Cleaved Variant of Plasmacytoma with Myelomonocytic Differentiation - Immunohistochemical and Ultrastructural Studies -

Although plasma cells are terminally differentiated B cells, neoplastic plasma cells frequently express not only pre-B cell antigen, but also megakaryocytic, myelomonocytic, or erythroid markers. Since morphologic diagnosis of plasmacytoma is based on the recognition of neoplastic cells closely resembling normal plasma cells, unusual morphologic variants of neoplastic cells associated with these aberrant immunohistochemical features frequently cause diagnostic difficulty. The authors report a case of plasmacytoma with cleaved nuclei and myelomonocytic features occuring in the clavicle. The tumor was composed of immature plasma cells showing irregular, cleaved, and multilobated nuclei and abundant cytoplasm with prominent eosinophilic granules. A few tumor cells showing recognizable plasmacytic differentiation were admixed within the tumor. Immunohistochemically, the tumor cells expressed CD45RB, CD68, lysozyme, myeloperoxidase and kappa light chain with focal positivity for lambda chain. Ultrastructurally, the tumor cells contained numerous membrane bound electron dense lysosomal granules, some of them resembling Auer rods, as well as rough endoplasmic reticula arranged in lamellated stacks. Small biopsied nasal mucosal tissue in same patient revealed well differentiated plasmacytoma composed of tumor cells showing round, eccentric nuclei devoid of marked nuclear cleavage and cytoplasmic granularity. Immunohistochemically, these cells were kappa(+), lambda(−), myeloperoxidase(−), lysozyme(−) and CD68(−). *(JKMS 1997; 12: 443~6)*

Key Words : *Plasmacytoma; Antigens, Differentiation, Myelomonocytic; Immunohistochemistry*

Jai Hyang Go, Young Hyeh Ko, Howe J. Ree

Department of Diagnostic Pathology, Samsung Seoul Hospital

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Address for correspondence
Jai Hyang Go, M.D., Department of Diagnostic Pathology, Samsung Seoul Hospital, 50, Ilwon-dong, Kangnam-gu, Seoul 135-710, Korea
Tel : (02) 3410-2800, Fax : (02) 3410-0025

INTRODUCTION

Most plasma cell myelomas are composed of mature-looking plasma cells (1). Plasma cell myeloma with cleaved nuclei is an uncommon subtype accounting for 8% of multiple myeloma (2). Morphologically, the tumor cells have notched, cleaved, or even convoluted nuclei of variable size and abundant cytoplasm which resemble myelomonocytic leukemia cells (2). Although some reports (2, 3) have emphasized diagnostic difficulty and a worse prognosis for this subtype as compared to the usual well differentiated myeloma, immunohistochemical and ultrastructural features have not been well characterized yet. We report a cleaved subtype of plasmacytoma occuring in the clavicle, with immunohistochemical and ultrastructural evidence of myelomonocytic differentiation.

CASE REPORT

A 39-year-old woman was admitted to the department of orthopedic surgery with the complaint of a painful right shoulder mass of one year duration. She had a history of right nasal polypectomy one year before admission. On admission, hemoglobin concentration was 13.5 g/dl, platelet count $240 \times 10^3/\mu l$ and white blood cell count 6.13×10^3/dl. The peripheral blood smear revealed neither blasts nor atypical lymphocytes. Total protein was 7.4 g/dl, and globulin was 2.9 g/dl with an albumin /globulin ratio of 1.6.

The shoulder MR image revealed a lobulated, multiseptated mass with an expansile contour in the lateral end of the right clavicle in T1WI. The entire mass excluding septa showed slightly increased signal intensity on T2WI and dense contrast enhancement.

The resected clavicle revealed an irregular reddish yellow soft tissue mass (2.5×1 cm) involving the marrow space with cortical bone destruction and periosteal soft tissue extension. The sections showed monotonous infiltration of large atypical cells with cleaved, convoluted and lobulated nuclei, some of them forming multinucleated giant cells (Fig. 1A). The nucleoli were inconspic-

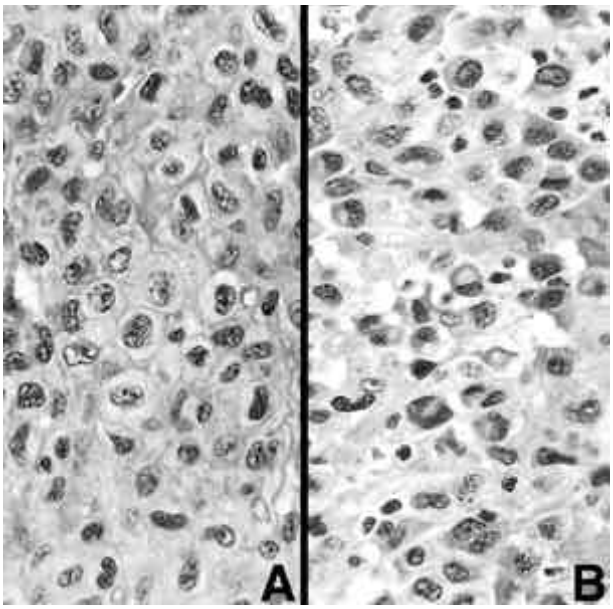

Fig. 1. The tumor of the clavicular bone was composed of monotonous large atypical cells with cleaved, convoluted and lobulated nuclei (A). Focal plasmacytic differentiation was evident within the tumor (B).

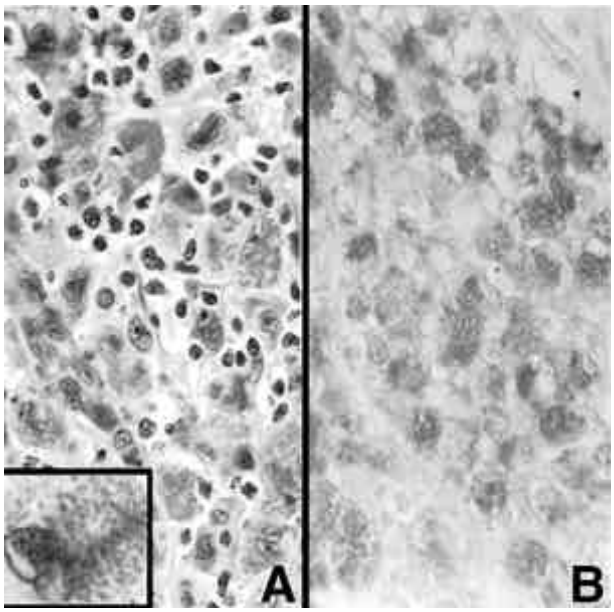

Fig. 2. The cytoplasms of the tumor cells were abundant and granular with eosinophilic granules (A). The tumor cells were diffusely positive for myeloperoxidase (B).

uous in most cells. The cytoplasm was abundant and granular with eosinophilic granules (Fig. 2A). Under the impression of granulocytic sarcoma, reticulum cell sarcoma or Langerhan's cell histiocytosis, immunostaining using paraffin sections with avidin-biotin-peroxidase complex method was performed for CD45RB, CD45RO, CD3, CD20, CD68, lysozyme, myeloperoxidase and S-100 protein (DAKO, Denmark). Many of the tumor cells were positive for CD45RB, CD68, lysozyme and myeloperoxidase (Fig. 2B), but negative for CD3, CD45RO, CD20 and S-100 protein. Ultrastructurally, the nuclei of the tumor cells were irregularly cleaved with prominent marginated heterochromatin and occasional nucleoli. The cytoplasm contained abundant organelles including many dilated rough endoplasmic reticula, some of which were arranged in lamellated stacks, and numerous membrane bound electron dense lysosomal granules (110 - 420 nm) thought to be primary granules. Some granules had finely lamellated tubular inner structures. Needle-like elongated Auer rods were also present (Fig. 3). Some cells had several large granules containing rectangular crystalline cores of eosinophilic precursor. These findings were suggestive of both myelomonocytic and plasma cell differentiation. During pathologic workup, nasal polypoid mass was developed. Orbitomeatal unit CT showed an expansile soft tissue mass in the right maxillary sinus antrum and right nasal cavity. Right inferior and middle turbinates were compressed by this mass. The right medial wall of the orbit seemed to be destructed focally.

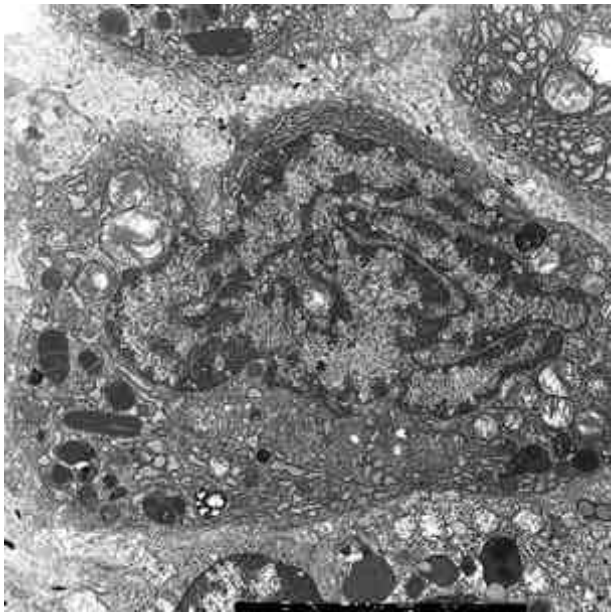

Fig. 3. Ultrastructurally, the nuclei of the tumor cells were irregularly cleaved with prominent marginated chromatin. The cytoplasm contained many membrane bound electron dense lysosomal granules, some of them forming needle like Auer rods (× 5000).

Small biopsied nasal mucosal tissue revealed well differentiated plasmacytoma composed of tumor cells showing round, eccentric nuclei devoid of marked nuclear cleavage

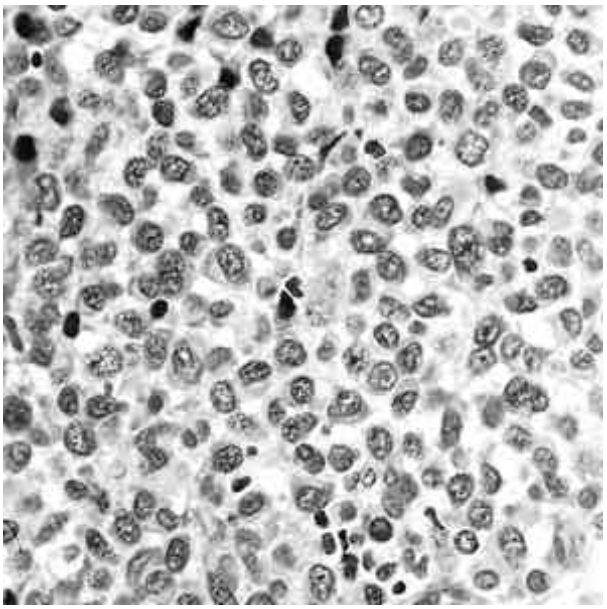

Fig. 4. The tumor of the nasal mass was composed of well differentiated plasma cells.

and cytoplasmic granularity (Fig. 4). Immunohistochemically, these cells were kappa (+), lambda (−), myeloperoxidase (−), lysozyme (−) and CD68 (−). Immunostaining for kappa and lambda light chains (DAKO, Denmark) was performed on the tumor of the clavicular bone. The cells were diffusely positive for kappa light chain with focal positivity for lambda chain. Also, the cells expressed IgD heavy chain. Polymerase chain reaction for IgH chain gene rearrangement showed oligoclonal bands. On careful histologic review of the clavicular mass, a few tumor cells showing recognizable plasmacytic differentiation were admixed within the tumor (Fig. 1B). With all these findings, the clavicular tumor was diagnosed as anaplastic plasmacytoma, cleaved type with myelomonocytic differentiation. Serum electrophoresis disclosed no abnormal findings. Bone marrow biopsy revealed no evidence of neoplastic infiltration.

After operation, radiotherapy was carried out at the total dose of 3600 cGy/20 fraction for 1 month on the right shoulder and for 2 months on the right nasal cavity at the total dose of 5940 cGy/33 fraction. Follow up CT revealed marked decrease in the size of the maxillary sinus and nasal cavity masses.

DISCUSSION

In multiple myeloma or plasmacytoma, no single classification has yet been widely accepted (3). Most cases of multiple myeloma or plasmacytoma are composed of mature-looking plasma cells, while tumors with marked cellular atypia are encountered infrequently (1). A variety of terms has been proposed to classify these two types. The former were named diversely as differentiated (4, 5), plasmacytic (6, 7, 8), or mature subtype (9) whilst the latter were called poorly differentiated (4, 5), plasmablastic (6, 7, 8) and immature subtype (9). The latter subtype, in which the neoplastic cells have a high nuclear to cytoplasmic ratio and prominent nucleoli, has been shown to have a worse prognosis than the usual well differentiated myeloma (6, 7, 8, 9). Contrary to the above classification, Bartl et al. (3) divided multiple myeloma into six histologic types and three histologic grades. The low grade group included the "Marschalko and small cell types"; the intermediate grade, the cleaved, polymorphous and asynchronous types; and the high grade the plasmablastic type. Especially cleaved/monocytoid and multilobated/multinucleated variant may lead to erroneous diagnosis, such as cleaved lymphoid cells, myelomonocytic leukemia cells, metastatic carcinoma cells, neutrophil or histiocyte-like cells (2).

Until recently, plasma cells were thought to express only a few antigens, in particular intracytoplasmic immunoglobulin and CD38. However, there is increasing evidence that the neoplastic plasma cells express a variety of hemopoietic and non-hemopoietic cell markers (1). Myeloma tumor cells show frequent expression of the pre-B cell antigen CALLA (58%), megakaryocytic (88%), myelomonocytic (65%), and erythroid (39%) surface markers (10, 11). The proportion of tumor cells expressing the different markers varied among patients from 2 to 100% of recognizable tumor cells (10).

The myeloid specific cell surface antigens such as CD33 and CD13, the early B cell antigen identified by CD10 are expressed on a proportion of normal plasma cells of human bone marrow. These observations imply that the expression of myeloid and early B cell markers described in multiple myeloma is not associated with neoplasia but is rather a normal phenomenon (12). However, an actual synthesis of lysozyme within myeloma cells appears to have taken place. A particular pattern of lysozyme positivity mainly in the peripheral RER containing area and to a lesser degree within the Golgi zone are suggestive of active synthesis and turnover in these compartments (11). Experiments reveal that the myelomonocytic cells in peripheral blood differentiate into both macrophages and plasma cells in suspension culture, and the CD14+ myelomonocytic cells synchronously produce IgG and show rearrangement of IgH gene (13). Based on these results, many authors suggested a common leukemic progenitor origin for all hematologic cancers and a mechanism of "lineage infidelity" in the development of "bilineal" differentiation of the common progenitor (10, 13). This type of lineage

infidelity represents a general phenomenon seen even in other types of neoplasms, particularly in leukemias (9).

There are several reports claiming that the immonohistochemical staining pattern and frequency are related to tumor differentiation. In poorly differentiated plasmacytoma more tumor cells expressed myelomonocytic markers (11). Multiple myeloid antigen expression was associated with more aggressive disease and shorter survival. The poorly differentiated plasmacytoma also had other prognostic factors including high labelling index and CALLA positivity (14).

In our case, many of the tumor cells showed prominent cytoplasmic eosinophilic granules, which were suspicious of myeloid origin. Intracytoplasmic inclusions, quite distinct from the splinter shaped azurophilic Auer rods found in acute myeloid leukemias, have been described in circulating malignant lymphocytes of various lymphoproliferative disorders. However, needle like crystals, which morphologically and ultrastructurally resemble Auer rods, have been found in the cytoplasm of neoplastic lymphocytes in one case of chronic lymphocytic leukemia, one case of prolymphocytic leukemia, two cases of multiple myeloma and small cleaved follicular center cell lymphoma in leukemic phase. In these cases, the inclusions were mostly negative for Sudan black B, PAS, myeloperoxidase or immunoglobulin and considered as a lysosomal origin ultrastructurally (15). However, most tumor cells in our case were positive for myeloid markers, such as CD68, lysozyme and myeloperoxidase.

The tumor in our case was likewise composed of intermediate grade plasma cells having cleaved, convoluted or multilobated nuclei. Thus we diagnosed it as an uncommon cleaved variant of plasmacytoma. Another notable feature of this tumor is its myelomonocytic differentiation displayed by eosinophilic cytoplasmic granules, positivity to markers such as CD68, lysozyme and myeloperoxidase, and the presence of Auer rod-like structures observed by electron microscopy. Due to its unusual morphologic features, this subtype is frequently confused with granulocytic sarcoma, reticulum cell sarcoma or Langerhan's cell histiocytosis. However, definite plasmacytic differentiation could be found within the tumor in contrast to granulocytic sarcoma. Therefore, a careful histologic review is mandatory for a correct diagnosis.

In conclusion, plasma cell myeloma can present with cleaved nuclear configuration and myelomonocytic features, which may mimick granulocytic sarcoma.

REFERENCES

1. Petruch UR, Horny HP, Kaiserling E. *Frequent expression of haemopoietic and non-haemopoietic antigens by neoplastic plasma cells: an immunohistochemical study using formalin-fixed, paraffin-embedded tissue. Histopathology 1992; 20: 35-40.*
2. Zuwrence LR, Ferry JA, Conlon M, Harris NL. *Plasma cell myeloma with cleaved, multilobated, and monocytoid nuclei. Am J Clin Pathol 1989; 93: 657-61.*
3. Bartl R, Frisch B, Fateh-Moghadam A, Kettner G, Jaeger K, Sommerfeld W. *Histologic classification and staging of multiple myeloma. A retrospective and prospective study of 674 cases. Am J Clin Pathol 1987; 87: 342-55.*
4. Bayrd ED. *The bone marrow on sternal aspiration in multiple myeloma. Blood 1948; 3: 987-1018.*
5. Pasmantier MW, Azar HA. *Extraskeletal spread in multiple plasma cell myeloma. A review of 57 autopsied cases. Cancer 1969; 23: 167-74.*
6. Bartl R, Frisch B, Burkhardt R. *Bone marrow histology in myeloma: Its importance in diagnosis, prognosis, classification and staging. Br J Hematol 1982; 51: 361-75.*
7. Ludwig H, Fritz E, Radaszkiewicz T. *The prognostic relevance of morphologic classification of myeloma cells, Abstracts of the International Society of Hematology and International Society of Blood Transfusion. Budapest, Akademiai Nyomda p179.*
8. Wutke K, Vabrio M, Rudiger KD, Kelenyi G. *Cytological and histological calssification of multiple myeloma. Hematologia 1981; 14: 315-29.*
9. Greipp PR, Raymond NM, Kyle RA, O'Fallon WM. *Multiple myeloma: significance of plasmablastic subtype in morphologic classification. Blood 1985; 65: 305-10.*
10. Epstein J, Xiao H, Xiao YH. *Markers of multiple hematopoietic cell lineages in multiple myeloma. N Engl J Med 1990; 322: 664-8.*
11. Safadi LA, Hellerich U, Schaefer HE. *The expression of lysozyme in multiple myeloma. Pathol Res Pract 1994; 190: 578-83.*
12. Terstappen LW, Johnsen S, Segers-Nolten IMJ, Loken MR. *Identification and characterization of plasma cells in normal human bone marrow by high resolution flow cytometry. Blood 1990; 76: 1739-47.*
13. Akashi K, Harada M, Shibuya T, Fukagawa K, Kimura N, Sagawa K, Yoshikai Y, Teshima T, Kikuchi M, Niho Y. *Simultaneous occurrence of myelomonocytic leukemia and multiple myeloma: involvement of common leukemic progenitors and their developmental abnormality of "lineage infidelity". J Cell Physiol 1991; 148: 446-56.*
14. Grogan TM, Durie BGM, Spier CM, Richter L, Vela E. *Myelomonocytic antigen positive multiple myeloma. Blood 1989; 3: 763-9.*
15. Groom DA, Wong D, Brynes R, Macaulay LK. *Auer rod-like inclusions in circulating lymphoma cells. Am J Clin Pathol 1991; 96: 111-5.*