

Case Report

Journal of Cancer Biology and Therapeutics

Multiple Myeloma and Primary Sjogren's Syndrome Combined with Unexplained Elevation of CA-125 Levels

Jun Du, ShuHui Deng, LuGui Qiu and Gang An*

Institute of Hematology & Blood Disease Hospital, Chinese Academy of Medical Science & Peking Union Medical College, China

***Correspondence:** Gang An, Institute of Hematology & Blood Disease Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Tianjin 300020, China, E-mail: dujunglobe@gmail.com

Received: December 03, 2018; Accepted: January 04, 2019; Published: January 10, 2019

Abstract

Background: Multiple myeloma (MM) and its precursor, monoclonal gammopathy of undetermined significance (MGUS), have been linked with several autoimmune conditions like primary Sjögren's Syndrome (pSS). Several studies link MM with autoimmune disorders. However, the data has not yet been fully analyzed or systematized.

Case presentation: We described a 60-year-old Chinese woman diagnosed as multiple myeloma who presented with ocular and oral sicca symptoms, unexplained elevation of CA-125. In this patient, there was an inner connection between MM and pSS remaining to be investigated further.

Conclusions: Multiple myeloma and primary Sjögren's Syndrome could be coexisting due to the similar physiopathologic mechanism, which might be the explanation of bortezomib's effectiveness. Moreover, tumor marker like CA-125 might be elevated owing to the secretion of CD-138+ve plasma cells.

Introduction

Multiple myeloma (MM) is a clonal malignancy of plasma cells characterized by an overproduction of monoclonal antibodies. Clinically, this entity is manifested as hypercalcemia, renal failure, anemia, and bone lesions, commonly abbreviated to "CRAB" symptoms. 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 [1]. Although monoclonal gammopathy of undetermined significance (MGUS) occurs in approximately 3% of persons 50 years of age or older. In a recent study, during 14,130 person-years of follow-up, MGUS progressed in 147 patients (11%), a rate that was 6.5 times (95% confidence interval [CI], 5.5 to 7.7) as high as the rate in the control population [2].

Primary Sjogren's syndrome (pSS) with a female preponderance is a systemic autoimmune disorder with secretory gland dysfunction characterized by dryness of the main mucosal surfaces including the mouth, eyes, nose and vagina. The disease is one of the three most common autoimmune disorders [3].

Herein, we provide a case report and literature review of multiple myeloma combined with primary Sjogren's syndrome, aiming at inspiring readers to dig the profound connection and distinction between them.

Case Report

A 60-year-old Chinese woman presented in January 2018 with dryness of the mouth and eyes for 2 years. She had a previous history of ovariogram 30 years ago, with ovariogram surgery removed. In addition, owing to the unexplained evaluation of carcinoembryonic antigen-125

(CA-125: 1935 U/ml), laparoscopic bilateral adnexectomy was operated, without the detection of neoplasm lesion.

The patient was referred to the Rheumatology Department, and a diagnosis of primary Sjögren's syndrome (pSS) was made based on ocular and oral sicca symptoms for 2 years, positive lower lip gland biopsy, and FANA (1:1000+), and rheumatoid factor (10.6 IU/mL) positivity. Anti-SSA/SSB were negative. Lower lip gland biopsy was performed, with the finding of moderate-to-severe atrophy of partial lobules, scattered and focal lymphocytes and plasma cells infiltration (Grades 3) in mesenchymal region. PET-CT (Positron Emission Tomography-Computed Tomography) revealed diffuse metabolism increases, 4.9 of the maximal standard uptake value (SUVmax), and the discontinuation of bilateral rib cortex, especially in the third and fifth rib on the right and the third rib on the left.

After admission to the Dept of Hematology, bone marrow aspiration was carried out, alongside the finding of 19.5% plasma cells in the nucleated cells (Figure 1). Biopsy of bone marrow, as stated in figure 2A and 2B, revealed 40% plasma cell infiltration. Immunohistochemical staining demonstrated: CD38 (+), CD138 (+), Kappa (-), Lambda (+), CD56 (-), CD3 (-), CD20 (-). Flow Cytometry revealed 1.93% abnormal plasma cells with the significant expression of CD38, CD138, CD28 and c-Lambda, weak expression of CD19, CD81, CD27. Moreover, CD56, CD200, CD117, CD20 and c-Kappa was not expressed. The karyotype was: 46, XY (20). The monoclonal immunoglobulin (M protein) is 10.665 g/L. Physical examination revealed multiple enlargement of lymph nodes, including the region of neck, axilla and groin. Laboratory investigations showed hemoglobin of 15.3 g/dL, white cell count of 4,800/L, platelet of 201,000/L, and MCV of 93.2 fL. She had a total protein of 79 g/L with 36.5 g/L of globulin. β 2-microglobulin (β 2-MG) was elevated to 2.89 mg/L. CA-125 elevated to 3067.7U/mL. Serum electrophoresis demonstrated a polyclonal pattern with increased amount of IgA (15.2 g/L). Multiple myeloma was diagnosed without doubt, staged as IgA-, D-S II A, ISS I, RB-1 loss, CDKN2C loss. We treated this patient with BCD chemotherapy protocol (body surface area: 1.64 m²; height: 162 cm; weight: 60 kg), bortezomib 2.1 mg d1.4.8.11, cyclophosphamide 0.8 g d1.8, dexamethasone d1.2.4.5.8.9.11.12, in detail (Table 1).

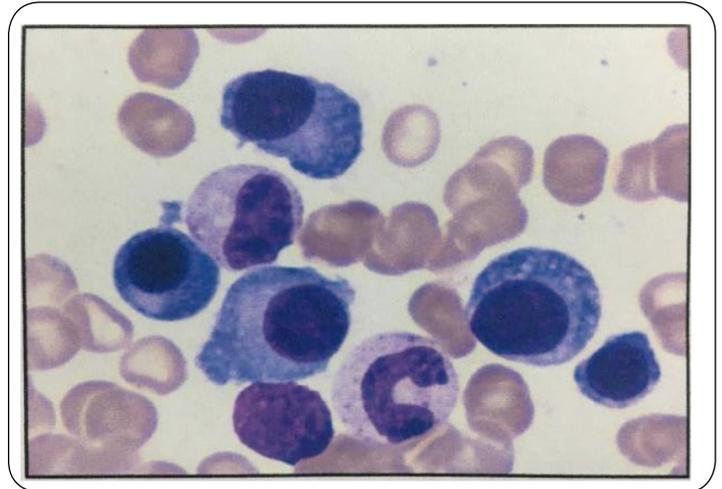


Figure 1: Plasma cells (primary 0.5% + immature 13.5% + mature 5.5% = 19.5%) detected by aspiration at the ilium bone.

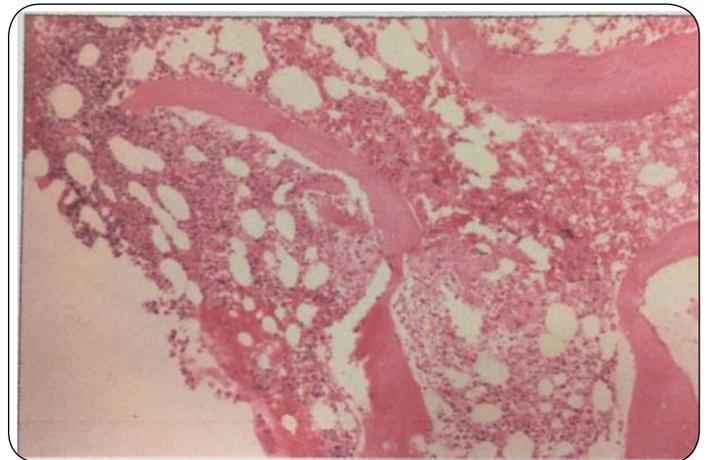
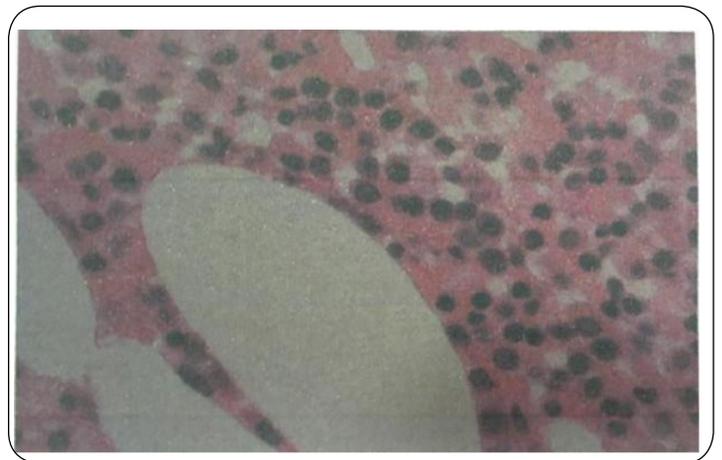


Figure 2: Bone marrow biopsy revealed normocellular marrow with multifocal increase of plasma cells (40%). Immunohistochemical staining: CD38 (+), CD138 (+), Kappa (-), Lambda (+), CD56 (-), CD3 (-), CD20 (-).

Table 1: Laboratory data (February, 2018).

Data	Value	Data	Value
WBC	4.8×10 ⁹ /L	ANA	0.736
ANC	2.84×10 ⁹ /L	Anti-nRNP Ab	negative
Lymph	1.43×10 ⁹ /L	Anti-Jo-1 Ab	negative
RBC	4.72×10 ¹² /L	Anti-SS-A-Ab	negative
HGB	153 g/L	Anti-SS-B Ab	negative
HCT	44%	Anti-ds-DNA Ab	negative
PLT	201×10 ⁹ /L	β-2-MG	2.89 mg/L
RET	1.60%	IgG	8.59 g/L
TP	79 g/L	IgA	15.2 g/L
ALB	42.5 g/L	IgM	0.46 g/L
GLO	36.5 g/L	carbamide	3.81 mmol/L
T-Bill	9.5 umol/L	creatinine	63.9 umol/L
D-Bill	1.9 umol/L	Uric acid	378.8 umol/L
CA-125	3067.7 U/ml	CA-125	1978.8 U/mL
(2018.01.17)		(2018.02.09)	

Discussion

Incidence of multiple myeloma in primary sjogren's syndrome

As is well known, patients suffering primary Sjögren's syndrome (pSS) are at a higher risk of developing non-Hodgkin's lymphoma (NHL). Nevertheless, the relative risk of advancing to cancers other than NHL (for example: multiple myeloma) is unrecognized.

In 2011, The Taiwan National Health Insurance (NHI) established a cohort of 7852 patients with pSS (from 2000 to 2008) who did not have cancer prior to diagnosis of pSS, in addition, calculated the incidence and standardized incidence ratios (SIRs) for multiple myeloma. The conclusion that female patients with pSS had a higher risk of NHL (SIR 7.1, 95% CI 4.3 to 10.3), multiple myeloma (SIR 6.1, 95% CI 2.0 to 14.2) is obtained. Overall, women with pSS had a significantly higher risk of MM. Theoretically, based on the observation that many patients with pSS had benign monoclonal gammopathy, the association between pSS and MM was well established, even though the solid evidence is deliquescent [4].

Another study, conducted by Tomi et al., found an increased risk of monoclonal gammopathy in patients suffering pSS, where a longer duration and higher severity of pSS is related to the highest risk [5].

Clinical manifestations of laboratory examination

In Caucasians, IgM or a free light chain, especially λ-type, is the most predominant monoclonal protein found in patients with pSS. In contrast, over 50% of the monoclonal proteins are members of the IgA or IgG class in Japanese patients with pSS [6]. Besides, there has been a growing incidence of free monoclonal light chains and proteins detected in serum and urine in patients with pSS, with monoclonal IgG as the most frequent immunoglobulin monitored [7].

Tomohiro Akimoto, in 1999, reported a case of a 62-year-old female patient with primary Sjögren's syndrome (pSS) who developed multiple myeloma (MM) of the IgA k-type, which is the same as the case we presented. It is of interest that the titers of anti-SS-A and anti-SS-B antibodies gradually increased during the clinical course of this patient at the same time as the increase in IgA level and the decrease in IgG and IgM levels were found [8].

Molecular mechanism underlying the progression of multiple myeloma in primary sjogren's syndrome

Early in 1978, with immunoperoxidase technology, Jules Zulman had demonstrated that in some patients with primary Sjögren's Syndrome, there may be a progression in the lymphoproliferative lesions from a polyclonal infiltrate to a monoclonal neoplasm. Besides,

Intracytoplasmic immunoglobulin identifies six of the nine cases as being B-cell in origin, which subsequently and logically, could be a rational explanation for disease progression [9].

By contrast, multiple myeloma, the only pure post germinal center (GC) type, showed infrequent associations with autoimmune diseases (ADs), as a retrospective analysis conducted by Kari Hemminki in 2016. During their studies, the risk of B-cell neoplasms after any of 33 ADs in Sweden was analyzed. Conclusion is the fact that primary non-GC neoplasms were associated with 2 ADs only. Accordingly, these data may suggest that autoimmune stimulation critically interferes with the rapid cell division, somatic hypermutation, class switch recombination and immunological selection of maturing B-cell in the GC and delivers damage contributing to transformation [10].

Recent studies involving pSS patients have demonstrated that reduction in the circulating memory B cell compartment is related to an elevation in serum IgG levels, suggesting plasmacytosis and overactive differentiation of memory B cells to plasma cells [11]. Put it in another way, chronic antigenic stimulation of B-lymphocytes present in autoimmune disorders might eventually lead to clonal proliferation of monoclonal gammopathy, and ultimately to MM.

Well known to us, plasma cells are specialized terminally differentiated B cells that synthesize and secrete antibodies to maintain humoral immunity. Via the production of pathogenic antibodies, plasma cells contribute to numerous conditions, such as autoimmune disorders, transplant rejection and allergies, and more than that, multiple myeloma, a malignant hematological which are life-threatening [12]. A further investigation of cellular events in B-cell neoplasia will be conducive to validate the molecular mechanism.

In addition, chronic inflammation, the core mechanism of autoimmune diseases, as a potential trigger for the development of multiple myeloma is hypothesized, although the exact correlation remains unclear [13]. One interesting and obvious phenomenon, described by U.P. Kulkarni, is that patients with concurrent pSS and MM demonstrated clinical improvement of pSS after treatment with thalidomide and dexamethasone, which suggests a possible causal relationship between the two disorders [14]. Consequently, MGUS/MM could develop due to chronic inflammation in the setting of autoimmune disorders.

Increased serum tumor markers (CA-125) in multiple myeloma

CA-125, is a mucin-like glycoprotein with a 200,000 Da molecular weight expressed in coelomic epithelium during embryonic development. In several malignant, non-malignant, and certain physiological states, including multiple myeloma, the expression of CA-125, secreted by the mesothelial cells, could be detected [15].

Mariam Boota, in 2016, reported a 55-year-old female diagnosed as IgG kappa Durie Salmon stage II-A MM, manifesting an asymptomatic elevation of CA-125 level to 500 U/mL. The back pain appeared later, and skeletal survey and CT-scan of the abdomen revealed a 3-inch tumor lesion in the pelvis which was subjected to a CT guided biopsy revealing plasmacytoma on pathology. Further work up revealed bone marrow plasmacytosis of 20%, IgG 2470 mg/dL, serum M-protein 2.4 g/dL, beta-2-microglobulin 2.5 mg/L, and hemoglobin of 11.2 g/dL. Serum and urine immunofixation was positive for IgG kappa free light chains. Multiple myeloma is diagnosed and the other cause for the elevation of CA-125 is excluded [16]. MM with CA-125 elevation is thought to be infrequent, yet CA-125 monitoring is not routinely performed and elevated CA-125 might be missed easily. One possible theory is that CA-125 is secreted by CD-138 +ve plasma cells. In our case, the value of CA-125 is dramatically dropped from 3067.7 U/mL to 1979.8 U/mL after only one course of chemotherapy, which may indicate a deep connection between CA-125 and multiple myeloma.

Bortezomib: An incidental successful treatment for refractory primary sjögren's syndrome?

Primary Sjögren's Syndrome (pSS) is a chronic autoimmune disease characterized by sicca complex and various systemic manifestations, in which plasma cell plays a vital role, equivalent to the core function of B lymphocytes. It is for this reason that, in a case of a patient with refractory primary Sjögren's syndrome and without the expression of CD20, as Juan JO reported in 2015, the decision was taken to pioneered treatment with bortezomib, a proteasome inhibitor mainly used in multiple myeloma and having effect against plasma cells. After treatment, a satisfactory therapeutic effect was achieved, with a significant clinical improvement and the recovery of the patient to her usual activities. Hence, the use of bortezomib in a refractory case of pSS broadens our scopes of mind to remedy autoimmune disease like

primary Sjögren's Syndrome, demystifies a profound connection between autoimmune disease and plasma cell disorder like multiple myeloma as mentioned above, in addition [17].

Essence of the connection and distinction of multiple myeloma and autoimmune disorders: still beneath the sea

Many autoimmune diseases, like primary Sjögren's Syndrome, could be preliminary, and may play a role in the pathogenesis of MGUS/MM. Conversely, autoimmune conditions may develop after the diagnosis of MGUS/MM. The autoimmune conditions can pose significant clinical threats for the MM patients and health care providers; In consequence, a catalogue of this information is important to raise awareness and improve timely diagnosis and management. Essence of the connection and distinction known to us is merely the tip of the iceberg; therefore, future investigations are needed to fully understand the underlying relationship between MM and autoimmune disorders [18].

Declaration statements

Ethics approval and consent to participate was obtained. Consent for publication was accepted. There is availability of data and material. No competing interests were involved. There was no funding for this paper. The author has investigated and written this manuscript.

Acknowledgements

This project was funded by [NSFC-81630007, 81570181; CIFMS:2017-12M-1-015, 2017-12M-1-005, 2016-12M-3-013; Basic Scientific Research Operating Expenses of Central Universities of China: 3332018156] Thanks for the assistants of Professor LuGuiQiu, GangAn, ShuHuiDeng in Lymphoma/Myeloma center of Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital.

References

1. Ries LAG, Eisner MP, et al. SEER cancer statistics review, 1975-2000. Bethesda (MD): National Cancer Institute; 2003.
2. Kyle RA, Larson DR, Therneau TM, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2018;378(3):241-249. doi: <https://dx.doi.org/10.1056/NEJMoa1709974>

3. Mariette X, Criswell LA. Primary Sjögren's syndrome. *N Engl J Med*. 2018;378(10):931-939. doi: <https://dx.doi.org/10.1056/NEJMcp1702514>
4. Weng M-Y, Huang Y-T, Liu M-F, Lu T-H. Incidence of cancer in a nationwide population cohort of 7852 patients with primary Sjögren's syndrome in Taiwan. *Ann Rheum Dis*. 2012;71(4):524-527. doi: <https://dx.doi.org/10.1136/annrheumdis-2011-200402>
5. Tomi A-L, Belkhir R, Nocturne G, et al. Brief Report: Monoclonal gammopathy and risk of lymphoma and multiple myeloma in patients with primary Sjögren's syndrome. *Arthritis Rheumatol*. 2016;68(5):1245-1250. doi: <https://dx.doi.org/10.1002/art.39534>
6. Sugai S, Konda S, Shoraski Y, Murayama T, Nishikawa T. Non-IgM monoclonal gammopathy in patients with Sjögren's syndrome. *Am J Med*. 1980;68(6):861-866. <https://www.ncbi.nlm.nih.gov/pubmed/6770683>
7. Brito-Zerón P, Ramos-Casals M, Nardi N, et al. Circulating monoclonal immunoglobulins in Sjögren syndrome: prevalence and clinical significance in 237 patients. *Medicine (Baltimore)*. 2005;84(2):90-97. <https://www.ncbi.nlm.nih.gov/pubmed/15758838>
8. Akimoto T, Kobayashi S, Tamura N, et al. Sjögren syndrome associated with multiple myeloma of the IgA κ-type. *Mod Rheumatol*. 2000;10(2):110-113. doi: <https://dx.doi.org/10.1007/s101650050008>
9. Zulman J, Jaffe R, Talal N. Evidence that the malignant lymphoma of Sjögren's syndrome is a monoclonal B-cell neoplasm. *N Engl J Med*. 1978;299(22):1215-1220. doi: <https://dx.doi.org/10.1056/NEJM197811302992204>
10. Hemminki K, Liu X, Ji J, Försti A. Origin of B-cell neoplasms in autoimmune disease. Dolcetti R, ed. *PLOS ONE*. 2016;11(6):e0158360. doi: <https://dx.doi.org/10.1371/journal.pone.0158360>
11. Bohnhorst JØ, Bjørgan MB, Thoen JE, Jonsson R, Natvig JB, Thompson KM. Abnormal B cell differentiation in primary Sjögren's syndrome results in a depressed percentage of circulating memory B cells and elevated levels of soluble CD27 that correlate with Serum IgG concentration. *Clin Immunol*. 2002;103(1):79-88. doi: <https://dx.doi.org/10.1006/clim.2002.5199>
12. Hiepe F, Alexander T, Voll RE. [Plasma cells]. *Z Rheumatol*. 2015;74(1):20-25. doi: <https://dx.doi.org/10.1007/s00393-014-1438-4>
13. Tazi I, Rachid M, Benchekroun S. Sjögren's syndrome associated with multiple myeloma. *Singapore Med J*. 2008;49(8):e215-216. <https://www.ncbi.nlm.nih.gov/pubmed/18756337>

14. Kulkarni U, Gokhale Y, Raut P, Dargad R. An unusual cause for sicca syndrome. *J Postgrad Med.* 2011;57(2):129-130. doi: <https://dx.doi.org/10.4103/0022-3859.81872>
15. Bischof P. What do we know about the origin of CA 125? *Eur J Obstet Gynecol Reprod Biol.* 1993;49(1-2):93-98. doi: [https://dx.doi.org/10.1016/0028-2243\(93\)90131-U](https://dx.doi.org/10.1016/0028-2243(93)90131-U)
16. Boota M, Schinke C, Ledoux S, Alapat D, Khan R, Barlogie B. CA-125 secreting IgG kappa multiple myeloma: CA-125 Elevation in MM. *Am J Hematol.* 2016;91(10):E457-E458. doi: <https://dx.doi.org/10.1002/ajh.24456>
17. Jakez-Ocampo J, Atisha-Fregoso Y, Llorente L. Refractory primary Sjögren syndrome successfully treated with bortezomib: *J Clin Rheumatol.* 2015;21(1):31-32. doi: <https://dx.doi.org/10.1097/RHU.0000000000000210>
18. Shimanovsky A, Alvarez Argote J, Murali S, Dasanu CA. Autoimmune manifestations in patients with multiple myeloma and monoclonal gammopathy of undetermined significance. *BBA Clin.* 2016;6:12-18. doi: <https://dx.doi.org/10.1016/j.bbacli.2016.05.004>



Copyright: © **Du et al.** This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.