



CASE REPORT

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



Ana María Ávila^{a,*}, Sergio Giralt^b

^a La Sabana University School of Medicine, Bogota, Colombia

^b Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, United States of America

Received 17 March 2017; accepted 21 July 2017

Available online 30 August 2017

KEYWORDS

Myeloma;
Neoplasia;
Autoimmunity;
Response to self antigen;
Immunobiology;
Myasthenia

PALABRAS CLAVE

Mieloma;
Neoplasia;
Autoinmunidad;
Respuesta a antígeno propio;
Inmunobiología;
Miastenia

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.

© 2017 Instituto Nacional de Cancerología. Published by Elsevier España, S.L.U. All rights reserved.

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.

© 2017 Instituto Nacional de Cancerología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

* Corresponding author.

E-mail address: anita.maria.avila@hotmail.com (A.M. Ávila).

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 erythematosus, 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

Table 1 Summary of clinical characteristics in 26 reported cases of MM associated with autoimmune conditions (AC).

Autoimmune conditions (AC)	Authors (ref)	age/sex	Age of MM	Age of AC	Diagnostic delay	Type of mm	Extra medullary involvement	MM treatment	AC treatment	Evolution	Autoimmune symptoms evolution	Cases reported in the literature
SLE	Choi(13)	31/F	31	26	MM 5 years after SLE.	IgA λ	Both cervical, paratracheal, both inguinal LN	VAD x2: BTD x2 -> ASCT	HCQ	VGPR	-	17
IAS	Waldrón-Lynch(14)	63/M	63	63	MM Several months after IAS	IgG3/ λ	No	Dexamethasone + lenalidomide -> BD	MM treatment	Favorable	Resolved	5
TTP	Yao (15)	74/F	74	74	Simultaneous	IgG κ	No	Melphalan + dexamethasone	FFP + plasma-pheresis	CR	Resolved	5
MG+thymoma	García-Fernández (16)	54/M	54	30	MM 24 years after MG	IgG κ	No	Melphalan+ Prednisone x2 -> Cyclophosphamide + Vincristine + prednisone	Resection + physostigmine	Relapse	Improved	1
SLE+MG+PK	Urbańska-ryś (17)	25/F	45	25	MM 20 years after MG/PK and 7 years after SLE.	IgG κ	Abdominal, inguinal, cervical and mediastinal LN.	VAD x4 -> CHOP x6	Physostigmine + CS+azathioprine+cyclophosphamide	PR	Improved	0
Acquired free PS deficiency	Deitcher(18)	46/M	40	46	Acquired PS deficiency 6 years after MM.	IgG κ	No	-	-	-	-	0
Acute interstitial nephritis + RA-like polyarthritis	Ardalan(19)	47/M	47	47	MM 2 months after RA and 4 months after AIN	-	No	VAD x4	CS	CR	Resolved	0
SS	Tazi (20)	63/F	63	58	MM 5 years after SS	IgA λ	No	VAD	Artificial tears + MM treatment	CR	Resolved	15
SLE+SS	Wang (21)	47/F	47	44	MM 3 years after SS+SLE	IgG κ	No	VAD	HCQ+CS+ cyclophosphamide	Death	Death	0

Table 1 (Continued)

Autoimmune conditions (AC)	Authors (ref)	age/sex	Age of MM	Age of AC	Diagnostic delay	Type of mm	Extra medullary involvement	MM treatment	AC treatment	Evolution	Autoimmune symptoms evolution	Cases reported in the literature
RA	Alexopoulou(22)	74/F	47	74	MM 27 years after RA	IgG λ	-	-	HCQ, gold, MTX.	-	-	-
Scleromyxedema	Shen (23)	79/M	79	79	Simultaneous	IgA λ	No	-	-	-	-	-
MG	Rowland(24)	54/M	54	54	MM 5 months after MG	IgG	No	Melphalan	Neostigmine and pyridostigmine	Death	Resolved	0
AHA	Wada(25)	57/M	57	57	Simultaneous	IgG κ	No	MCNU-VMP	CS	-	Resolved	8
AN	Aryal (26)	54/M	54	54	Simultaneous	IgG κ	No	BTD -> carfilzomib	Filgastrim	PR	Improved	0
Urticarial Vasculitis	Highet (27)	44/M	44	40	MM 4 years after Urticarial Vasculitis	IgA λ	No	Mephalan +Prednisone	Prednisone	-	Resolved	5
SPD-type IgA pemphigus	España(28)	37/M	37	35	MM 2 years after pemphigus	IgA κ	No	Cyclophosphamide+BD->VRD->BCNU	Prednisone	-	Resolved	5
SSc	Owlia(29)	58/M	58	43	MM 15 year after SSc	IgA	No	VAD x 2->Bortezomide x2	Calcium channel blockers + prostaglandin E1	Death	-	13
Urticaria pigmentosa	Ogg. (30)	44/M	44	36	MM 8 year after urticarial pigmentosa	IgG	No	Doxorubicin, carbamustina, melphalan and cyclophosphamide.	-	-	-	0

Table 1 (Continued)

Autoimmune conditions (AC)	Authors (ref)	age/sex	Age of MM	Age of AC	Diagnostic delay	Type of mm	Extra medullary involvement	MM treatment	AC treatment	Evolution	Autoimmune symptoms evolution	Cases reported in the literature
Urticaria + complete C1q deficiency	Tokumitsu (31)	75/F	75	75	Simultaneous	IgG3	No	-	-	-	-	1
DM+SLR	Chakraverty (32)	46/M	46	46	DM+SLR 10 months after MM	IgG λ	Testicular	VAD x6-> melphalan ASCT	CS	CR	Resolved	0
CPV	Jain (33)	53/M	53	-	-	IgG κ	No	VAD x 6	Topics CS.	-	Improved	11
Eosinophilic dermatosis	Two (34)	50/M	49	50	Dermatosis 1 year after MM	-	No	ASCT-> brotezomib, carfilzomib and dexamethasone.	CS	-	Resolved	-
EBA	Radfar (35)	71/M	64	69	EBA 5 years after MM	IgG κ	No	-	CS + cyclosporine.	Relapse	Improved	-
CLA + leukocytoclastic vasculitis	Turner (36)	29/M	29	29	Simultaneous	IgA λ	No	-	CS + cyclophosphamide	Death	Persisted	-
Urticarial erythema	Zhang(37)	79/M	79	79	Simultaneous	IgA	No	Melphalan+ Prednisone	-	-	Resolved	-
ITP	Tabata(38)	78/M	78	80	ITP 23 months after MM	IgG κ	No	Melphalan+ prednisone.	Cepharanthine	Death	Resolved	7

Abbreviations: AC Autoimmune condition, AHA Autoimmune Hemolytic Anemia, AN Autoimmune neutropenia, AIN Acute interstitial nephritis, ASCT autologous stem cell transplantation, AvWD Acquired Von Willebrand disease, BCNU Melphalan, Cyclophosphamide, Adriamycin and Carmustine, BD Bortezomib and Dexamethasone, BTD Bortezomib, Thalidomide, and Dexamethasone, CLA Cutis laxa acquisita, CPV Cutaneous paraneoplastic vasculitis, CR Complete remission, CS Corticosteroids, DM Dermatomyositis, EBA Epidermolysis bullosa acquisita, F Female, FFP Fresh frozen plasma, HCQ Hydroxychloroquine, IAS Insulin autoimmune syndrome, ITP Immune thrombocytopenic purpura, LN Lymph node, MCNU-VMP Ranimustine, Vindesine, Melphalan and Prednisolone, MG Myasthenia gravis, MM Multiple myeloma, M Male, PK Palmoplantar keratoderma, PR Partial response, PS Protein S, SLE Systemic lupus erythematosus, SLR Sarcoid-like reaction, SPD Sucroeneal pustular dermatosis, SS Sjögren syndrome, SSc Systemic sclerosis, RA Rheumatoid Arthritis, TTP Thrombotic thrombocytopenic purpura, VAD Vincristine, Doxorubicin and Dexamethasone, VRD Bortezomib, Lenalidomide, Dexamethasone, VGPR Very good partial response.

The concurrence of autoimmuned conditions and MM is rare and has not been fully investigated. We herein describe the course of two patients with MM who presented with two different autoimmune conditions: myasthenia gravis and angioedema. To date, more than 25 different autoimmune conditions related to MM have been reported in the literature, which are summarized in Table 1.¹³⁻³⁸ In the review of reported cases, the mean age of diagnosis of MM and the autoimmune condition was 55 and 54 years old, respectively. One third of the cases had the diagnosis of their autoimmune condition before the onset of MM, and 40 percent (10 of 25 cases) the diagnosis were made simultaneously. Among the autoimmune conditions related to MM, SLE was the most common with 17 reported cases, followed by SS and SSc with 15 and 13 respectively. The autoimmune symptoms resolved or improved with MM treatment in the majority of cases, as in the case of patient 2.

B-cell hyperactivity, considered a trademark of autoimmune conditions, favors the escape of abnormal cell clones from normal regulatory mechanisms.¹³ Therefore, it has been suggested that immune related conditions can be associated with an elevated MM risk.^{12,21} In the case of SLE, the mouse lupus model showed an increased prevalence of MM, and more than 30% of the specimens showed monoclonal gammopathy.¹³ It has been recently reported that plasma cell growth factors such as B lymphocyte stimulator (BLYS) are elevated in patients with SLE.

Several theories have been proposed to explain the coexistence of MM and an immune condition. One hypothesis suggests that a spontaneous autoreactive clone of B cells undergoes physiological maturation and produces monoclonal auto antibodies.^{14,39}

The association of Myasthenia Gravis and MM was first reported by Rowland et al.²⁴ who diagnosed the plasma cell dyscrasia in a patient five months after the diagnosis of MG. Because the protein abnormality was considered to be possibly related to the myasthenic syndrome, therapy for MM was instituted and caused a remission of myasthenic symptoms. In this regard, our reported case (patient 2) is similar because treatment of MM resulted in resolution of MG.

The incidence of monoclonal gammopathy developing during the course RA has been estimated to be 1-2%.²² Moreover, Srinivasulu et al.⁴⁰ reported the case of two patients who presented with inflammatory arthritis as the initial manifestation of MM. Reza-Ardalan et al. studied the similarity in the cytokine milieu of MM and RA. They showed that in the context of MM, an immunologic reaction directed against light chain molecules and tumoral antigens deposited within the synovium could result in RA-like polyarthritis.¹⁹ Another biologically plausible association between autoimmune thyroid disease (ATD) and MM has been reported regarding the cytokine milieu. IL-6 in particular appears to contribute to the growth of myeloma cells and has a role in the initiation and perpetuation of ATD.⁴¹

In a prospective study, less than 4% of AHA cases were due to MM, and only eight cases of AHA at MM presentation have been reported in the literature.^{40,42} Wada et al.²⁵ demonstrated that the antibody binding to erythrocytes was similar to myeloma M protein.

Among the paraneoplastic syndromes and cutaneous manifestations of MM, angioedema is exceptional (only 4 cases in the literature).^{43,44} Angioedema with acquired C1

esterase inhibitor (C1-INH) deficiency is a rare disorder usually identified as acquired angioedema (AAE). It was first described in 1972 by Caldwell et al and is characterized by episodes of bradykinin-mediated angioedema without urticarial.^{43,45,46} In the acquired form, the deficiency results from markedly increased catabolism of C1 inhibitor due to its consumption by the neoplastic lymphatic tissues (AAE type 1) or by autoantibody mediated inactivation (AAE type 2).^{46,47} Geha et al.⁴⁸ presented a patient with IgA MM and acquired C1-inhibitor deficiency who had circulating anti-idiotypic antibodies that reacted with the M component. This interaction appeared to cause increased consumption of C1-inhibitor. There is evidence that the M components detected frequently correspond to the C1-inhibitor auto antibodies. Castelli et al.^{42,44} study group has shown that patients with MGUS and C1-inhibitor auto-antibodies frequently have the same heavy and light chain histotypes. This suggests that a single B cell clonal disorder with different potential clinical evolutions underlies all AAE.⁴⁹

In correlation with patient 1, it has been documented that C1- INH antigen values can be normal due to elevated amounts of cleaved inactive C1-INH in plasma or normal function levels between angioedema attacks. C1q reduction confirms the diagnosis of AAE, but a minority of patients can present with normal C1q. In this case, the presence of autoantibodies to C1- INH can be investigated. Limits to these procedures are the inadequate standardization of C1-INH functional measurements and the availability to look for anti-C1-INH autoantibodies.^{49,50}

In summary, autoimmunity appears to have an association with multiple myeloma. We reviewed several cases of autoimmune conditions related to multiple myeloma documented in the literature. The heterogeneous set of conditions, diversity among presentations and severity explains the lack of epidemiological data and clinical features. In the majority of cases, the diagnoses were made simultaneously; SLE was the most common AD associated with MM. Myeloma treatment in general improved the autoimmune symptoms. As the pathogenesis is still not clear, different hypotheses have emerged although none proven. Based on only a few studies, it appears that autoimmunity favors the escape of abnormal clones of B cells from regulatory mechanisms leading to emergence of neoplastic B cell clones. On the other hand, other data suggests a spontaneous transformation of an autoreactive clone of B cells that later on undergoes physiological maturation and production of autoantibodies, therefore, explaining the autoimmune manifestations.

This association needs further clinical studies in order to provide an important foundation in understanding the physiology of B cell in MM. In addition, larger retrospective studies could favor the discernment of risk factors, prognosis and essential epidemiologic data in the setting of autoimmune conditions related to myeloma.

Ethical responsibilities

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicto de intereses

The authors have no conflicts of interest to declare.

Acknowledgments

Dr. Avila and Dr. Giralt performed the research, designed the research study and wrote the paper. We considered the ethical responsibilities dictated by Revista Colombiana de Cancerología and we do not have any conflict of interest to declare.

References

- Shen K, Xu G, Wu Q, Zhou D, Li J. Risk of multiple myeloma in rheumatoid arthritis: a meta-analysis of case-control and cohort studies. *PLoS One* [Internet]. 2014;9:e91461.
- Benedek TG, Zawadzki ZA. Ankylosing spondylitis with ulcerative colitis and amyloidosis. *Am Med.* 1966;40:431–9.
- Blanc AP, Gastaut JA, Sebahoun G, Carcassonne Y. Association spondylarthrite ankylosante maladie de Kahler: a propos d'une observation. *Semin HOp Paris.* 1979;55:1335–7.
- Danon F, Clauvel JP, Seligmann M. Les 'paraproteines' de type IgG et IgA en dehors de la maladie de Kahler. *Rev Fr Etudes Clin Biol.* 1967;12:681–701.
- Damali NM, Isis SM, Landgren O. Autoimmunity and hematologic malignancies: associations and mechanisms. *Leuk Lymphoma.* 2009;50:541–50.
- Smedby KE, Askling J, Mariette X, Baecklund E. Autoimmune and inflammatory disorders and risk of malignant lymphomas - An update. *J Intern Med.* 2008;264:514–27.
- Dimopoulos MA, Kastiris E, Anagnostopoulos A. Hematological malignancies: Myeloma. *Ann Oncol.* 2006;17 Suppl 10:x137–43.
- Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. *Blood.* 2008;111:3388–94.
- Dalamaga M, Karmaniolas K, Papadavid E, Pelecanos N, Migdalis I. Association of thyroid disease and thyroid autoimmunity with multiple myeloma risk: a case-control study. *Leuk Lymphoma* [Internet]. 2008;49:1545–52.
- Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood.* 2010;116:679–86.
- Rajkumar SV. Doublets, triplets, or quadruplets of novel agents in newly diagnosed myeloma? *ASH Education Book.* 2012;2012:354–61.
- Cho SY, Yang HS, Jeon YL, You E, Lee HJ, Yoon HJ, et al. A case series of autoimmune diseases accompanied by incidentally diagnosed monoclonal gammopathy: Is there a link between the two diseases? *Int J Rheum Dis* [Internet]. 2014;17:635–9.
- Choi JW, Han SW, Kwon KT, Kim GW. Early onset multiple myeloma in a patient with systemic lupus erythematosus: A case report and literature review. *Clin Rheumatol* [Internet]. 2010;29:1323–6.
- Waldron-Lynch F, Inzucchi SE, Menard L, Tai N, Preston-Hurlburt P, Hui P, et al. Relapsing and remitting severe hypoglycemia due to a monoclonal anti-insulin antibody heralding a case of multiple myeloma. *J Clin Endocrinol Metab* [Internet]. 2012;97:4317–23.
- Yao H, Monge M, Renou M, Lecaque C, Jauréguy M, Presne C, et al. Thrombotic thrombocytopenic purpura due to anti-ADAMTS13 antibodies in multiple myeloma. *Clin Nephrol* [Internet]. 2014;81:210–5.
- García Fernández M, Sanz MA, Vilela C, Rafecas J, Yaya Huaman R. A case of association of myasthenia, thymoma and multiple myeloma. Review of the cases published. *Rev Clin Esp.* 1979;153:465–9.
- Urbańska-ryś H, Robak E, Kordek R, Bartkowiak J, Rieszke P, Woźniacka A, et al. Multiple Myeloma in a Patient with Systemic Lupus Erythematosus, Myasthenia Gravis and Non-Familial Diffuse Palmoplantar Keratoderma. *Leuk Lymphoma* [Internet]. 2004;45:1913–8.
- Deitcher SR, Erban JK, Limentani SA. Acquired free protein S deficiency associated with multiple myeloma: a case report. *Am J Hematol.* 1996;51:319–23.
- Reza-Ardalan M, Mohajel-Shoja M. Multiple myeloma presented as acute interstitial nephritis and rheumatoid arthritis-like polyarthrititis. *Am J Hematol.* 2007;82:309–13.
- Tazi I, Rachid M, Benchekroun S. Sjögren's syndrome associated with multiple myeloma. *Am J Hematol.* 2008;49:215–6.
- Wang J, Xie X, Li F, Chen J. Multiple myeloma secondary to systemic lupus erythematosus and Sjögren's syndrome: a case report. *Arch Rheumatol* [Internet]. 2014;29:65–8.
- Alexopoulou A, Dourakis SP, Apostolopoulou A, Kandyli A, Pandelidaki H, Archimandritis AJ. Light chain multiple myeloma in a patient with long-standing rheumatoid arthritis. *Clin Rheumatol* [Internet]. 2005;24:669–70.
- Shen M, Ng SC. Multiple myeloma masquerades as rheumatic diseases. *Proc Singapore Healthc.* 2013;22:64–9.
- Rowland LP, Osserman EF, Scharfman WB, Balsam RF, Ball S. Myasthenia gravis with a myeloma-type, gamma-G (IgG) immunoglobulin abnormality. *Am J Med* [Internet]. 1969;46:599–605.
- Wada H, Yata K, Mikami M, Suemori S, Nakanishi H, Kondo T, et al. Multiple myeloma complicated by autoimmune hemolytic anemia. *Intern Med.* 2004;43:595–8.
- Aryal MR, Bhatt VR, Tandra P, Krishnamurthy J, Yuan J, Greiner TC, et al. Autoimmune neutropenia in multiple myeloma and the role of clonal T-cell expansion: evidence of cross-talk between B-cell and T-cell lineages? *Clin Lymphoma Myeloma Leuk* [Internet]. 2014;14:e19–23. Elsevier Inc.
- Highet AS. Urticarial vasculitis and IgA myeloma. *Br J Dermatol.* 1980;102:355–7.
- España A, Gimenez-Azcarate A, Ishii N, Idoate MA, Panizo C, Hashimoto T. Antidesmocollin 1 autoantibody negative subcorneal pustular dermatosis-type IgA pemphigus associated with multiple myeloma. *Br J Dermatol* [Internet]. 2015;172:296–8.
- Owlia MB, Distler O, Foratyazdi M, Akhtari M. Visual problem and low back pain as initial manifestation of multiple myeloma complicating pre-existing systemic sclerosis. *J Coll Physicians Surg Pakistan* [Internet]. 2014;24:S29–31.
- Ogg GS, Rosbotham JL, MacDonald DM. Urticaria pigmentosa coexisting with multiple myeloma. *Clin Exp Dermatol.* 1996;21:365–6.
- Tokumitsu S, Yoshio F, Kobayashi T, Tetsuki A, Shinya S, Zensuke O. Complete C1q Deficiency Associated with IgG Multiple Myeloma. *Jpn J Med.* 1989;28:216–8.
- Chakraverty R, Rabin N, Peggs K, Robinson S, Duncan JR, Yong K. Dermatomyositis and sarcoid-like reaction associated with multiple myeloma treated effectively by high-dose chemother-

- apy and autologous peripheral blood stem cell transplantation. *Bone Marrow Transpl* [Internet]. 2001;27:1215-7.
33. Jain P, Kumar P, Parikh PM. Multiple myeloma with paraneoplastic leucocytoclastic vasculitis. *Indian J Cancer*. 2009;46:173-4.
 34. Two AM, Li C, Hata T. A case of eosinophilic dermatosis of hematologic malignancy in a patient with multiple myeloma. *Dermatol Online J*. 2014;20:15.
 35. Radfar L, Fatahzadeh M, Shahamat Y, Sirois D. Paraneoplastic epidermolysis bullosa acquisita associated with multiple myeloma. *Spec Care Dent* [Internet]. 2006;26:159-63.
 36. Turner RB, Haynes HA, Granter SR, Miller DM. Acquired cutis laxa following urticarial vasculitis associated with IgA myeloma. *J Am Acad Dermatol* [Internet]. 2009;60:1052-7.
 37. Zhang Y, Morita E, Matsuo H, Ueda D, Dekio S. Urticarial erythema associated with IgA myeloma. *J Dermatol*. 2004;31:661-5.
 38. Tabata R, Tabata C, Tazoh A, Nagai T. Low dose cepharanthine ameliorates immune thrombocytopenic purpura associated with multiple myeloma. *Int Immunopharmacol* [Internet]. 2012;13:242-4. Elsevier B.V.
 39. Kashyap R, Singh A, Kumar P. Prevalence of autoimmune hemolytic anemia in multiple myeloma: A prospective study. *Asia Pac J Clin Oncol*. 2016;2:319-22.
 40. Srinivasulu N, Sharma V, Samant R. Monoclonal gammopathies presenting as inflammatory arthritis: uncommon but important- a case series. *Int J Rheum Dis* [Internet]. 2012;15:336-9.
 41. Frémeaux-Bacchi V, Guinépain MT, Cacoub P, Dragon-Durey MA, Mouthon L, Blouin J, et al. Prevalence of monoclonal gammopathy in patients presenting with acquired angioedema type 2. *Am J Med* [Internet]. 2002;113:194-9. Elsevier.
 42. Collet E, Dalac S, Guy H, Tavernier C, Lorcerie B, Besancenot JF, et al. Manifestations cutanées au cours du myélome multiple. *Ann Dermatol Veneréol* [Internet]. Masson;118(1):35-44.
 43. Taddei S, Caraccio N, Viridis A, Dardano A, Versari D, Ghiadoni L, et al. Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis. *J Clin Endocrinol Metab*. 2006;91:5076-82.
 44. Castelli R, Deliliers DL, Zingale LC, Pogliani EM, Cicardi M. Lymphoproliferative disease and acquired C1 inhibitor deficiency. *Haematologica*. 2007;92:716-8.
 45. Caldwell JR, Ruddy S, Schur PH, Austen KF. Acquired C1 inhibitor deficiency in lymphosarcoma. *Clin Immunol Immunopathol*. 1972;1:39-52.
 46. Benjilali L, Essaadouni L. Un myélome multiple associé à une anémie hémolytique auto-immune. *Presse Med* [Internet]. 2013;42:1533-5.
 47. Castelli R, Zanichelli A, Cicardi M, Cugno M. Acquired C1-inhibitor deficiency and lymphoproliferative disorders: A tight relationship. *Crit Rev Oncol Hematol* [Internet]. 2013;87:323-32. Elsevier Ireland Ltd.
 48. Geha R, Quinti I, Austen F, Gicardi M, Sheffer A, Rosen FS. Acquired C1- Inhibitor Deficiency Associated with Antiidiotypic Antibody to Monoclonal Immunoglobulins. *N Engl J Med*. 1985;534-40.
 49. Wu MA, Castelli R. The Janus faces of acquired angioedema: C1-inhibitor deficiency, lymphoproliferation and autoimmunity. *Clin Chem Lab Med*. 2016;54:207-14.
 50. Zeerleder S, Levi M. Hereditary and acquired C1-inhibitor-dependent angioedema: from pathophysiology to treatment. *Ann Med*. 2016;48:256-67.