfus (July-Sept 2019) 35(3):580–583
https://doi.org/10.1007/s12288-019-01128-3

CORRESPONDENCE

Cortical Venous Thrombosis as an Initial Presentation of Multiple Myeloma: Report of a Case and Literature Review

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Received: 27 February 2019 / Accepted: 23 April 2019 / Published online: 2 May 2019

Dear Editor,

Multiple Myeloma (MM) is a potential thrombophilic state. Incidence of venous thromboembolism (VTE) in MM is variable, and can be as high as 25% with the use of immunomodulatory drugs [1, 2]. Thrombosis has been associated with an inferior survival in MM [3]. Commonest presentations of VTE include lower extremity deep vein thrombosis (DVT), catheter-related thrombosis, pulmonary embolism, and upper limb DVT [4]. Association of cerebral venous thrombosis (CVT) with MM is uncommon.

A 52-year-old lady presented in the emergency department with generalized tonic-clonic seizures. She complained of headache and fatigue for 1 month. On examination, she was in post-ictal state. Her vitals were: blood pressure—120/80 mm hg, pulse rate—98/min, and respiratory rate—16/min. Physical exam revealed marked pallor, and absence of signs of dehydration. Her blood investigations were: hemoglobin—47 g/l, white cell counts—5.5 $\times$ 10^9/l, platelets—196 $\times$ 10^9/l, and erythrocyte sedimentation rate—60 mm/h (0–10 mm/h). Peripheral blood smear showed rouleaux formation. Serum biochemistry was: sodium—136 mmol/l (135–145 mmol/l), creatinine—159 µmol/l (53–106 µmol/l), calcium—2.15 mmol/l (2.05–2.55 mmol/l), phosphorous—1.29 mmol/l (0.74–1.72 mmol/l), total protein—74 g/l (64–82 g/l), albumin—30 g/l (35–52 g/l), and lactate dehydrogenase—233 U/L (< 250U/L). Non-contrast CT scan of the head revealed a large expansile lytic lesion at the skull base (Fig. 1a). Magnetic resonance imaging (MRI) of brain revealed a large heterogeneously enhancing destructive lesion at the skull base (3.5 cm $\times$ 3.0 cm $\times$ 2.4 cm) involving the right occipital bone, extending to the right temporal bone and clivus. Absent flow void was seen in the right transverse and sigmoid sinus, which was confirmed to be a thrombus on MR venography (Fig. 1b). Serum protein electrophoresis and immunofixation identified a monoclonal band (1.9 g/dl, IgGκ). Urine protein electrophoresis, and Bence Jones protein testing were unrevealing. PET-CT scan showed multiple FDG-avid bone lesions. Serum β2-microglobulin was 4.8 mg/l. Bone marrow aspirate showed 27% plasma cells, and trephine biopsy revealed sheets of clonal plasma cells (Fig. 1c, d). Conventional cytogenetics of the marrow aspirate revealed tetrasomy of chromosomes 5, 7, 8, and 20, and Fluorescent in situ hybridisation (FISH) was negative for high-risk aberrations. A diagnosis of Multiple Myeloma (IgGκ, R-ISS-II) with skull base plasmacytoma, and CVT was made. Anti-coagulation (Enoxaparin—1 mg/kg q12 h, subcutaneous) and anti-myeloma therapy (CyBorD regimen: Cyclophosphamide—300 mg/m^2, oral; Bortezomib—1.3 mg/m^2, subcutaneous and dexamethasone—40 mg, oral; administered weekly as 4-weekly cycles) were initiated. Patient denied autologous stem cell transplant. After an initial overlap of 5 days with Enoxaparin, oral warfarin was continued, maintaining a therapeutic INR between 2 and 3. Patient attained complete remission (negative serum immunofixation, < 5% clonal plasma cells in marrow aspirate, and no skull base plasmacytoma on repeat MRI scan) and recanalization of the dural venous sinuses after 12 cycles of CyBorD, following which warfarin was stopped. Currently, she continues to be in complete remission on 2-weekly bortezomib maintenance. Thrombophilia work-up done after stopping warfarin was: Protein

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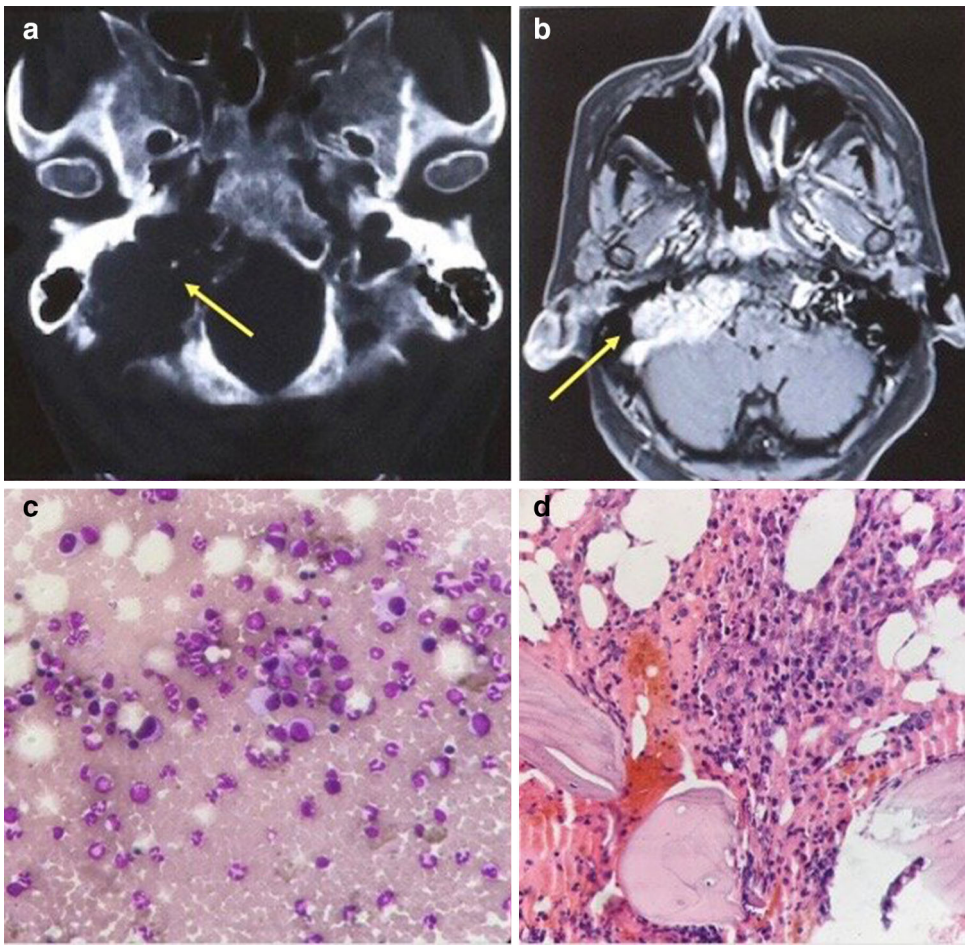

Fig. 1 **a** High resolution CT scan of the temporal bone showing a large lytic lesion in the right temporal bone (yellow arrow), **b** Post contrast MRI brain image showing a large homogeneously enhancing lesion in right temporal bone reaching up to the clivus. The lesion is compressing the right sigmoid sinus (yellow arrow), **c** microphotograph of the bone marrow aspirate showing increased numbers of immature plasma cells, (Romanowsky stain, 100×), and **d** microphotograph of the bone marrow biopsy showing replacement of normal hematopoietic cells by sheets of immature plasma cells (H&E, 400×) (colour figure online)

C antigen—91% (70–160%), free Protein S antigen—120% (50–130%), Leiden Factor V mutation-negative, anti-cardiolipin/lupus anti-coagulant/anti-β2 glycoprotein-1 antibodies- negative, antinuclear antibody-negative, Factor VIII activity—86% (50–150%), fibrinogen—6.47 µmol/l (5.8–11.8 µmol/l), von Willebrand antigen—141% (47–197%). Thyroid function test was normal, and Paroxysmal nocturnal hemoglobinuria clone was undetectable. VTE has been reported in about 20% of cancer patients, and history of malignancy increases the risk of thrombosis by four–sevenfold [4, 5]. Haematological neoplasms have a similar or even higher thrombotic risk as compared to solid cancers [1, 6]. MM and its precursor, monoclonal gammopathy of undetermined significance are independent risk factors for VTE [4]. Risk of both venous and arterial thrombosis is increased in MM before diagnosis, during treatment, after completion of the therapy, and at the relapse [1, 7, 8]. A population-based study identified a 9.2-fold increased risk of DVT associated with MM, being highest during first year following the diagnosis. Risk decreases to 7.5-fold and 4.1-fold after 1-year and 10-year follow-up, respectively [9]. Etiopathogenesis of thrombosis in MM is driven by cytokines, and unique properties of the paraprotein (Table 1) [4–8]. Disease-related factors are present at the baseline, and worsened by induction chemotherapy. Newly diagnosed status, chromosome 11 abnormalities, elevated C-reactive protein, and light chain disease have been identified as independent risk factors for thrombosis in MM [7]. In a case–control study, out of 594 CVT cases, 53 (8.9%) had a history of cancer, and only 2 cases had MM [10]. Four reported cases of CVT in association with MM till date have been summarised in Table 2 [11–14]. All were elderly females, median age—60 years (range, 52–83 years). CVT was an initial presentation of MM in only one case. Thrombophilic work-up, although not done at the time of diagnosis was unrevealing in our case. Skull base plasmacytoma was possibly responsible for CVT in our patient by means of compression or invasion. We report an uncommon site of VTE in MM, describe the pathophysiology of hypercoagulable state associated with it, and review the association of CVT with MM.

Table 1 Proposed mechanisms of underlying hypercoagulable state in Multiple Myeloma [4–8]

Factor associated with hypercoagulable state	Comments
Patient related factor	Age
	Immobilisation (secondary to infection, fracture)
	Central venous catheters
Disease-related factor	Changes in coagulation cascade: Elevated inflammatory cytokines (IL-6, CRP, and TNF), FVIII, VWF, fibrinogen, VEGF, tissue factor, increased blood viscosity, microparticle associated-tissue factor activity, increased thrombin generation
	Anti-coagulation system: reduced protein S, anti-thrombin, and tissue-plasminogen activator, acquired resistance to activated protein C
	Fibrinolysis: impaired fibrinolysis
	Paraprotein-related: Lupus anti-coagulant property, hyperviscosity, platelet inhibition, interference with fibrin polymerisation, and coagulation proteins
	Enhanced platelet aggregation and activation
	Genetic pre-disposition: SNP in NFκB1
Treatment-related factor	Thalidomide: increases FVIII, VWF, VEGF, and bFGF levels, impaired fibrinolysis, reduced thrombomodulin, stimulate tissue factor in monocytes, platelet activation
	Lenalidomide: increased P-selectin, fibrinogen, homocysteine, upregulation of cathepsin-G
	Pomalidomide
	High-dose dexamethasone (> 450 mg/month): increases circulating P-selectin, FVIII, and VWF levels
	Doxorubicin: endothelial dysfunction, monocyte activation, and increased plasma thrombin generation
	Vincristine-based therapy: impaired fibrinolysis
	Recombinant erythropoietin

IL-6, Interleukin-6; CRP, C-reactive protein; TNF, tumor necrosis factor; FVIII, Factor VIII; VWF, von Willebrand factor; VEGF, vascular endothelial growth factor; SNP, single nucleotide polymorphism; bFGF, basic fibroblast growth factor

Table 2 Review of the five reported cases of cerebral venous thrombosis in Multiple Myeloma (including the present case)

S. no.	References	Age (year), sex	Time of occurrence of CVT	Treatment
1	Khurana et al. [11]	52, F	At the initial presentation	Melphalan plus prednisolone, LMWH, warfarin
2	Eudo et al. [12]	83, F	After starting Lenalidomide	Lenalidomide discontinued, LMWH
3	Fernandes et al. [13]	62, F	After autologous stem cell transplant (ASCT)	Anti-coagulation
4	Macintosh et al. [14]	60, F	Relapse after ASCT, associated with skull base plasmacytoma	Chemotherapy and radiotherapy, warfarin
5	Jain et al. [present case]	52, F	At the initial presentation, associated with skull base plasmacytoma	Bortezomib, dexamethasone, cyclophosphamide, LMWH, warfarin

Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interests to declare.

Informed Consent The authors state that a written and informed consent was obtained from the patient prior to publication.

Ethical Standards Authors state that the article has not been submitted elsewhere for publication, and the article follow the guidelines of Helsinki declaration.

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