Pure red cell aplasia in a patient with lupus-like disease and thymoma

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Abstract

Pure red cell aplasia (PRCA) is a rare complication of autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE). Thymoma occurs in 5–13% of patients with PRCA and in 2% of patients with SLE. The simultaneous occurrence, however, of all 3 disorders is rare. We report a patient with lupus-like disease who developed PRCA in association with a thymoma and explore the management challenges that ensued.

Keywords

Pure red cell aplasia; lupus-like disease; thymoma; anaemia; rituximab.

Introduction

Pure red cell aplasia (PRCA) is a rare haematologic disease characterized by severe progressive normochromic normocytic anaemia and a deficiency of red cell precursors in the bone marrow, with normal white cell and platelet cell lines. It can arise as a complication of autoimmune rheumatic diseases (ARD) such as systemic lupus erythematosus (SLE) and may also occur in association with thymoma. Patients are considered to have SLE when they satisfy at least 4 of 11 possible clinical and laboratory classification criteria[1]. If a patient has some features of SLE but less than 4 of the classification criteria they are considered to have lupus-like disease (LLD). We report a patient with the rare triad of PRCA, thymoma and LLD who was treated with corticosteroids and thymectomy followed by B cell depletion therapy with rituximab (RTX).

Case history

A 76-year-old woman with a 9-year history of LLD (positive antinuclear antibody (ANA), raised erythrocyte sedimentation rate (ESR) and arthralgia) presented to her local hospital with arthralgia and fatigue. She was found to be anaemic (Hb 7.4 g/dl) and was transfused with 4 units of red cells, then commenced on prednisolone (15 mg/day) as well as hydroxychloroquine 200 mg daily and referred to our hospital.

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One month later she presented with breathlessness and fatigue. Blood tests revealed a
normocytic anaemia (Hb 7 g/dl), raised ESR (121 mm/h) with normal white blood cells, platelets,
C-reactive protein and complement levels. ANA (1:1280, diffuse pattern), anticardiolipin IgM
(76.6 MPLU/ml) and lupus anticoagulant were positive but more specific tests for SLE such as anti-
dsDNA and extractable nuclear antigen were negative. Therefore, her LLD was considered to be
quiescent and other causes for her anaemia were sought.

Despite a positive direct antiglobin test there was no evidence of autoimmune-mediated
haemolysis, with normal bilirubin, haptoglobin and low reticulocyte counts (3.6×10⁹/l, 0.2%).
Therefore a bone marrow aspirate and trephine were performed which revealed erythroid
hypoplasia with normal megakaryocyte and myeloid cell lines. These findings coupled with a
raised serum erythropoietin level (835 IU/l) were consistent with PRCA. There was no evidence of
current infection with parvovirus B19, cytomegalovirus or Epstein–Barr virus. Screening computed
tomography to examine for an associated thymoma demonstrated a non-invasive anterior
mediastinal mass without lymphadenopathy (Fig. 1). Mediastinoscopy and biopsy subsequently
confirmed a thymoma.

During a 3-week admission she was transfused with 5 units of red cells and her breathlessness
resolved. Post-discharge she required further transfusions (6 units of red cells over 7 weeks) and
underwent an elective thymectomy 2 months later, the histology of which confirmed a type B3
thymoma. Surgery was complicated by phrenic nerve palsy and bilateral pulmonary emboli for
which she commenced anticoagulation. Post-thymectomy there was no reduction in transfusion
requirements (8 units of red cells over 11 weeks), so a single dose of RTX (375 mg/m²) was given.
Initially, she required 3 further red cell transfusions during the first 4 weeks post-RTX and
continued on low-dose steroid (prednisolone 5 mg/day). During the following 6 weeks, however,
her haemoglobin stabilized (>9.5 g/dl) and she did not require any further red cell transfusions.
Her LLD was quiescent throughout this period.

Unfortunately, her condition subsequently deteriorated with increasing breathlessness due to a
combination of pulmonary emboli, fluid overload, worsening anaemia requiring 3 further red cell
transfusions and she died 4 weeks later from pneumonia.

**Discussion**

To our knowledge there are only 3 previous reports of patients with PRCA, thymoma and SLE, one
of which developed PRCA 3 years after thymoma resection[2–4]. All patients were female with an
average age of 55 years (range 49–66 years) at PRCA diagnosis. All patients had quiescent SLE at
the time of PRCA diagnosis and were treated with red cell transfusions as well as corticosteroids
but no patients received biologic therapy. Two patients died from pneumonia within 2 months of
PRCA diagnosis and 1 patient died from pulmonary embolism 1 year after PRCA was diagnosed.

SLE and LLD are multisystem autoimmune diseases associated with immune abnormalities
and characterized by autoantibody formation leading to a variety of different clinical and

![Fig. 1.](image_url)
laboratory manifestations including anaemia. Common causes of anaemia in lupus are autoimmune-mediated red cell haemolysis, bone marrow suppression and drug-induced gastrointestinal blood loss. PRCA is a rare cause of anaemia in lupus and should prompt the search for an associated thymoma, the most common tumour of the mediastinum. Thymoma-related autoimmune disease may be due to induction of autoreactive T cell clones in abnormal thymic tissue or due to suppression of regulatory T cells. Thymoma-associated PRCA is the most recognized form of secondary PRCA, found in 5–13% of such patients. The reported incidence of thymoma with SLE is 2% and the association of PRCA with SLE is rare. Habib et al. analysed 24 reported cases of PRCA and SLE, including the 3 cases associated with thymoma and found that the onset of PRCA did not correlate with SLE disease activity, which was often quiescent.

PRCA has also been described in association with the antiphospholipid syndrome (APS). The APS is diagnosed when a patient develops vascular thrombosis and/or pregnancy morbidity in the presence of persistently positive antiphospholipid antibody (aPL) tests. Although our patient had positive aPL (lupus anticoagulant and high titre IgM anticardiolipin antibodies) and a thrombotic event, the aPL were only tested on one occasion and the pulmonary emboli occurred post-operatively. Therefore, a secure diagnosis of APS in the presence of persistently positive aPL cannot be confirmed in our patient.

Immunosuppression with corticosteroids, alongside red cell transfusions, is the mainstay of treatment of PRCA. Limitations include secondary infections from high-dose immunosuppression and the need for prolonged therapy due to relapse after steroid cessation. Habib et al. reported the remission of 2 patients with SLE-associated PRCA following treatment with intravenous immunoglobulin after failure to respond to corticosteroid. If a thymoma is present then thymectomy may provide long-term remission of PRCA in 50% of cases.

In patients with thymoma-associated ARD, the benefits of thymectomy are less clear. Boonen et al. reported 1 case and reviewed a further 11 reports of patients with SLE and thymoma who underwent thymectomy. In 5 cases, thymectomy had no clear effect on SLE disease activity, 3 cases had an exacerbation of SLE after thymectomy, 1 case showed an improvement and 3 cases did not comment. SLE may also develop following thymectomy for myasthenia gravis and PRCA onset has been reported after thymectomy in a patient with SLE. Therefore the development of SLE, thymoma and PRCA can occur in variable temporal relations and the therapeutic efficacy of thymectomy is uncertain. Our patient’s LLD was quiescent pre- and post-thymectomy, however the PRCA failed to remit and she suffered from post-operative complications.

B cell depletion with RTX has been shown to be useful in treating autoimmune-mediated cytopenias such as haemolytic anaemia and thrombocytopenia, and there are several reports of successful treatment of PRCA associated with B cell lymphoproliferative disorders with RTX. However, the results of RTX therapy in 3 patients with severe, resistant idiopathic PRCA refractory to conventional immunosuppression have been disappointing. There has also been substantial recent interest in the use of RTX for the treatment of SLE. Encouraging results have been obtained from open-label studies, however 2 recent double-blind randomized placebo-controlled trials (EXPLORER and LUNAR) on non-renal and renal lupus, respectively, failed to reach their primary objectives. We report the first use of RTX for PRCA associated with lupus and thymoma. Although the initial clinical response to treatment was promising at weeks 4–10 post-RTX, we are unable to assess a long-term response due to the patient’s later complications from multiple existing co-morbidities.

This case highlights the rare association of PRCA, thymoma and ARD. A reduced reticulocyte count should prompt consideration of bone marrow examinations in patients with LLD and SLE presenting with anaemia. These patients with co-existing PRCA frequently have relatively inactive lupus. The search for a thymoma should also be instigated in patients with PRCA due to the described association and implications on management. Immunosuppression and thymectomy are potential definitive therapeutic options, however thymectomy has uncertain implications on ARD activity. RTX is an established therapy for various types of ARD and autoimmune-mediated cytopenias and further studies are warranted to assess efficacy and safety data for B cell depletion in these patients.

Teaching points

- PRCA may arise as a complication of SLE or LLD and can be associated with thymoma.
- A reduced reticulocyte count in patients with lupus presenting with anaemia should alert the treating physician to consider the diagnosis of PRCA.
The current mainstay of management of patients with PRCA associated with thymoma and ARD, such as SLE or LLD, is corticosteroids. Further studies are warranted to assess the efficacy and safety profiles for thymectomy and B cell depletion with RTX.

References