Cytologic Diagnosis of Multiple Myeloma and Macroglobulinemia in Effusions

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ABSTRACT

The presence of effusion in association with multiple myeloma or macroglobulinemia is an unusual finding which generally occurs late in the course of the disease. Occasionally, cytologic detection is a diagnostic problem. In both conditions, the fluid is characterized by a high specific gravity and high protein content. In myeloma, plasma cells at varying stages of differentiation are present, while in macroglobulinemia atypical lymphocytes and plasma cells resembling those found in the blood and bone marrow are seen. Generally, the diagnosis can be readily made on the basis of clinical features, characteristics of the fluid and cytologic findings. In difficult cases, additional procedures helpful in establishing a definite diagnosis include methyl green pyronine stain, fluid electrophoresis and electron microscopy.

Introduction

The occurrence of extramedullary lesions in multiple myeloma is well known.1,5–8,10,11,17–20,25,29,30,32,35,37,38 Pleuropulmonary manifestations in Waldenström's macroglobulinemia have also been described.12,31,34,36,41,47,49 However, in both conditions malignant effusion is considered unusual. Nevertheless a review of the literature reveals a number of cases in which myeloma cells have been found in association with pleural effusion,2,9,11,13,15,24,26,39,43,48 pericardial effusion14,16,39 and ascites2,9,23,27,32,40 and in which macroglobulinemia has been associated with pleural effusion.4,31,33,42,44,45,49,50

In the present report, four additional cases of malignant pleural effusion occurring in association with multiple myeloma are presented, with a discussion of the pertinent cytologic findings important in the diagnosis of myeloma and macroglobulinemia in effusions.

Case Reports

Case 1. A 68 year old woman with a diagnosis three years previously of multiple myeloma was admitted to the hospital with pneumonia, gastrointestinal bleeding and anemia. At the time of initial diagnosis, serum proteins were 7.5 g per dl and immunoelectrophoresis demonstrated an IgA gammopathy, lambda type. The patient was treated with melphalan and plasmapheresis to decrease blood viscosity. On the current admission, bilateral pleural effusions were noted on chest x-ray and
thoracentesis revealed hazy yellow fluid with specific gravity of 1.026 and protein 7.1 g per dl. Cytologic examination showed many cells in the plasma cell series varying in appearance from immature myeloma cells to mature plasma cells (figure 1). In the background were occasional mesothelial cells, lymphocytes and red blood cells. She was discharged on steroids and supportive treatment and expired at home three months later. No autopsy was performed.

Case 2. A 65 year old man developed multiple bony lesions and bone marrow examination revealed numerous immature plasma cells consistent with multiple myeloma. Serum electrophoresis was normal, except for a slightly decreased gamma globulin, but urine electrophoresis revealed a spike in the beta-gamma globulin region, IgA type. Chest x-ray showed the presence of pleural effusion. The fluid removed was yellow and slightly bloody with specific gravity of 1.017.

Malignant plasma cells similar to those present in the bone marrow were found in the pleural fluid, both in smears (figure 2a) and in cell block preparations (figure 2b). Methyl green pyronine stain performed on the cell button was positive. A pleural biopsy done at the same time revealed an atypical plasma cell infiltrate consistent with multiple myeloma. The patient subsequently developed multiple skin nodules in the chest, back and abdomen presumed to be metastatic tumor.

Treatment included a variety of chemotherapeutic agents. After a period of increasing lethargy, the patient went into acute congestive heart failure and expired approximately one year after initial diagnosis. At autopsy, there was extensive myelomatosis involving bones, skin, lungs, pleura, epicardium, spleen, lymph nodes and testes.

Case 3. A 44 year old man with a previous diagnosis of multiple myeloma was admitted for congestive heart failure and severe dyspnea secondary to recurrent pleural effusion. The patient had a long history of drug abuse, treated with methadone, and episodes of hepatitis. Four years prior to the current admission, he was hospitalized for weight loss and low back pain and bone marrow was found to be replaced by plasma cells. This was associated with leukopenia and thrombocytopenia and an IgA fraction of 11 g per dl in the serum. He subsequently developed cardiomegaly, anemia and a right pleural effusion. He was treated with transfusions and cyclophosphamide without success. Over the next several years he experienced numerous bouts of pneumococcal pneumonia, treated with penicillin.

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found on thoracentesis (figure 3a). The fluid was slightly bloody with specific gravity of 1.018. The patient developed a right upper lobe infiltrate, fever, altered mental status and abnormal liver function studies. His condition rapidly deteriorated and he expired two months later, death attributed to hepatic encephalopathy. At autopsy, in addition to a variety of hepatic, cardiac and pulmonary abnormalities, there was extensive myelomatous involvement of the calvarium, ribs, sternum and vertebrae (figure 3b).

Case 4. A 59 year old woman with anemia, thrombocytopenia and mild azotemia was found to have multiple myeloma, IgG kappa type. Total serum protein was 14.3 g per dl, with gamma globulin 9.3 g per dl. Bence-Jones protein was present in the urine. She had experienced weakness, shortness of breath and a history of repeated lung infections. On her last of many admissions, she was found to have a left pleural effusion with loculated fluid and bilateral pleural masses. Pleural fluid had a specific gravity of 1.029, protein 9.2 g per dl.

On cytologic examination, there were numerous pleomorphic plasma cells of neoplastic type (figure 4). Scattered multinucleated cells and many red blood cells were present. Because of the presence of an empyema and fibropothorax, thoracotomy and left lower lobectomy were performed. There was considerable blood loss during and after surgery and the patient expired two days postoperatively, five months after the initial diagnosis of multiple myeloma. At autopsy, there was myelomatous involvement of sternal and vertebral bone, lungs and peripancreatic lymph nodes.

Discussion

The cases presented illustrate the usual manner of detection of myelomatous effusion, that is in patients with previously diagnosed disease. In rare instances, effusion may appear as an initial or early manifestation. Generally, visceral involvement is a later event in the progression of multiple myeloma and, consequently, diagnosis of malignant effusion rests on identification of abnormal plasma cells in fluid removed from a patient with known myeloma.

It is particularly important, however, to distinguish myelomatous effusion from...
effusion associated with other conditions in which plasma cells may be observed, such as lymphomas, especially Hodgkin's disease, chronic inflammatory processes, eosinophilic granuloma, rheumatoid arthritis, pulmonary infarct and congestive heart failure. In general, effusions associated with myeloma will show clusters of plasma cells exhibiting varying degrees of differentiation. Occasional binucleate and multinucleate cells are present. While the majority of cells generally retain their resemblance to mature plasma cells, the principal diagnostic feature is the variety in degree of differentiation. In other conditions, the plasma cells are generally of mature type and are scattered randomly in the specimen. However, any of the conditions listed may be associated with a prominent plasma cell component, and it is therefore advisable to consider history and other findings before arriving at a diagnosis.

Myelomatous effusions are characterized by a high specific gravity, greater than 1.015 and often above 1.025, and a high protein content, generally above 5 g per dl. Electrophoresis and immunoelectrophoresis usually reveal the same monoclonal protein found in the serum. It is of interest that in three of our four patients the protein was of IgA type. This finding is consistent with results of our literature survey, indicating a preponderance of IgA type myeloma in cases with malignant effusion. In contrast, only 23 percent of all cases of myeloma have an IgA gammapathy. The reason for such a discrepancy is not clear. The suggestion has been made that plasma cells in IgA cases have a larger diameter and smaller nucleus than those in IgG cases, but this could not be verified in a recently reported cytometric analysis.

The presence of high specific gravity and high protein content are particularly helpful in distinguishing myelomatous effusion from effusion owing to chronic inflammation. This is especially true in cases where pneumonia might be superimposed on myeloma and plasma cells could be found in the fluid as the result of a benign inflammatory process. In inflammation, specific gravity and protein content of the fluid are generally in a lower range than the values indicated for myeloma.

Also important in the differential diagnosis is distinction from other types of malignant cells. A second malignancy has been found in 7 percent of patients with myeloma. Therefore, a prior diagnosis of myeloma is not sufficient to assume that malignant cells present in the fluid of such a patient are attributable to the myeloma. Generally, the more common types of tumors seen in body cavity fluids are metastatic adenocarcinomas. These should be readily distinguishable on the basis of specific cellular characteristics not seen in myeloma, such as close aggregation, papillary formation, mucin production, etc. Electrophoresis of the fluid can also be done to determine if a monoclonal gammapathy is present. Another procedure that may be utilized is electron microscopy, which can reveal the characteristic ultrastructural features of cells in the plasma cell series as well as other tumor cell types.

Myeloma cells and mesothelial cells may occasionally be difficult to distinguish. Both occur as individual oval to polygonal cells with rounded nuclei and abundant cytoplasm and both show a wide range in size and appearance. Atypical mesothelial cells can closely mimic myeloma cells, and thus may present a problem in nonmalignant effusions associated with myeloma. The usual staining procedures, such as Papanicolaou, Wright's and hematoxylin and eosin stains, generally reveal a darker staining cytoplasm in plasma cells than in mesothelial cells and the latter do not show the eccen-
tric nucleus with cartwheel pattern and perinuclear halo characteristic of plasma cells. However, under certain circumstances these distinctions may be extremely subtle or absent.

PAS stain is not particularly helpful, since both cell types contain positively staining acid mucopolysaccharides in their cytoplasm. A stain that is useful is methyl green pyronine, since white plasma cells are pyroninophilic, mesothelial cells are not. Electron microscopy would also indicate specific differences, particularly in the amount of endoplasmic reticulum, which is much greater in plasma cells than in mesothelial cells.

There were no cases of malignant effusion associated with Waldenström's macroglobulinemia in our files. However, from analysis of cases reported in the literature it is evident that the diagnosis of macroglobulinemia in effusions is based on principles similar to those indicated for multiple myeloma. These include correlation with clinical findings, the presence of fluid with high specific gravity and high protein content, identification of atypical lymphocytes and plasma cells resembling those seen in the blood and bone marrow and demonstration of an IgM spike in the fluid.

Acknowledgment

Photographic assistance was provided by Clifford E. Lai.

References


