Clinical Case Reports

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CASE REPORT

Acrocyanosis revealing chronic lymphocytic leukemia

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Funding Information
No sources of funding were declared for this study.

Received: 6 February 2015; Revised: 23 December 2015; Accepted: 7 February 2016

Clinical Case Reports **2016; 4(4): 404–405**

doi: 10.1002/ccr3.529

Key Clinical Message

Cold agglutinin disease arising in the context of chronic lymphocytic leukemia can misdiagnose a warm autoimmune hemolytic anemia.

Keywords

Autoimmune hemolytic anemia, chronic lymphocytic leukemia, cold agglutinin disease, peripheral blood film.

Report

A 61-year-old man was referred in December (cold winter season in the east area from France) for assessment of fatigue and a bronchitis that had been dragging on for 3 weeks. The physical examination revealed acrocyanosis but neither lymphadenopathy nor hepatosplenomegaly. Laboratory findings were: hemoglobin 7.9 g/dL, mean cell volume 91 fL, leukocytes 17.770 × 10^9/L, platelets 546 × 10^9/L.

The blood differential demonstrated 57% (10.129 × 10^9/L) lymphoïd cells (21% of which showing nuclear clefts; Fig. 1B). The immunophenotype pointed out monoclonal B-cells expressing dimly surface IgM κ light chains. The lymphoid cells co-expressed CD19 and CD5 markers, and were CD20 (weak), CD22/CD79b (weak), CD23, CD24, CD43, CD38, CD200 (high), and FMC7 (weak) positive. CD10, CD11c, CD25, and CD103 were negative. ZAP-70 detection was not performed. Serum electrophoresis and immunofixation showed hypogammaglobulinemia and a M-component at 5.8 g/L. The karyotype was 46, XY, +12. Molecular analysis of immunoglobulin variable heavy chains (IGVH) found nonmutated B-cells. The retained diagnosis was chronic lymphocytic leukemia (CLL), Matutes score 4 [1], with trisomy 12.

Unexpectedly, the peripheral blood smear observation also showed red blood cells with moderate anisocytosis, some spherocytes, polychromatophilia, and mainly, numerous clumped erythrocytes (Fig. 1A). Investigations confirmed a mild hemolytic anemia (direct bilirubin 41 μmol/L, LacticoDesHydrogenase 460 U/L, haptoglobin below the level of detection). The direct antiglobulin test (DAT) was positive for C3d only (negative for anti-IgG). A high titer of 4.096 at 4°C agglutinin with anti-I specificity was affirmed. The thermal amplitude testing at 30°C (with and without albumine) was positive. A cold agglutinin disease (CAD) was evoked.

No blood cell transfusion was performed. The patient responded poorly to the prevention of cold exposure, but improved after the administration of high-dose prednisolone (80 mg daily). The treatment was tapered after 3 weeks, when partial response was achieved (improvement of clinical symptoms, Hb 10.5 g/dL, IgM 3.6 g/L). Unfortunately, the patient was then lost of sight.

A clinical condition not commonly seen in CLL is reported here. Autoimmune disorders may precede or follow the diagnosis of CLL [2]. In our case, the cold agglutinin and the increased lymphocytes were discovered at the time of the diagnosis. The association of CAD and CLL is a scarce finding. The autoantigens usually belongs to the I/i system [3, 4]. Since the B cells of our case were not somatically mutated, one might speculate that the cold agglutinin might not be a paraprotein synthesized by the neoplastic clone, but an other IgM Kappa which is

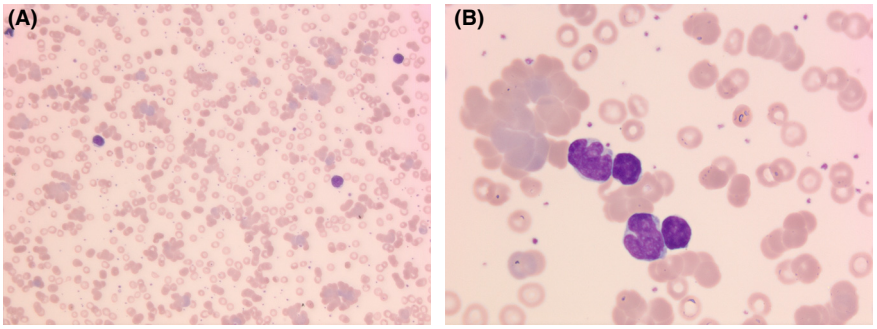

Figure 1. Clumped erythrocytes (A) along with abnormal lymphoïd cells (B). Peripheral blood film, MGG ×200 and ×500.

not sharing the same idiotype as expressed on the clonal B-cells. Nevertheless, IgM antibodies can be produced without somatic IGVH hypermutation and our speculation remains unproved. Although patients with CAD typically have cold agglutinin with high titer at 4°C, not all patients with high titer cold agglutinin have CAD and the thermal amplitude of the cold agglutinin is a critical result. The cold antibody may be pathogenic if it reacts at 30°C or above, and a CAD can then be affirmed [5]. Steroids are not usually effective in CAD and successful avoidance of cold is the first-line therapy. Though unspecific, our patient's response to treatment (poor with prevention of cold exposure but partial response after steroids) could had better matched with the diagnosis of a warm autoimmune hemolytic anemia (AIHA) [6]. But, in that hypothesis, the only DAT positivitv for C3d would had unfitted the picture of a warm antibody AIHA. A super Coombs investigation could have helped for classification but had not been performed in our case. Only a minority of CLL patients harboring a positive DAT test will develop AIHA [7]. Though a few patients with warm AIHA have been found to present with positive DATs with anti-C3d only, the CAD diagnosis was affirmed in our case by the thermal amplitude of the antibody.

Conflict of Interest

None declared.

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