Multiple Myeloma in Association With Sarcoidosis

A Case Report and Review of the Literature

Filiz Şen, MD; Karen P. Mann, MD, PhD; L. Jeffrey Medeiros, MD

- The association of sarcoidosis with Hodgkin disease and non-Hodgkin lymphoma is well known. However, multiple myeloma also can occur rarely in association with sarcoidosis. We describe a patient with sarcoidosis who subsequently developed multiple myeloma. The patient was a 49-year-old woman with a 4-year history of severe, chronic, active sarcoidosis involving her lungs, lymph nodes, eyes, and bone marrow. During the initial clinical workup, a serum monoclonal paraprotein was detected and bone marrow aspiration revealed a monoclonal paraprotein, immunoglobulin (Ig) G type, and quantification revealed an IgG level of 46.67 g/L (normal, 5.88–15.73 g/L). Bone marrow aspiration and biopsy revealed multiple myeloma and sarcoidosis. Including this patient, 11 cases of sarcoidosis and multiple myeloma have been reported to date, including 3 patients with monoclonal gammopathy of undetermined significance preceding the onset of multiple myeloma. In this case, as in most of the cases reported previously, sarcoidosis preceded the development of multiple myeloma.

(Arch Pathol Lab Med. 2002;126:365–368)

Sarcoidosis is a chronic systemic disorder of unknown etiology characterized histologically by the presence of nonnecrotizing granulomas. This disease most often affects young adults and is often more severe and acute in African Americans than in other racial groups. The clinical manifestations of sarcoidosis are protean and reflect the large number of organ systems that can be involved. Of these, the respiratory tract is most invariably affected, and hilar lymph nodes are also enlarged in up to 90% of patients. Other organs commonly involved include the liver, heart, skin, and eyes. Sarcoidosis is associated with disturbances of the immune system, including decreased CD8-positive T-cell suppressor/cytotoxic cells, activation of CD4-positive T-cell helper/inducer cells, abnormal cytokine production, cutaneous anergy to particular antigens such as tuberculin purified protein derivative, and hypergammaglobulinemia. An association between sarcoidosis and malignant neoplasms has been suggested. In particular, patients with sarcoidosis may also develop a lymphoproliferative disorder. Usually, the lymphoproliferative disorder follows the onset of sarcoidosis by more than one year. Hodgkin disease is the most common lymphoid neoplasm; however, many different types of non-Hodgkin lymphomas and lymphoid leukemias also have been reported in patients with sarcoidosis. Brincker suggested the term sarcoidosis-lymphoma syndrome for this association in 1986.

Rarely, cases of sarcoidosis associated with multiple myeloma also have been reported, mostly in the clinical literature. In this report, we describe a woman who developed multiple myeloma 4 years after the diagnosis of sarcoidosis, and we review the relevant literature.

REPORT OF A CASE

A 49-year-old black woman was admitted to the hospital in June 1998 for severe low back pain and weakness of her lower extremities.

The patient's past medical history was significant for severe disabling sarcoidosis, first diagnosed in January 1994, involving the lungs, eyes, lymph nodes, and bone marrow. Complete blood cell count revealed the following values: white blood cell count, $3.5 \times 10^9/L$ (reference range, $3.2–9.8 \times 10^9/L$); hemoglobin, 83 g/L (reference range, 120–155 g/L); hematocrit, 0.26 (reference range, 0.35–0.45); and platelet count, $224 \times 10^9/L$ (reference range, 150–450 $\times 10^9/L$). The patient's total serum protein level was 84 g/L (reference range, 60–80 g/L). Serum protein electrophoresis revealed a monoclonal band, shown by immunofixation to be immunoglobulin (Ig) G k. Quantification of serum immunoglobulin levels showed a high IgG level of 35.2 g/L (reference range 5.88–15.73 g/L) with normal levels of IgA (reference range, 0.46–2.87 g/L) and IgM (reference range, 0.57–2.37 g/L). Bone marrow aspiration and biopsy revealed numerous noncaseating granulomas, active hematopoiesis, and 4% plasma cells (slides not available for review). The diagnoses of sarcoidosis and monoclonal gammopathy of undetermined significance (MGUS) were established. The patient also complained of recurrent urinary tract and upper respiratory tract infections. She was treated with prednisone and showed clinical improvement. Nine months later, persistent lymphadenopathy prompted biopsy of a right supraclavicular lymph node that revealed complete replacement of normal architecture by noncaseating granulomas. Acid-fast and me-
thenamine silver stains were negative for organisms, and the diagnosis of sarcoidosis involving lymph node was established.

At the time of the current hospitalization, a complete blood cell count revealed a white blood cell count of 1.8 x 10^9/L; hemoglobin, 93 g/L; hematocrit, 0.30; and platelet count, 192 x 10^9/L. Total serum protein was 87 g/L and albumin was 38 g/L (reference range, 39.7–53.4 g/L). Serum and urine protein electrophoresis demonstrated a prominent monoclonal band in the gamma region, confirmed by immunofixation to be IgG k. Serum immunoglobulin quantification showed an increased IgG level of 46.67 g/L and a decreased IgM level of 0.34 g/L. The serum IgA was normal. Magnetic resonance imaging of the spine revealed moderate narrowing of the intervertebral disk space at L5-S1 with arthritic changes and cervical stenosis. Bone marrow aspiration and biopsy were performed, which revealed multiple myeloma and numerous noncaseating granulomas consistent with sarcoidosis. The patient was treated with melphalan and prednisone and responded clinically after 2 cycles of chemotherapy.

In July 1999, follow-up bone survey showed multiple lytic bone lesions involving the thoracic and lumbar spine and a sclerotic lesion overlying the sacroiliac joint. At last follow-up, the patient was in stable condition 30 months after the diagnosis of multiple myeloma.

**PATHOLOGIC FINDINGS**

Bone marrow aspirate smears obtained in 1998 were amanulate. Hematoxylin-eosin–stained sections of the core biopsy specimen showed markedly hypocellular bone marrow with severely decreased hematopoiesis. Approximately 50% of the medullary space was involved by well-formed epithelioid granulomas without necrosis (Figure 1). Acid-fast and methenamine silver stains were negative for acid-fast bacilli and fungi, respectively. In addition, an interstitial infiltrate of atypical plasma cells was present, representing approximately 40% to 50% of the cellularity. These plasma cells were large and many were multinucleated. Small nucleoli were visible in a subset of plasma cells (Figure 2). These findings were interpreted as involvement by sarcoidosis and multiple myeloma. The percentage of plasma cells, the interstitial pattern, and the well-differentiated cytologic features are compatible with a relatively good prognosis, as described by others.11

Immunohistochemical studies were performed using fixed, paraffin-embedded tissue sections of the bone marrow biopsy specimen, a standard avidin-biotin peroxidase
The occurrence of sarcoidosis and multiple myeloma in the same patient is rare. In our review of the literature, we identified 10 patients with sarcoidosis who also developed multiple myeloma. One case of sarcoidosis followed by extramedullary plasmacytoma also has been reported. Data from these 11 cases and the current case are summarized in the Table. In 10 (83.3%) of the patients with sarcoidosis and multiple myeloma (including the case of plasmacytoma), the diagnosis of sarcoidosis preceded the diagnosis of multiple myeloma. The median interval from the time of diagnosis of sarcoidosis to the time of diagnosis of multiple myeloma was 6 years, with a range of 2 to 27 years. In 2 patients, both disorders developed simultaneously. Three cases, including the patient we describe, had both MGUS and multiple myeloma. In the case reported in this article, MGUS was diagnosed simultaneously with sarcoidosis. In the other 2 cases, sarcoidosis preceded the diagnosis of MGUS by 3 years and 6 years. Slides of the 1994 bone marrow aspiration and biopsy specimen for our case were not available for review, and thus we cannot completely exclude the possibility that this patient had clinically indolent, so-called smoldering multiple myeloma at the time of the initial diagnosis of sarcoidosis. In fact, the serum IgG level reported in 1994, 35.2 g/L, is relatively high for MGUS and is more in keeping with immunoglobulin levels observed in patients with smoldering myeloma, that is, greater than 30 g/L. The reported plasma cell count of 4%, however, is lower than the 10% cutoff required for the diagnosis of smoldering myeloma.

In the 11 patients with sarcoidosis and multiple myeloma, including the case we report, the median age at time of diagnosis of sarcoidosis was 56 years. This age is significantly older than that of the general patient population with this disease. Sarcoidosis developing in older age groups is generally associated with a chronic active clinical course. In the case we report, the clinical course of sarcoidosis was severe and disabling, and required continuous treatment consistent with chronic active sarcoidosis. Information regarding the clinical course of sarcoidosis in most of the previously reported cases associated with multiple myeloma is not available. Patients with other lymphoproliferative disorders associated with sarcoidosis, such as Hodgkin disease and non-Hodgkin lymphoma, also have been older, and sarcoidosis was most often of the chronic active type.

As so few cases of sarcoidosis associated with multiple myeloma have been reported in the literature, no epidemiologic data are available to support the hypothesis that the risk of multiple myeloma is increased in sarcoidosis patients. However, available data do support the hypothesis that patients with sarcoidosis have an increased risk of lymphoproliferative disorders. In one epidemiologic study of 2544 sarcoidosis patients, Brincker and Wilbek reported that the risk of lymphoproliferative disorders in this patient population was 11.5 times higher than expected. In a subsequent letter in 1995, Brincker summarized the literature. At that time, 145 patients with sarcoidosis had developed a malignant neoplasm, including 66 cases of various types of lymphoproliferative disorders. The observed to expected ratio of lymphoid malignancies in sarcoidosis patients was 13.2. Hodgkin disease is most common, but a wide variety of B-cell non-Hodgkin lymphomas and leukemias and rare T-cell neoplasms also have been reported.

The explanation for the relationship between sarcoidosis and lymphoproliferative disorders, and potentially multiple myeloma, is unknown. There is abundant evidence that patients with sarcoidosis have immune system dysregulation, including activation of CD4-positive T-helper/inducer cells, increased secretion of various cytokines, and decreased CD8-positive T-suppressor/cytotoxic cells. B-cell function is relatively unaffected in sarcoidosis, but with defective T-cell suppression and increased cytokine secretion, B cells are likely to be stimulated continuously. In one relevant study, Hunninghake and Crystal showed that untreated patients with pulmonary sarcoidosis have greater numbers of IgG- and IgM-secreting cells per 10^6 lung lymphocytes, as compared with those of normal individuals. These investigators also showed that B lymphocytes of normal individuals, when cocultured with purified T lymphocytes from the lungs of patients with sarcoidosis, were induced to differentiate into immunoglobulin-secreting cells. Polyclonal hypergammaglobulinemia, often seen in sarcoidosis patients, may be explained by this mechanism. The extended half-life of B lymphocytes and plasma cells in sarcoidosis technique, and monoclonal antibodies specific for Igκ and λ light chains (Dako Corporation, Carpinteria, Calif). The neoplastic plasma cells expressed cytoplasmic monotypic Igκ light chain (Figure 3).

**COMMENT**

The occurrence of sarcoidosis and multiple myeloma in the same patient is rare. In our review of the literature, we identified 10 patients with sarcoidosis who also developed multiple myeloma. One case of sarcoidosis followed by extramedullary plasmacytoma also has been reported. Data from these 11 cases and the current case are summarized in the Table. In 10 (83.3%) of the patients with sarcoidosis and multiple myeloma (including the case of plasmacytoma), the diagnosis of sarcoidosis preceded the diagnosis of multiple myeloma. The median interval from the time of diagnosis of sarcoidosis to the time of diagnosis of multiple myeloma was 6 years, with a range of 2 to 27 years. In 2 patients, both disorders developed simultaneously. Three cases, including the patient we describe, had both MGUS and multiple myeloma. In the case reported in this article, MGUS was diagnosed simultaneously with sarcoidosis. In the other 2 cases, sarcoidosis preceded the diagnosis of MGUS by 3 years and 6 years. Slides of the 1994 bone marrow aspiration and biopsy specimen for our case were not available for review, and thus we cannot completely exclude the possibility that this patient had clinically indolent, so-called smoldering multiple myeloma at the time of the initial diagnosis of sarcoidosis. In fact, the serum IgG level reported in 1994, 35.2 g/L, is relatively high for MGUS and is more in keeping with immunoglobulin levels observed in patients with smoldering myeloma, that is, greater than 30 g/L. The reported plasma cell count of 4%, however, is lower than the 10% cutoff required for the diagnosis of smoldering myeloma.

In the 11 patients with sarcoidosis and multiple myeloma, including the case we report, the median age at time of diagnosis of sarcoidosis was 56 years. This age is significantly older than that of the general patient population with this disease. Sarcoidosis developing in older age groups is generally associated with a chronic active clinical course. In the case we report, the clinical course of sarcoidosis was severe and disabling, and required continuous treatment consistent with chronic active sarcoidosis. Information regarding the clinical course of sarcoidosis in most of the previously reported cases associated with multiple myeloma is not available. Patients with other lymphoproliferative disorders associated with sarcoidosis, such as Hodgkin disease and non-Hodgkin lymphoma, also have been older, and sarcoidosis was most often of the chronic active type.

As so few cases of sarcoidosis associated with multiple myeloma have been reported in the literature, no epidemiologic data are available to support the hypothesis that the risk of multiple myeloma is increased in sarcoidosis patients. However, available data do support the hypothesis that patients with sarcoidosis have an increased risk of lymphoproliferative disorders. In one epidemiologic study of 2544 sarcoidosis patients, Brincker and Wilbek reported that the risk of lymphoproliferative disorders in this patient population was 11.5 times higher than expected. In a subsequent letter in 1995, Brincker summarized the literature. At that time, 145 patients with sarcoidosis had developed a malignant neoplasm, including 66 cases of various types of lymphoproliferative disorders. The observed to expected ratio of lymphoid malignancies in sarcoidosis patients was 13.2. Hodgkin disease is most common, but a wide variety of B-cell non-Hodgkin lymphomas and leukemias and rare T-cell neoplasms also have been reported.

The explanation for the relationship between sarcoidosis and lymphoproliferative disorders, and potentially multiple myeloma, is unknown. There is abundant evidence that patients with sarcoidosis have immune system dysregulation, including activation of CD4-positive T-helper/inducer cells, increased secretion of various cytokines, and decreased CD8-positive T-suppressor/cytotoxic cells. B-cell function is relatively unaffected in sarcoidosis, but with defective T-cell suppression and increased cytokine secretion, B cells are likely to be stimulated continuously. In one relevant study, Hunninghake and Crystal showed that untreated patients with pulmonary sarcoidosis have greater numbers of IgG- and IgM-secreting cells per 10^6 lung lymphocytes, as compared with those of normal individuals. These investigators also showed that B lymphocytes of normal individuals, when cocultured with purified T lymphocytes from the lungs of patients with sarcoidosis, were induced to differentiate into immunoglobulin-secreting cells. Polyclonal hypergammaglobulinemia, often seen in sarcoidosis patients, may be explained by this mechanism. The extended half-life of B lymphocytes and plasma cells in sarcoidosis.
osis patients may increase their risk of undergoing genetic events that result in neoplastic transformation.

The 2-hit hypothesis of carcinogenesis, as it applies to multiple myeloma, postulates that a first oncogenic event results in MGUS and that a second event is necessary for the development of multiple myeloma.13 Up to 16% of patients with MGUS develop multiple myeloma with long-term follow-up (30 years or more). The annual actuarial risk of developing multiple myeloma subsequent to MGUS is 0.8% in an unselected patient population.13 In this study, the median interval between MGUS and multiple myeloma in the 3 cases of MGUS associated with sarcoidosis is 4 years. This finding may suggest that MGUS in sarcoidosis patients more rapidly progresses to multiple myeloma than does MGUS in other patients, although the small number of patients precludes any definite conclusions. It is also likely that patients with sarcoidosis in association with MGUS who do not develop multiple myeloma are underreported in the literature.

In summary, we describe a patient with sarcoidosis and MGUS who developed multiple myeloma 4 years later to call attention to this rare occurrence. Eleven other cases have been reported to date, mostly in the clinical literature. The explanation for this association is unknown. Although a coincidental relationship cannot be excluded, the number of cases and the temporal relationship between sarcoidosis and multiple myeloma suggest a true association. Immune dysregulation, currently considered to explain the increased risk of lymphoproliferative disorders in patients with sarcoidosis, also may be involved in the pathogenesis of multiple myeloma in this patient group.

References