

# Cytologic Diagnosis of Malignant Pleural Effusion in Multiple Myeloma – Two Case Reports –

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Malignant pleural effusion in multiple myeloma (MM) is extremely rare and is associated with poor prognosis. We experienced two cases of MM IgA type with malignant pleural effusion. The diagnoses were based on characteristic cytology and CD138 immunocytochemistry. The patients received several cycles of combination chemotherapy, since symptoms were more aggressive with an uncontrolled pleural effusion. We review the clinical features of these cases and literature concerning myelomatous pleural effusion.

**Key Words :** Cytology; Malignant pleural effusion; Multiple Myeloma

Malignant pleural effusion in patients with multiple myeloma (MM) is rare and occurs as a late complication during disease progression.<sup>1</sup> Recognition of malignant plasma cells in pleural fluids from MM is important both therapeutically and prognostically. Here, we describe two cases diagnosed cytologically as having myelomatous pleural effusion.

## CASE REPORTS

### Case 1

A 59-year-old woman presented with a 5-month history of back and anterolateral chest pain. At a local hospital, the patient was diagnosed as MM of immunoglobulin (Ig) A and kappa type by bone marrow biopsy and immunoglobulin analysis. The patient was transferred to our hospital for combination chemotherapy. However, during chemotherapy, the patient presented with

dyspnea and radiologic evidence of pleural effusion associated with both lungs. Thoracentesis was performed, which revealed serosanguineous fluid with a glucose level of 89.0 mg/dL, lactate dehydrogenase 601.0 IU/L, protein 4.8 g/dL, IgA 20.1 g/L, IgG 1.4 g/L, and IgM 0.1 g/L. Serum protein electrophoresis revealed a monoclonal peak in the gamma Ig region and urinary immunoelectrophoresis showed an abnormal arc in the kappa light chain. Pleural fluid cytology showed numerous immature and atypical plasma cells mixed with more mature forms. The abnormal cells typically displayed an abundant dense blue cytoplasm and large eccentric nucleus (Fig. 1A). Immunocytochemical staining of a cell block for CD138 revealed a positive reaction for neoplastic plasma cells (Fig. 1B). However, immunocytochemical staining for cytokeratin (CK), CD30, and CD56 were negative. Although the patient received several cycles of combination chemotherapy with thalidomide, cyclophosphamide, and dexamethasone (TCD), chest radiograph monitoring showed no change during therapy. The treatment was unsuccessful and

she was discharged.

### Case 2

A 49-year-old man was admitted to our hospital with a 2-month history of right ankle pain. Magnetic resonance imaging revealed multiple lesions in vertebral bodies, right iliac body, and right tibia. A bone marrow biopsy and protein electrophoresis revealed MM. Serum Ig levels were: IgG 340 mg/dL, IgA 2,480 mg/dL, IgM 18 mg/dL, kappa light chain <0.06 mg/L, lambda light chain 2,810 mg/L, and beta2-microglobulin 48,938.7  $\mu$ g/L. Serum protein electrophoresis and Ig analysis revealed an IgA lambda monoclonal gammopathy, and urine electrophoresis revealed a monoclonal lambda chain proteinuria. After eight cycles of TCD combination chemotherapy, the patient's condition was improved. After 2 months, the patient presented with

severe dyspnea and pain in both flanks. Chest radiography revealed massive right side pleural effusion. Thoracentesis was performed and straw-colored fluid was aspirated. Ig analysis of the pleural fluid showed elevated IgA, identical to the result of the earlier serum Ig analysis. A cytologic examination of the pleural fluid revealed variously sized immature and mature-looking plasma cells (Fig. 2A). Frequent binucleated and multinucleated forms, mitotic figures, and scattered plasmablasts with prominent nucleoli were also seen. These neoplastic cells demonstrated positive immunocytochemical staining for CD138 (Fig. 2B), but were negative for CK, CD56, and CD30. Pleurodesis was performed to prevent additional pleural fluid formation and the patient was given modified chemotherapy in the form of methylprednisolone and cyclophosphamide due to his deranged renal profile and general condition. However, the patient's condition deteriorated rapidly and death occurred one month later as a

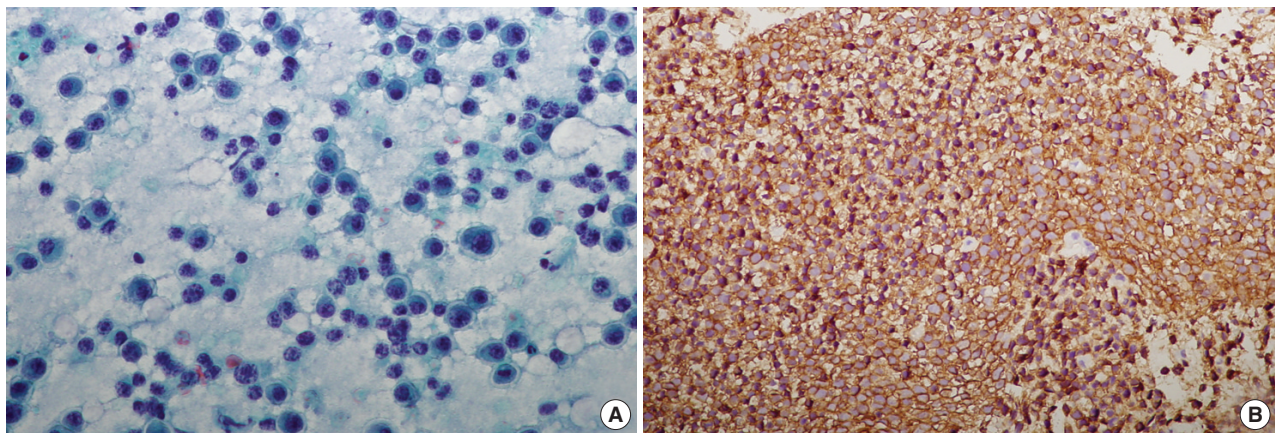


Fig. 1. Cytologic features of the pleural fluid of case 1. (A) Numerous mature and immature plasma cells are shown (Papanicolaou). (B) Immunocytochemical staining of a cell block for CD138 reveals a positive reaction for neoplastic plasma cells (Immunocytochemical stain).

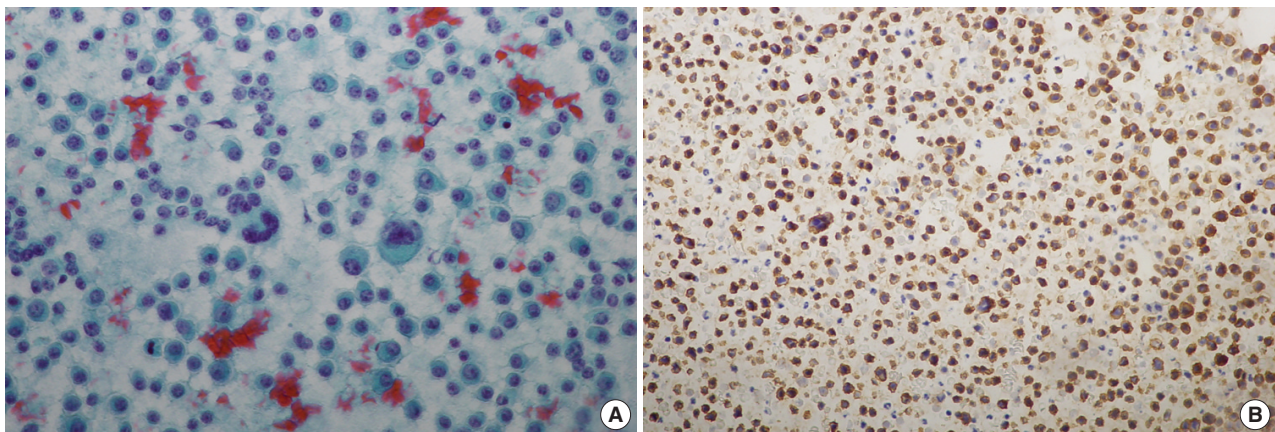


Fig. 2. Cytologic features of the pleural fluid of case 2. (A) Variously sized immature plasma cells with eccentric nuclei and occasional multinucleated cells are noted (Papanicolaou). (B) These neoplastic cells demonstrate positive immunocytochemical staining for CD138 (Immunocytochemical stain).

result of complicated renal failure.

## DISCUSSION

MM is a malignant proliferation of plasma cells that primarily affects the bone marrow and skeletal system.<sup>2</sup> Pleural effusions occur in approximately 6% of MM patients.<sup>3</sup> Most pleural effusions in multiple myeloma are benign and are due to congestive heart failure, chronic renal failure, hypo-albuminemia, cardiac amyloidosis, pulmonary infection, or pulmonary infarction.<sup>4</sup> In a Mayo Clinic review of 958 MM cases including 58 with pleural effusion, only 8 (0.8%) were found to have effusions due to myeloma.<sup>5</sup> Thus, myelomatous pleural effusion is rare and most are of the IgA type, which shows a major tendency to invade extra-osseous structures,<sup>3</sup> as was observed in our two cases. Ig analysis in our cases showed an elevated IgA level compared to other Ig levels.

A diagnosis of myelomatous pleural effusion is typically confirmed by cytologically identifying malignant plasma cells within the pleural fluid. However, the morphology of plasma cells in patients with myelomatous pleural effusion can be quite variable. A purely morphologic diagnosis of myelomatous pleural effusion can be made if the cytologic features are sufficiently distinctive, as presently occurred. Immunocytochemistry may be useful when the number of plasma cells in the pleural fluid is low, when plasma cells do not display atypical features, or when the cells are so bizarre as to mimic other malignancies. When atypical cells are predominantly demonstrated, other malignancies like malignant lymphoma and poorly differentiated carcinoma should be considered. Alternatively, when only mature plasma cells are observed, reactive plasmacytosis, as seen in tuberculosis, viral infection, collagen vascular disease, and Hodgkin's lymphoma, should be included in the differential diagnosis. Immunocytochemical staining can be useful in these conditions. Specifically, CD138 (Syndecan-1), a member of the transmembrane heparin sulfate proteoglycan family, is expressed in normal and neoplastic plasma cells.<sup>6</sup> CD56, a neural cell adhesion molecule, is expressed in 70-80% of MM, but not in reactive plasma cells.<sup>7</sup> Moreover, when malignant plasma cells spread to the extramedullary sites, CD56 is frequently not expressed within the extramedullary sites, but is expressed in the medullary part of MM.<sup>8,9</sup> In our cases, CD56 was not detected by immunocytochemical staining. The cytologic diagnosis may be further supplemented by flow cytometric evaluations for plasma cell markers (CD38 and CD138) and by demonstrating the monoclonal protein in

pleural fluid that is identical to that found in patient serum.

In a recent report, plasmablastic myeloma, defined as plasmablasts comprising  $\geq 2\%$  of all nucleated cells in bone marrow, was associated with poor outcome.<sup>10</sup> Many plasmablasts were detected in effusion fluid of our second case. This case could be classified as the plasmablast subtype. The clinical outcome of this case also supports the fact that this subtype has an especially poor outcome.

As in these two cases, MM associated with myelomatous pleural effusion has a poor prognosis. Myelomatous pleural effusion has been thought to be a late manifestation in the natural history of MM or to be a feature of aggressive behavior.<sup>2,11</sup> In such cases, aggressive therapy including high dose chemotherapy and peripheral blood stem cell support appears to offer no advantage. Reported survival in such cases is generally <4 months.<sup>4</sup> Several reports of MM treated using conventional chemotherapy have suggested that CD56 negative MM is associated with aggressive disease and a poor prognosis.<sup>12,13</sup> The association between a lack of CD56 expression and a higher frequency of extramedullary involvement in MM seems to indicate a poor prognosis for CD56 negative MM.

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