Bence Jones proteinuria (lambda type) and mild pancytopenia but no other abnormalities were found. In particular, serum calcium and comprehensive metabolic, renal, hepatic, and coagulative panel results were normal. In addition, skeletal survey showed neither lytic nor sclerotic lesions throughout the axial and appendicular skeleton. The diagnosis of MM coexisting with secondary acute biphenotypic phenotype was made. The patient was evaluated as a possible candidate for treatment with hypomethylating agents, but his condition suddenly deteriorated and he died of pneumonia.

This case lacks practical therapeutic implications and reliable indications for the management of this uncommon occurrence, and our report has only anecdotal value. However, the overlapping occurrence of acute biphenotypic leukemia transformed from ET and MM is extremely rare. We speculate that the synchronous evolution of ET and MGUS along with coexpression of lymphoid antigens by blastic cells could suggest a common origin of these 2 malignancies, potentially evolving from a common precursor by progressive transformation to more aggressive disorders [5]. However, this hypothesis remains to be investigated.

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REFERENCES

1. Montefusco E, Monarca B, Tribalto M. Coexistent idiopathic thrombocythaemia and monoclonal component: a causal association? Scand J Haematol 1985;35:584.
2. Kyrtsonis MC, Kokoris SI, Kontopidou FN, Siakantaris MP, Kittas C, Pangalis GA. Development of a myeloproliferative disorder in a patient with monoclonal gammopathy of undetermined significance secreting immunoglobulin of the M class and treated with thalidomide and anti-CD20 monoclonal antibody. Blood 2001;97:2527-8.
3. Tosato F, Fossaluzza V, Rossi P, et al. Monoclonal gammopathy of undetermined significance in a case of primary thrombocythemia. Haematologica 1986;71:417-8.
4. Prosper F, Borbolla JR, Rifon J, et al. Coexistence of essential thrombocythemia and multiple myeloma. Ann Hematol 1992; 65:103-5.
5. Majhail NS, Lichtin AE. Rare coexistence of multiple myeloma with essential thrombocythemia: report of two cases. Haematologica 2003;88:ECR09.
6. Kuroda J, Matsumoto Y, Tanaka R, et al. JAK2V617F-positive essential thrombocythemia and multiple myeloma with IGH/CCND1 gene translocation coexist, but originate from separate clones. Acta Haematol 2008;120:177-81.
7. Holtan SG, Hoyer JD, Buadi FK. Multiple myeloma with concomitant JAK2-positive essential thrombocythemia post-successful autologous peripheral blood hematopoietic stem cell transplant. Bone Marrow Transplant 2011;46:615.
8. Eskazan AE, Ongoren S, Ar MC, et al. Essential thrombocythemia and multiple myeloma: two rare diseases in one patient. Clin Lymphoma Myeloma Leuk 2011;11:442-5.
9. Dispenzieri A. How I treat POEMS syndrome. Blood 2012;119: 5650-8.

Waldenstrom's macroglobulinemia presenting with lytic bone lesions: a rare presentation

TO THE EDITOR: Lymphoplasmacytic lymphoma (LPL) is a neoplasm of small B lymphocytes, plasmacytoid lymphoid cells, and plasma cells that usually involves bone marrow, and sometimes, the lymph nodes and spleen; which does not fulfill the criteria for any other small B cell lymphoid neoplasms that may also have plasmacytic differentiation [1]. Waldenstrom's macroglobulinemia (WM) comprises a significant proportion of LPL cases and is characterized by bone marrow involvement and an IgM monoclonal gammopathy of any concentration [2].

When WM was first described, the general belief was that it did not extend to the skeletal system. However, following several reports of lytic bone lesions in WM [3-6], this belief has been challenged. It is now considered that bone involvement in WM may not be unusual. The abnormal feature that was commonly observed in these previously reported cases was the presence of a predominant plasmacytic morphology in the bone marrow of the WM patients with lytic bone lesions. Contrary to these reports, we hereby report a rare case of WM with lytic bone lesions, showing a predominant presence of lymphocytic infiltration of the bone marrow, and very few plasmacytic cells.

CASE

A 65-year-old male patient, who had a 10-year history of hypertension and type II diabetes mellitus, presented with complaints of pain and a tingling sensation in both lower limbs over the previous year and in both upper limbs over the previous 6 months. He also had a history of weight

loss and an intermittent low-grade fever during the previous 6 months.

On examination, the patient was pale, conscious, alert, and oriented with a pulse of 72 beats per minute and blood pressure at 140/90 mmHg. Nothing unusual was found on examination of the chest and cardiovascular systems. Abdominal examination revealed mild hepatomegaly without splenomegaly. Examination of the nervous system showed normal mental status (patient was conscious and well oriented in time, place, and person). Sensations were diminished below the knees in both lower limbs. Power in all of the muscles was 4/5. Fundoscopy revealed a grade 4 hypertensive retinopathy.

Investigations revealed pancytopenia and normocytic normochromic anemia with a hemoglobin of 6.8 g/dL; a total leukocyte count of $1.5\times10^3/mm^3$; a differential leukocyte count with 23% neutrophils, 71% lymphocytes, 5% monocytes, and 1% eosinophils; a platelet count of 21,000/mm^3; and a markedly raised erythrocyte sedimentation rate of 140 mm/hr. Biochemical investigations provided the following results: blood sugar, 92 g/dL; total bilirubin, 0.6 mg/dL; alkaline phosphatase/aspartate transaminase/alanine transaminase, 126/74/55 IU/mL; blood urea, 74 mg/dL; serum creatinine, 1.7 mg/dL; and serum uric acid, 11 mg/dL. The serum protein level was 10.0 g/dL, albumin level was 1.76 g/dL, and the albumin/globulin ratio was 0.2 (reference range, 0.9–2.0). Serum calcium levels ranged from 8.4 to 9.2 mg/dL on different occasions. The venereal disease research laboratory (VDRL), antinuclear antibody, and rheumatoid factor tests were negative, while C-reactive protein was raised. The Coombs test and the test for cold agglutinins were also negative. In addition, the serological markers for hepatitis B and hepatitis C were negative. The skull radiograph revealed multiple lytic lesions.

The chest radiograph showed cardiomegaly with prominent bronchovascular markings. Ultrasonography revealed mild hepatomegaly (15.5 cm in size), while the spleen and both kidneys were within normal limits. The wall of the rectum and sigmoid colon demonstrated thickening. Contrast enhanced computed tomography (CECT) revealed atrophy of the brain and multiple lytic lesions in the skull. The rectal wall was also edematous. There was mild hepatomegaly with the presence of minimal ascites. A clinical diagnosis of multiple myeloma was considered due to the presence of lytic bony lesions, increased total protein values, decreased serum albumin, and low albumin to globulin ratio.

Bone marrow aspiration, bone marrow biopsy, and serum protein electrophoresis were simultaneously performed to confirm the diagnosis of multiple myeloma. Bone marrow imprint smears were hypercellular with the presence of numerous bare nuclei, which were predominantly lymphoid cells with a few plasmacytoid cells (Fig. 1). The bone marrow biopsy revealed a hypercellular marrow with diffuse infiltration of a spectrum of lymphoid cells that were predominantly small lymphocytes, plasmacytoid lymphocytes, a few plasma cells, and mast cells (Fig. 2). The erythroid, myeloid, and megakaryocytic series were markedly suppressed. Therefore, a diagnosis of lymphoplasmacytic lymphoma was considered. Immunohistochemical staining revealed 2 populations of cells; the predominant population was strongly positive for CD20 (lymphocytic cells) (Fig. 2 inset) while the other population was positive for CD138 (plasmacytic cells). CD5 and CD23 were negative, which ruled out chronic lymphocytic leukemia/small lymphocytic lymphoma. The serum protein electrophoresis revealed the following: total protein, 10.5 g/dL (range, 6.4–8.1); albumin, 1.76 g/dL (range, 3.50–5.64); gamma globulin, 7.18 g/dL (range, 0.62–

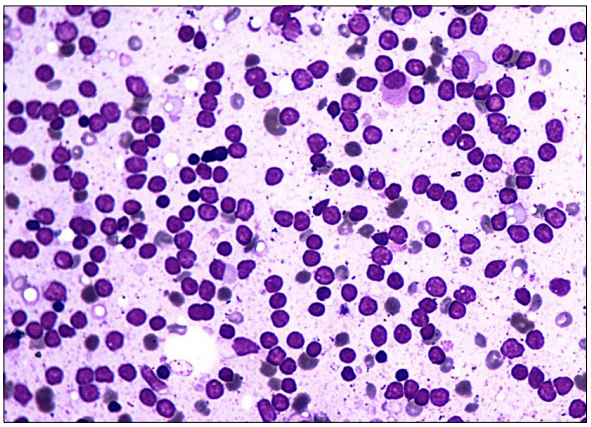

Fig. 1. Photomicrograph showing hypercellular bone marrow smears with the presence of mostly bare nuclei, few lymphoid cells, and plasmacytic cells (Wright's stain, ×1,000).

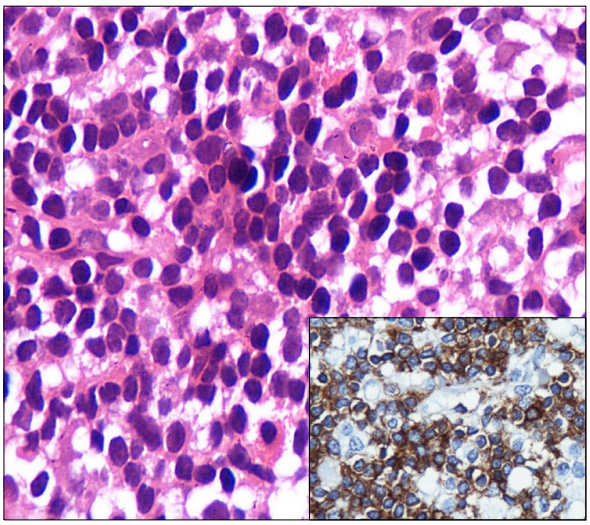

Fig. 2. Photomicrograph showing hypercellular marrow with diffuse infiltration by lymphoid cells, plasmacytoid lymphocytes, a few plasma cells, and mast cells (hematoxylin and eosin stain, ×1,000); inset photomicrograph showing strong cytoplasmic positivity for CD20 in the majority of the lymphoid cells (immunohistochemical stain for CD20, ×400).

1.53); and albumin to globulin ratio, 0.2 (range, 0.9–2.0), with an M spike of 5.98 g/dL. Immunofixation electrophoresis revealed IgM kappa light chains. Thus, a final diagnosis of WM was established.

DISCUSSION

A Swedish physician named Waldenstrom first described WM in 1944. WM, also known as LPL, is one of the rare subtypes of non-Hodgkin's Lymphoma (NHL), accounting for only 1–2% of all NHL cases [7, 8].

WM is defined as LPL with bone marrow involvement and an IgM monoclonal gammopathy of any concentration, and it is found in a significant proportion of patients with LPL [1].

WM occurs in adults with a median age between 60 and 70 years. Common presentation includes weakness and fatigue with an IgM serum paraprotein. The complications of LPL/WM include serum hyperviscosity, cryoglobulinemia, bleeding diathesis, amyloidosis, and pancytopenia; and these are related to the presence of increased levels of serum IgM and to tissue infiltration by lymphoplasmacytic lymphoma [1, 9-12].

Initially, it was believed that the skeletal system was not affected by WM. Moreover, absence of bone involvement in WM was considered a differentiating feature from multiple myeloma. Several subsequent reports indicated that skeletal involvement might be more common than previously believed [3-6]. Ju *et al.* [13] reported a case of a patient with WM, aged 50 years, who presented with a compression fracture of the spine . In multiple myeloma, plasma cells produce a monoclonal immunoglobulin as well as an osteoclast activating factor (OAF), which is a calcium mobilizing substance. OAF stimulates osteoclasts and therefore local bone resorption around the foci of myeloma while inhibiting local osteoblastic activity, leading to increased serum calcium levels. Marks *et al.* [5] suggested that, despite the fact that the lytic bone involvement in WM resembles that of multiple myeloma, the serum calcium levels in WM were consistently normal, suggesting that OAF was not present. Moreover, it has been observed that lytic lesions in WM are more common when there is a predominance of plasmacytic morphology [5, 6]. However, this was not reflected in the present case where the cell population was comprised primarily of lymphoid cells.

Involvement of the gastrointestinal system in WM is also rare [14, 15]. In our case, the CT scan indicated a thickening of the rectal wall and the wall of the sigmoid colon, suggesting a possible involvement of WM. The patient passed away; therefore, a biopsy could not be performed to confirm it.

In the present case, a clinical diagnosis of multiple myeloma was considered due to lytic bone lesions, decreased serum albumin, and low albumin to globulin ratio. However, there were a number of findings indicating that WM would have been a more appropriate diagnosis. These included the high percentage of lymphoid cells on the bone marrow biopsy, with only a few plasmacytic cells, and the increase in mast cells, a feature commonly observed in WM. In addition, the immunohistochemistry indicated a strong positivity for CD20 with only focal staining for CD138 which is contrary to the strong diffuse staining for CD138 observed in multiple myeloma. Lastly, the consistently normal serum calcium levels, despite the presence of multiple lytic lesions in the bone, also favored WM.

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REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press, 2008:194-5.
2. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol 2003;30: 110-5.
3. Leb L, Grimes ET, Balogh K, Merritt JA Jr. Monoclonal macroglobulinemia with osteolytic lesions: a case report and review of the literature. Cancer 1977;39:227-31.
4. Krausz Y, Zlotnick A. Macroglobulinemia of Waldenstrom associated with severe osteolytic lesions. Acta Haematol 1977;58: 307-11.
5. Marks MA, Tow DE, Jay M. Bone scanning in Waldenstrom's macroglobulinemia. J Nucl Med 1985;26:1412-4.
6. Schlesinger N, Neustadter L, Schumacher HR. Lytic bone lesions as a prominent feature in Waldenstrom's macroglobulinemia. J Clin Rheumatol 2000;6:150-3.
7. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89: 3909-18.
8. Owen RG, Parapia LA, Higginson J, et al. Clinicopathological correlates of IgM paraproteinemias. Clin Lymphoma 2000;1: 39-43.
9. Dimopoulos MA, Panayiotidis P, Moulopoulos LA, Sfikakis P,

Dalakas M. Waldenstrom's macroglobulinemia: clinical features, complications, and management. J Clin Oncol 2000;18:214-26.
10. Dimopoulos MA, Hamilos G, Zervas K, et al. Survival and prognostic factors after initiation of treatment in Waldenstrom's macroglobulinemia. Ann Oncol 2003;14:1299-305.
11. Dimopoulos MA, Kyle RA, Anagnostopoulos A, Treon SP. Diagnosis and management of Waldenstrom's macroglobulinemia. J Clin Oncol 2005;23:1564-77.
12. Gertz MA, Fonseca R, Rajkumar SV. Waldenstrom's macroglobulinemia. Oncologist 2000;5:63-7.
13. Ju KT, Bang SM, Song KS, et al. A case of Waldenstrom's macroglobulinemia presented as a compression fracture of spine. Korean J Hematol 2001;36:257-61.
14. Gad A, Willen R, Carlen B, Gyland F, Wickander M. Duodenal involvement in Waldenstrom's macroglobulinemia. J Clin Gastroenterol 1995;20:174-6.
15. Yasui O, Tukamoto F, Sasaki N, et al. Malignant lymphoma of the transverse colon associated with macroglobulinemia. Am J Gastroenterol 1997;92:2299-301.

Relationship between bortezomib-containing regimens and the incidence of tuberculosis in patients with myeloma

TO THE EDITOR: Despite the growing concern for the increased risk of infection associated with the use of new drugs for patients with myeloma, only few data have been reported until recently, especially for tuberculosis infections [1]. A recent analysis demonstrated the relationship between the use of bortezomib and the occurrence of tuberculosis in Korean patients with myeloma [2]. Investigating this relationship might be important in tuberculosis-prevalent areas such as Asian countries because it might influence physician decision-making with regard to the appropriate treatment regimen. Furthermore, previous study results showed a considerable incidence (7.0%) of tuberculosis during the course of treatment with a bortezomib-containing regimen. Considering the importance of this topic, we retrospectively analyzed our data to investigate the incidence of tuberculosis in patients treated with a bortezomib-containing regimen in our institute. Between October 2004 and August 2012, 285 patients with myeloma received 349 courses of bortezomib-containing regimens. The regimens administered are summarized in Table 1.

Table 1. Bortezomib-containing combination regimens (N=349).

Regimen	N (%)
Bortezomib+dexamethasone	201 (57.6)
Bortezomib	52 (14.9)
Bortezomib+melphalan+prednisolone	27 (7.7)
Bortezomib+doxorubicin+dexamethasone	26 (7.4)
Bortezomib+cyclophosphamide+dexamethasone	16 (4.6)
Bortezomib+thalidomide+dexamethasone	9 (2.6)
Others	18 (5.2)

The median age of the patients included in our analysis was 60 years (range, 22–86 years). Of the patients, 50.9% were male. No occurrence of tuberculosis was encountered during the course of treatment with bortezomib-containing chemotherapy. However, we found 6 patients who developed tuberculosis during the follow-up period after myeloma diagnosis. Of the 6 tuberculosis cases, 4 were documented by acid-fast bacilli culture and 2 by tuberculosis pleurisy with increased adenosine deaminase levels. Of the 6 patients, 3 were previously exposed to bortezomib-containing treatment; the time interval from their last exposure to bortezomib to the tuberculosis diagnosis was from 5 to 21 months (5, 12, and 21 months, respectively). The other 3 patients developed tuberculosis during the course of their treatment with a thalidomide-containing regimen or alkylating agents. They were never exposed to bortezomib before developing tuberculosis. Thus, we found no case of tuberculosis during the course of treatment with a bortezomib-containing regimen in our study, except for the 3 patients who were previously exposed to bortezomib (3/285, 1.1%). The incidence rate of tuberculosis among our patients was lower than that in a recent study (7.0%). Although it cannot be directly compared with that of our study, the higher incidence of tuberculosis in the previous study might be associated with the other drugs combined with bortezomib. In our series, the most commonly combined drug was dexamethasone (57.6%), with 14.9% of the patients receiving bortezomib alone. Only 7.2% of the patients received bortezomib combined with cyclophosphamide or thalidomide. However, the study by Ahn *et al.* [2] showed that most patients received bortezomib in combination with thalidomide and cyclophosphamide. Our data imply that the addition of more combination drugs that may affect immune function, such as thalidomide or cyclophosphamide, might increase the patient's susceptibility to tuberculosis. To clarify this finding, a more extensive survey of the incidence of tuberculosis and the various myeloma treatment regimens is required. In conclusion, tuberculosis infection in the patients treated with a bortezomib-containing regimen was not common in our series. The increase in the susceptibility to tuberculosis by bortezomib-containing regimens might be more dependent on the other combination drugs.

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