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Case Report

Low-grade B cell lymphoma in the perirenal space of the left kidney associated with high titer cold agglutinin disease

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Abstract: Cold agglutinin disease (CAD) is a subgroup of autoimmune hemolytic anemia caused by monoclonal cold agglutinins produced by clonally expanded B lymphocytes. In primary CAD, lymphoproliferative bone marrow disorder is noted, while as one of the secondary cold agglutinin syndromes (CAS), the initial manifestation of CAD is followed by development of lymphoma. Here, we report a case of low-grade B cell lymphoma developed 3 months after an initial CAD diagnosis. The patient had an extremely high serum cold agglutinin titer (1:16,384) and slightly elevated serum IgM (452 mg/dL; reference, 31-200) with positive monoclonal IgM-kappa chain. After diagnosis of lymphoma-associated CAS, he was managed successfully with six cycles of a BR (bendamustine and rituximab) regimen. Cold agglutinin titers fell rapidly to 1:2048 at 5 months and to 1:512 at 10 months after chemotherapy, and the patient has been in a complete remission for 34 months.

Keywords: Cold agglutinin disease, low-grade lymphoma, perirenal lymphoma, IgM-kappa

Introduction

Cold agglutinin disease (CAD) is a subgroup of autoimmune hemolytic anemia triggered by cold reactive immunoglobulins against red blood cells (RBC) surface antigens in the pathogenesis. CAD can be divided into two categories: primary CAD and secondary cold agglutinin syndrome (CAS) [1]. The major cold autoantibody in CAD/CAS is directed against the I antigen of RBC and can cause peripheral RBC agglutination and acrocyanosis, resulting in hemolysis via activation of the classical complement cascade [2]. As symptoms/signs, patients present with hemolytic anemia (increased lactate dehydrogenase, bilirubin, and reticulocytes, along with decreased haptoglobin) and/or acrocyanosis, which is occasionally associated with peripheral gangrene following exposure to cold. Primary CAD is a clonal B cell disorder characterized by clonally expanded B cells in the bone marrow [3, 4]. By contrast, CAS shows a similar picture of cold-hemolytic anemia, but occurs secondary to hematological malignancies (lymphomas, leukemias) [5-13] or infectious diseases (particularly *Mycoplasma pneumoniae* and Epstein-Barr virus infections) [14, 15]. In the majority of patients with primary CAD, monoclonal IgM-kappa antibodies are noted while lymphoma-associated CAS shows IgM-lambda type [3, 5]. In addition, some of primary CAD and lymphoma-associated CAS may show chromosomal abnormalities [16-18]. In lymphoma-associated CAS, symptoms/signs of CAD are noted as initial manifestation of disease before lymphoma can be identified. In terms of treatment/outcome of CAD/CAS, for primary CAD, B-cell directed therapies against the clonal B-lymphocytes have been employed including anti-CD20 antibody rituximab, as well as complement modulation with use of a novel agent sutimlimab [19, 20]. On the other hand, for lymphoma-associated CAS, anti-lymphoma chemotherapy for specific types is required. In terms of outcome of CAD/CAS, in the past, sur-

vival time was shorter in lymphoma-associated CAS than primary CAD [5]. Here, we report a case of low-grade B cell lymphoma with IgM-kappa chain diagnosed during the search for the cause(s) of CAD in an adult patient with cold-related circulatory symptoms showing a significantly high cold agglutinin titer.

Case report

The patient was a 59-year-old male who received percutaneous catheter myocardial ablation for the treatment of persistent atrial fibrillation. During this procedure, a blood smear revealed Rouleaux formation. His cold agglutinin titer was extremely high at 1:16,384 (reference: <1:64). It remained unknown for how long the patient had CAD; however, he developed cold-related circulatory symptoms (such as Raynaud phenomenon) at least 6 months earlier. On referral to our hematology clinic, examination revealed that he was 176 cm tall and weighed 82.9 kg. His blood pressure was 128/81 mmHg and his heart rate was 93/min. He was neither anemic nor icteric, with normal hepatic function and slightly exacerbated renal function. Laboratory data were as follows: white blood cell count (WBC), 6,700/μL (no abnormal cells on the smear); Hb, 14.5 g/dL; mean corpuscular volume (MCV), 107 fL; platelet count, 235 K/μL; reticulocyte count, 1.7%; haptoglobin, 95 mg/dL; C-reactive protein, 0.30 mg/dL; aspartate aminotransferase (AST), 25 U/L; alanine aminotransferase (ALT), 23 U/L; lactate dehydrogenase (LDH), 338 U/L; total bilirubin, 0.51 mg/dL; total protein, 7.6 g/dL; albumin, 4.2 g/dL; blood urea nitrogen, 15.3 mg/dL; creatinine, 1.23 mg/dL; uric acid, 6.8 mg/dL. Thus, hemolytic anemia was not significant. Immunological studies revealed the following: serum IgG, 1,366 (reference value; 820-1740) mg/dL; IgA, 237 (90-400) mg/dL; and IgM, 452 (31-200) mg/dL with positive monoclonal IgM-kappa protein. Complement was normal. He was negative for anti-nuclear-antibody and other autoimmune antibody levels were within normal. Serum soluble IL-2 receptor (sIL-2R) was elevated at 1,831 (122-496) U/L, with a high free kappa/lambda ratio of 2.18 (0.26-1.65). There was no evidence of active Epstein-Barr virus or cytomegalovirus infection. Since he had compensated hemolysis [1], he was put on non-pharmacological management with thermal protection alone. A bone marrow aspirate showed a few (<5% of nuclear cell counts) moderately large lymphoblastoid cells with a high N/C ratio, which characterization was not possible. There were no clusters of lymphoblastoid cells as those in lymphoplasmacytic lymphoma (data not shown) and the karyotype of the bone marrow was normal, which ruled out primary CAD. We thus searched for cause(s) of CAD in this case. Three months later, a contrast-enhanced computed tomography (CT) scan of the abdomen revealed a soft tissue mass at the perirenal space of the left kidney, which was associated with swelling of neighboring lymph nodes (**Figure 1A**). A repeat assay of cold agglutinin at this point revealed the same high (1:16,384) titer. A CT-guided needle (18-gauge TEMNO) biopsy of this region (**Figure 1B**) was performed, which obtained a lympho-proliferative tissue (**Figure 1C**). Histopathology showed lymphoma tissue (**Figure 2A**), immunostaining analyses of which revealed tumor cells were positive for CD20, BCL-2, Ki-67 (approximately 30%), and smIg-kappa (**Figure 2B**, **2C**, **2E**, **2F**), but negative for BCL-6 (**Figure 2D**), smIg-lambda (figure not shown) and BCL2-IgH fusion by fluorescence in situ hybridization method. Regarding the clonality of lymphoma cells, PCR showed rearrangement of the IgH gene (data not shown). However, no karyotype was obtained from the lymphoma tissue. The above findings led to a diagnosis of low-grade B cell lymphoma. Eventually, the patient was diagnosed as lymphoma-associated CAS. Regarding the therapeutic choice, though splenic marginal lymphomas among low-grade B cell lymphomas were successfully managed with rituximab alone [10, 11], we selected a BR (bendamustine and rituximab) regimen considering the unusual location of lymphoma and based on the article in which this regimen was effective even for the refractory low- grade B cell lymphoma [21]. The patient was managed successfully with six cycles of a BR regimen, with grade 1/2 of adverse events (CTCAE Version 5.0). After chemotherapy, along with decline of sIL-2R, cold agglutinin titers also fell rapidly to 1:2048 at 5 months and to 1:512 at 10 months. The patient remains in a complete remission at 34 months from the diagnosis of lymphoma without any symptoms/signs of CAD.

Discussion

Differential diagnosis between primary CAD and secondary CAS (infectious disease or leu-

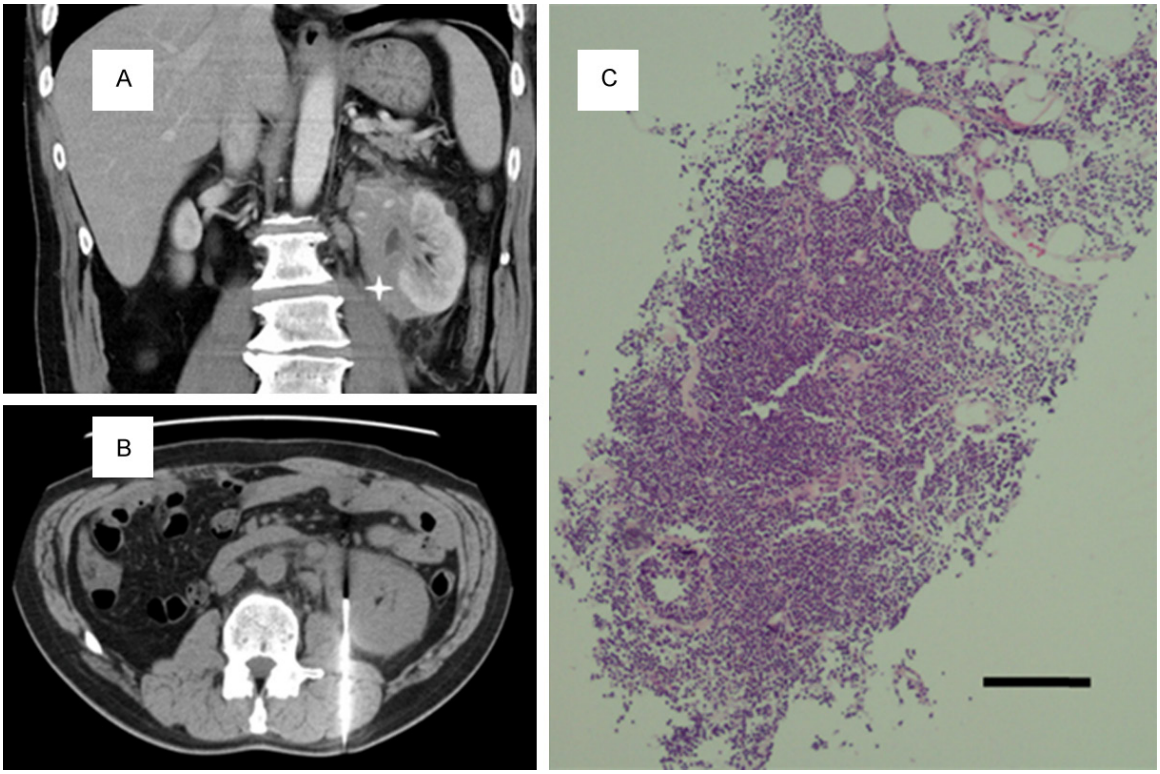

Figure 1. Contrast-enhanced CT image of the abdomen showing a soft tissue mass in the perirenal space of left kidney (A. Coronal view; asterisk). The actual CT-guided biopsy procedure is shown in axial view (B). Biopsied specimen is shown in (C), of which histopathology shows a lymphomatous lesion with lymphocyte aggregates stained with H&E (C. Original magnification; ×200). Scale bar indicates 250 μm.

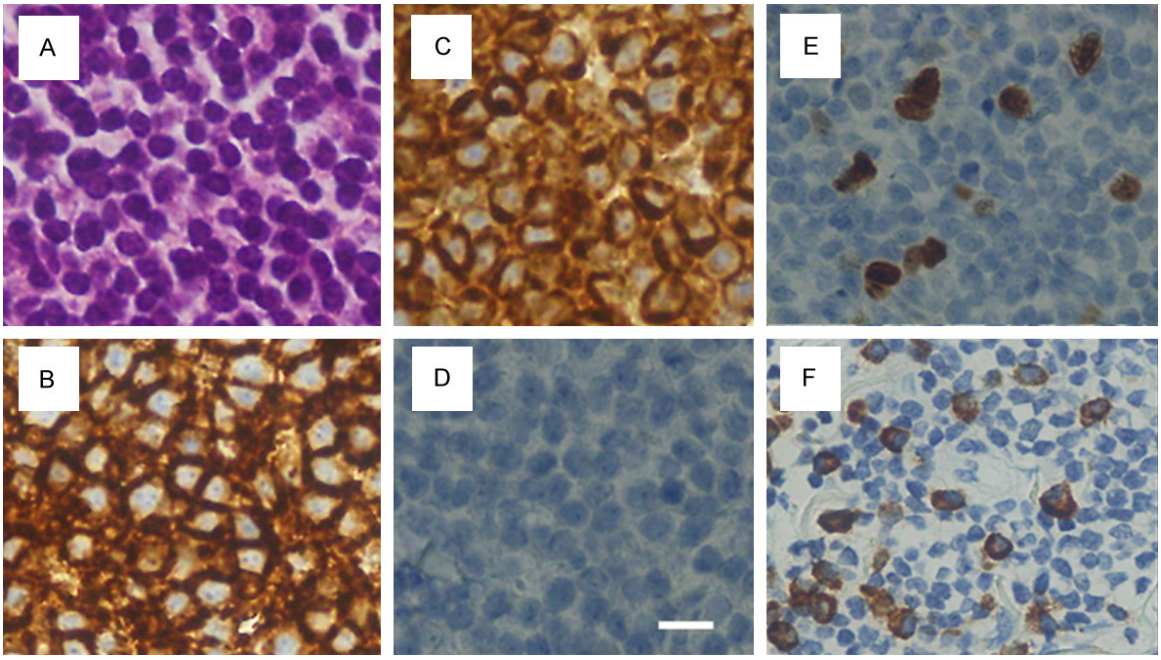

Figure 2. Lymphoma cells were small to medium-sized (A. H&E stain original magnification ×400), with immunostaining positive for CD20 (B. ×400), and for BCL-2 (C. ×400) while negative for BCL-6 (D. ×400). Immunostaining for Ki-67 was approximately 30% (E. ×400) and positive for smIg-kappa (F. ×400), but negative for smIg-lambda (data not shown). Scale bar indicates 20 μm.

kemia/lymphoma) is essential but often difficult in patients with CAD. In lymphoma-associated CAS, lymphoma may become apparent after the initial CAD presentation, suggesting occult lymphoma as an etiology of CAD. When our patient was diagnosed as CAD, he had cold-related circulatory symptoms with a high cold agglutinin titer (1:16,384), but without severe anemia or jaundice, suggesting compensated hemolysis [1]. Three months later, the patient was identified to have lymphoma at the left perirenal area resulting in the diagnosis of lymphoma-associated CAS.

In terms of CAD/CAS, among the 78 patients reported by Crisp et al. [5], 31 (39.7%) had lymphoma, of which 71% of cold agglutinins had lambda light chains, while 29% had kappa light chains. As lymphoma types, low-grade B cell type [10, 11], small lymphocytic lymphoma [12], hepatosplenic alpha/beta T-cell lymphoma [7], large cell lymphoma [17], or diffuse large B cell lymphoma [6, 8, 9] were previously described. In addition, reports on abnormal karyotypes in lymphoma-associated CAS have been made, such as trisomy 3q or t(8;22) [16, 17]. Michaux et al. underlined the importance of the long arm of chromosome 3 in the pathogenesis of primary CAD as well as lymphoma-associated CAS [6]. Our case was diagnosed as low-grade B cell lymphoma with kappa light chain with unidentified karyotype. Lastly, the lymphoma was located at the perirenal space around the left kidney, a region in which only 3-10% of lymphomas develop [22, 23]; in our case, the tissue in this region was successfully obtained via CT-guided percutaneous needle biopsy, resulting in the final diagnosis.

Management of CAD is similar for primary CAD and CAS. In general, CAD therapy comprises thermal protection, complement modulation by B cell-directed therapies [1-3, 19] and by stimulimab [20]. As pathogenesis of CAD, the IgM antigen complex is a potent trigger of the classic complement pathway by binding to the C1 complement complex and activating C1s (a C1 complex serine protease). Identification of this pathogenetic mechanism has led to use of stimulimab in patients with CAD. This treatment significantly alleviates clinical symptoms [20]. However, though it prevents hemolysis, it does not prevent acrocyanosis, which is not related to complement activation. B cell-directed therapies, such as rituximab alone, rituximab plus fludarabine, BR regimen [19] or ibrutinib [24] could be employed for management of CAD/CAS. When our patient was referred to us, he was successfully managed with thermal protection alone and we searched for any underlying disease(s) causing CAD symptoms/signs. Eventually, the patient was diagnosed as lymphoma-associated CAS. In the management of lymphoma-associated CAS, various regimens have been employed for specific subtypes of lymphoma; rituximab alone [10, 11] or a BR regimen [21] for low grade B cell lymphoma, rituximab-CHOP (cyclophosphamide, Adriamycin, vincristine, prednisolone) for cases of DLBCL [6, 8, 9], a BR regimen for small lymphocytic lymphoma [12], CHOP for hepatosplenic alpha/beta T cell lymphoma [7], rituximab-CVP (cyclophosphamide, vincristine, prednisolone) for large cell lymphoma [17] and even autologous hematopoietic stem cell transplantation was used for aggressive lymphoma [25]. Our patient was successfully treated with 6 cycles of a BR regimen. After chemotherapy, the patient remains in remission for 34 months at this writing, and is doing well, with rapidly declined cold agglutinin titers (1:512) without any symptoms/signs of CAD.

Conclusions

In summary, whenever physicians are presented with a patient with chronic CAD and high cold agglutinin titers, they should search for cause(s) such as lymphoma within/outside the bone marrow. If cases of lymphoma-associated CAS are appropriately treated with chemotherapy, symptoms/signs of CAD disappear and cold agglutinin titers decline rapidly.

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The patient provided written informed consent to publish this case study (including publication of images).

Disclosure of conflict of interest

None.

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