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Fatty but starving marrow! Gelatinous transformation of bone marrow secondary to plasma cell disorder and all-trans-retinoic acid therapy: A report of two cases

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Dear Editor,

Gelatinous transformation of the bone marrow (GMT) also known as "starvation marrow" or "serous fat atrophy" is a rare hematological disorder characterized by fat cell atrophy with focal loss of hematopoietic cells and extracellular deposition of gelatinous material which histochemically is mucopolysaccharide and is rich in hyaluronic acid.[1] It was first described in 1976 in bonemarrow (BM) of patients suffering from prolonged starvation and cachexia.[2] We describe GMT in two cases, one each of plasma cell myeloma and acute promyelocytic leukemia (APML) treated with all-trans-retinoic acid (ATRA).

Apparently healthy 55-year-old female with no known co-morbidities presented with complaints of severe backache. Magnetic resonance imaging showed multiple lytic lesions in the thoracic and lumbar vertebrae with largest lesions in T8 and L2. Computed tomography-guided biopsy from the L2 lesion showed sheets of plasma cells with round to oval nucleus, moderate amount of eosinophilic cytoplasm, clumped nuclear chromatin, and inconspicuous nucleoli. BM biopsy done subsequently showed interstitial prominence of plasmacytoid cells, at places forming small clusters with one large focal collection surrounded by stromal myxoid change [Figure 1a]. This extracellular material stained positive for alcian-blue at 2.5 pH and the cells on immunohistochemistry showed positivity for CD138 with kappa light chain restriction [Figure 1b]. Serum electrophoresis and immunofixation showed M-band of IgG kappa. Patient was started on lenalidomide-based chemotherapy and is presently under follow-up.

A 33-year-old male presented with history of generalized weakness, fever, and breathlessness. He was diagnosed as APML with presence of 81% abnormal promyelocytes and blasts. Flow-cytometry complemented the morphological diagnosis and PML/RARα hybrid transcript was detected in the BM sample by qualitative polymerase chain reaction and gel electrophoresis. Patient was started on the induction therapy with ATRA, Daunorubicin and Cytarabine. Following post induction remission, the patient was continued with the consolidation therapy with single agent ATRA. However, patient developed severe pancytopenia after 1 month triggering a repeat BM aspirate and biopsy evaluation. BM aspirate smears were hypocellular and hemodilute. BM biopsy showed presence of prominent and extensive gelatinous change with few scattered foci of hematopoiesis [Figure 1c and d]. No blast or promyelocyte prominence was seen. The gelatinous material stained positive for alcian-blue at pH 2.5. There were no other co-morbid conditions. ATRA was stopped for 6 weeks with subsequent improvement of his peripheral blood counts. Patient was later lost to follow-up.

Gelatinous transformation of the bone marrow is a rare disorder with unknown pathogenesis. Seaman *et al*. reported GMT in 5.2% of his autopsy cases while Bohm found GMT in 1.9% of his 80,000 BM cases.[1] An Indian study reported an incidence of 4.39%.[3] Malnutrition including anorexia nervosa and chronic infections were the predominant cause in these studies. GMT has been found to increase with age, a phenomenon that may be attributed to more number of bone biopsies with age.[1] Histochemical studies have demonstrated this gelatinous substance to stain strongly with alcian-blue at a pH of 2.5. Pretreatment with bovine testicular hyaluronidase and varidase results in loss of alcian-blue staining.[3]

Gelatinous transformation of the bone marrow has also been described in other nutritional states like alcoholism, iron deficiency anemia, celiac disease, psychiatric illnesses, and metabolic disorders such as diabetes mellitus, hypothyroidism, and renal failure. Chronic infections including AIDS and collagen vascular diseases like SLE have also

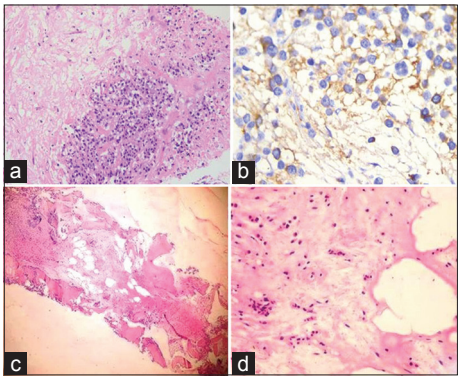

Figure 1: (a) Bone marrow biopsy showing collection of plasma cell in a background of gelatinous transformation (H and E, ×20). (b) Immunohistochemistry using antibodies to CD138 showing positivity in the plasma cell surrounded by gelatinous transformation in the marrow (×40). (c) Bone marrow biopsy showing extensive gelatinous transformation with scattered foci of hematopoiesis (H and E, ×4). (d) Higher magnification of the bone marrow biopsy as in Figure 1c (H and E, ×40)

been associated with GMT. Literature search showed its description in occasional cases of myelodysplastic syndromes, Non-Hodgkin's lymphomas, Hodgkin lymphomas, acute leukemia, and carcinomas like that of rectum. Rare reports of chemotherapeutic agents leading to GMT suggest it to be a manifestation of systemic disease rather than a disease itself.[1,3] It has been postulated that GMT in nutritional disorders and chronic debilitating diseases occurs due to excessive production of mucopolysaccharide as a mechanism to compensate for the loss of BM fat to meet nutritional requirements.[2] Electron microscopy reveals the gelatinous substance to consist of randomly aggregated non-amyloid fibrillar and granular material while other studies have proposed that this extra-cellular substance is a normal constituent of BM ground substance and starvation seems to stimulate its biosynthesis. GMT is not considered to carry any prognostic significance.[1] Mant and Faragher proposed GMT to be a temporary change as it is reversible after improvement of the clinical condition.[4]

Gelatinous transformation of the bone marrow till date has been described in six cases of multiple myeloma, four of which were reported in elderly males with an age range of 64–75 years while two were elderly females 71 and 79 years old. In one case, the GMT was reported after chemotherapy for multiple myeloma.[1] Our case of multiple myeloma was relatively younger and had never received any chemotherapy. The BM biopsy showed the presence of GMT in the region surrounding the neoplastic plasma cells [Figure 1a and b] while rest of the biopsy was free of any such change. Ifrah *et al*. have proposed that even some malignant cells may produce or stimulate the production of hyaluronic acid leading to GMT.[5] The morphological presence of GMT around the neoplastic plasma cell collection and with no such change in the other part of the BM biopsy substantiates this proposal.

All-trans-retinoic acid is a relatively safe drug. Headache, hypercholesterolemia, hypercalcemia, hypertriglyceridemia, transient elevations of liver enzymes, and acute pancreatitis has been described as important side effects of ATRA therapy besides retinoic acid syndrome which is a potentially fatal complication of ATRA monotherapy. Necrosis and fibrosis due to ATRA have been described as ATRA induced complications in the BM.[6] To the best of our knowledge, no case of GMT associated with ATRA causing severe pancytopenia has ever been reported. As ATRA was used as a single agent, GMT seen in the BM done for evaluation of pancytopenia can be attributed to ATRA. This case emphasizes the need of GMT to be kept as a differential diagnosis in patients undergoing treatment with ATRA as pancytopenia due to GMT is reversible.

Gelatinous transformation of the bone marrow is a benign condition which may be precipitated by multiple factors and presents with variable degree of cytopenias. It does not require any specific treatment and resolves with management of the underlying condition only.

Manu Goyal, Anurag Gupta, Swathi Yarlagadda, Anil Handoo[1]

Department of Hematopathology, AmPath, American Oncology Institute and Citizens Hospital, Hyderabad, Telangana, [1]Department of Laboratory Hematology, BLK Super specialty Hospitals, New Delhi, India

Correspondence to: Dr. Anurag Gupta,
E-mail: anuragg@ampath.com

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