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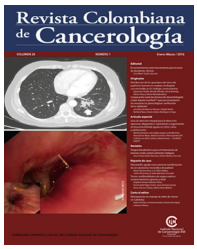

CASE REPORT

Autoimmune Disorders and Multiple Myeloma- Two Illustrative Case Reports and a Literature Review

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Abstract Several autoimmune disorders have been associated with a variety of hematopoietic malignancies, particularly lympho-proliferative disorders. Multiple myeloma (MM) is one of the most common hematologic malignancies and has been described in the context of a variety of autoimmune conditions. Due to their diversity and rarity, the clinical features of autoimmune conditions associated with MM have not been elucidated and the pathogenesis remains unclear. In this report, we describe two cases of autoimmune conditions in the setting of MM and review the current literature.
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PALABRAS CLAVE
Mieloma;
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Miastenia

Trastornos autoinmunes y Mieloma Múltiple- Dos Reportes de Casos Ilustrativos y una Revisión de la Literatura

Resumen Varios trastornos autoinmunes se han asociado a una variedad de neoplasias malignas hematopoyéticas, particularmente trastornos linfoproliferativos. El mieloma múltiple (MM) es una de las neoplasias malignas hematológicas más comunes y ha sido descrito en el contexto de una variedad de condiciones autoinmunes. Debido a su diversidad y rareza, las características clínicas de las condiciones autoinmunes asociadas con el MM no han sido aclaradas y la patogénesis sigue siendo poco clara. En este artículo se describen dos casos de condiciones autoinmunes en el marco del MM y se realiza una revisión de la literatura actual.
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Introduction

The relationship between autoimmune diseases and myeloma was initially observed in the 1960's.[1–4] Multiple retrospective and cohort studies have shown that the incidence of lymphoproliferative diseases is greater in patients carrying autoimmune disorders. Multiple myeloma (MM), a plasma cell neoplasia and the second most common lymphoproliferative disorder, has been associated with a wide spectrum of autoimmune related conditions. [5–8]A retrospective cohort study of more than 4000 white and black male veterans postulated that various types of immune-mediated conditions such as pernicious anemia, systemic sclerosis and systemic lupus erythematosus were related to MM development.[9]

Herein we report on two patients with MM presenting with autoimmune conditions rarely described in conjunction with MM (angioedema and myasthenia gravis) as autoimmune disorders associated with MM and summarize the current literature regarding autoimmune manifestations of MM.

Patient and Methods

This review is based on information from the Medline/PubMed and Scopus database using combinations of the keywords multiple myeloma, auto antibodies, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematous, urticaria, paraneoplastic and autoimmunity. We included reports that were published in English, Spanish and French and specifically described autoimmune disorders associated with MM. Forty-four articles met our selection criteria.

Patient 1

A 70 year old male was seen for initial consultation in 2013 for history of free lambda chain monoclonal gammopathy as well as focal episodes of angioedema. He initially developed intermittent episodes of facial swelling involving different parts of his face in 2008. He was noted to have proteinuria during one of his angioedema episodes and was referred to a hematologist. Over the next few years, the attacks involved also his forehead, cheek, tongue and sometimes the bottoms of the hands and feet. These episodes occurred without any antecedent triggers or associated factors and were relieved with Benadryl. Involvement of the upper respiratory or gastrointestinal tracts was never observed.

A full workup for multiple myeloma (MM) was then performed, and he was noted to have immune globulins within normal limits except for IgG of 648 mg/dl, free lambda elevated to 27.85 mg/dl with a decreased kappa lambda ratio to 0.02 and serum and urine immunofixation revealing free lambda light chains. The percentage of plasma cells was 15% by bone marrow examination with immunohistochemistry demonstrating lambda restriction and a normal karyotype with an extra copy of 1q25 in 75% of plasma cells.

At that time the diagnosis of lambda light chain multiple myeloma ISS I was confirmed without any evidence of anemia, bone disease, hypercalcemia or impaired renal function. Nonetheless, the question remained of whether the episodes of focal angioedema may be related to an acquired C1q inhibitor antibody related to multiple myeloma. Further testing noted normal levels of C1 esterase inhibitor, C3 complement, C4 complement and C1q complement. Although there was no direct evidence that could confirm the association, it has not been effectively ruled out either. Patient has not received antimyeloma therapy and angioedema episodes have been controlled symptomatically.

Patient 2

A 53 year old African American male presented with a 30 year history of myasthenia gravis; he initially experienced upper body weakness, ptosis, diplopia, loss of peripheral vision and was treated with pyridostigmine. He was assessed in 2011 for a progressive hemoglobin drop from 14.7 to 13 with normal levels of serum iron, B12, folic acid and elevated total protein. Further workup revealed a paraprotein peak in the blood (IgG of 3786 mg/dl with an IgG Kappa peak of 2.65 mg/dl), bone marrow with 29% plasma cells, and no high risk cytogenetic abnormalities with the exception of deletion of ETV6 stain in 8% of the cells. At that time the diagnosis of asymptomatic IgG Kappa multiple myeloma ISS II (normal albumin and B2 3.7) was confirmed without any evidence of anemia, bone disease, hypercalcemia or impaired renal function.

Therefore he continued with close observation; during his nine month follow up he had recurrence of his old symptoms of myasthenia gravis (only right eye ptosis) and was treated with pyridostigmine by his neurologist. Two months later, he demonstrated progression of the disease with an increasing paraprotein peak, kappa free light chain of 67.21 mg/dl, kappa:lambda ratio of 93.35 as well as progressive cytopenias. He started to have symptoms— in particular, fatigue and mild back pain. CT scans revealed punctate lytic lesions at the vertebral bone and nondisplaced fractures in the fourth and fifth ribs. A repeat bone marrow biopsy showed 30% plasma cells and complex cytogenetic abnormalities including p11 deletion,p12 addition, and additional copies of chromosomes 3, 5, 9 and 15. MLL gene loss was seen in 35% of the cells.

The patient received 4 cycles of bortezomib, lenalidomide, and dexamethasone (RVD)[10] with suboptimal response. He then underwent stem cell mobilization with bortezomib, dexamethasone, thalidomide, platinum, adriamycin, cyclophosphamide and etoposide (VDTPACE) for stem cell mobilization and collection.[11] Subsequently undergoing an autologous stem cell transplantation with a high dose melphalan based conditioning regimen and achieved a very good partial response (VGPR).

His symptoms of myasthenia gravis recovered completely off all treatment, noticing less fatigue and muscular weakness compared to before his transplant. He discontinued pyridostigmine and denies any other symptoms related to this disease.

Discussion

Multiple myeloma is a B cell malignancy characterized by clonal expansion of malignant plasma cells in bone marrow. Although the etiology is poorly understood, there is some evidence for immune dysregulation or sustained immune stimulation in the pathogenesis of this disease.[12]

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