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CASE REPORT

Refractory cold agglutinin-immunohaemolytic anaemia associated to marginal zone lymphoma responding to rituximab

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Cold agglutinin immunohaemolytic anaemia (CAIA) responds poorly to standard treatment. We report a case of marginal zone lymphoma complicated by CAIA that responded to rituximab after failing to respond to corticosteroids and chlorambucil.
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(CAIA) is far less common than warm-antibody immunohaemolytic anaemia and may complicate the course of B-cell lymphomas, in which CA is supposedly produced by the malignant clone itself. In other instances, CA disease (CAD) may precede the development of lymphoma. Immunologic abnormalities in marginal zone lymphoma include autoimmune haemolytic anaemia,[1] immune thrombocytopenia, IgM monoclonal gammapathy,[1] and CAs.[2] Treatment of CAD is unsatisfactory in many instances. Corticosteroids, chorambucil, cyclophosphamide, and splenectomy are usually ineffective. Few reports indicate the effectiveness of rituximab in idiopathic[3,4] and lymphoma-associated CAD.[5–8]

Case report

A 66-year-old woman was admited for severe anaemia on March 2001. Past history revealed insulin-dependent diabetes since she was 46 years. Autoimmune haemolytic anaemia was detected in another hospital in May 1999 (Hb 90 g/l, haptoglobins 8 mg/dl (normal 30–200 mg/dl), positive direct antiglobulin test, and autoagglutination of RBC). A nodular lung lesion was noted in July 1999 but two fine-needle aspirations were nondiagnostic. In December 2000, a CT scan revealed a 3 cm mass beside the upper pole of the right kidney; lymphadenopathies were not seen. A right nefrectomy was carried out and morphologic, immunohistochemical, and molecular studies were diagnostic of marginal zone lymphoma, nodal type, with clonal heavy chain rearrangement; hilar lymph nodes were negative. When we saw the patient for the first time her blood counts were: RBC 2.0×10^{12}/l, Hb 68 g/l, haematocrit 0.18 l/l, MCV 88 fl, normal platelet and WBC counts and differential. A diagnosis of CA autoimmune haemolytic anaemia was made on the bases of intense reticulocytosis (140.1×10^9/l), haptoglobins <20 mg/100 ml (normal 30–200 mg/100 ml), total bilirubin 21 μmol/l (normal $\leqslant 18$ μmol/l), LDH 18.1 μkat/l (normal $\leqslant 3.5$ μkat/l), positive direct antiglobulin test (anti-C_3 positive, anti-C_4, -IgG and -IgM negative), and CA (titre 1 : 10, 240; thermal range 4–37°C; specificity anti-I). Blood samples were warmed up to 37°C to perform complete blood counts; the serological techniques used for the demonstration, specificity, and titration of CAs were performed as previously described.[9] A thin $\mu\kappa$ monoclonal serum component was evident. Immunofixation of urine showed a κ monoclonal chain. Quantitative serum immunoglobulins were IgG 904 mg/100 ml, IgA 119 mg/100 ml, and IgM 246 mg/100 ml (normal ranges: IgG 690–1400, IgA 74–370, IgM 40–240). Cryoimmunoglobulins were negative. Bone marrow smear showed erythroid hyperplasia and 11% lymphocytes; the immunophenotype showed positivity for CD19, CD20, CD38, CD79b, and κ light chains, and negativity for CD5, CD10, and λ light chains. Bone marrow biopsy showed discrete lymphoid infiltration in an interstitial pattern. A final diagnosis of marginal zone lymphoma, nodal type, stage IV (bone marrow involvement) was made.

On March 2001, the patient started treatment with prednisone 1 mg/kg and folinic acid, and haemolysis decreased with an increase in Hb up to 89 g/l, lowering

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of the reticulocyte count to 51.3×10^9/l, and normalisation of haptoglobins, bilirubin, and LDH by the 13th day of therapy. Chlorambucil 5 mg/day was started and prednisone tapered, but severe anaemia (58 g/l) supervened while receiving prednisone 40 mg/day and chlorambucil 5 mg/day by day 25 of treatment. On 5 April, 2001 the patient received transfusion of two red cell units throughout a line warmer without incidences. The following day, she received the first infusion of rituximab (375 mg/kg/week/4 weeks). No other immunosuppressive or cytostatic therapy was given from that moment. The response was slow but steady and 6 months after receiving rituximab, the haemolytic picture had ceased (Hb 122 g/l, Hct 38.1 l/l, reticulocytes 68×10^9/l, haptoglobins 236 mg/100 ml, LDH 3 μkat/l). This response was still evident 17 months after therapy, although the direct antiglobulin test and serum immunofixation (μ/κ) remained positive.

Discussion

Several immunological abnormalities have been described in marginal zone lymphoma. Autoimmune haemolytic anaemia is seen in up to 11% of patients and monoclonal gammopathy, mainly of IgM type, in 15% of the cases.[1] CA is very rare in marginal zone lymphoma; it has been described as complicating the course of two patients before the availability of rituximab;[2] one of these patients also had an IgM λ paraprotein and her haemolysis disappeared after spleen removal. Rituximab has been successfully used in few cases of CA autoimmune haemolytic anaemia, mostly reported as letters or abstracts. Four out of six patients responded (one complete, three partial responses) in a small Norweigan series of clonal, CD20+ immunoproliferative disorders indluding haemolytic CAD and IgM paraprotein.[6] Another patient had a lasting response after anti-CD20 treatment for her CA autoimmune haemolytic anaemia associated to low-grade bone marrow lymphoma with monoclonal serum IgM.[8] Rituximab has also shown efficacy in idiopathic CAD.[3,4] The present case adds more information about the safety and efficacy of rituximab in the management of refractory severe CA autoimmune haemolytic anaemia associated with low-grade lymphoma. Of note, this diabetic patient was able to get free of prednisone once rituximab was started; the cessation of haemolysis is durable but the response incomplete since 17 months after rituximab therapy the direct antiglobulin test remains positive and a small μ/κ monoclonal immunoglobulin is still evident only by immunofixation. The patient has not received further therapy and there is no evidence of progression of the lymphoma.

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