Monoclonal Gammopathy Associated with Multiple Sclerosis

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ABSTRACT

A 52-year-old white male with a 26-year history of multiple sclerosis developed a monoclonal gammopathy of the IgA class, with reciprocal depression of normal immunoglobulins. A bone marrow aspirate and biopsy showed a marked increase in plasma cells, many of which appeared immature. These findings fulfilled the diagnostic criteria for multiple myeloma. The association of multiple myeloma with multiple sclerosis may not be coincidental. Mechanisms regarding this association are discussed.

The development of simple rapid techniques for measuring immunoglobulins, immunoelectrophoresis and serum protein electrophoresis has fostered the publication of an increasing number of case reports dealing with the occurrence of monoclonal gammopathy. The purpose herein is to describe a patient who had a monoclonal gammopathy coexistent with multiple sclerosis.

Case History

A 52-year-old Caucasian male, with a 26-year history of multiple sclerosis, was admitted to Veterans Administration Center, Milwaukee, WI, in February 1970. He complained of fever, chills, frequency of urination and some painful swelling of his right scrotum. He appeared obese and paraplegic. The right epididymis was tender and swollen. Laboratory data, including an SMA-12 chemistry profile and hematology work-up, were within normal limits. Urinalysis showed evidence of a urinary tract infection and he was treated with penicillin. He became afebrile and results of the urinalysis became normal. He was followed in the multiple sclerosis clinic where his course deteriorated progressively.

On readmission in May 1972, the patient was first noted to have an elevated level of serum protein of 8.3 g per dl on an SMA-12. Serum protein electrophoresis revealed a monoclonal spike (figure 1). The 24-hour urine protein excretion was normal. Bence Jones protein was not found by the heat test. The bone survey was negative. Serum immunoglobulin quantitation was as follows: IgG, 410 mg per dl (normal, 570 to 2000 mg per dl); IgA, 4350 mg per dl (normal, 68 to 310 mg per dl); IgM, 40 mg per dl (normal, 45 to 145 mg per dl); IgD, 0 mg per dl (normal, 0 to 6 mg per dl). A serum immunoelectrophoresis showed increased IgA with a bowed precipitin arc. The arc developed by anti-kappa serum presented a triphasically bowed abnormal pattern indicating the presence of the kappa Bence Jones protein (figure 2). Bone marrow aspiration and biopsy were not performed.

On October 7, 1974, the patient was again admitted for treatment of an urinary tract infection. His hemoglobin level was 10 g per dl, and the hematocrit 30 percent. The total white count and the differential were within normal limits. The platelet count was 20,000 per mm. The cryoglobulin was negative. An SMA-12 showed a serum protein of 9.2 g per dl. A serum protein electrophoresis again showed a monoclonal spike. Immunoglobulin quantitation was as follows: IgG, 240 mg per dl; IgA, 3000 mg per dl; IgM, 20 mg per dl; IgD, 0 mg per dl. A bone marrow aspirate and trephine biopsy specimen from the posterior iliac crest showed a markedly hypercellular marrow with diffuse plasma cells, many of which appeared immature (figure 3). It was felt that he had multiple myeloma. Urine Bence Jones protein by the heat test was again negative. Chemotherapy with Melphalan, 10 mg daily, and prednisone,
100 mg daily, was initiated. When the patient was seen in the hematology clinic on July 1, 1975, his condition was stable.

Discussion

Osserman and Fahey\(^1\) defined multiple myeloma by the following three main criteria: (1) the proliferation of immunologically competent cells, usually identifiable as plasma cells, in the absence of a recognizable antigenic stimulus; (2) the elaboration of "M-type" gamma globulins with characteristics of structural homogeneity and/or comparably homogenous polypeptide subunits of these gamma globulins, usually of the Bence Jones type; and (3) generally, an associated decrease in the synthesis of the normal gamma immunoglobulins. The patient described herein fulfilled all the criteria when he was seen on October 7, 1974. He also met the three criteria for multiple sclerosis\(^6\): age of onset between 15 and 45 years; signs indicative of damage to at least two different parts of the central nervous system; and a course with at least two exacerbation and one remission. To my knowledge, this is the first report of an association between multiple sclerosis (MS) and multiple myeloma (MM).

Michaux and Heremans\(^10\) proposed a classification for monoclonal gammopathy and divided this disorder into three major groups: (I) primary malignancy: this group comprises multiple myeloma, Waldenstrom’s macroglobulinemia, Franklin’s disease and monoclonal gammopathy associated with malignancies of the blood-forming tissues; (II) secondary monoclonal immunoglobulin disorders: in this category, patients had a variety of diseases and (III) primary benign monoclonal immunoglobulin disorder. Monoclonal gammopathy, unless it is a benign form, has a variable rate of progression.

Stevens\(^17\) described a patient who was followed from the asymptomatic phase of six years into the typical clinical state of multiple myeloma. The monoclonal spike of the patient described was first noted on May 13, 1972. The point of the onset of this spike was not tested.

Despite extensive studies, the basic mechanisms involved in the etiology of multiple myeloma still remains unknown. It has been suggested that if an antigenic
stimulus persists for a long time, one of the stimulated plasma cell clones might escape the normal control mechanisms and become autonomous, producing a homogenous monoclonal immunoglobulin.\textsuperscript{10,12}

There has been recent interest in the possibility that an immunodeficiency exists in patients with multiple sclerosis.\textsuperscript{7,8} It has also been found that leukocytes from MS patients do not respond to measles virus as efficiently as leukocytes from healthy individuals.\textsuperscript{20} These studies suggested that patients with MS might have a deficiency in cellular immunity as well as humoral immunity. In the literature, it has been observed that a malignant process developed in a higher incidence in patients with an immunodeficiency than in normal individuals.\textsuperscript{14} If patients with MS indeed have an immunodeficiency, a malignant disease would develop in a higher incidence in patients with multiple sclerosis than in normal individuals.

A study was carried out in Finland to investigate the frequency of combinations of MS and malignant process.\textsuperscript{15} However, the results revealed a low prevalence and mortality rate of cancer among MS patients. Therefore, it does not support the interrelation between MS and MM based on the assumption that MS patients have a defect in immunity. A similar study should be performed in the United States to confirm the low frequency of combinations of MS and malignant processes. Although toxic, metabolic, dietary and viral etiologies have been proposed,\textsuperscript{5,4,9,11} they are only speculative.

Tissue culture studies of human and experimental demyelinating diseases
have contributed to speculations about pathogenetic mechanisms of multiple sclerosis, including the role of both circulating antibodies and delayed hypersensitivity factors. Increased levels of immunoglobulins in cerebrospinal fluid (CSF) were found in patients with multiple sclerosis. In two series, IgG elevation in CSF was found in 55.6 percent and 73 percent of patients, respectively. Only occasional elevation of IgA and IgM in the CSF was found. In a study by Eickhoff et al, an elevation of IgG in CSF of MS patients was from 75 percent to 85 percent, taking into account the albumin and IgG pattern in CSF and in serum. This incidence was much higher than if analysis of CSF alone was performed (51.5 percent).

The findings of increased immunoglobulins in CSF of MS patients are keeping up with the results of tissue culture studies. The question remains of what meaning can be attached to the immunoglobulins. It is possible, for example, that these immunoglobulins are formed in response to destruction of myelin and, as such, may be an indicator of the occurrence of demyelination but not a factor in the pathogenesis of the disease.

Regardless of what role these immunoglobulins may play in the pathogenesis, it is evident that the immune system of most MS patients has been stimulated. It is conceivable that if antigenic stimulus persists for a long time, one of the plasma cell clones might escape the normal control mechanisms and become neoplastic. Therefore, the association of MS and MM may be casually related.

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References