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Multiple myeloma presenting as cerebral venous sinus thrombosis

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Abstract

A 52-year old lady presented with acute onset headache, seizures, confusion and was found to have anemia, albumin/globulin ratio reversal and cerebral venous sinus thrombosis. On further investigations, multiple myeloma was found to be the underlying cause. The patient recovered fully with anticoagulation and chemotherapy. This case indicates that cerebral venous sinus thrombosis can be an unusual presenting manifestation of myeloma.

INTRODUCTION

Cerebral venous sinus thrombosis is a common condition associated usually with hypercoagulable states such as puerperium and inherited as well as acquired coagulopathies. We report a case of a 52-year-old woman who presented with cerebral venous sinus thrombosis and was discovered to have multiple myeloma. Cerebral venous sinus thrombosis as a presenting manifestation of multiple myeloma is unreported, to the best of our knowledge.

CASE REPORT

A 52-year old lady presented with acute onset, global, moderately severe headache of 2 weeks duration without associated vomiting, fever, neck pain or stiffness. She was admitted in a confused state following three episodes of left focal seizures with secondary generalization. There was no history of diabetes, hypertension, cardiac disease, chronic headache, drug abuse or documented thrombosis in the past. She was postmenopausal for last 8 years and did not receive hormonal replacement therapy or any other drugs. Examination revealed pallor and a delirious state, in the absence of lymphadenopathy, hepatosplenomegaly, bony or sternal tenderness, papilledema, focal neurological or meningeal signs. Her cardiovascular, respiratory and gynecological examinations were unremarkable.

Hemogram revealed anemia (Hb=8.3 g/dl), normal leukocyte and platelet counts and a mixed normocytic and microcytic, hypochromic picture on the peripheral blood smear. ESR was 65 mm in the first hour. Biochemistry revealed total proteins of 8 g/dl with albumin/globulin reversal (A/G=0.67). Renal parameters, serum calcium and phosphate levels, fasting blood sugar, prothromin time (PT) and activated partial thromboplasting time (aPTT) were normal. ELISA for HIV was non reactive. X ray skull revealed punched out osteolytic bone lesions (Figure 1A). The rest of the skeletal survey was normal. Non-contrast CT of the brain revealed hemorrhagic infarct of the right temporo-parietal area; bone windows did not show any evidence of bone destruction. Post-contrast CT head revealed an empty delta sign (Figure 1B). Cranial MR imaging showed hemorrhagic infarcts in the right temporo-parietal and left frontal and parietal areas. MR venography showed superior sagittal and right transverse sinus thromboses (Figure 2A, B). Bone marrow aspiration revealed 50% plasma cells (Figure 3) and trephine biopsy showed mildly hypercellular marrow with interstitial increase in plasma cells. Serum and urinary electrophoresis (by Polyacrylamide gel method) were negative. Serum viscosity and fibrinogen levels could not be done. Also, procoagulant workup for protein C and S and anti-thrombin III levels could not be done since patient was already started on anticoagulant therapy by the time the possibility of a plasma cell disorder was considered.

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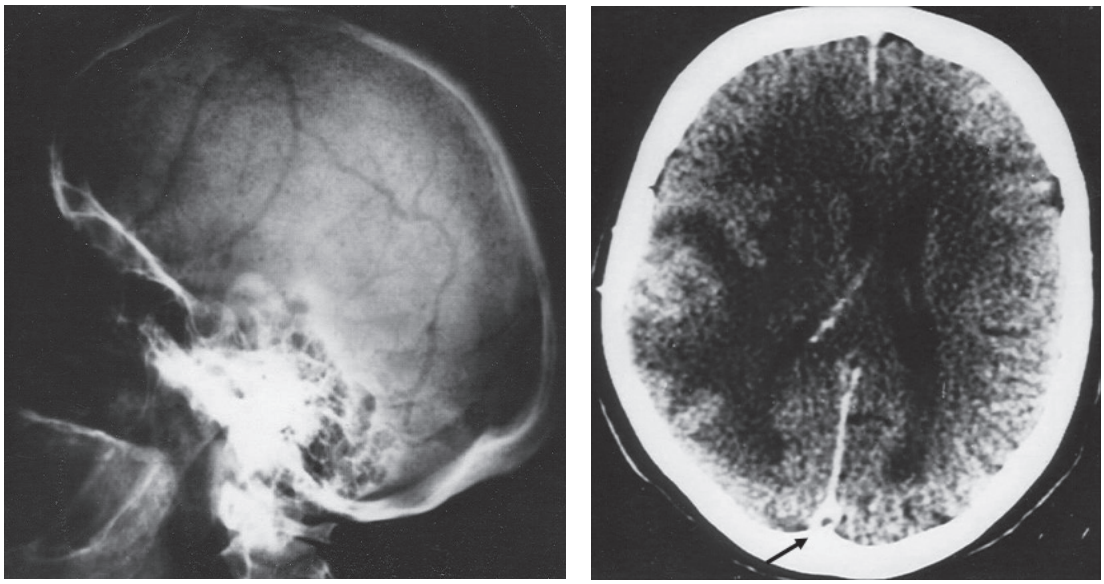

Figure 1: **(A)** X-Ray skull-lateral view showing multiple"punched out" bony lesions. (**B**) Contrast enhanced cranial computerized tomography, axial section, showing "empty delta sign"(arrow) in superior sagittal sinus.

The patient received antiedema measures in the form of IV mannitol 0.25 g/Kg every six hours for five days and anticoagulation with low molecular weight heparin followed by oral warfarin maintaining INR between 2-2.5, following which she had good clinical recovery. She received melphalan 5 mg/day and prednisolone 1 mg/kg/day for one and a half years. Her repeat bone marrow aspiration after two years revealed 5% plasma cells. Investigations for protein C and S and anti-thrombin III deficiency, factor V Leiden mutation, anticardiolipin antibodies and lupus anticoagulant 3 months after stopping anticoagulation was negative. Prothrombin PT20210A mutation was not tested as this facility was not available in our institute.

DISCUSSION

Multiple myeloma is a disorder in which malignant plasma cells accumulate, generally derived from one clone in the bone marrow. Neurological manifestations in myeloma include peripheral neuropathies, spinal radiculopathies, cranial nerve

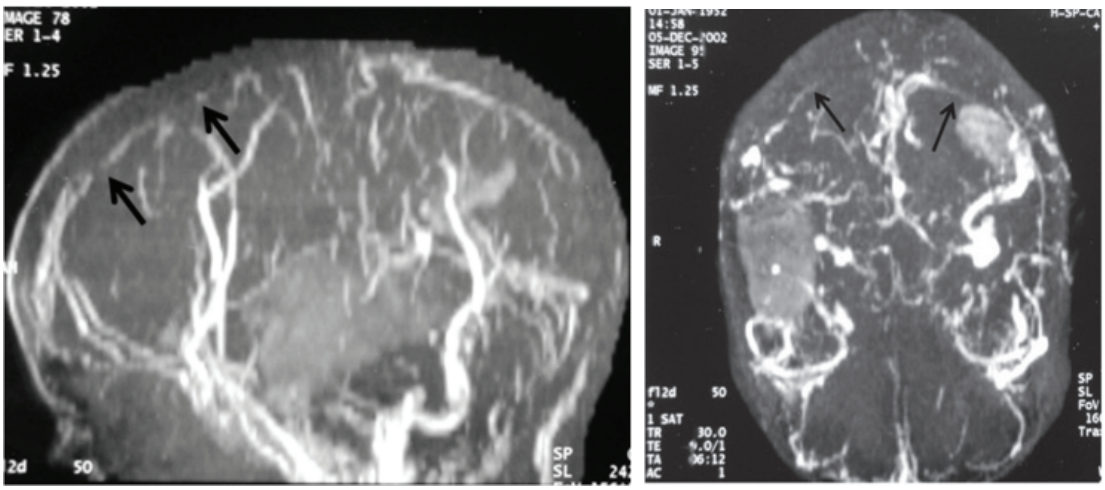

Figure 2: **(A)** & **(B)** Magnetic Resonance Venogram, sagittal and axial views, showing the thromboses in superior sagittal and transverse sinuses (arrows) respectively.

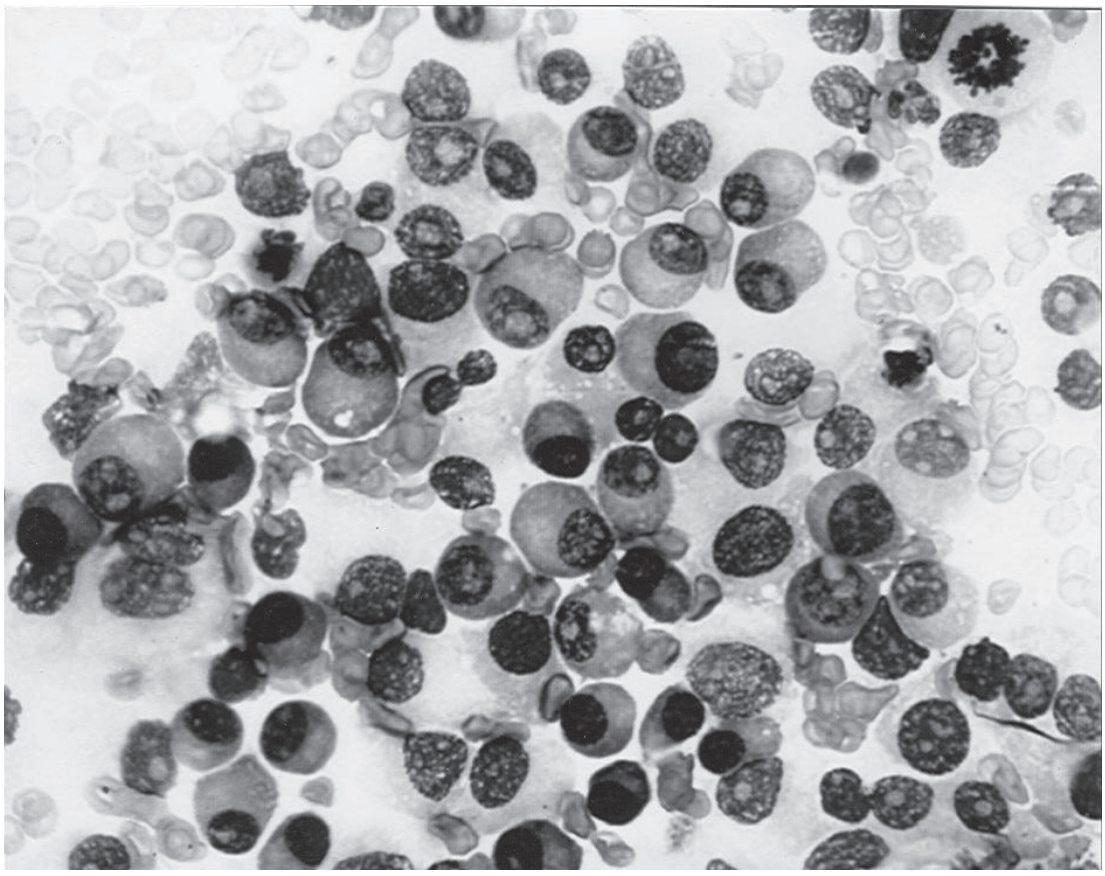

Figure 3: Bone marrow aspirate showing increased number of plasma cells(~50%). M x G-100.

palsies, spinal cord compression, and a host of metabolic encephalopathies.[1] Thrombosis and thromboembolism is not uncommon in myeloma, especially during treatment. Various thrombotic manifestations include deep vein thrombosis[2], central retinal vein occlusion[3], pulmonary thromboembolism[4], Budd-Chiari syndrome[5], and localized skin gangrene[6], attributed to patient immobility, low grade disseminated intravascular coagulation, antiphosholipid antibodies or hyperviscosity.[7]

In most cases of myeloma, the pathogenesis of thrombotic complications remains unexplained. The major reasons for hypercoagulability described in these patients include interference of immunoglobulins on fibrin structure, procoagulant autoantibody production, effects of inflammatory cytokines on endothelium and acquired activated protein C resistance. Extremely high levels of von Willebrand factor antigen and procoagulant factor VIII[8], acquired activated protein C resistance in the absence of factor V leiden mutation[9], acquired protein S deficiency[10], and the lupus anticoagulant activity of light chain paraproteins[11] have been reported in these patients.

Our patient lacked any obvious predisposing factors for cerebral venous sinus thrombosis like use of hormonal replacement therapy or dehydration. The clinical picture of anemia and albumin/globulin reversal on investigations led to suspicion of a plasma cell disorder.

The predisposing cause for hypercoagulable tendency in our patient is not clear. We did not find any evidence of thrombocytosis known to occur as overcompensation in response to low grade disseminated intravascular coagulation and thrombocytolysis. We could not perform baseline hypercoagulable state work up although baseline PT and aPTT levels and hypercoagulable state work up done after stopping anticoagulants was normal. Robert *et al*[12] analyzed 42 patients with lymphoplasmacytic disorders to confirm the association of monoclonal gammopathies with hemostatic defects and have reported a high incidence of abnormal coagulation tests in patients with myeloma. These abnormalities are known to reverse completely after treatment and disease control.

The urine and serum electrophoreses in our patient were normal. A 24-hour urinalysis by protein electrophoresis is done to determine the presence of Bence Jones proteinuria and kappa or lambda light chains. The possible reasons for a negative result include poor preservation of sample, low concentration of proteins, inadequate concentration or a non-secretory myeloma. The serum electrophoresis identifies M-protein in around 80-90% of patients with multiple myeloma. The remaining 10-20% usually show only free monoclonal light chains or IgD paraprotein present at very low level or have non-secretory myeloma.[13] We could not do immunofixation study in our patient to detect low levels of paraprotein.

Cerebral venous sinus thrombosis in myeloma may also occur due to metastasis into the skull, which may spread to subjacent duramater and dural sinuses. We did not find any evidence of bony destruction compressing the sinuses in our patient, as reported by Plant *et al*.[14] Although we did not do CSF study in our patient, leptomeningeal myelomatosis as cause of cerebral venous sinus thrombosis in myeloma is unlikely in view of good recovery on treatment. Schluterman *et al*, in their series of 23 patients with leptomeningeal myelomatosis, did not find venous sinus thrombosis in any of them and reported a poor prognosis, despite aggressive and systemic treatment.[15]

Hence, we feel that even though we could not demonstrate hypercoagulability in our patient at outset, hypercoagulability secondary to paraproteins resulted in cerebral venous sinus thrombosis as there were no other possible reasons found in her.

In conclusion, cerebral venous sinus thrombosis is an unusual presenting manifestation of multiple myeloma and the latter should be considered in the differential diagnosis of cerebral venous sinus thrombosis, whenever appropriate.

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