Review article

Autoimmune manifestations in patients with multiple myeloma and monoclonal gammopathy of undetermined significance☆

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ABSTRACT

Background: Multiple myeloma (MM) and its precursor, monoclonal gammopathy of undetermined significance (MGUS), have been linked with several autoimmune conditions in the medical literature. Yet, significance of these associations is not well understood.
Methods: Herein, we provide a comprehensive literature review on autoimmune disorders identified in patients with MM and MGUS. Most relevant papers were identified via searching the PubMed/Medline and EMBASE databases for articles published from inception until May 1, 2016.
Findings: Scientific literature on autoimmune conditions in patients with MM and MGUS consists of several case series and a multitude of case reports. Our analysis suggests an increased prevalence of autoimmune conditions in patients with MM and monoclonal gammopathy of undetermined significance (MGUS), including various autoimmune hematologic and rheumatologic conditions among other entities. Conversely, persons with various autoimmune conditions tend to have a higher prevalence of MGUS and MM than the general population.
Conclusions: Future research is required to explore further the link between MGUS/MM and autoimmune disorders. Inflammation in the setting of autoimmunity may serve as a trigger for MGUS and MM. In addition, a common genetic susceptibility for developing both an autoimmune disease and MM/MGUS might also exist. Autoimmune hematologic and rheumatologic diseases may pose important clinical problems for the MM patients. Therefore, a catalogue of these problems is important so that physicians are able to consider, identify and address them promptly.

Contents

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1. Introduction

Multiple myeloma (MM) is a clonal malignancy of plasma cells characterized by an overproduction of monoclonal antibodies. Clinically, this entity is characterized by skeletal lesions, anemia, hypercalcemia and renal failure. According to the United States Surveillance, Epidemiology and End Results (SEER), the incidence of MM is 6.1/100,000 people per year and increases to 30.4/100,000 people per year in those older than 65 years. The median age of diagnosis of MM is 71 years in whites, and 67 years in blacks [1]. As a rule, monoclonal gammopathy of undetermined significance (MGUS) precedes MM and carries an average 1% annual risk of progression to MM or other lymphoproliferative disorder [2]. While the etiology of both MGUS and MM remains unknown, risk factors such as advanced age, family history, male gender and environmental factors have been present in both conditions [3].

Several studies link MM with autoimmune disorders; however, the data has not yet been fully analyzed or systematized. Herein, we review comprehensively autoimmune conditions that have been associated with MM and MGUS in the medical literature.

2. Materials and methods

We performed a systematic search on PUBMED/MEDLINE, EMBASE and foreign articles published from inception to May 1, 2016. We searched for papers using the following keywords: 'multiple myeloma' and 'monoclonal gammopathy of undetermined significance' with each of the following keywords: 'autoimmune', 'autoimmunity', 'autoimmune hemolytic anemia', 'immune thrombocytopenia', 'vasculitis', 'polyarthritis', 'rheumatoid arthritis', 'rheumatologic disease', 'nephrotic syndrome', 'autoimmune neutropenia', 'thrombocytopenia', 'pure red cell aplasia', 'systemic lupus erythematosus', 'Sjogren's syndrome', 'myasthenia gravis', 'multiple sclerosis' and 'inflammatory bowel disease'. Several articles were also obtained via cross-reference checking and "snowball" method, when databases different from PUBMED and MEDLINE were accessed.

3. Overview and pathophysiology of autoimmunity and multiple myeloma

Immune dysregulation plays a key role in lymphomagenesis. Of note, chronic autoimmune inflammatory conditions have been associated with lymphoproliferative disorders such as lymphoma and chronic lymphocytic leukemia [4–5].

Indeed, chronic inflammation plays an important role in the development of lymphoproliferative diseases and other cancers [6]. In fact, there is current interest in development of targeted therapies that aim to control inflammation, such as with the toll-like receptor (TLR) pathway. For survival, B-cells in multiple myeloma depend on inflammation pathways involving interleukin (IL)-6, IL-13, and Tumor Necrosis Factor (TNF)-α. Furthermore, TLR and TLR-ligands expressed by B lymphocytes promote their proliferation and survival [7]. Other important components that help maintaining a favorable microenvironment for malignant B-cells in MM include the B-cell activating factor (BAFF) which participates in the activation of the nuclear factor κ-B (NF-κB), an important B-cell malignancy pathway [8].

In recent years, a number of reports and case studies have hinted at the association between plasma cell dyscrasias and autoimmune disorders [9]. Osserman and Takatsuki were the first ones to hypothesize that chronic antigen stimulation may trigger the development of plasma cell dyscrasias [10]. As a result, chronic immune stimulation may lead to the development of hematological malignancies by randomly introducing pro-oncogenic mutations in rapidly dividing cells, including plasma cells [11].

4. Autoimmune hematologic conditions in multiple myeloma

Anemia is almost invariably present patients with MM, either at diagnosis or as the disease progresses. The pathogenesis of anemia in MM is usually multifactorial, including a component anemia of inflammation due to myeloma itself, bone marrow replacement with malignant plasma cells and anemia of renal failure due to erythropoietin deficit. However, such entities as pernicious anemia, autoimmune hemolytic anemia and pure red cell aplasia have also been described in these patients (Table 1).

Thrombocytopenia occurs frequently in patients with plasma cell dyscrasias. The pathogenesis usually involves marrow replacement by the myeloma cells or treatment with anti-myeloma agents. Neutropenia in MM is often due to the use of traditional chemotherapy agents, immunomodulating agents and, less frequently, other agents. Notwithstanding, there are cases of immune thrombocytopenia and autoimmune neutropenia in MM patients described in the literature (Table 1).

4.1. Pernicious anemia

Pernicious anemia is characterized by an autoimmune destruction of gastric parietal cells and antibody-mediated inactivation of the intrinsic factor resulting in malabsorption of cobalamin (vitamin B12), thus leading to megaloblastic anemia. Some studies established that incidence of cobalamin deficiency in patients with IgA multiple myeloma and MGUS is approximately 13.6% (Table 1) [12]. Several publications, including meta-analysis studies, suggest that pernicious anemia may represent a risk factor for MM [9,13–14]. In addition, a recent case-control study found a 1.47 times increase in risk of developing MM in patients with pernicious anemia [13]. While the exact steps of pathogenesis of plasma cell dyscrasias in patients with pernicious anemia is not well described, several hypotheses exist. One of them favors occurrence of immune alterations and chromosome abnormalities in the bone marrow of patients with pernicious anemia [15]. Another one postulates that cobalamin deficiency may promote carcinogenesis and development of plasma cell dyscrasias by causing abnormal DNA methylation [16]. Indeed, aberrant DNA methylation patterns have been demonstrated in patients with MM [17].

Table 1
Hematologic autoimmune disorders associated with multiple myeloma and MGUS in the literature.

Disease	Proposed mechanism	Epidemiology	Therapy	References
Pernicious anemia	Disruption of B12-mediated methylation	Increased prevalence of IgA MM/MGUS in these patients	Vitamin B12 therapy has not been proven to impact the multiple myeloma outcome	[9,12–17]
AIHA	Occurrence of auto-reactive B-cell clones	Prevalence 4–10%	Improves after MM therapy	[18–22,88]
PRCA	Marrow precursor suppression by monoclonal antibody or paraprotein	Unknown	Refractory to immunosuppression; improves with MM therapy	[23–25]
ITP	Clonal autoantibody production	Unknown	May improve with MM therapy	[27,28]
Evans' syndrome	Associated with MM and IgA monoclonal gammopathy	Unknown	May improve with MM therapy	[29–31]
AIN	Clonal expansion of light chain-restricted anti-neutrophil antibodies Can be induced by MM therapy (e.g. lenalidomide, etc.)	Rare	No change	[33–35]

AIHA: autoimmune hemolytic anemia. AIN: autoimmune neutropenia. ITP: immune thrombocytopenia. MM: multiple myeloma. PRCA: pure red cell aplasia, MGUS: Monoclonal gammopathy of undetermined significance.

4.2. Autoimmune hemolytic anemia (AIHA)

Autoimmune hemolytic anemia (AIHA) is known to be associated with B-cell lymphoproliferative neoplasms. Some studies claim that 4% of patients MM also have AIHA [6,18], while others suggest that AIHA is only rarely associated with MM [19]. However, a more recent case series reported that 7 of the 66 (10.6%) MM cases were complicated by AIHA and carried red cell autoantibodies in their serum [20]. In addition, another 10 cases of AIHA associated with MM have been recently reported in literature [21]. Of those, seven patients had IgG myeloma and four - IgA myeloma [20–21]. Interestingly, one patient in this series had a biclonal (IgG2 and IgA) MM. With the exception of two patients with relapsed myeloma, all patients demonstrated remission of AIHA after therapy for myeloma [20–21]. While the pathogenesis of AIHA in MM is unclear, it has been hypothesized that significant immune disturbances may allow the development of clones that produce auto-antibodies against erythrocyte surface antigens [22].

4.3. Pure red cell aplasia

Pure red cell aplasia (PRCA) is an acquired autoimmune condition [23]. PRCA in patients with MM has traditionally been considered a rare occurrence. Recently, three case reports have described a PRCA associated with MM [24–26]. In all cases, the diagnosis of PRCA was made concurrently with the diagnosis of MM. Sarathy et al. described a patient with PRCA refractory to immunosuppressive therapy that improved only after the patient was treated with bortezomib [26]. This finding suggested that PRCA was secondary to MM.

4.4. Immune thrombocytopenia

Immune thrombocytopenia (ITP) has been reported in patients with lymphoproliferative disorders such as chronic lymphocytic leukemia and non-Hodgkin's lymphoma (NHL). While uncommon, ITP is also described in patients with MM [27–28]. In a series of six patients, thrombocytopenia was the initial presentation in two, with myeloma being diagnosed at a later stage [27–28]. Although the pathogenesis of ITP in lymphoproliferative disorders is poorly understood, it has been proposed that intrinsic immune alterations promote generation of specific autoreactive platelet antibodies [27]. In addition, ITP can be associated with AIHA as Evans' syndrome, with hemolysis usually preceding thrombocytopenia [29]. Two cases of Evans' syndrome have been described in patients with MM/MGUS [30–31]. However, one of the cases occurred in a patient with extramedullary plasmacytoma, a relatively rare plasma cell tumor not uncommonly preceding MM. The patient had IgA monoclonal gammopathy in serum and urine which was consistent with the diagnosis of MM [30]. The diagnosis of Evans' syndrome in this case preceded the diagnosis of MM by four years.

Interestingly, the second case of Evans' syndrome was also described in a patient with IgA MGUS [31].

4.5. Autoimmune neutropenia

Therapy for MM can result in neutropenia. For instance, lenalidomide-induced neutropenia occurs in up to 35% of patients [32]. Autoimmune neutropenia (AIN), characterized by the presence of autoantibodies directed against neutrophils and an absolute neutrophil count of less than 1500 cells/μL, rarely occurs secondary to myeloma itself [33]. Aryal et al. [34] have recently reported a rare case of AIN associated with MM [34]. The authors hypothesized that the cross talk between T- and B-cells in MM can induce a clonal T-cell expansion and T-cell receptor gene rearrangement leading to the development of AIN. Shastri et al. [35] identified the presence of a clonal expansion of lymphoid cells that led to light chain-restricted neutrophil-binding autoantibodies in patients with antibody-induced neutropenia.

5. Rheumatologic disorders in multiple myeloma

Increased prevalence of several rheumatologic conditions has been linked with multiple myeloma and MGUS (Table 2).

5.1. Rheumatoid arthritis

Rheumatoid arthritis (RA), systemic scleroderma, Sjogren's syndrome (SS) and systemic lupus erythematosus (SLE) have all been linked to MM and plasma cell dyscrasias (Table 2) [6,36–37]. Nonetheless, the association between MM and RA is rather weak according to several cohort studies and case reports [9,36–37]. Two recent meta-analyses did not find a statistically significant increase in the risk for MM in patients with RA [9,13]. However, both studies showed a high level of between-study heterogeneity ($I^2 > 50\%$) that could have affected their conclusions. A subgroup analysis of the study by Shen et al. [13] revealed that patients with RA are more likely to be diagnosed with subsequent MM (relative risk [RR] = 1.32). McShane et al. [9] found an increased risk of MM in patients with RA (RR = 1.18) as well, although they were not able to show statistical significance. In addition, several case-control studies found that there was an increased risk of developing MM after being diagnosed with RA [38–40]. The discrepancy between the studies could be due to reverse causality bias. Indeed, RA preceded the development of MM in case studies and most case reports in the literature [37–38]. Consequently, it is conceivable that prolonged antigenic stimulation present in RA could lead to the development of MM.

5.2. Systemic lupus erythematosus

The association between SLE and lymphoproliferative disorders is well known. In a cohort study, nearly 11% of patients with MM were

Table 2
Rheumatologic autoimmune disorders associated with multiple myeloma in the literature.

Disease	Proposed mechanism	Epidemiology	Therapy	References
RA	RA usually precedes MM; prolonged antigenic stimulation induced by RA can lead to MM.	Conflicting data	No change	[37–40]
SLE	Similar to RA In addition, defective immune surveillance in SLE may lead to uncontrolled clonal proliferation of plasma cells.	MM tends to be diagnosed at an earlier age.	No change	[41–43]
DM and PM	Chronic immune stimulation leading to B-cell clonal expansion	2.29 relative risk of developing plasma cell dyscrasias	No change	[45–49]
SS		IgG myeloma is the most common subtype.	SS symptoms may improve with MM therapy	[13,53–60]
AS	Unknown	Unknown	No change	[46,61–66]
LCV	Overexpression of IL-6 genes in MM may lead to development of LCV.	IgG myeloma is more prevalent than other subtypes.	No change	[67–73]

DM: dermatomyositis. HM: hematologic malignancy. IL-6: interleukin-6. MM: multiple myeloma. PM: polymyositis. RA: rheumatoid arthritis. SLE: systemic lupus erythematosus. SS: Sjogren's syndrome. AS: ankylosing spondylitis. LCV: leukocytoclastic vasculitis.

reported to have clinico-laboratory features of SLE [41]. In addition, increased prevalence of SLE in family members of patients with MM has also been reported [42]. Review of literature revealed more than a dozen cases of MM in patients with SLE [43]. In all of them, SLE either preceded or was diagnosed concurrently with MM. The median age of diagnosis of MM in patients with SLE was 45 years, which is younger than the median age of 64 years seen in the general population [44]. The pathophysiology underlying the association between SLE and MM is unclear. Similar to RA, it is plausible that prolonged antigenic stimulation present in SLE leads to development of MM. Conversely, defective immune surveillance in SLE may lead to selection of specific B-cell clones, thus leading to the development of MM.

5.3. Dermatomyositis and polymyositis

Dermatomyositis (DM) and polymyositis (PM) are associated with hematologic malignancies [45]. A recent retrospective cohort study of 4641 patients with MM/MGUS found that DM and PM are associated with an increased risk (relative risk = 2.29) of developing plasma cell dyscrasias [46]. Several researchers even reported cases of DM-related MM [47–48]. Similarly, a few case reports described PM associated with MM [49–50]. Unlike the situation in DM, the diagnosis of PM occurred either simultaneously or after the diagnosis of MM. Chronic immune stimulation that occurs in PM/DM is thought to cause T-cell and B-cell activation, thus leading to the development of certain hematologic malignancies including MM [51].

5.4. Sjogren's syndrome

There have been reports in literature linking Sjogren's syndrome (SS) and MM [6,13]. SS is a chronic autoimmune disease featuring a progressive lymphocytic proliferation and destruction of the salivary and lacrimal glands causing xerostomia and xeropthalmia. An increased risk of NHL and thyroid cancer has been reported in patients with SS [52]. Several cohort studies found an increased risk of MM and MGUS in patients with primary SS, while several reports described SS preceding MM [53–55]. In addition, there has been an increased incidence of free monoclonal light chains and proteins detected in serum and urine in patients with SS, with monoclonal IgG as the most frequent immunoglobulin detected [56–58]. Another study by Tomi et al. [59] found an increased risk of monoclonal gammopathy in patients with SS, where a longer duration and higher severity of SS correlated with the highest risk. Although exact mechanism remains unclear, chronic inflammation as a potential trigger for the development of MM is hypothesized [53]. Patients with concurrent SS and MM demonstrated clinical improvement of SS after treatment with thalidomide and dexamethasone [60]. This suggests a possible causal relationship between the two disorders.

5.5. Ankylosing spondylitis

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease involving the axial skeleton. A retrospective cohort of over 4 million United States (US) white and black male veterans followed for 27 years found a significantly increased relative risk of 2.29 of developing MM and MGUS in subjects with AS [46]. Several reports describe development of MM in patients with longstanding AS [61–66]. Among those cases, one patient had IgA lambda and five patients had IgA kappa multiple myeloma. In all reported cases the diagnosis of AS preceded the diagnosis of MM. While the exact mechanism for this association is unclear, persistent plasma cell stimulation and activation in AS has been proposed as a potential trigger for IgA MM [61].

5.6. Leukocytoclastic vasculitis

Leukocytoclastic vasculitis (LCV) represents a small vessel vasculitis that may present as palpable purpura. Although data is limited on the relationship between vaculitides and MM, several studies suggested an association between the two. A case series by Bayer-Garner and Smoller [67] evaluated eight patients with concomitant MM and LCV. This study found that all patients had IgG myeloma associated with LCV. In contrast, several case-reports described IgA myeloma associated with LCV [68–72]. Another report describes a patient who developed MM, retinal vasculitis and temporal arteritis [73]. While the exact pathogenesis for the development of LCV in MM is unknown, some authors postulated that overexpression of IL-6 genes in MM may contribute to the development of LCV [67].

6. Autoimmune neurologic disorders in multiple myeloma

Several retrospective cohort studies have reported the presence of autoimmune neurologic disorders including myasthenia gravis (MG) and multiple sclerosis (MS) in patients with plasma cell dyscrasias, including MM (Table 3) [9,74–75]. One report described MM that developed in a patient suffering from MS for 26 years [76]. Similarly, a case of Waldenstrom's macroglobulinemia was described in a patient suffering from MS for 39 years [77]. Conversely, MS and peripheral demyelinating neuropathies have been described in patients with monoclonal gammopathies [78]. These findings suggest a possible association between monoclonal gammopathies and demyelinating neuropathies, which is thought to be due to shared genetic susceptibility. Indeed, one study demonstrated increased frequency of MS in relatives of 1317 MM patients [79].

Cases of coexistence of MG and MM in the literature are rare. In one case report, MG preceded the development of MM by 20 years [80]. In addition, MG was described in a patient with extramedullary plasmacytoma and in another patient with MM [81–82].

Table 3
Neurologic and other autoimmune disorders associated with multiple myeloma in the literature.

Disease	Proposed mechanism	Epidemiology	Therapy	References
MG	MG usually precedes MM	Very rare	May improve with MM therapy	[74,75,80–82]
MS	Genetic susceptibility	Unknown	No change	[74–76,78,79]
MGN	Monoclonal immunoglobulin deposition	Unknown	May improve with MM therapy	[85]
IBD	Increased B-cell and plasma cell activation may lead to MM	Unknown	No change	[87,88]

IBD: inflammatory bowel disease. MG: myasthenia gravis. MGN: membranous glomerulonephritis. MM: multiple myeloma. MS: multiple sclerosis.

7. Immunomodulatory drugs and multiple myeloma

Published data have suggested that some agents used to treat auto-immune disorders might confer an increased risk of myeloma. In partic-ular, a case-control study found a 5-, 3-, and 6-fold increased risk of developing multiple myeloma in women taking prednisone, insulin, and gout medications (e.g. sulphinpyrazone and colchicine), respectively [1,9].

On the other hand, some multiple myeloma therapies can also lead to the development of autoimmune conditions. In 2009, for the first time, Dasanu *and* Alexandrescu reported a case of lenalidomide-induced aplastic anemia that resolved spontaneously after the discontinuation of lenalidomide [83]. In 2014, a retrospective study by Montefusco et al. [84] found a 4.3% absolute risk of autoimmune disorders in MM patients treated with lenalidomide. Most autoimmune conditions devel-oped within six months of starting therapy. These diseases included AIHA, ITP, Evans syndrome, optic neuritis, autoimmune thyroiditis, polymyositis, and cutaneous vasculitis. In that study, autologous stem cell transplantation for multiple myeloma was also associated with a statistically significant increased risk of developing autoimmune disorders.

8. Other autoimmune disorders in multiple myeloma

Renal abnormalities such as tubular light-chain deposition disease, interstitial nephritis, primary amyloidosis and monoclonal deposition disease are well-recognized in patients with MM [85]. However, nephrotic syndrome is a rare presentation in MM. A case-series by Thachil et al. [86] describes two MM patients who developed membranous glomerulonephritis. Nephrotic syndrome resolved after the myeloma therapy, suggesting an association between MM and membranous glomerulonephritis. Monoclonal immunoglobulin deposition is thought to play a role in the pathogenesis of nephrotic syndrome in MM [86].

A large, retrospective cohort study of patients with multiple myelo-ma suggested that inflammatory bowel disease (IBD) may be associated with the development of MM [9] (Table 3). Minami et al. described instances of MM in patients with ulcerative colitis (UC) and Crohn's dis-ease [87]. In both cases, MM developed during a long-term observation of patients with IBD. There have been nine additional reported cases of MM developing in the setting of IBD [88]. In these cases, the diagnosis of MM was made between 6–30 years after the diagnosis of IBD. While anti-TNF therapies (i.e. infliximab) could have played a role in the development of MM, only 3 of 9 patients were treated with such agents. This suggests that mechanisms involving increased B-cell activation might be responsible for the development of MM in IBD [88].

9. MGUS and autoimmunity

MGUS is known to precede MM, and carries an average 1% annual risk of progression to MM. Indeed, on a molecular level, MM is consis-tently preceded by MGUS [89]. Nonetheless, most cases of MGUS never progress to a full-blown MM. While the pathogenesis of MGUS and MM is still not well-understood, there is evidence that immune dysregulation and/or sustained immune stimulation may play a role in the development of these two hematologic entities [90]. A recent population-based study and a case-series showed clearly that several immune-mediated conditions were associated with a significant risk of developing MGUS [91,92].

A recent meta-analysis demonstrated that autoimmune conditions were associated with a nearly 42% increase in risk of MGUS [9]. Similar to the situation in MM, patients with pernicious anemia display a signif-icantly increased risk of developing MGUS [9]. Furthermore, this study found a non-significant association between ankylosing spondylitis and polymyositis/dermatomyositis with MGUS [9].

A study of United States veterans suggested that subjects with autoimmune conditions where autoantibodies are detectable are at increased risk of developing MGUS [46]. Furthermore, a recent population-based study found that personal or family history of autoim-mune disease increases the risk of developing MGUS [91]. In that study, history of giant cell arteritis, polymyalgia rheumatica and rheumatoid arthritis was associated with a significantly increased risk of MGUS [91]. Two additional case-series demonstrated an increased prevalence of autoimmune axonal or peripheral demyelinating neuropathy in patients with MGUS [93,94].

In a recent prospective study, 15% patients with MGUS were found to have a preceding autoimmune disorder [95]. Sjogren's syndrome, polymyositis and vitiligo have been reported to precede the develop-ment of MGUS in three patients from Senegal [92]. Interestingly, their monoclonal components stabilized after the treatment of their autoim-mune conditions. Another case series reported four patients with Sjogren's syndrome , Kikuchi disease, neuromyelitis optica and ankylos-ing spondylitis, respectively, who developed MGUS either coincidently or up to 10 years after the diagnosis of the autoimmune condition [90].

Several studies have found that inflammatory/infectious conditions such as pneumonia, sepsis, meningitis and osteoarthritis increase the risk of developing MGUS and in some cases - of MM [46,91]. This suggests that an overwhelming inflammatory process can trigger the development of MGUS and myeloma. It had been proposed that infections can lead to a clonal proliferation by serving as a trigger for certain genetic translocations [96].

Taken together, these findings suggest that autoimmune diseases and inflammatory conditions may increase the risk of developing MGUS. As a result, chronic antigen stimulation may trigger the develop-ment of a plasma cell dyscrasia. Alternatively, there might be a common genetic or environmental susceptibility for developing both an autoim-mune disease and a MGUS.

10. Discussion and conclusions

Patients with MM appear to be at increased risk for various autoim-mune conditions. Nonetheless, information available in the literature on autoimmune conditions in patients with MM/MGUS consists largely of retrospective analyses of case series or isolated reports. This might limit the accuracy of our analysis. Some conclusions of our review might render an overestimation of the association between autoim-mune conditions and MM due to the retrospective nature of most studies on this topic in the published literature. Presence of publication bias is another concern, reflecting the fact that studies reporting positive associations are more likely to be published than studies reporting negative associations. Finally, some associations between instances of autoimmunity and MM/MGUS could represent a mere coincidence.

Etiopathogenesis of autoimmune conditions and MM appears multifactorial and complex. Furthermore, insights from pathophysiology could explain the risk for both diseases. In most cases, development of an autoimmune condition precedes the development of MM. This echoes the hypothesis made by Rudolf Virchow who, in 1863, stated that the origin of cancer at different sites was due to chronic inflammation. Consequently, MM/MGUS could develop due to chronic inflammation in the setting of autoimmune disorders. Chronic antigenic stimulation of B-lymphocytes present in autoimmune disorders might eventually lead to clonal proliferation, and ultimately to MM. In addition, defective immune surveillance in autoimmunity may lead to pre-selection of specific B-cell clones, thus triggering development of MM. Moreover, some studies suggested shared genetic susceptibility for both conditions.

Many autoimmune diseases could be primary, and may play a role in the pathogenesis of MGUS/MM. Conversely, autoimmune conditions may develop after the diagnosis of MGUS/MM has been made. Future studies are needed to better understand the relationship between MM and autoimmune disorders. The autoimmune conditions can pose significant clinical problems for the MM patients and health care providers; therefore, a catalogue of this information is important to raise awareness and improve timely diagnosis and management.

Transparency document

The Transparency document associated with this article can be found, in online version.

Conflict of interest

The authors of this manuscript certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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