bjh research paper

Pure red cell aplasia associated with thymoma: clinical insights from a 50-year single-institution experience*

Carrie A. Thompson and David P. Steensma
Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN, USA

Received 22 May 2006; accepted for publication 31 July 2006
Carrie Thompson, MD, Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
E-mail: thompson.carrie@mayo.edu
*The authors have no potential conflicts of interest to disclose.

Summary

Acquired pure red cell aplasia (PRCA) is a rare disorder of erythropoiesis that can develop in association with a thymoma. Optimal management of this subgroup is unclear, and there have been few series reporting long-term clinical outcomes. Here, we report features of 13 patients treated for PRCA associated with thymoma over 50 years at our institution. Surgical resection of the thymoma was insufficient for normalisation of erythropoiesis in all cases. T-cell gene rearrangement studies did not routinely demonstrate a clonal process, and ciclosporin and anti-thymocyte globulin were effective adjuvant treatments. However, treatment-related morbidity was high, with frequent infectious complications.

Keywords: pure red cell aplasia, erythropoiesis, thymoma.

Acquired pure red cell aplasia (PRCA) is an uncommon condition characterised by erythropoietic failure with preserved granulopoiesis and megakaryopoiesis. PRCA can be associated with various medications, viral infections, immune disorders, ABO-incompatible haematopoietic stem cell transplantation, and malignancies, including a well-described association with thymomas (Fisch *et al*, 2000). In contemporary series, <10% of patients with PRCA had an associated thymoma (Charles *et al*, 1996; Lacy *et al*, 1996). Due to the extreme rarity of the concurrent diagnosis of PRCA and thymoma, the relevant medical literature is restricted to case reports and small case series. Thus, conclusions regarding the optimal patient management strategies and expected clinical outcomes are limited. Here, we review our single centre experience in 13 patients with both PRCA and thymoma over a 50-year period.

Materials and methods

Between 1950 and 2005, 13 adult patients with PRCA and thymoma were treated at our institution. After Institutional Review Board approval, a retrospective chart review was performed, extracting patient characteristics, bone marrow biopsy and surgical pathology reports, treatment regimens, outcomes and complications. These patients were identified through the Mayo Clinic medical record retrieval service, searching for patients with both the diagnosis of 'pure red cell aplasia' and 'thymoma' who were treated at Mayo Clinic between the years 1950 and 2005. All of these patients had previously allowed their records to be reviewed for the purpose of clinical research. An earlier review of all patients with PRCA at Mayo Clinic between 1980 and 1994 reported that 8·5% patients (4/47) had thymoma as the presumed cause of PRCA (Lacy *et al*, 1996).

Results and discussion

The median age at PRCA diagnosis was 65 years (range 31–76 years) with no gender predilection (seven males and six females) and median haemoglobin concentration of 6·1 g/dl (range 4·8–9·1). All but one patient underwent surgical excision of the thymoma. The patient who did not undergo resection had significant medical co-morbidities that precluded operative intervention.

Thymoma histology was varied, with four cases of mixed epithelial-lymphocytic type, two lymphocytic type, two spindle cell type, one thymolipoma, one malignant/invasive neoplasm, and three unspecified subtype. This contrasted with early reports, which suggested that spindle cell histology was most commonly associated with PRCA, but was consistent with more recent observations (Kuo & Shih, 2001). Bone marrow biopsies were available for review from 12 of 13 patients and demonstrated selective decrease in erythroid precursors without other characteristic morphological features, consistent with PRCA.

Marrow karyotype was normal in all patients tested, and T-cell gene rearrangement studies were normal in six of seven

  doi:10.1111/j.1365-2141.2006.06295.x

cases where they were performed. A clonal T-cell receptor gene rearrangement was detected by PCR analysis in one patient, while Southern blotting was normal. The pathophysiology of PRCA is not well understood, and there are probably several distinct pathways that can lead to the clinical syndrome. Aetiological theories have included a humoral factor (e.g. IgG antibody) suppressing the erythroid lineage, antibodies against erythropoietin, cell-mediated suppression (including T-cells, large granular lymphocytes, and natural killer cells), and (for drug-associated and virus-associated cases) direct toxic effects of virus and drug on erythroid precursors (Dessypris, 1991; Marmont, 1991; Fisch *et al*, 2000). Studies of patients with PRCA have found frequent abnormal karyotypes as well as the presence of clonal cell populations on T-cell receptor gene rearrangement studies (Lacy *et al*, 1996). However, in this study population, T-cell clonality was not routinely detectable via T-cell gene rearrangement studies, and karyotypes were uniformly normal, suggesting that these features are uncommon when PRCA arises in association with thymoma.

Most patients were diagnosed with PRCA and the thymoma within 1 month of each other, but in four of 13 patients there was a delay between thymoma resection and development of anaemia (range, 4–117 months). Anaemia that presented years following the diagnosis of thymoma – particularly in the setting of a recurrent thymoma – has been reported occasionally by others (Murakawa *et al*, 2002).

The optimal therapy of PRCA complicating thymoma is unknown, given the rarity of this clinical situation. Surgical thymoma resection has been recommended as the initial treatment of choice, and reportedly led to remission of PRCA in 25–30% of patients (Zeok *et al*, 1979). However, none of the 12 patients in our series who underwent surgery experienced complete anaemia remission (CR, defined as haemoglobin concentration >11·0 g/dl without transfusions) after resection alone. Subsequent therapeutic interventions in the present series included danazol, corticosteroids, other immunosuppressants [ciclosporin, anti-thymocyte globulin (ATG), and azathioprine], cytotoxic agents (low-dose cyclophosphamide), androgens, splenectomy and rituximab. One patient received multiple cytotoxic agents and mediastinal irradiation without effect, due to initial incorrect diagnosis of lymphoma at another institution. Other authors have observed that epoetin-associated PRCA has been difficult to treat, with corticosteroids and intravenous immunoglobulins being ineffective, but more intensive immunosuppressant therapies offering response (Grigg & O'Flaherty, 2001).

At last follow-up (median 26 months, range 1–124 months), four patients were in CR, eight remained transfusion-dependent, and one patient was lost to follow-up. In the four patients in continuous CR, one was treated with prednisone alone, one received ATG and prednisone and remained in CR off all treatment, and the other two were treated with ATG followed by ciclosporin. Two other patients achieved transfusion independence on ciclosporin: one for 6 months, and the other for 6 years, before doses had to be decreased due to drug toxicity, and the patients then relapsed. Seven patients have died, with two deaths attributed to infection (one empyema, and one pneumonia in a patient with underlying bronchiectasis), one to progressive metastatic thymoma, one to bleeding complications, one to cardiopulmonary decompensation, and two unknown causes. The two deaths due to infection occurred soon after the diagnosis of PRCA (2 and 5 months), while the patient with cardiopulmonary decompensation died 3 months after splenectomy.

Treatment-related complications included frequent infections related to immunosuppression (including two cases of Pneumocystis carinii pneumonia), renal insufficiency, and thrombotic thrombocytopenic purpura (TTP). Renal insufficiency and TTP were associated with ciclosporin use and seen in two of six patients who received ciclosporin. Careful monitoring of patients receiving long-term ciclosporin for PRCA seems prudent.

Due to the presumed immune pathogenesis in PRCA, various immunosuppressive therapies have been attempted (Clark *et al*, 1984). In this series, ciclosporin and ATG were effective treatments, but nine of 13 patients in this series remained transfusion-dependent until death or last follow up, despite therapy. However, two of these patients succumbed to infection within 5 months of PRCA diagnosis and therefore were unable to receive an adequate therapeutic regimen. Of note, newer therapies, such as rituximab, were not prescribed in this series of patients. Experience has shown rituximab to be efficacious in treatment of multiple haematological disorders, including autoimmune-related anaemia, and may have potential benefit in management of patients with PRCA.

In summary, PRCA and thymoma are rarely associated, and the associated anaemia is probably due to an immune phenomenon and may respond to immunosuppressive medications. T-cell receptor and karyotype abnormalities are unusual in these patients. While surgical resection of the thymoma is still recommended, it does not reliably lead to remission. Anaemia usually presents at the same time as the thymoma is diagnosed, but there are cases in which anaemia can present years later. Ciclosporin and ATG are effective treatments, but can lead to significant morbidity, particularly pulmonary infections. Close follow up of these patients is recommended.

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