Case Report and Case Series

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2024, Vol. 52(11) 1–12

DOI: 10.1177/03000605241285228
journals.sagepub.com/home/imr
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Type II cryoglobulinemia in a patient with chronic lymphocytic leukemia/small lymphocytic lymphoma and Sjögren's disease

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Abstract

Type II cryoglobulinemia is a rare disorder characterized by abnormal immunoglobulins (Igs) precipitating in the blood at low temperatures and redissolving upon warming. Sjogren's disease (SjD) is an autoimmune disorder involving secretory gland malfunction that leads to persistent dryness of the mouth and eyes. Here, we report the case of a 61-year-old woman with a 7-year history of SjD who was diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). However, her complicated clinical features could not be sufficiently explained by this disease alone. Immunofixation electrophoresis revealed monoclonal IgM-κ and polyclonal IgG-κ. The presence of precipitated cryoglobulin and elevated rheumatoid factor levels confirmed a diagnosis of type II cryoglobulinemia for this patient. To the best of our knowledge, this case represents the first report of a patient with CLL/SLL, SjD, and type II cryoglobulinemia, which increased our understanding of immune system-related disorders. Because certain similar mechanisms are involved in the pathogenesis of these three diseases, a combination treatment of rituximab, ibrutinib, and dexamethasone resulted in a favorable prognosis for this patient.

Keywords

Cryoglobulinemia, cryoglobulin, chronic lymphocytic leukemia, small lymphocytic lymphoma, Sjögren's disease, rituximab, ibrutinib, dexamethasone

Date received: 12 June 2024; accepted: 2 September 2024

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Introduction

Cryoglobulinemia is a rare disorder characterized by the presence of circulating immunoglobulins (Igs) in the serum that precipitate at low temperatures and redissolve upon warming.[1,2] The well-accepted classification by Brouet and colleagues categorizes cryoglobulinemia into three types.[3] In type I cryoglobulinemia, the abnormal Igs, called cryoglobulins, are commonly monoclonal IgM and occasionally monoclonal IgG. Type I cryoglobulinemia has been associated with patients with hematological malignancies, including myeloma, B-cell lymphoma, and chronic lymphocytic leukemia (CLL).[1,4,5] The cryoglobulins in type II cryoglobulinemia consist of a mixture of monoclonal IgM (or IgG/IgA) and polyclonal Igs with rheumatoid factor (RF) activity, while the cryoglobulins related to type III cryoglobulinemia only contain polyclonal Igs with RF activity.[1,6] Accordingly, type II and III cryoglobulinemia are also referred to as mixed cryoglobulinemia. The manifestations of mixed cryoglobulinemia are broad, ranging from systemic vasculitis, peripheral neuropathy, purpura, arthralgia, and weakness to cutaneous necrosis and ulcers.[7] Mixed cryoglobulinemia has been associated with chronic infections, most frequently with hepatitis C virus (HCV), B-cell malignancies, such as B-cell non-Hodgkin's lymphoma (B-NHL), and autoimmune diseases, including lupus and Sjögren's disease (SjD).[1,2,6,8]

The most recognizable symptoms of SjD are dryness of the eyes and mouth because of chronic lymphocyte infiltration into the exocrine glands, which thereby damages the gland functions.[9] Other common features of SjD include fatigue, polyarthralgia, salivary gland enlargement, and Raynaud's phenomenon.[10] Notably, these clinical features can be from either primary SjD (pSjD) or secondary SjD associated with other diseases, such as systemic lupus erythematosus, rheumatoid arthritis, scleroderma, or NHL.[11] The incidence of SjD is approximately 1 in 400, with a female-to-male patient ratio of 10:1.[12,13]

CLL and small lymphocytic lymphoma (SLL) are considered as one disease with different clinical presentations. In CLL patients, a large number of abnormal lymphocytes typically manifest in the peripheral blood, bone marrow, and lymphoid tissues, while immature lymphocytes predominately accumulate in the lymph nodes and bone marrow in SLL patients.[14] CLL/SLL is the most prevalent form of adult leukemia in individuals of European descent. However, it is 10- to 20-fold less common among Asians, including Chinese.[14–16] Here, we report a unique case in which a female patient manifested type II cryoglobulinemia, SjD, and CLL/SLL. To the best of our knowledge, this is the first report of one patient with all three disorders. We implemented a therapeutic plan of rituximab, ibrutinib, plus dexamethasone. The patient responded well and was released from the hospital after treatment. This reporting meets the requirements of the CARE case report guidelines.[17]

Case presentation

A 61-year-old Chinese woman presented in the emergency department with fever, chills, and severe skin ulcers on both lower legs. Ulceration, scabs, hyperpigmentation, and inflammation occurred simultaneously (Figure 1(a)). She had obvious fatigue, shortness of breath, and enlarged left axillar lymph nodes. The leg ulcers had developed over a period of almost three years. Initially, red papules about the size of a grain of rice appeared on both lower limbs without itching or pain. These then enlarged and ruptured, eventually developing into ulcers over six months that led to pain after walking. The ulcers failed to heal and became repeatedly infected, but the

inflammation subsided following treatment with antibiotics. A computed tomography (CT) scan of the lungs showed interstitial changes that indicated decreased lung permeability, ground-glass density changes in both lungs, and pleural effusion (Figure 1(b)).[18] The F-fluoreodeoxyglucose positron emission tomography/CT scans in Figure 1(c) revealed multiple highly metabolically active lymph nodes (SUVmax 9.31) in the paracentral lung, mediastinum, bilateral axilla, right ventricular septum, bilateral superior pleural lateral retroperitoneum, hepatic portal area, splenic portal area, bilateral pelvic cavity, abdominal wall, and inguinal area, as well as skin in the right lower leg (SUVmax 5.67).

A complete blood count analysis showed pancytopenia with a hemoglobin level of 35 g/L, white blood cell count of 3.4×10^9/L, and platelet count of 113×10^9/L. The total protein level was 48.1 g/L, albumin level was 28.9 g/L, and globulin level was 19.2 g/L, with a main increase in IgM (3.27 g/L) and slight decreases in the other Igs. The urinalysis showed proteinuria and hematuria. Tests for anti-glomerular basement membrane antibodies, anti-neutrophil cytoplasmic antibody 1 (ANCA1), and ANCA2 were negative. Serum electrophoresis showed a slight monoclonal band in the gamma zone. Immunofixation electrophoresis data for blood and urine samples showed a monoclonal IgM-κ band and

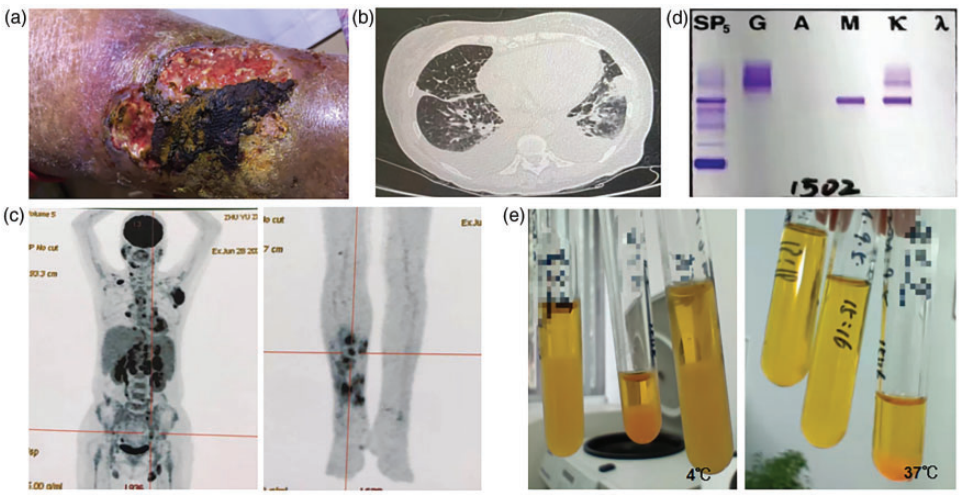

Figure 1. The clinical features of the patient. (a) Ulceration, scabs, hyperpigmentation, and inflammation occurred simultaneously on her right lower leg. (b) The lung computed tomography (CT) scan showed interstitial changes and pleural effusion in both lungs. (c) 18F-fluoreodeoxyglucose positron emission tomography/computed tomography (18FFDG-PET/CT) revealed multiple highly metabolically active lymph nodes and skin on the right lower leg. (d) The results of immunofixation electrophoresis analysis of the serum. A small cluster of monoclonal bands can be seen in the far-left lane. The lanes labeled as G, M, and κ demonstrated a monoclonal IgM-κ band and polyclonal IgG-κ band, respectively. The lambda anti-sera were performing normally and the tests were conducted using serum and urine separately, with equivalent results observed and (e) the cryoglobulin testing showed positive results and the cryocrit was approximately 65%. Specifically, 20 mL of blood was drawn into collection tubes that were prewarmed to 37°C without anticoagulants. After clotting at 37°C for 30 minutes, the serum was separated by centrifugation at 37°C, placed into a graduated tube, and refrigerated at 4°C to allow cryoglobulin precipitation after 24 hours.

polyclonal IgG-κ band (Figure 1(d)). HAV, HBV, HCV, and human immunodeficiency virus (HIV) serologies were all negative. Complement tests demonstrated reduced C4 levels (0.05 g/L [normal, 0.10–0.40 g/L]), slightly reduced C3 levels (0.56 g/L [normal, 0.70–1.40 g/L]), and increased RF levels (588 IU/mL). The patient complained of dryness of the eyes and mouth over the last 5 years, with salivary scintigraphy showing damaged intake functions of the parotid and submandibular glands. Evaluations of serum antibodies against Sjögren's syndrome A (SSA) and Ro-52 showed strong positivity, approximately 3+, indicating that the patient also suffered from SjD.[9] The antinuclear antibodies were positive at a dilution of 1:100, while the anti-double-stranded DNA antibody was negative. However, the observed severe anemia and skin ulcers are not typical features of SjD patients. We further performed cryoglobulin testing, bone marrow aspiration, as well as skin and lymph node biopsies. The cryoglobulin testing showed positive results and the cryocrit was approximately 65% (Figure 1(e)). Flow cytometry analysis of the bone marrow revealed 12.95% of monoclonal B cells with the classical CLL immunophenotype (4–5 scores): CD5+, CD19+, CD20+, CD23±, FMC7−, CD22±, CD79b−, and slg−. Flow cytometry analysis of the blood revealed this phenotype in 0.7% of total cells (Figure 2(a)). *IGHV*, *EGR2*, and *SPEN* mutations were detected. Biopsy of the inguinal lymph nodes indicated SLL, with immunophenotyping analysis of cell surface markers revealing CD20+, Ki-67 (1%+), CD10−, CD5+, CD19+, CD3(partial+), CD23+, Bcl2+, Bcl6−, and CyclinD1− (Figure 2(b/c)). The skin biopsy indicated sclerosing panniculitis with SLL cell infiltration (Figure 2(d)). The immunophenotyping markers were CD19+, CD20+, CD3−, CD5+, CyclinD1−, SOX11−, CD23+, CD10−, LEF1+, and Ki-67 (20%+). From the collected data, the patient was therefore diagnosed with CLL/SLL with type II cryoglobulinemia.

The ibrutinib–rituximab regimen has been shown to result in superior overall survival and progression-free survival for CLL patients.[18] For patients with moderate-to-severe mixed cryoglobulinemia syndrome, treatment with glucocorticoids in combination with rituximab is effective.[19] The pathogenesis of pSjD is characterized by B cell activation, with rituximab treatment demonstrating positive clinical efficacy for this disease. Because of the patient's diagnosis and poor general health, she was administered ibrutinib 420 mg per day, rituximab 375 mg/m^2 on day 1 of a 21-day cycle, and dexamethasone 5 mg per day. Her shortness of breath and pulmonary inflammatory exudate symptoms were significantly alleviated after two cycles of therapy (Figure 3 (a)). Her performance status was improved and the hemoglobin level increased to 82 g/L, which further increased to 102 g/L after four cycles. Additionally, the enlarged lymph nodes became much smaller. The skin ulcers and cyanosis on both lower legs were improved (Figure 3(b)). The patient obtained partial remission and continued to take oral ibrutinib for 6 months, then stopped treatment because of severe mouth ulcers. She has remained in a stable condition to date.

Discussion and conclusions

Cryoglobulinemia is defined as the persistent presence of cryoglobulins in the serum that precipitate at low temperatures (<37°C) and redissolve when the temperature is increased. Cryoglobulinemia is classified into three types (I, II, and III) according to Brouet's classification based on the Ig composition. Type II and type III are referred to as mixed cryoglobulinemia.[3] HCV infection is the most common

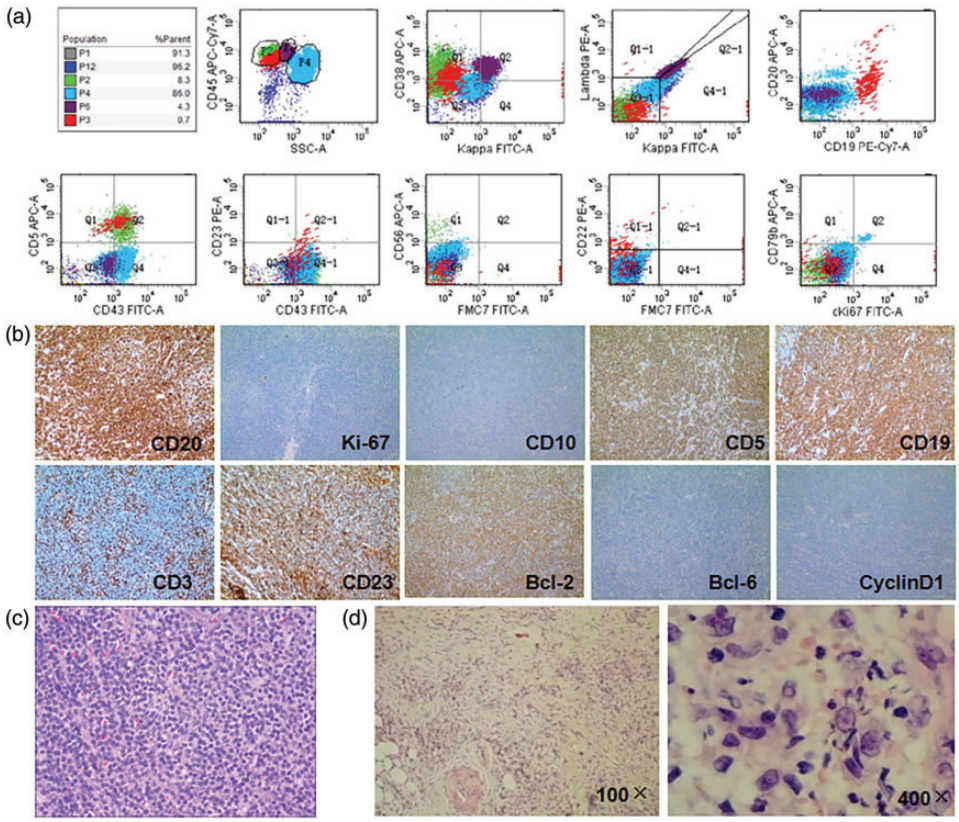

Figure 2. The diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) was made through pathological and flow cytometry analyses. (a) Flow cytometry analysis of P3 of the blood revealed CD5+, CD19+, CD20+, CD23±, FMC7−, CD22±, CD79b−, and slg− in 8.4% of all lymphocytes and 0.7% of the total cells. P2 was lymphocytes; 8.3% of the total cells. P4 was granulocytes; 86.0% of the total cells. P6 was monocytes; 4.3% of the total cells. (b) Immunophenotyping analysis of the lymph node revealed CD20+, Ki-67(1%+), CD10−, CD5+, CD19+, CD3(partial+), CD23+, Bcl2+, Bcl6−, and CyclinD1−. (c) Inguinal lymph node biopsy indicated SLL (hematoxylin and eosin [H&E] stain, 40×) and (d) skin biopsy indicated sclerosing panniculitis with SLL/CLL cell infiltration (H&E stain, 100× and 400×).

cause of mixed cryoglobulinemia, while other causes include systemic autoimmune diseases, lymphoproliferative disorders, and other viral infections (HBV, HIV).[20]

Here, we reported the case of a cryoglobulinemia patient with both SjD and lymphoproliferative disorders, which is a very rare clinical scenario that has not been reported previously. The manifestations of mixed cryoglobulinemia vary and often depend on small vessel involvement in the skin, musculoskeletal system, nervous system, kidneys, gastrointestinal tract, and lungs. Only about a third of patients present with the representative triad of purpura, arthralgia, and weakness, with purpura being the most common manifestation.[21] If cryoglobulin deposition in small blood vessels leads to clinical manifestations, then it is referred to as cryoglobulinemia vasculitis. This patient presented with recurring ulcers on both lower legs, with the pathological examination revealing sclerosing panniculitis with infiltration of SLL cells.

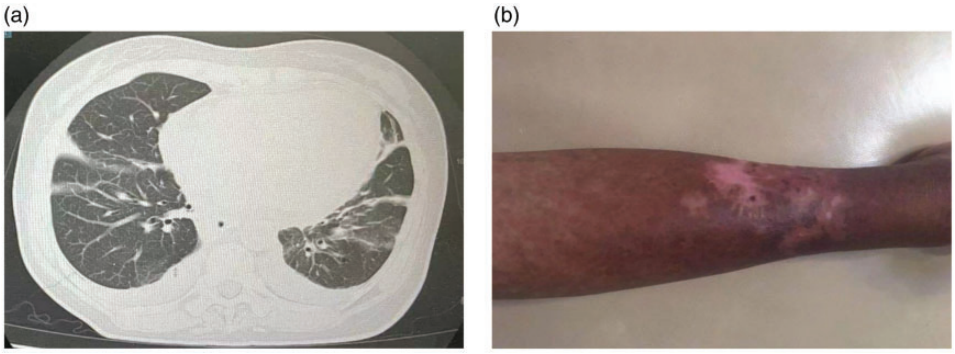

Figure 3. Patient improvement after treatment. (a) The pulmonary inflammatory exudate was significantly alleviated after two cycles of therapy and (b) the skin ulcers and cyanosis on the patient's right lower leg were improved.

We believed that the sclerosing panniculitis was partially caused by cryoglobulinemia vasculitis. The patient also presented with interstitial lung disease and nephritis, which could be caused by SjD and cryoglobulinemia. Notably, the involvement of organs other than the kidneys suggests mixed, rather than type I, cryoglobulinemia. The prognosis is usually poor in patients with gastrointestinal and pulmonary involvement.[21] We believed that this patient's pancytopenia, especially the severe anemia, was potentially caused by SjD and CLL/SLL. Taken together, the complicated conditions of this case caused the diagnosis to be difficult.

Compared with other autoimmune diseases, pSjD is associated with an increased risk of lymphoproliferative malignancies, especially B-NHL.[22,23] The most common type of SjD-associated lymphoma is parotid gland marginal zone lymphoma, followed by diffuse large B cell lymphoma and follicular lymphoma.[24] In addition, SjD combined with cryoglobulinemia, palpable purpura, low C4, lymphopenia, lymphadenopathy, persistent salivary gland enlargement, or cutaneous vasculitis is associated with a notably higher incidence of NHL, with cryoglobulinemia being the strongest independent lymphoma-associated factor.[25]

SjD patient cryoglobulins are represented by monoclonal IgM-κ and polyclonal IgG.[26] In our case, the cryoglobulins included monoclonal IgM-κ and polyclonal IgG-κ.[27] CLL/SLL has rarely been related to SjD or type II cryoglobulinemia, which is notable.[28] The clinical features and treatment methods of CLL/SLL patients with cryoglobulinemia described in the literature are summarized in Table 1. In CLL/SLL with cryoglobulinemia, the most common type is monoclonal IgG-κ, then monoclonal IgM-κ with or without poly IgG. The cryocrit is generally between 2% and 7% in type II and between 1% and 3% in type III disease.[27] We speculated that the presence of monoclonal IgG-κ and significantly high percentage of cryoglobulins in the patient were associated with CLL/SLL. Alternatively, this phenomenon was caused by SjD, an autoimmune disorder,[29] or both.

Compared with HCV-related cryoglobulinemia, the pathogeneses of other mixed cryoglobulinemia cases, such as those caused by autoimmune diseases, are still under investigation.[6] Overactivity or overgrowth of B cells may cause B cell clonal expansion, thus producing cryoglobulins.[8] Oncogene translocation to Ig loci or tumor suppressor gene inactivation in B

Table 1. Summary of reported cases with cryoglobulinemia and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

No.	Ref.	Year	No. of patients	Age/Sex	Type	Cryoglobulins	Related diseases	Treatment	Clinical consequence
1	[30]	1949	1	43/M	N/A	N/A	No	N/A	N/A
2	[31]	1979	2	62/M	I	Monoclonal IgG-κ	No	CS, CTX, and CLB	Deceased
				53/F	I	Monoclonal IgG-κ	No	CS and CTX	Deceased
3	[32]	1992	5	41/M	II/III	IgG and IgM	No	CLB and CS	Deceased
				60/M	II/III	IgG and IgM	No	N/A	Deceased
				74/M	II/III	IgG and IgA	No	MOPP	Deceased
				63/F	I	Monoclonal IgG-κ	No	CLB and CS	CR
				71/M	N/A	N/A	No	CLB and CS	CR
4	[33]	2002	1	52/M	I	Monoclonal IgG-κ	No	CLB	PR
5	[34]	2002	1	70/M	I	Monoclonal IgM-κ	No	N/A	N/A
6	[35]	2005	1	53/M	I	Monoclonal IgG-λ	No	Ituximab and fludarabine	PR
7	[36]	2007	1	58/F	I	Monoclonal IgG-κ	No	N/A	N/A
8	[37]	2010	1	53/M	III	Polyclonal IgG	No	RFC	CR
9	[38]	2011	1	70/M	N/A	N/A	Parvovirus infection	CS, CTX, rituximab, alemtuzumab, hemodialysis	Progression
10	[39]	2014	1	90/N/A	II	Monoclonal IgM and polyclonal IgG	No	CS	Deceased
11	[40]	2015	5	N/A	I	Both monoclonal IgG	No	N/A	N/A
12		2015	3	67/F	II	N/A	No	Not treated	Progression
	[41]			65/F	I	Monoclonal IgG-κ	No	CLB and rituximab	CR and relapse
				63/F	I	Monoclonal IgG-κ	No	CLB	CR and relapse
13	[42]	2016	1	60/F	I	Monoclonal IgG-κ	No	R-CVP and plasma exchange	Deceased
14	[43]	2018	1	60/M	I	Monoclonal IgM-λ	No	Iloprost, CS, plasma exchange, and rituximab	N/A
15	[44]	2018	1	63/M	I	Monoclonal IgG-κ	No	Not treated	N/A

(continued)

Table 1. Continued.

No.	Ref.	Year	No. of patients	Age/Sex	Type	Cryoglobulins	Related diseases	Treatment	Clinical consequence
16	[45]	2019	1	56/M	I	Monoclonal IgM-λ	HCV infection	CS, rituximab, bendamustine, plasma exchange, and CTX	CR
17	[4]	2019	1	69/M	I	Monoclonal IgM-κ	No	Plasma exchange, rituximab, CS, and ibrutinib	CR
18	[46]	2021	1	91/M	I	Monoclonal IgG-κ	hMPV infection	Not treated	N/A
19	[47]	2022	1	59/F	II	Monoclonal IgM-κ and polyclonal IgG	No	R-COP and ibrutinib	CR
20	This case		1	61/F	II	Monoclonal IgM-κ and polyclonal IgG-κ	Sjögren's disease	Ibrutinib, rituximab, and CS	PR

CS, corticosteroids; CTX, cyclophosphamide; CLB, chlorambucil; R-COP, rituximab, cyclophosphamide, verodoxin, and dexamethasone; CR, complete remission; hMPV, human metapneumovirus; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; RFC, ituximab, fludarabine, and cyclophosphamide; PR, partial remission; MOPP, nitrogen mustard, vincristine, procarbazine, and prednisone; N/A, not available.

cell dysregulation may also contribute to the initiation and development of B-NHL. Chronic antigenic stimulation has been suggested to lead to the activation of abnormal B cells in the salivary glands and appearance of auto-reactive B cell clones in SjD patients, with the emergence of cryoglobulins potentially accelerating this process.[48] Type II cryoglobulinemia has also been suggested to represent a transition phase between autoimmune disorders and malignancies.[49]

Treatment of the disease underlying the cryoglobulinemia, especially hematological malignancies, is the priority. Immunosuppressive therapy is the cornerstone of care for patients with severe manifestations, including the first-line immunosuppressant rituximab or cyclophosphamide and corticosteroids. However, more aggressive plasmapheresis is needed if life-threatening diseases develop, such as rapidly progressive glomerulonephritis, gastrointestinal ischemia, central nervous system involvement, and pulmonary hemorrhage.[50] Bruton's tyrosine kinase inhibitors are effective therapies for CLL/SLL. Barot et al. reported a case of refractory monoclonal gammopathy of undetermined significance related to type II cryoglobulinemia that was treated with ibrutinib, resulting in a complete clinical response and durable therapeutic effect that reversed kidney damage.[51] Here, we used ibrutinib, rituximab, and dexamethasone for a patient with complicated type II cryoglobulinemia, SLL/CLL, and pSjD, obtaining a good response. Remarkably, this treatment plan worked well for the patient, although the therapeutic mechanism of ibrutinib for cryoglobulinemia requires further investigation.

Acknowledgements

We thank our colleagues, Dr. Shuang Wang and Dr. Jinxing Wang, for their contributions to clinical and lab data collection. We are grateful to Dr. Hongcang Gu for reviewing the manuscript.

Author contributions

RB and XY wrote the main manuscript text. The figures were prepared by CZ and YT, while XW prepared Table 1. All authors contributed to the writing and final approval of the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics statement

This study was reviewed and approved by the Institutional Review Board (IRB) of the First Hospital of China Medical University (Approval No. 2023546). The patient provided written informed consent to participate in this study. The written informed consent is ready for review upon request.

Funding

This work was supported by the Natural Science Foundation of Liaoning Province (Grant No. 2022-YGJC-62) and the Project on the xinrui cancer support therapy (Grant No. cphcf-2022-102).

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References

1. Desbois AC, Cacoub P and Saadoun D. Cryoglobulinemia: An update in 2019. *Joint Bone Spine* 2019; 86: 707–713. 2019/02/08. DOI: 10.1016/j.jbspin.2019.01.016.
2. Ferri C. Mixed cryoglobulinemia. *Orphanet J Rare Dis* 2008; 3: 25. DOI: 10.1186/1750-1172-3-25.
3. Brouet JC, Clauvel JP, Danon F, et al. Biologic and clinical significance of cryoglobulins. A report of 86 cases. *Am J Med* 1974; 57: 775–788. DOI: 10.1016/0002-9343(74)90852-3.
4. Wright N, Voshtina E, George G, et al. Cryoglobulinemic vasculitis with interruption of ibrutinib therapy for chronic

lymphocytic leukemia (CLL). *Int J Hematol* 2019; 110: 751–755. 2019/09/09. DOI: 10.1007/s12185-019-02729-4.
5. Terrier B, Karras A, Kahn JE, et al. The spectrum of type I cryoglobulinemia vasculitis: new insights based on 64 cases. *Medicine (Baltimore)* 2013; 92: 61–68. 2013/02/23. DOI: 10.1097/MD.0b013e318288925c.
6. Roccatello D, Saadoun D, Ramos-Casals M, et al. Cryoglobulinaemia. *Nat Rev Dis Primers* 2018; 4: 11–08. 2018//04. DOI: 10.1038/s41572-018-0009-4.
7. Terrier B, Krastinova E, Marie I, et al. Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. *Blood* 2012; 119: 5996–6004. DOI: 10.1182/blood-2011-12-396028.
8. Takada S, Shimizu T, Hadano Y, et al. Cryoglobulinemia (review). *Mol Med Rep* 2012; 6: 3–8. 2012/04/10. DOI: 10.3892/mmr.2012.861.
9. Thorne I and Sutcliffe N. Sjogren's syndrome. *Br J Hosp Med* 2017; 78: 438–442. DOI: 10.12968/hmed.2017.78.8.438.
10. Goules AV, Argyropoulou OD, Pezoulas VC, et al. Primary Sjogren's Syndrome of Early and Late Onset: Distinct Clinical Phenotypes and Lymphoma Development. *Front Immunol* 2020; 11: 594096–17. 2020/11/ DOI: 10.3389/fimmu.2020.594096.
11. Sebastian A, Szachowicz A and Wiland P. Classification criteria for secondary Sjogren's syndrome. Current state of knowledge. *Reumatologia* 2019; 57: 277–280. 2019/12/18. DOI: 10.5114/reum.2019.89520.
12. Brito-Zeron P, Retamozo S, Flores-Chavez A, et al. Practical diagnostic tips for the Sjogren Clinic: pearls, myths and mistakes. *Clin Exp Rheumatol* 2022; 40: 2413–2427. DOI: 10.55563/clinexprheumatol/3bvq48.
13. Kelly AL, Nelson RJ, Sara R, et al. Sjogren Syndrome: New Insights in the Pathogenesis and Role of Nuclear Medicine. *J Clin Med* 2022; 11: 5227. DOI: 10.3390/jcm11175227.
14. Wierda WG, Byrd JC, Abramson JS, et al. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 4.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2020; 18: 185–217. 2020/02/06. DOI: 10.6004/jnccn.2020.0006.
15. Gale RP. Chronic lymphocytic leukemia in China. *Chin Med J (Engl)* 2022; 135: 883–886. 2021/10/13. DOI: 10.1097/CM9.0000000000001811.
16. Boggs DR, Chen SC, Zhang ZN, et al. Chronic lymphocytic leukemia in China. *American J Hematol* 1987; 25: 349–354. DOI: 10.1002/ajh.2830250317.
17. Gagnier JJ, Kienle G, Altman DG, CARE Group, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *J Med Case Rep* 2013; 7: 223. DOI: 10.1186/1752-1947-7-223.
18. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. *N Engl J Med* 2019; 381: 432–443. DOI: 10.1056/NEJMoa1817073.
19. De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 2012; 64: 843–853. 2011/12/08. DOI: 10.1002/art.34331.
20. Pakula AS, Garden JM and Roth SI. Mixed cryoglobulinemia and hepatitis C virus infection. *J Am Acad Dermatol* 1994; 30: 143. DOI: 10.1016/s0190-9622(08)81907-x.
21. Muchtar E, Magen H and Gertz MA. How I treat cryoglobulinemia. *Blood* 2017; 129: 289–298. 2016/11/02. DOI: 10.1182/blood-2016-09-719773.
22. Prochorec-Sobieszek M and Wagner T. Lymphoproliferative disorders in Sjogren's syndrome. *Otolaryngol Pol* 2005; 59: 559–564. 2005/11/09.
23. Zintzaras E, Voulgarelis M and Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med* 2005; 165: 2337–2344. DOI: 10.1001/archinte.165.20.2337.
24. Ekstrom Smedby K, Vajdic CM, Falster M, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood* 2008; 111: 4029–4038. DOI: 10.1182/blood-2007-10-119974.
25. Tzioufas AG, Boumba DS, Skopouli FN, et al. Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-

reactive idiotypes as predictive factors for the development of lymphoma in primary Sjogren's syndrome. *Arthritis Rheum* 1996; 39: 767–772. DOI: 10.1002/art.1780390508.
26. Ramos-Casals M, Cervera R, Yague J, et al. Cryoglobulinemia in primary Sjogren's syndrome: prevalence and clinical characteristics in a series of 115 patients. *Semin Arthritis Rheum* 1998; 28: 200–205. 1999/01/01. DOI: 10.1016/s0049-0172(98)80037-1.
27. Retamozo S, Gheitasi H, Quartuccio L, et al. Cryoglobulinaemic vasculitis at diagnosis predicts mortality in primary Sjogren syndrome: analysis of 515 patients. *Rheumatology (Oxford)* 2016; 55: 1443–1451. 2016/04/24. DOI: 10.1093/rheumatology/kew194.
28. Ho CH, Chiang YM, Chong LL, et al. Development of chronic lymphocytic leukaemia in a case of Sjogren's syndrome with systemic lupus erythematosus. *Scand J Haematol* 1985; 35: 246–248. DOI: 10.1111/j.1600-0609.1985.tb01582.x.
29. Musset L, Duarte F, Gaillard O, et al. Immunochemical characterization of monoclonal IgG containing mixed cryoglobulins. *Clin Immunol Immunopathol* 1994; 70: 166–170. DOI: 10.1006/clin.1994.1025.
30. Schwartz RB and Jager BV. Cryoglobulinemia and Raynaud's syndrome in a case of chronic lymphocytic leukemia. *Cancer* 1949; 2: 319–328. DOI: 10.1002/1097-0142(194903)2:2<319::aid-cncr2820020210>3.0.co;2-f.
31. Gilboa N, Durante D, Guggenheim S, et al. Immune deposit nephritis and single-component cryoglobulinemia associated with chronic lymphocytic leukemia. Evidence for a role of circulating IgG-anti-IgG immune complexes in the pathogenesis of the renal lesion. *Nephron* 1979; 24: 223–231. DOI: 10.1159/000181721.
32. Moulin B, Ronco PM, Mougenot B, et al. Glomerulonephritis in chronic lymphocytic leukemia and related B-cell lymphomas. *Kidney Int* 1992; 42: 127–135. DOI: 10.1038/ki.1992.270.
33. Galea HR, Bridoux F, Aldigier JC, et al. Molecular study of an IgG1kappa cryoglobulin yielding organized microtubular deposits and glomerulonephritis in the course of chronic lymphocytic leukaemia. *Clin Exp Immunol* 2002; 129: 113–118. DOI: 10.1046/j.1365-2249.2002.01896.x.
34. Gray Y, Bruno N, Badiavas EV, et al. Type I cryoglobulinemia presenting as hemorrhagic crusted leg ulcers. *Cutis* 2002; 70: 319–323.
35. Mantha S, Jacobs MI and Savage DG. Unusual leukemia presentations. Case 3. Type I IgGlambda cryoglobulinemia associated with chronic lymphocytic leukemia. *J Clin Oncol* 2005; 23: 5841–5843. DOI: 10.1200/JCO.2005.07.004.
36. Nasr SH, Snyder RW, Bhagat G, et al. Chronic lymphocytic leukemia and cryoglobulinemic glomerulonephritis. *Kidney Int* 2007; 71: 93. DOI: 10.1038/sj.ki.5001891.
37. Favre G, Courtellemont C, Callard P, et al. Membranoproliferative glomerulonephritis, chronic lymphocytic leukemia, and cryoglobulinemia. *Am J Kidney Dis* 2010; 55: 391–394. DOI: 10.1053/j.ajkd.2009.06.021.
38. Purhonen AK, Mikkola M, Karjalainen L, et al. Cryoglobulinaemia and rapidly deteriorating renal function in chronic lymphocytic leukaemia. *Nephrol Dial Transplant* 2011; 26: 1101–1103. DOI: 10.1093/ndt/gfq701.
39. Gracia-Cazana T, Pastushenko I, Morales-Moya AL, et al. Increased complement levels in cryoglobulinemia as a marker of chronic lymphocytic leukemia progression in a nonagenarian patient. *Rev Esp Geriatr Gerontol* 2014; 49: 194–195. DOI: 10.1016/j.regg.2014.01.005.
40. Harel S, Mohr M, Jahn I, et al. Clinico-biological characteristics and treatment of type I monoclonal cryoglobulinaemia: a study of 64 cases. *Br J Haematol* 2015; 168: 671–678. DOI: 10.1111/bjh.13196.
41. Poitou-Verkinder AL, Francois A, Drieux F, et al. The spectrum of kidney pathology in B-cell chronic lymphocytic leukemia / small lymphocytic lymphoma: a 25-year multicenter experience. *PLoS One* 2015; 10: e0119156. DOI: 10.1371/journal.pone.0119156.
42. Arora S, Levitan D, Regmi N, et al. Cryoglobulinemia in a patient with chronic lymphocytic leukemia - A case report and review of literature of renal involvement in CLL. *Blood Cells Mol Dis* 2016; 60: 7–11. DOI: 10.1016/j.bcmd.2016.05.009.

43. McCay J and Scott J. Type 1 cryoglobulinaemia presenting as digital ischaemia in chronic lymphocytic leukaemia. *BMJ Case Rep* 2018; 2018. DOI: 10.1136/bcr-2018-224488.
44. Tang C, Kumar P and Mackinlay N. Cryoglobulin crystals in a patient with chronic lymphocytic leukaemia. *Pathology* 2018; 50: 670–671. DOI: 10.1016/j.pathol.2018.03.012.
45. Raj N. Type 1 Immunoglobulin M Cryoglobulinemic Vasculitis in a Patient with Chronic Lymphocytic Leukemia and a History of Hepatitis C Virus: Is There a Link? *Cureus* 2019; 11: e4729. DOI: 10.7759/cureus.4729.
46. Barben J, Putot A, Mihai AM, et al. The Pivotal Role of Viruses in the Pathogeny of Chronic Lymphocytic Leukemia: Monoclonal (Type 1) IgG K Cryoglobulinemia and Chronic Lymphocytic Leukemia Diagnosis in the Course of a Human Metapneumovirus Infection. *Viruses* 2021; 13. DOI: 10.3390/v13010115.
47. Ma T, Wang H, Su T, et al. Case Report: Chronic Lymphocytic Leukemia With Recurrent Complement-Mediated Thrombotic Microangiopathy and C3 Glomerulonephritis. *Front Med (Lausanne)* 2022; 9: 813439. DOI: 10.3389/fmed.2022.813439.
48. Stergiou IE, Poulaki A and Voulgarelis M. Pathogenetic Mechanisms Implicated in Sjogren's Syndrome Lymphomagenesis: A Review of the Literature. *JCM* 2020; 9: 3794. 2020/12/02. DOI: 10.3390/jcm9123794.
49. Anand A, Krishna GG, Sibley RK, et al. Sjogren Syndrome and Cryoglobulinemic Glomerulonephritis. *Am J Kidney Dis* 2015; 66: 532–535. 2015/02/11. DOI: 10.1053/j.ajkd.2014.11.032.
50. Ringheim GE, Wampole M and Oberoi K. Tyrosine Kinase (BTK) Inhibitors and Autoimmune Diseases: Making Sense of BTK Inhibitor Specificity Profiles and Recent Clinical Trial Successes and Failures. *Front Immunol* 2021; 12: 662223. DOI: 10.3389/fimmu.2021.662223.
51. Barot SV, Lee SS, Patel BJ, et al. Ibrutinib is Effective in Refractory Type II Cryoglobulinemia. *Clin Lymphoma Myeloma Leuk* 2019; 19: e629–e632. 2019/10/06. DOI: 10.1016/j.clml.2019.07.442.