Waldenström's macroglobulinaemia complicated by pure red cell aplasia: a case report

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Introduction

Waldenström's macroglobulinemia (WM), a lymphoplasmacytic lymphoma and immunoglobulin M (IgM) monoclonal gammopathy, is a subtype of plasma cell disorder, an indolent mature B-cell neoplasm associated with bone marrow involvement[1]. Pure red cell aplasia (PRCA) is characterised by the near complete absence of erythroid precursors in the bone marrow but normal megakaryocytes and granulocytes[2]. About 80% cases of WM are complicated by normocytic normochromic anaemia, while PRCA, an unusual cause of anaemia in patients with chronic lymphoproliferative disorders, is extremely rare in WM. So far, very few cases of concomitant WM and PRCA have been reported. Here we describe a new patient with acquired PRCA and concurrent WM with the purpose of providing further insight into this rare association.

Case report

On June 20, 2012, a 59-year old man, who was 172 cm tall and weighed 67 kg, was admitted to our hospital because of progressive fatigue, dizziness, palpitations, and shortness of breath for over a year, which had worsened in the preceding 20 days. He also complained of a poor appetite, a general deterioration in health and a significant weight loss of more than 5 kg. His past medical history was unremarkable. On examination, the patient had facial pallor and pretibial pitting oedema on both legs. Physical examination revealed moderate splenomegaly (4 cm below the left costal margin), and a swollen lymph node under the left armpit (diameter 4 cm). Other superficial lymph nodes and the liver were not palpable.

The complete blood count was as follows: red blood cells, 1.59×10^{12}/L; haemoglobin, 43 g/L; mean cell volume, 85.5 fL; mean cell haemoglobin concentration, 316 g/L; white blood cells, 10.1×10^{9}/L; platelets, 223×10^{9}/L, and reticulocyte count, 0.11%, thus showing profound anaemia. Serum iron and ferritin concentrations were high, being 30.8 μmol/L and 914.0 μg/L, respectively. The direct antiglobulin test was positive, showing *in vivo* coating of red blood cells with IgG antibodies and complement (C3d). Folic acid and vitamin B12 levels were within the normal limits. Serology was negative for viral infections (hepatitis B virus, hepatitis C virus, Epstein Barr virus, cytomegalovirus and parvovirus B19). No immunological abnormalities suggestive of an underlying systemic autoimmune disease were detected. A peripheral blood smear revealed normocytic normochromic anaemia. Bone marrow aspiration and biopsy were performed, revealing severe erythroid hypoplasia with 0.2% erythroblasts but normal myeloid and megakaryocytic cell lineages. The myeloid: erythroid ratio was 139:1 (Figure 1A). As a result, an initial diagnosis of PRCA was made, relying mainly on the absence of erythroblasts from the bone marrow combined with reticulocytopenia and anaemia.

Blood chemistry tests showed a lactate dehydrogenase concentration of 188 U/L, total protein of 95.3 g/L, albumin of 30.4 g/ L, globulin 64.9 g/L and normal liver and kidney function tests. The serum levels of IgG, C3, and C4 were normal (IgG, 10.2 g/L [normal 7.0-16.0 g/L], C3, 1.12 g/L [normal 0.9-1.8 g/L], C4, 0.258 g/L [normal 0.1-0.4 g/L]), but IgA was slightly decreased (0.58 g/L [normal 0.7-4 g/L]) while IgM was significantly elevated (43.6 g/L [normal 0.4-2.3 g/L]). Biological analyses showed high levels of C-reactive protein (60.5 mg/L) and β2-microglobulin (6.33 mg/L) together with a fast erythrocyte sedimentation rate (140 mm/hour), which are findings suggestive of an inflammatory condition. Levels of kappa and lambda light chains in blood were 5.56 g/L (normal 1.7-3.7 g/L) and 0.71 g/L (normal 0.9-2.1 g/L), respectively. A flow cytometric analysis of peripheral blood lymphocyte subsets showed CD3

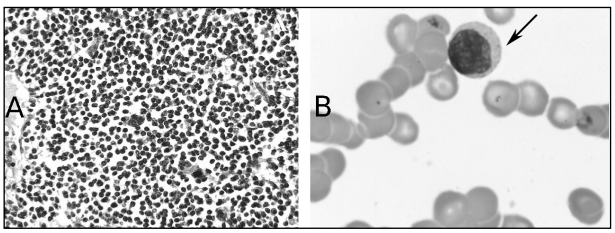

Figure 1 - A) Bone marrow biopsy showed marked erythroid hypoplasia with haemosiderin deposition (haematoxylin-eosin stain, 400X). B) The red blood cells were arranged in rouleaux formation. Identification of plasmacytoid cells (haematoxylin-eosin stain, 1,000X).

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on 85.9% of cells, CD4 on 13.9%, CD8 on 70.2%, and CD19 on 0.3%. Immunofixation electrophoresis showed IgM-kappa gammopathy (Figure 2). MYD88 L265P mutation was not found by sequencing of the polymerase chain reaction product. Bence-Jones proteins were not found in urinalysis, while the 24-hour proteinuria was 0.61 g/L. The levels of kappa and lambda light chains in the urine were 297 mg/L (normal 0-7.1 mg/L) and 7.48 mg/L (normal 0-3.9 mg/L), respectively. Positron emission tomography - computed tomography revealed bilateral multiple enlarged lymph nodes in the neck, jaw, clavicular area, axilla, mediastinum, retroperitoneal region around the abdominal aortic artery, pelvic wall, and the inguinal area, with a maximum standardised uptake value (SUV) of 5.2.

The red blood cells in a smear of sternal bone marrow formed rouleaux. The smear also showed diffuse infiltration of small lymphoid cells and plasmacytoid differentiation, with lymphocytes accounting for 53.6% of the cells (Figure 1B). Flow cytometric immunophenotypic studies performed on the same bone marrow aspirate detected 20.2% lymphocytes, expressing CD3 on 77.6%, CD4 on 13%, CD8 on 62.1%, CD5 on 73.3% and CD7 on 73.6%, and CD2 on 81.8%; the CD4+/CD8+ ratio was abnormal and there was a deficiency of CD4 lymphocytes. The cells were negative for CD10, and no abnormalities of TCRvβ were found. Immunohistochemical examination of trephine biopsies of bone marrow showed that the small lymphocytes and the plasmacytoid lymphocytes were CD20+++, CD79a++++, CD10–, and plasma cells were CD38+, CD138+. Cytogenetic analysis revealed a normal karyotype of 46,XY [20]. The patient was positive for the IgH rearrangement (Figure 3). Thus, based on symptoms, signs, laboratory findings, flow cytometric analysis and bone marrow examination, we diagnosed this case as WM complicated by PRCA.

The patient was treated with one cycle of fludarabine and cyclophosphamide chemotherapy. Meanwhile, recombinant human erythropoietin was administered subcutaneously at a dose of 10,000 IU every other day.

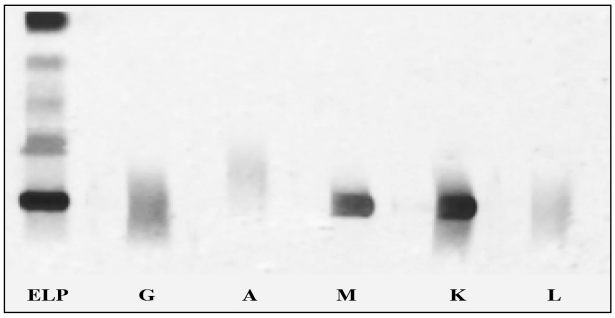

Figure 2 - Immunofixation electrophoresis showed IgM-kappa gammopathy.

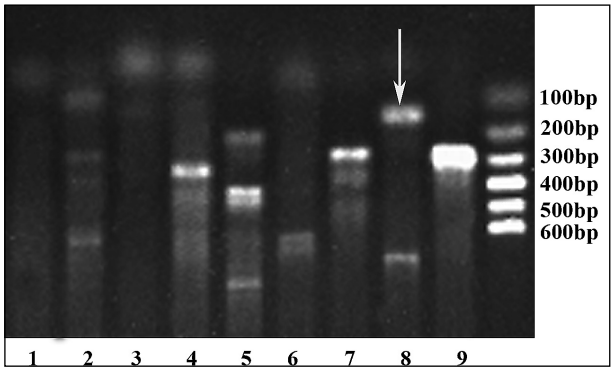

Figure 3 - IgH gene rearrangement showing the distinct band at 140-170 bp on ethidium bromide stained acrylamide gel.

Prednisone 30 mg/day, thalidomide 100 mg/day and cyclosporine A 200 mg/day were given orally. After uninterrupted treatment for 3 months, the patient's symptoms improved obviously, accompanied by an increase in haemoglobin concentration and a decrease in the levels of IgM. Repeated blood tests showed a red cell count of 3.4×10^{12}/L, haemoglobin of 98 g/L, platelet count of 203×10^{9}/L, reticulocyte count of 0.6% and an IgM level that had decreased to 13.4 g/L. The patient is currently under follow-up.

Discussion

PRCA, whether congenital or acquired, is a rare bone marrow failure syndrome characterised by progressive normocytic anaemia and reticulocytopenia but normal myeloid and megakaryocytic cell lineages[3]. It is seldom idiopathic; acquired PRCA is further divided into primary and secondary forms. Secondary PRCA can be associated with various haematological disorders, such as T-cell large granular lymphocyte leukaemia, chronic lymphocytic leukaemia and diffuse large B-cell lymphoma. However, PRCA is a rare complication of WM and there are only a few case reports in the literature[4-6]. PRCA can present simultaneously with the lymphoid neoplastic disease, may precede the appearance of it, or might appear following the disorder. In this case, PRCA was diagnosed co-existent with WM. Although rare, clinicians should be alert to this combination, considering PRCA as a possible cause of severe normochromic and normocytic anaemia in patients with WM, even at diagnosis.

The pathogenesis between PRCA and WM is complex and remains to be elucidated. Parvovirus B19 infection, which has been advocated as a possible cause of previously reported cases of PRCA accompanying WM, was excluded, indicating that different mechanisms may underlying this extremely rare association. The increased ferritin in our patient could have been a spurious result in our patient and be due to inflammation (the patient

was documented to have had elevated C-reactive protein levels). Nevertheless, one particular point we must pay attention to is that the patient's direct antiglobulin test was positive with no evidence of haemolytic anaemia, which suggests the involvement of immune mechanisms in WM associated with PRCA. Furthermore, there are reports of favourable outcomes of cases of refractory PRCA treated with rituximab, suggest the role of B-cell involvement[7,8]. Some reports suggested that the factors in patients' sera that inhibit erythropoiesis *in vivo* could be IgG antibodies directed against erythroblasts. These autoreactive antibodies could be polyclonal or might derive from a malignant B-cell clone[9] and could be directly cytotoxic, complement-binding, targeting erythroblasts, or inhibiting haemoglobin synthesis[10]. The targets for autoantibodies have not been clearly identified, since various stages of erythroid differentiation could be affected. Although the exact mechanism underlying the association between PRCA and WM is not precise, it is possible that multiple factors contribute to the disease, and so further investigation is required to define it at a molecular level and to provide convincing evidence.

The optimal treatment of PRCA complicating WM is not known, given the rarity of the condition. Treatment of PRCA consists mainly of immunosuppressive drugs, including corticosteroids, cyclophosphamide, cyclosporine A, intravenous immunoglobulins and antithymocyte globulin, of which cyclosporine A, a T-cell targeted therapy, is believed to be the most efficacious agent for disease management[3]. The anti-CD20 monoclonal antibody, rituximab, has been reported to show promising results in patients with PRCA associated with B-cell lymphomas[7,8]. WM usually follows a relatively indolent course with a median survival ranging from 60 to 120 months, so not all patients need treatment. However, in some patients, the disease may be more aggressive[11], and immediate therapy should be initiated. An International Prognostic Scoring System for WM (IPSSWM) was formulated based on five adverse factors: older age (>65 years), haemoglobin (≤115 g/L), platelet count (≤100×10^9/L), β2-microglobulin (>3 mg/L), and monoclonal IgM (>70 g/L)[1]. Based on haemoglobin and β2-microglobulin levels our patient belonged to the intermediate risk-group of the IPSSWM. There is no standard treatment for symptomatic WM. Various reports have recommended the combination of rituximab with alkylating agents and/or nucleoside analogues, or the combination of rituximab with thalidomide[12]. Bortezomib, alemtuzumab and new agents, such as bendamustine can be considered as alternative regimens[13]. Since rituximab-based chemotherapy was an economic problem for our patient, we treated him with fludarabine and cyclophosphamide chemotherapy. Meanwhile, immunosuppressive treatment modalities, including corticosteroids, cyclosporine A and thalidomide were administered and showed favourable efficacy. The standard treatment for PRCA in indolent lymphoproliferative disorders should be established through further accumulation of cases.

Acknowledgements

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Key words: Waldenström's macroglobulinemia, pure red cell aplasia, diagnosis.

The Authors declare no conflicts of interest.

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