have suggested monitoring lymphocyte or CD4 counts for patients receiving bendamustine. For example, Brugger and Ghielmini [11] recommend bimonthly monitoring of CD4-helper T-cell counts during bendamustine-containing chemotherapy and initiation of PJP prophylaxis for patients with counts of <200/μL. When deciding whether to employ prophylactic treatment, it is also important to consider concomitant drugs, patient age, underlying diseases, and previous chemotherapy history.

As bendamustine is increasingly used in lymphoma patients, physicians should be aware of its potentially serious infectious complications. Considering the fatality rate of PJP, prophylaxis and monitoring for PJP are required for patients on bendamustine chemotherapy who are elderly, heavily pre-treated, or currently in a refractory/relapsed status.

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Received on Feb. 17, 2015; Revised on Mar. 27, 2015; Accepted on Apr. 20, 2015

http://dx.doi.org/10.5045/br.2016.51.1.61

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Oligosecretory multiple myeloma: a case report

TO THE EDITOR: Approximately 95–97% of myelomas are of the secretory type, i.e., they exhibit monoclonal (M) band in the γ region on either urine or serum protein electrophoresis [1, 2]. Non-secretory myelomas were first described in 1958 by Serre, and they constitute 1–5% of myelomas. These do not show M band on serum or urine immunofixation electrophoresis. However, on immunohistochemistry (IHC), 85% of non-secretory myelomas stain for cytoplasmic M protein, indicating immunoglobulin synthesis. The remaining 15% are non-producers. The proposed pathophysiology for non-secretory multiple myeloma includes diminished immunoglobulin synthesis, secretion defects, and rapid immunoglobulin degradation, either intracellularly or extracellularly [3]. With newer serum free light chain (FLC) assays, approximately three-fourths of these non-secretory myelomas were found to have elevated FLC levels and/or abnormal FLC ratios [4]. These cases may be considered to be minimally secretory, hyposecretory, or oligosecretory. Since these patients do not present with classical multiple myeloma symptoms, diagnoses may be delayed. We hereby present a case of non-secretory myeloma with increased kappa (κ) FLC levels, i.e., an oligosecretory myeloma. The rare and unique clinical presentation of this case prompted us to report this case. We also discuss the diagnostic and

prognostic issues along with the staging dilemmas often associated with non-secretory oligosecretory myelomas.

CASE

A 60-year-old man presented with a history of lower back pain that had persisted for 2 years and difficulty walking for 2 months. The patient received a complete hemogram as well as routine biochemical and radiographic imaging studies. His hemoglobin level was 15.3 g/dL, his total leukocyte count was 6.1×10^9/L, his platelet count was 160×10^9/L, and his erythrocyte sedimentation rate (ESR) was 15 mm. No rouleaux formation was seen on a peripheral smear. Serum blood urea nitrogen (27 mg/dL), creatinine (1.06 mg/dL), calcium (9.9 mg/dL), and albumin (5.1 g/dL) were all within normal limits. Serum uric acid levels were high (7.6 mg/dL), Alkaline phosphatase levels were slightly increased (134 U/L), and the patient had subnormal vitamin D3 levels. Ultrasonography findings were within normal limits, except for mild prostatomegaly. Serum prostate specific antigen and carcinoembryogenic antigen levels were within normal limits.

A radiograph of the dorsolumbar spine showed diffuse osteoporosis and wedging of the D12 vertebra. Multiple small permeative lesions were seen in the pelvic bones and proximal femoral shafts. MRI findings showed diffuse degenerative changes in the cervical and lumbar spine and D12 vertebral collapse. Bone scan showed increased uptake in the anterior region of the 6th rib, left sacroiliac joint, and occipital region. Serum protein electrophoresis did not show any M spike, and gamma globulin levels were normal (8.8 g/L). Urine protein electrophoresis showed protein levels of less than 60 mg/L and no M spike. The bone scan findings, together with increased serum uric acid and alkaline phosphatase levels, and negative myeloma workup suggested possible diffuse skeletal metastasis. The patient underwent bone marrow aspiration from the bilateral posterior iliac spines and unilateral trephine biopsy to look for any secondary causes of bone scan findings and to rule out the presence of a plasma cell neoplasm. The aspirates from both sides showed similar findings, with numerous plasma cells ranging from 60–70% (Fig. 1). Binucleated or multinucleated forms, plasmablasts, and occasional mitotic figures were also observed in those plasma cells. Additionally, intranuclear Dutcher bodies and occasional Mott cells were observed. The Congo red stain for amyloid on the trephine biopsy was negative. IHC was performed on the trephine biopsy, revealing cells positive for CD138, MUM 1, and cytoplasmic κ and negative for CD3, CD20, LCA, CD56, and lambda (λ). The Ki-67 labelling index was 15%. The mean λ FLC level was 11.2 mg/L (range, 5.5–26.3 mg/L), and that of κ was 176.8 mg/L (range, 3.3–19.4 mg/L). The mean κ/λ ratio was 15.78 (range, 0.2–1.65). Patient had high β2-microglobin levels, at 2,557 mg/mL (range, 609–2,366 mg/mL).

The patient was in clinical stage I according to the International Staging System (ISS) for plasma cell myeloma and stage IIIA according to the Durie-Salmon staging system.

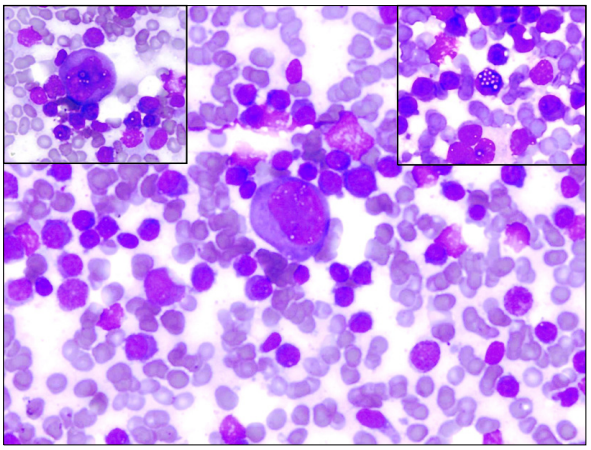

Fig. 1. Bone marrow aspirate showing numerous plasma cells. Intranuclear Dutcher bodies and occasional Mott cells were observed (WG; ×400).

The patient was referred to the oncology center for further management. There the patient was treated with a chemotherapy regimen that included the proteasome inhibitor bortezomib and dexamethasone.

DISCUSSION

Non-secretory multiple myeloma (NSM) is a symptomatic myeloma without detectable monoclonal immunoglobulin protein in serum or urine by immunofixation electrophoresis [1, 5]. The clinical picture of NSM is different from that of secretory myeloma, as NSM patients usually have improved hemoglobin levels, lower ESR values, higher neurological presentation incidence, less aggressive osteolysis, low risk of renal myeloma, lower hypercalcemia incidence, and improved immunoglobulin levels. All these findings were present in the current case.

A high index of suspicion for NSM must be born in mind when excluding multiple myeloma as the cause of pain, pathologic fractures, lytic lesions, and positive bone scans. A positive bone scan indicates osteoblastic activity and increased blood flow to the affected area and thus suggests the possibility of metastatic disease, as was seen in our case [6]. However, positive bone scans in multiple myeloma cases have been well reported, and bone scan is considered superior to radiography in detecting lesions in the ribs, scapula, and spine of patients with multiple myeloma [6, 7].

The diagnosis of NSM depends on the demonstration of clonal/atypical plasma cells in bone marrow aspiration, bone marrow biopsy, or biopsy of the osteolytic lesion [2, 7, 8]. In our case, bone marrow aspirates from the posterior superior iliac spine contained excess plasma cells, and permeative lesions were observed in the pelvis. Additionally, secretory activity was indicated by the presence of inclusions and Mott cells and was later confirmed by IHC and FLC assays. As per the literature, κ nonsecretory myelomas are 4 times more common than those of the λ type [4]. Our

case exhibited κ light chain oligosecretion.

The prognosis for patients with NSM has been a subject of debate in the available literature [1, 2, 7, 9]. Albumin levels are not decreased, and thus, the NSM infection rate is lower than that for secretory myelomas. Renal tubular damage due to FLC proteinuria is also not present in patients with NSM. These patients may have anemia because of marrow hematopoietic cell replacement, but unlike patients with secretory myelomas, their erythropoietin levels are not low. Hypercalcemia is usually observed at presentation; however, it was not observed in our case. There is usually some delay in diagnosis of such cases, as patients normally do not have paraprotein in blood or urine. The prognoses of patients with NSM cases are generally at least as good as those for patients with secretory myelomas.

Cytogenetic analysis is more frequently used for prognostication of plasma cell neoplasms [4]. Using cytogenetic techniques, isolated case reports have shown a high percentage of t(11;14)(q13:q32) in NSM cases [10, 11]. However, the implication of cytogenetics in prognostication of these cases would need further studies. Cytogenetic evaluation was not performed for this patient because at the time of bone marrow aspiration, hematolymphoid malignancy was not a priority diagnosis, and thus, no sample was collected for cytogenetics. The patient refused reaspiration.

Staging discrepancies, similar to that found in our case, have also been reported earlier [7, 12]. Because NSM tends to be less involved serologically, the ISS system is less able to properly stage these patients. Further studies or retrospective reviews of NSM cases are needed to determine the best staging system for patients with this disease.

Treatment for oligosecretory NSM is generally no different than that for classic multiple myeloma [2]. FLC assays, i.e., nephelometric assessment of κ chain, λ chain, and calculation of κ/λ ratio, are useful adjuncts not only in establishing diagnosis of NSM but also for monitoring therapy [13].

In conclusion, paraprotein absence does not exclude a multiple myeloma diagnosis. FLC assays can suggest oligosecretory type NSM, which can be confirmed by bone marrow aspiration/biopsy or osteolytic lesion biopsy. Additionally, a pre-treatment FLC assay should be performed because serial FLC values are helpful in monitoring treatment effects.

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Received on Feb. 16, 2015; Revised on Mar. 29, 2015; Accepted on Apr. 23, 2015

http://dx.doi.org/10.5045/br.2016.51.1.63

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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