Monoclonal gammopathy and rheumatic diseases

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ABSTRACT

It is common to find monoclonal gammopathy in the investigation workout for an unrelated disorder. There are studies relating rheumatic diseases and therapies which show an increased risk of monoclonal gammopathy. The specific mechanisms are not well understood but chronic antigen stimulation assumes an important role.

Specific rheumatic diseases have consistently been associated with lymphoproliferative disorders but less attention has been paid to the possible association between monoclonal gammopathy of undetermined significance and multiple myeloma.

We reviewed previous studies regarding monoclonal gammopathy and different rheumatic diseases and treatments associated focusing on prevalence, risk factors and possible pathogenic mechanisms. The clinical approach of a monoclonal gammopathy and its follow-up are explained.

Keywords: Monoclonal gammopathy; rheumatic diseases; multiple myeloma.

INTRODUCTION

Monoclonal immunoglobulins with a benign course may occur in chronic inflammatory disorders such as chronic infections and autoimmune disorders[1].

Monoclonal gammopathy of undetermined significance (MGUS) is one of the most prevalent premalignant disorders in the world among people aged 50 years or older. The high prevalence in the general population has made the incidental diagnosis of MGUS with numerous other diseases a common clinical occurrence. It is impossible to determine if a causal relationship exists without accurate expected rates of MGUS in a given patient population[2].

Multiple myeloma (MM) and MGUS are grouped together as plasma cell disorders[3]. MGUS is an asymptomatic premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder[4], with an average risk of progression to MM or other lymphoproliferative disorders of 1% per year. MGUS is defined by the presence of a serum monoclonal protein, at a concentration <3 g/dl, and bone marrow with < 10% monoclonal plasma cells, in the absence of end-organ damage (lytic bone lesions, anemia, hypercalcemia, renal insufficiency or hyperviscosity related to the proliferative process[4].

Smoldering MM (SMM), or asymptomatic MM, according to the 2010 International Myeloma Working Group diagnostic criteria, is defined as a serum monoclonal protein (IgG or IgA) ≥3g/dL and/or clonal bone marrow plasma cells ≥10%, and absence of end-organ damage that can be attributed to a plasma cell proliferative disorder[5].

Being MGUS one of the most prevalent premalignant disorder and considering its occurrence in association with a specific rheumatic diseases, understanding the possible mechanisms relating MGUS and rheumatic diseases, potential etiologic factors and risk factors is important in the management of each other.

PREVALENCE, RISK FACTORS AND PATHOGENESIS OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

The prevalence of MGUS among general white population is estimated to be about 1,5% in those above the age of 50 years and increases to 3% by 70 years of age[6]. In the first and largest systematic study focusing on SMM, retrospective data from 276 patients seen at the

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Mayo Clinic between 1970 and 1995 were collected. In that study, SMM patients had a 10% average annual risk of progression to MM for the first five years following diagnosis, decreasing to 3% annually for the following five years, and then lowering to the same 1% annual rate of progression as MGUS thereafter. The risk of progression from smoldering multiple myeloma to symptomatic disease was related to the proportion of bone marrow plasma cells and the serum monoclonal protein level at diagnosis[7].

The first step in the pathogenesis of MGUS is likely an abnormal response to antigenic stimulation, mediated possibly by aberrant expression of toll-like receptors and overexpression of interleukin (IL) 6 receptors and IL-1 [8,9].This results in the development of primary cytogenetic abnormalities, either hyperdiploidy or immunoglobulin heavy chain (IgH) translocations. The progression of MGUS to myeloma is likely secondary to a random second hit, the nature of which is unknown. Ras and p53 mutations, p16 methylation, myc abnormalities and induction of angiogenesis are all associated with progression. In addition, there is increased osteoblast RANKL (receptor activator of nuclear factor B ligand) expression and reduction in the level of its decoy receptor, osteoprotegerin, which results in osteoclast activation and increased bone resorption and turnover[10].This is accompanied by increased levels of IL-3, IL-7, and dickkopf 1 that simultaneously inhibit osteoblast differentiation, leading to the characteristic pure lytic lesions typical of myeloma[11-13].

The etiology of MGUS is unknown, and previous studies support a role of both genetic and environmental factors. A family history of MGUS or MM increases the risk of MGUS by approximately 3.3 - and 2-fold, respectively, suggesting a shared environmental and/or genetic effect[14-16]. Radiation exposure, particularly at a younger age, increases the risk of MGUS significantly, but not that of malignant progression[17]. The use of certain pesticides[18], as well as obesity, and increasing age are associated with an excess risk of MGUS[19].The prevalence of both MGUS and MM is 2--3 fold higher in African-Americans than Caucasians, whereas there is no difference in the frequency of progression to MM in these two populations of MGUS patients[20].

Convincing evidence shows immune dysregulation to play a major role in lymphomagenesis; however, much less is known regarding immune-related conditions and risk of plasma cell disorders[21].

A Spanish study found rheumatic diseases to be the third associated pathology with higher incidence of MGUS, after infections and heart diseases. Malignant transformation was associated with heavy chain IgA, high erythrocyte sedimentation rate, age < 70, bone marrow percentage of plasma cells and osteoporosis[22].

To understand the impact of immune-related conditions and plasma cell disorders, the largest study to date was performed. It was a population-based, case-control study, involving males and females diagnosed with MM and MGUS over a 40-year period. Significantly elevated risk of MGUS was found in patients with a history of all subcategories of autoimmune diseases and the specific conditions rheumatoid arthritis, systemic sclerosis, Sjögren syndrome, pernicious anemia, immune thrombocytopenia, Guillain-Barré syndrome, celiac disease, chronic rheumatic heart disease, ankylosing spondylitis, polymyalgia rheumatica, giant cell arteritis and aplastic anemia. Family history of autoimmune disease was associated too with a significantly increased risk of MGUS, but not with MM. Both family history and personal history of autoimmune disease were independent predictors of risk of MGUS[23].

A population-based study had already shown the association of autoimmune conditions and the risk of specific lymphoid malignancies[24]. The strongest associations observed by Non-Hodgkin lymphoma subtypes were diffuse large B-cell lymphoma with rheumatoid arthritis and Sjögren syndrome; T-cell lymphoma with hemolytic anemia, psoriasis, discoid lupus erythematosus, and celiac disease; and marginal zone lymphoma with Sjögren syndrome, systemic lupus erythematosus and hemolytic anemia. Hodgkin lymphoma was associated with several autoimmune conditions[24].

PRESENCE OF MGUS AND SPECIFIC CONDITIONS

Sjögren's Syndrome (SS) and Systemic Lupus Erythematosus (SLE) are among the diseases in which monoclonal gammopathy is more frequent[4].

Sjögren syndrome (SS) is a systemic autoimmune disease characterized by chronic inflammation of exocrine glands, causing xerostomia and keratoconjunctivitis sicca among other manifestations. This exocrinopathy can be encountered alone (primary SS) or in the presence of other systemic autoimmune disorders (secondary SS). SS is characterized by two main immune-

mediated phenomena: B-cell hyperactivity and lymphocytic infiltration of the exocrine glands. B-cell lymphoma develops in 5% of patients[25]. Hyperimmune reaction has been assumed to play an important role in the lymphoma genesis in SS. Polyclonal gammopathy is almost always present[25,26]. Although the finding of a monoclonal gammopathy is not rare, demonstrated either in the urine or serum, MM is very rare[27]. Most of the reported monoclonal gammopathies in patients with SS involve the IgM class being the non-IgM class infrequent[28].

SLE is another autoimmune disease of unknown etiology that affects primarily women, often in their reproductive years. It is characterized by a systemic involvement, profound B-cell hyperactivity, autoantibody formation, and hypergammaglobulinemia. As in SS, a monoclonal gammopathy may be identified in some patients[29]. The prevalence of monoclonal gammopathy in a large cohort of 1083 SLE patients followed at the University of Toronto Lupus Clinic, was 5.4%. There were no differences in disease manifestations, treatment approaches, or malignancies between SLE patients with and those without monoclonal gammopathy. The authors found statistically significant differences in the erythrocyte sedimentation rate (ESR) between monoclonal gammopathy patients and controls, being higher in the first group. As so, an unexplained persistently elevated ESR in a patient with SLE should trigger an investigation with serum protein electrophoresis. As well as SS, there have been however, few reports of multiple myeloma in SLE[29]. A recent review described 12 previous cases with MM in SLE patients. The mean age for the diagnosis was 54 years old, which is nearly 10 years earlier than that of general MM population[30].

Another common disease is rheumatoid arthritis (RA) of which the hallmark feature is a persistent characteristic symmetric polyarthritis that affects hands and feet, leading to substantial functional disability. Distinct mechanisms regulate inflammation and matrix destruction, including damage to bone and cartilage. T cells are assumed to play a pivotal role in the initiation of RA, and the key player in this respect is assumed to be T helper 1 (Th1) CD4 cells. B cells are also important in the pathologic process and may serve as antigen-presenting cells, producing autoantibodies and cytokines. As reported for SS and SLE the presence of monoclonal gammopathy seems to be slightly increased in RA, at about 1 to 2%[31,32]. The development of paraproteinaemia in patients with RA was related more to severity than to disease duration and the presence of an IgA paraprotein was associated with a special risk for myeloma[32]. Similar to SS, a polyclonal rise of immunoglobulins is a non-specific finding and is often found in patients with active RA. In addition to the hypergammaglobulinaemia seen in RA, the marked proliferation of lymphoid tissues, together with the increase in plasma cell numbers and the wide variety of autoantibodies present, all underline the hyperreactivity of the lymphoreticular system in this disease.

Other studies have focused on spondylarthropathies. Ankylosing spondylitis (AS) is a chronic systemic inflammatory disorder of the axial skeleton, mainly affecting the sacroiliac joint and spine, and can cause enthesitis. Chronic spinal inflammation leads to ankylosis, abnormal posture and permanent disability. The association of AS with monoclonal gammopathy has also been described in the literature[33]. Some investigators have suggested that malignant changes resulting from prolonged plasma cell stimulation and proliferation due to elevated levels of IgA associated with ankylosing spondylitis may be related to the pathogenesis of MGUS and progression to MM[34,35].

Psoriatic arthritis (PsA) is another spondylarthropathy that courses with an inflammatory arthritis and affects about one-third of patients with psoriasis[36]. T cells, particularly those from the CD8+ lineage, play an important role in the pathogenesis of both diseases, while B cell hyperactivity and autoantibody production are not characteristic features of either psoriasis or PsA[36]. Nonetheless, in a study among patients with PsA the prevalence of monoclonal gammopathy was 9,7%, which is high compared to the reported prevalence in the general population[6,36]. Despite of the prevalence of MGUS, only one case of MM in this large cohort was reported. The presence of monoclonal gammopathy was associated with measures of disease activity including longer disease duration and higher sedimentation rate[36]. Other two cases of MM in patients with PsA are found in the literature[37,38].

Polymyalgia rheumatica has also been associated to monoclonal gammopathy. It is the most common inflammatory rheumatic disease in the eldery, characterized by proximal myalgia of the hip and shoulder girdles with accompanying morning stiffness. However, as both conditions occur more commonly in older population, the relationship is questionable[39]. On the other way, population-based studies showed that polymyalgia rheumatica may in fact be associated with an increased risk of MM[24,40]. Interestingly, a personal

history of polymyalgia rheumatica and giant cell arteritis was associated with an increased risk of both MM and, for the first time, MGUS in another recent population-based study. In addition, a family history of these disorders was also associated with an increased risk of MGUS[23].

The association of monoclonal gammopathy with other rare rheumatic diseases has been studied. In inclusion body myositis an M-protein was found in 23% of the patients; in which 81% presented an IgG M-protein[41]. Monoclonal gammopathies have been also reported in polymyositis/dermatomyositis, discoid lupus erythematosus and systemic sclerosis[1].

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Certain drugs as disease-modifying antirheumatic drugs (DMARDs) reduce clinical disease activity, improve function and retard progression of some rheumatic diseases. For example, methotrexate is considered nowadays the mainstay of RA treatment and other inflammatory rheumatic diseases in which arthritis is present[42]. Other DMARDs include leflunomide, sulphasalazine, azathioprine and cyclosporine.

The advances in the understanding of the pathogenesis of many of these diseases have led to the development of new treatment targets. Biological agents, as for example the inhibitors of tumor necrosis factor (TNF)-α (infliximab, adalimumab, certolizumab and golimumab and a soluble TNF receptor fusion protein - etanercept) have emerged as a new therapeutic modality for chronic inflammatory disorders. These biologic DMARD with profound immunoregulatory effects have shown clinical efficacy and can prevent joint damage[43,44].

The immunomodulatory therapies promove the reduction of proinflammatory cytokines, chemokines and acute phase reactants, downregulation of adhesion molecule expression, attenuation of vascular permeability and angiogenesis, deactivation of epithelial, endothelial and dendritic cells, myofibroblasts and osteoclasts, increasing in circulating regulatory T cells, and diminished recruitment of inflammatory cells from blood to the inflamed tissue[42]. Since some of these inflammatory cells and cytokines play an important role in controlling tumor development and growth it is easily understandable the concern on these drugs in the possibility of acceleration of malignancy in patients with pre-malignant conditions[45].

TNF, for instance, is a known cytokine that mediates a broad range of cellular activities, including proliferation, survival, differentiation and apoptosis, is considered to be essential for the induction and maintenance of the inflammatory immune response[46].

Serum levels of monoclonal gamma-globulin have been reported to increase during treatment with ETN in a patient with rheumatoid arthritis[47,48]. Current guidelines suggest caution in the use of these drugs in patients with malignant or pre-malignant conditions. Unlike Barretts esophagus, for example, also a known pre-malignant condition, MGUS is not specifically mentioned in this guidance. Given the frequency of MGUS, if anti-TNF-α therapy is started in patients with monoclonal gammopathies, close monitoring of paraprotein levels is necessary.

Tocilizumab (TCZ), an IL-6 inhibitor, is indicated for rheumatoid arthritis and systemic juvenile inflammatory arthritis. There is a case report of a patient with refractory RA and worsening smoldering MM after anti-TNF-α treatment, in whom TCZ improved RA symptoms and stabilized the serum levels of monoclonal IgA[49].

Rituximab is a chimeric antibody that targets CD20, a molecule that is found on the surface of B-cells, with proved efficacy in RA[50]. In contrast to the demonstrated efficacy of anti-CD20 strategies in various B-cell lymphoproliferative disorders, the role of such therapy in multiple myeloma is undetermined and controversial. The expression of CD20 by myeloma cells is heterogeneous, and can be detected only in 13–22% of patients. Clinical trials showed that rituximab elicits a partial response in approximately 10% of CD20+ patients with multiple myeloma and evidence of disease stabilization in 50–57% of CD20+ patients for a period of 10 to 27 months[51]. The potential benefits of rituximab in these two conditions could be an argument for using it in the treatment of patients with RA and a monoclonal gammopathy.

Despite the description, in different case reports, of the improvement or worsening of the monoclonal protein, the effect of treatments for rheumatic diseases in patients with concomitant monoclonal gammopathy, including methotrexate, remains unproven to date.

DIAGNOSIS, MONITORIZATION AND MANAGEMENT OF MGUS AND SMOLDERING MULTIPLE MIELOMA

Screening of patients with suspected monoclonal gam-

mopathies include protein electrophoresis (PEL), immunofixation electrophoresis (IFE) of both serum and urine and quantitative serum assays for immunoglobulin free light chain (FLC)[52]. A complete blood count, serum calcium, creatinin, estimated glomerular filtration rate values and a qualitative test for urine protein are also required to rule out organ damage.

Low-risk MGUS is characterized by having an M protein <1.5 g/dl, IgG type and a normal free light chain (FLC) ratio. Patients should be followed with serum protein electrophoresis at six months and, if stable, can be followed every 2-3 years or when symptoms suggestive of a plasma cell malignancy arise. For patients with intermediate and high-risk MGUS (M protein above 1.5 g/dL, IgA or IgM isotype, or an abnormal FLC ratio) the International Myeloma Working Group state that a bone marrow aspirate and biopsy should be done at baseline to rule out underlying plasma cell malignancy; the patient should be followed with serum protein electrophoresis and a complete blood count in 6 months and then annually for life[53].

A skeletal survey and a bone marrow aspirate and biopsy should be carried out at baseline for SMM patients. Laboratory tests and clinical work-up should be done at diagnosis and 2-3 months after the initial recognition of SMM. If the results are stable, the patient should be followed every 4-6 months for 1 year and, if stable, every 6-12 months[53,54].

On the basis of the International Myeloma Working Group 2010 guidelines patients with MGUS and SMM should not be treated outside of clinical trials, because potential therapeutic toxicity must be weighed against benefits achieved by treating a precursor state[53]. Different clinical trials have been assessed for treatment of SMM, a condition with high risk of progression to MM, but no drugs have been approved yet[53].

CONCLUSION

MGUS and SMM may occasionally be found in association with SLE, SS, RA, spondylarthropathies and rarely with other specific rheumatic conditions. It does not seem a simple coincidence and different mechanisms, like antigenic stimulation and cytogenetic abnormalities have been postulated. Although the finding of MGUS is common following patients with immune-mediated inflammatory diseases, the development of MM in this setting seems unusual.

If a monoclonal gammopathy is found during the course of a rheumatic disease or during the etiology investigation of an articular manifestation, the serum and urinary electrophoresis with immunofixation and free light chain, laboratory and radiographic findings and eventually bone marrow aspiration is necessary. Distinguishing between MGUS or other condition is critical because patients with MGUS are conservatively treated instead of chemotherapy.

Follow-up care includes observing the patient for progression of MGUS to MM, other cell plasma dyscrasia or other lymphoproliferative disorders, described as being at higher risk in rheumatic diseases.

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