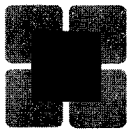

Lambda light chain myeloma with pleural involvement

SAMUEL L. ABBATE, MD; MICHAEL R. JAFF, DO, ANDREW J. FISHLEDER, MD; DAVID P. MEEKER, MD

■ A case is reported of lambda light chain multiple myeloma complicated by a myelomatous pleural effusion. Pleural effusions are uncommon in multiple myeloma, and most are secondary to nonmalignant causes. The clinical characteristics, natural history and pathophysiology of myelomatous pleural effusions are reviewed.

□ INDEX TERM: MULTIPLE MYELOMA □ CLEVE CLIN J MED 1991; 58:235–239

MULTIPLE MYELOMA is a malignant neoplasm characterized by the poorly controlled growth of a single cone of plasma cells. The clinical manifestations of multiple myeloma are due to the local effects of plasmacyte proliferation and the systemic effects of immunoglobulin accumulation. Although plasmacyte proliferation occurs primarily in the bone marrow and bones, autopsy series document extraosseous involvement in 70% of cases.[1] The most frequently involved extraosseous sites include the liver, spleen, and lymph nodes. Less frequently involved are the respiratory tract, oral cavity, and gastrointestinal tract.

Thoracic involvement has been clarified by Kintzer[2] and includes skeletal lesions (eg, osteolytic, osteoporotic, and pathological fractures); intramedullary and extramedullary plasmacytomas; pulmonary infiltrates (including those due to infections); and pleural effusions. Pleural involvement is rare, with an incidence of less than 1% reported in an autopsy series.[3]

From the Departments of Internal Medicine (S.L.A., M.R.J.), Laboratory Hematology (A.J.F.), and Pulmonary Disease (D.P.M.).

Address reprint requests to D.P.M., Department of Pulmonary Disease, A-90, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195.

We report a patient with lambda light chain myeloma who manifested a myelomatous pleural effusion. This is only the second report of lambda light chain myeloma as a cause of pleural effusion. Previously reported pleural effusions in multiple myeloma from the English literature are reviewed.

CASE REPORT

A 67-year-old black man with a history of atherosclerotic heart disease, hypertension, and alcohol abuse was admitted with chest discomfort, low back pain, and abdominal discomfort. He described shortness of breath and nausea. Sublingual nitroglycerin relieved the chest pain. He had recently been discharged from the hospital after a 9-day stay for evaluation of disabling low back pain of 12 months' duration. Medications on admission to the hospital included nifedipine (Procardia), 10 mg orally three times daily, sublingual nitroglycerin prn, and cyclobenzaprine (Flexeril), 10 mg at bedtime.

The patient appeared chronically ill on physical examination. His temperature was 36.7°C; pulse, 64 beats per minute; respirations, 22 per minute; and blood pressure, 150/90 mmHg. He had no palpable

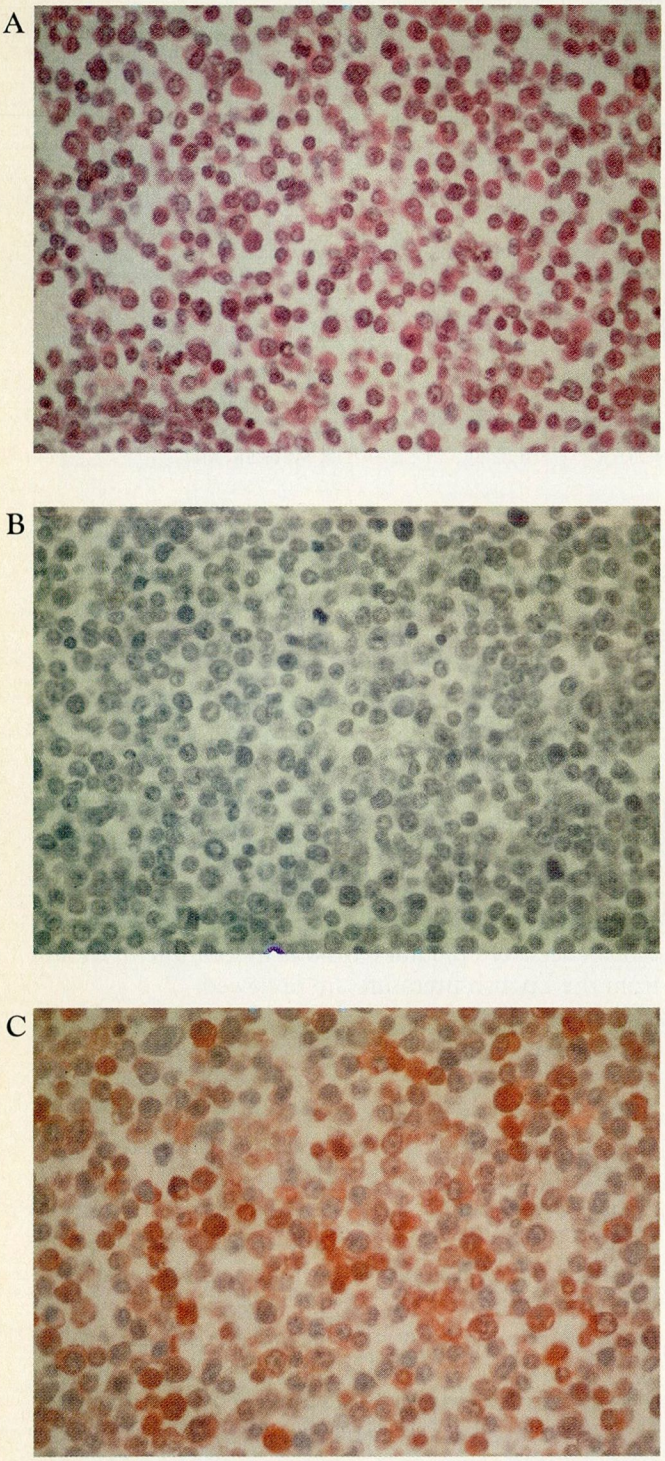

FIGURE (A) Wright's stain of pleural fluid revealing malignant plasma cells. (B) Immunoperoxidase staining of pleural fluid negative for Kappa light chains. (C) Immunoperoxidase staining of pleural fluid positive for lambda light chains (magnification × 100).

lymphadenopathy. His lungs revealed basilar rales one third up bilaterally. Cardiac examination revealed a regular rate and rhythm with an S_4 gallop. There was a systolic ejection murmur, grade II/VI, at the left sternal border without radiation.

There was no jugular venous distention. The abdomen was soft, nontender, and without organomegaly. Symmetric proximal lower extremity muscle weakness was present on active testing. The sensory examination was intact with diminished deep tendon reflexes in the lower extremities. Plantar responses were normal bilaterally. The musculoskeletal examination revealed tenderness over the lumbosacral spine region and lower flanks. The patient was admitted to a cardiac intensive care unit where a myocardial infarction was ruled out.

A workup for low back pain 1 month earlier included spine films, which revealed compression fractures at T7 and L2. A bone scan revealed increased radionuclide uptake at T8, T12, L2, and the left 11th rib posterolaterally. A serum protein electrophoresis was normal. Serum calcium 1 month prior to this admission was normal at 9.7 mg/dL.

The laboratory examination on this admission included a white blood cell count of 7,700 mm^3, hemoglobin of 8.4 g/dL, hematocrit of 24.1%, and a platelet count of $74\times10^3/mm^3$. Serum electrolyte levels included: sodium, 139 mEq/L; potassium, 4.0 mEq/L; chloride, 96 mEq/L; and a carbon dioxide content of 30 mEq/L. The blood urea nitrogen was 33 mg/dL with a creatinine of 2.1 mg/dL. The serum calcium was 14.2 mg/dL with a phosphorus of 3.7 mg/dL. Liver function tests revealed a total bilirubin of 0.6 mg/dL, aspartate aminotransferase of 45 U/L, lactate dehydrogenase (LDH) of 538 U/L, and an alkaline phosphatase of 127 U/L. Blood glucose was 137 mg/dL. Total protein was 6.6 g/dL (4.1 g/dL albumin and 2.5 g/dL globulin). A repeat serum protein electrophoresis was normal. Quantitative serum immunoglobulins revealed an IgG of 580 mg/dL, IgA of 212 mg/dL, and IgM of 23 mg/dL.

Bone marrow aspirate and biopsy demonstrated greater than 80% plasma cells consistent with plasma cell myeloma. A 24-hour urine protein revealed 5,236 mg of protein. Urine immunoelectrophoresis demonstrated free lambda light chains. A computed tomographic (CT) scan of the abdomen and pelvis revealed multiple soft tissue masses within the pelvis.

The patient began treatment with carmustine (BCNU), cyclophosphamide (Cytoxan), and prednisone. A left pleural effusion developed. During thoracentesis, 650 cc of bloody fluid was obtained. The

cell count revealed 80,000 red cells/mm^3 and 17,750 white blood cells/mm^3 with a cell differential of 100% atypical plasmacytoid cells. The pleural fluid to serum LDH ratio was 1.17. The pleural fluid to serum protein ratio was 0.64. Pleural fluid cytology revealed plasma cell myeloma. Immunoperoxidase staining was positive for lambda light chains only. Direct immunofluorescence of the pleural fluid cells stained positive for lambda light chains (*Figure*). Immunoelectrophoresis on the pleural fluid revealed an IgG of 392 mg/dL, IgA of 128 mg/dL, and IgM of 9 mg/dL.

CT of the chest revealed destruction of the 11th rib posterolaterally with a bulging mass extending into the extrathoracic muscles of the back. A large left pleural effusion was also identified. Despite continued chemotherapy, the left pleural effusion increased in size and a chest tube was placed. The patient deteriorated rapidly, requiring mechanical ventilation. A cardiac arrest ensued from which the patient could not be resuscitated.

TABLE
CHARACTERISTICS OF 35 FIVE MYELOMATOUS PLEURAL EFFUSIONS

Reference	Sex/age	Type	Location	Lung involvement	Duration of myeloma preceding effusion	Survival post-effusion
Safa[5]	M/60	NR	L	None	–	–
Galgano[7]	M/50	NR	R	None	–	–
Favis[8]	F/60	NR	R/L	Yes	0	–
Gabriel[9]	F/63	NR	R	Yes	–	1 mo
Edwards[10]	M/69	NR	L	Yes	0	1 mo
Safa[5]	F/56	IgG-κ	L	None	4 yr	7 wk
Kleinholz[3]	M/78	IgA-κ	L	None	10 yr	1 mo
Badrinas[11]	M/41	IgA-κ	L	None	2 wk	4 mo
Ghosh[12]	M/47	IgA-λ	L	Yes	0	6 mo
Mital[13]	M/55	NR			0	–
Kapadia[14]	M/65	IgG	L	None	0	1 mo
	M/70	IgG-κ, IgA-κ	R	None	18 mo	3 wk
Schoenfeld[4]	M/80	IgA-κ	R	None	3 mo	–
Kintzer[2]	–	NR	L	None	–	–
	–	NR	L	Yes	–	–
	–	NR	L	None	–	–
	–	IgA-λ	R	None	–	–
	–	NR	L	None	–	–
	–	IgG-κ	L	Yes	–	–
	–	NR	R/L	None	–	–
	–	NR	L	Yes	–	–
Hughes[15]	M/60	IgG-κ	R/L	None	5 mo	4 mo
	M/40	IgA-κ	R/L	None	15 mo	1 mo
Koss[16]	F/57	κ	R	None	0	–
Scullin[17]	F/59	IgG-κ	L		0	32 mo
Angrish[18]	M/66	IgG*	R	None	14 mo	–
Waddell[19]	M/49	IgG*	R/L	None	0	7 mo
Renau-Piqueras[20]	M/66	IgA-κ	NR	None	–	40 mo
Estrov[21]	F/60	IgA	L	None	0	>30 mo
Kwan[22]	F/60	κ	L	None	17 mo	1 mo
Chee[23]	F/48	IgA*	L	None	0	1 mo
Gupta[24]	M/60	IgG*	L	Yes	2 mo	–
Witt[25]	F/76	λ	R/L	None	0	1 mo
Kamal[6]	M/59	IgD	R	None	20 mo	4 mo
Present Case	M/66	λ	L	None	0	2 mo

NR, not reported
*Immunoelectrophoresis not performed on pleural fluid; diagnosis based on cytology

DISCUSSION

The patient described here had these features of plasma cell myeloma: extensive bone marrow infiltration by plasma cells, lytic bone lesions on skeletal survey, anemia and thrombocytopenia, back pain from vertebral involvement, hypercalcemia, renal insufficiency, a decrement in IgM on quantitative immunoglobulins, and a urine immunoelectrophoresis demonstrating the presence of free lambda light chains. In addition, he had ante mortem evidence of myelomatous involvement of the pleura. This was confirmed both by direct immunofluorescent staining as well as by cytologic examination of the malignant cells in the pleural fluid.

Pleural effusions in multiple myeloma were first reported in the early 1900s.[4,5] Despite frequent thoracic involvement in multiple myeloma, pleural effusions are rare, with only 35 previously reported cases in the English literature. Myelomatous pleural effusion has been reported twice in the Japanese literature as a result of IgD myeloma and once in the

Spanish literature resulting from light chain disease.[6]

Characteristics of the 35 cases reported in the English literature are summarized in *Table*.[5–25] Of the 27 cases where gender was specified, 18 occurred in males compared to only 9 in females. This 2:1 ratio is greater than would be expected, given that the incidence of multiple myeloma is only slightly higher in men than in women.[26] Age was reported in 26 cases, and ranged from 41 to 80 years with a median of 60. This range correlates well with median age (64 years) for the occurrence of multiple myeloma.

Type, location associated with effusion

Myeloma type was specified in 24 of the 35 cases. IgG myeloma was found in 9 cases; in 4 cases it was described in only the serum and not by immunoelectrophoresis of the pleural fluid.[18,19,23,24] In one case, the myeloma was found to secrete both IgG and IgA.[14] IgA myeloma was found in 10 cases (in one case the immunoglobulin was identified only in the serum and not in the pleural fluid). IgD myeloma was reported once, kappa light chain myeloma in two cases, and lambda light chain myeloma in two cases, including the one presently reported. Ordinarily, IgA accounts for 25% of myelomas; however, it accounted for a disproportionate 42% of myeloma cases with pleural effusions.

Myelomatous pleural effusions are found to occur more commonly in the left hemithorax. Of the 33 cases in which location was specified, 19 were in the left hemithorax, 8 were in the right hemithorax, and 6 were bilateral. Underlying lung involvement was noted in only 8 of the 33 cases. Duration of the myeloma prior to the finding of the pleural effusion was short, most frequently occurring at the time of diagnosis. However, it was found as late as 10 years after the diagnosis of multiple myeloma.[3] The presence of a myeloma-associated effusion was a poor prognostic sign. Of the 19 patients for whom this information was available, 16 died within seven months. The other 3 survived beyond 30 months.[17,20,21]

In the largest collected series, Kintzer described pleural effusions as occurring in only 58 of 958 patients with multiple myeloma.[2] In only half of these cases was an effusion present at the time of myeloma diagnosis. Analysis of the causes of these pleural effusions show that most (27/58) were due to congestive heart failure—amyloidosis (18/58) or presumed atherosclerotic heart disease (9/58). In 26% (15/58) no cause was ascertained. Fourteen percent of the pleural effusions (8/58) were found to be due to pleural involvement by the multiple myeloma. In this series, the diagnoses were based upon cytologic examination of the effusion and in only two cases was immunoelectrophoresis used to demonstrate a paraprotein. The remaining causes of pleural effusion in this series included infection (4/58), pulmonary infarction (3/58), and a single case of mesothelioma.

Contributing factors

Myelomatous pleural effusion is rarely an isolated event; the chest wall, mediastinum, or, less frequently, the pulmonary parenchyma, is simultaneously involved. Pleural involvement in multiple myeloma is thought to result either from implantation of tumor on the pleura or extension into the pleural space from adjacent skeletal or parenchymal plasmacytomas.[22,25] Waddell suggested that the major determinant in the development of the myelomatous pleural effusions is the production of a large quantity of immunoglobulins by the malignant cells in and near the pleura.[19] The presence of the immunoglobulins raises the colloid osmotic pressure of the fluid, which interferes with the normal absorption of fluid by the visceral pleura.

Evidence for the contribution of the proteins derived from the pleural plasmacytes and pleural fluid plasmacytomas can be found in the higher measured paraprotein to albumin ratio in the pleural fluid compared to simultaneous serum levels.[5,9,10] Furthermore, Scullin[17] demonstrated that the pleural fluid plasmacytes were viable, synthetically active cells which incorporated ^{3}H leucine into monoclonal immunoglobulins and secreted it with the same kinetics found in bone marrow plasma cells.

If excessive paraproteins caused the accumulation of fluid in the pleural space, then successful chemotherapy for multiple myeloma would decrease the production of the monoclonal proteins by decreasing the tumor burden, and lead to resolution of the effusion. Waddell[19] reported one patient in whom chemotherapy demonstrated this desired end.

In contrast to lymphomas, mediastinal lymphadenopathy is not believed to be a major contributing factor in the development of myelomatous pleural effusion. Mediastinal lymphadenopathy has been reported in only one case ante mortem.[2] In three autopsy cases where mediastinal lymph nodes were examined, malignant plasma cell involvement was minimal.[9-11]

The patient reported here had a lambda light chain myeloma with pleural involvement, giving rise to a myelomatous pleural effusion. Pleural effusions are uncommon in multiple myeloma and myelomatous ef-

fusions account for only 14% of those which are found. Pleural effusions are often a late manifestation in the natural history of multiple myeloma, and are associated with short survival. However, since prolonged survival has been documented in some cases, the presence of a myelomatous pleural effusion should not preclude therapeutic interventions to treat this complication as well as the underlying malignancy.

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