

Case Report

Successful Management of Post-Thymectomy Pure Red Cell Aplasia with Rituximab: A Case Report

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Keywords

Rituximab · Anemia · Pure red cell aplasia · Thymoma · Thymectomy

Abstract

Background: Pure red cell aplasia (PRCA) is a rare cause of anemia characterized by decreased red blood cell production, often associated with thymomas. While thymectomy is commonly performed to treat thymoma-associated PRCA, the development of PRCA post-thymectomy is less understood. **Case Presentation:** We present a case of a 25-year-old woman who developed PRCA and autoimmune diabetes mellitus (DM) following radical thymectomy for malignant thymoma. Initial treatment with prednisolone showed minimal improvement, leading to the inclusion of rituximab. This combination resulted in a significant increase in reticulocyte counts and transfusion independence. **Discussion:** This case highlights the potential for PRCA to develop after thymectomy and the challenges of treating PRCA in the context of additional conditions like autoimmune DM. While immunosuppressive therapies such as cyclosporin A and corticosteroids are standard, their side effects necessitated exploring alternative treatments. Rituximab proved effective and was well-tolerated, suggesting its potential as a primary option in similar cases. **Conclusion:** This case illustrates the occurrence of PRCA after thymectomy and highlights rituximab's effectiveness as a treatment option, offering a viable alternative to standard therapies in managing this complex condition.

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Published by S. Karger AG, Basel

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Introduction

Pure red cell aplasia (PRCA) is a rare type of anemia characterized by a severe decrease in red blood cell production and a notable reduction or absence of erythroid progenitor cells in the bone marrow [1]. It typically presents as normocytic normochromic anemia. PRCA can manifest in two forms: congenital and acquired. Diamond-Blackfan anemia represents a congenital form of PRCA. Acquired PRCA can be further categorized into primary (idiopathic) and secondary forms, where it is associated with an underlying disease [2]. Common underlying diseases linked with acquired PRCA include vascular or autoimmune conditions like systemic lupus erythematosus, lymphoproliferative disorders such as chronic lymphocytic leukemia or large granular lymphocytic leukemia, infections notably parvovirus B19, thymomas, other solid tumors, as well as various other diseases, medications, and toxic substances [3]. Thymoma is a rare neoplasm arising from the epithelial cells of the thymus gland; the association between PRCA and thymomas is well established, with anemia often improved following thymectomy. However, the development of PRCA after thymectomy is less frequent and not well-defined [4].

In primary PRCA, most cases are thought to be mediated by autoreactive T-cells. This is likely via selective T- or natural killer-cell-mediated killing of erythroid colony (CFU-E) and burst (BFU-E) forming units, thereby inhibiting red cell precursor progression to mature erythrocytes [5]. On the other hand, autoimmune PRCA, which is mediated by antibodies, is less common. Most anti-erythroid antibodies typically lead to immune hemolytic anemia. However, there is a specific form known as anti-erythropoietin antibody-mediated PRCA, which can be induced by recombinant erythropoietin [6]. Thymoma-associated PRCA can be categorized as either secondary or primary with an immune etiology. While some patients respond well to T-cell-directed immunosuppressive therapies, others have underlying conditions involving humoral immunity (such as myasthenia gravis and Good's syndrome). These cases are often less responsive to such treatments [7–9].

The optimal treatment for PRCA is still unclear due to the condition's rarity and the diverse underlying causes that lead to varying clinical presentations. While spontaneous remission can occur in some cases, those who do not experience this may require a combination of supportive care and treatment for the underlying disorders. For patients with severe anemia that persists despite addressing these underlying conditions, immunosuppressive or immunomodulatory therapies may be necessary [6]. Although there are no randomized clinical trials directly comparing different immunotherapies, a study involving 100 patients (comprising 60 percent primary PRCA and 40 percent secondary PRCA) revealed varying response rates. Notably, cyclosporin A, which primarily targets autoreactive T-cells, demonstrated the highest response rate at 71%, followed by glucocorticoids at 67% and other therapeutic approaches at 50% [10]. Additionally, Rituximab, which mainly acts against B cells and suppresses humoral immunity, has shown promising results in treating PRCA, particularly in cases associated with chronic lymphocytic leukemia [11–13].

Case Presentation

A 25-year-old woman with no personal or family history of blood disorders was diagnosed with malignant thymoma with left-sided pleural metastasis. She initially received neoadjuvant chemotherapy composed of five cycles of the CAP regimen (Cisplatin, Adriamycin, and Cyclophosphamide). Following chemotherapy, the patient underwent radical thymectomy followed by radiotherapy; subsequent whole-body PET-CT scan showed complete metabolic remission of her malignant thymoma. Two more cycles of adjuvant

chemotherapy were planned but were not given due to the development of fatigue, exertional dyspnea, and palpitations almost 3 months after the radical thymectomy. These symptoms were attributed to severe anemia, which improved following blood transfusions.

The initial investigation for anemia (Table 1) indicated normocytic normochromic anemia with a decreased reticulocyte count. Following this, an extensive workup was conducted, including peripheral blood evaluations such as a peripheral smear, viral screening, and an autoimmune panel. Subsequently, the patient underwent a comprehensive bone marrow examination involving aspirate analysis, flow cytometry, cytogenetic and molecular studies, and a core biopsy. The findings from this examination confirmed the diagnosis of PRCA and effectively excluded other differential diagnoses (Fig. 1).

Subsequently, the patient was observed to have high levels of blood sugar. Further evaluations led to the diagnosis of autoimmune diabetes mellitus, prompting the start of treatment with insulin. Considering the patient's history of malignancy, platinum-based chemotherapy and a newly diagnosed diabetes mellitus, the decision regarding the first-line therapy for PRCA was made after a careful assessment of the associated risks (the potential nephrotoxicity of cyclosporin A and uncontrolled diabetes with corticosteroids) and benefits, particularly given the absence of an established standard of care for this condition. Together with the patient we choose rituximab, as it was perceived to be a safer option with a shorter treatment duration compared to cyclosporine A. Additionally, the prolonged use of corticosteroids such as prednisolone was deemed inappropriate due to the risk of exacerbating the patient's diabetes.

The patient commenced treatment with 1 mg/kg of prednisolone. However, after 2 weeks, there was minimal improvement observed in the patient's reticulocyte counts. Consequently, rituximab was incorporated into the treatment regimen at a weekly dose of 375 mg/m². This regimen continued for four doses. Subsequently, there was a notable improvement in the patient's condition, particularly in the reticulocyte count, which increased from $9.9 \times 10^3/\mu\text{L}$ before rituximab to $289.9 \times 10^3/\mu\text{L}$ 6 days after rituximab administration. Moreover, the patient no longer required transfusions, achieving transfusion independence. As her hemoglobin levels nearly normalized, prednisolone gradually reduced by 10 mg weekly over the following weeks. However, when prednisolone was discontinued, there was an early detection of a decline in reticulocyte levels, suggesting a beginning relapse, although no transfusion was necessary at that point. In response, a second course of prednisolone and rituximab was administered, and the patient achieved a rapid response, once again (Fig. 2). Due to the early detection and mild nature of the relapse, prednisolone was tapered quickly, especially since the patient began to experience uncontrolled blood sugar. During the follow-up period of 12 months, she remained in complete remission.

Discussion

Thymoma has traditionally been considered the most common secondary cause of PRCA, with up to 50% of PRCA cases believed to be related to it. However, recent retrospective studies have revealed that PRCA occurs in fewer than 5% of thymoma patients, and the prevalence of thymoma among PRCA patients is estimated to be between 7% and 10%. PRCA can either appear before the detection of a thymoma or, in rare cases, after its surgical removal. The extent to which these cases occur after thymectomy is uncertain [4, 6, 10]. In our patient, the association between thymectomy and the development of PRCA was clear as her blood values were normal and anemia with PRCA developed after the operation.

Primary or secondary PRCA that does not respond to treatment of the underlying diseases is typically treated as an immunologically mediated disease. Several studies

Table 1. Showing basic anemia investigations

Test	Result	Normal range	Test	Result	Normal range
Hgb	6.6 g/dL	12.0–15.0 g/dL	Serum iron	33 µmol/L	6–3 µmol/L
WBC	$6.1 \times 10^3/\mu\text{L}$	$4\text{--}10 \times 10^3/\mu\text{L}$	Serum total iron binding capacity	38 µmol/L	45–80 µmol/L
Platelet	$350 \times 10^3/\mu\text{L}$	$150\text{--}450 \times 10^3/\mu\text{L}$	Serum transferrin	1.5 g/L	2.0–3.6 g/L
MCV	85.8 fL	83.0–101.0 fL	Fe% saturation	87%	15–45%
Absolute neutrophil count	$4.65 \times 10^3/\mu\text{L}$	$2.0\text{--}7.0 \times 10^3/\mu\text{L}$	Serum ferritin	807.0 µg/L	12–114 µg/L
Reticulocyte count	$3.1 \times 10^3/\mu\text{L}$	$50\text{--}100 \times 10^3/\mu\text{L}$	Serum folate	50 nmol/L	10–70 nmol/L
Retic %	0.2%	0.5–2.5%			
Serum EPO concentration	267.19 mIU/mL	2.5–18.5 mIU/mL	Serum vitamin B12	422.0 pmol/L	145–600 pmol/L

Hgb, hemoglobin; WBCs, white blood cells; MCV, mean corpuscular volume; EPO, erythropoietin; TIBC, total iron binding capacity.

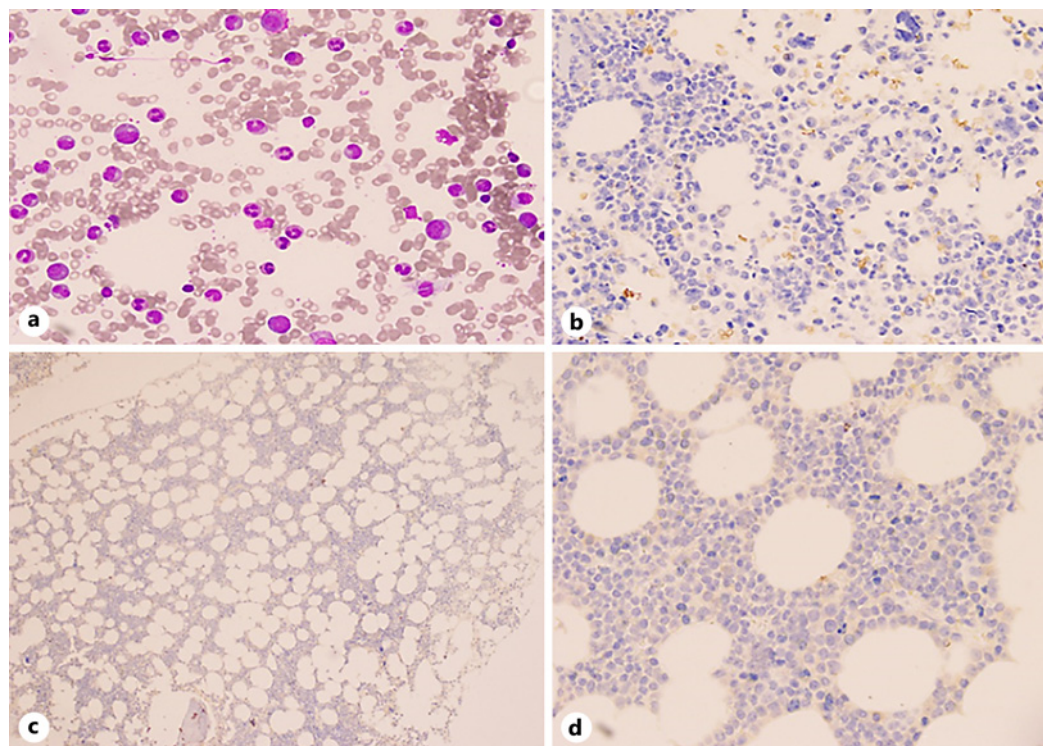


Fig. 1. Bone marrow aspirate and biopsy showing absence of erythroid precursor. **a** The bone marrow aspirate reveals decreased cellularity with a notable absence of erythroid precursors. **b** The biopsy shows minimal staining for glycophorin, an erythroid marker. **c, d** Both panels with E-cadherin immunostaining another erythroid marker reveal absent or reduced expression.

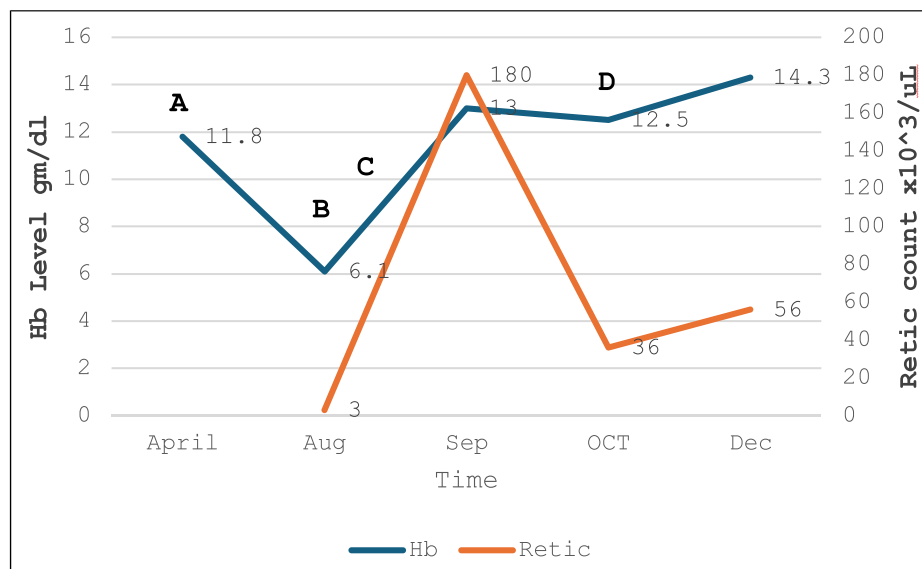


Fig. 2. Overview of the patient's clinical course from thymectomy to diagnosis and treatment response. A: Date of thymectomy. B: Diagnosis and commencement of steroid therapy. C: Initiation of rituximab treatment. D: Suspected relapse is indicated by changes in the reticulocyte count. Hb, hemoglobin; Retic, reticulocytes.

implicate a pathological role of serum auto-antibodies, natural killer cell-mediated or T lymphocyte-mediated effects impairing various stages and mechanisms of erythropoiesis as extensively reviewed by Fisch et al. [14]. Patients with PRCA associated with thymoma are usually treated with thymectomy as the first-line therapy [15, 16]. Although previous studies have reported positive outcomes, recent research has highlighted several limitations. For instance, less than one-third of patients experience complete remission, treatment response may be incomplete, and hemoglobin levels may not return to normal. Additionally, relapses are frequent, and PRCA may sometimes occur after thymoma removal in patients who did not have PRCA before [3, 13]. Immunosuppressive therapy with various medications has shown promising results in various retrospective studies. Repeated trials with immunosuppression using a series of agents can lead to a response in approximately two-thirds of patients with PRCA [17].

Currently, no widely accepted guidelines dictate the choice of immunosuppressive therapies in the treatment of PRCA. However, there is a growing consensus that cyclosporine A should be considered for initial treatment due to its significant efficacy, as it is regarded as the most effective immunosuppressive agent in several retrospective studies, demonstrating an overall response rate of over 75%. This response rate is particularly noteworthy given that many early studies included patients who had previously failed multiple therapeutic modalities. An alternative option is oral corticosteroids, specifically prednisone, which is typically administered at a dose of 1 mg/kg and yields an overall response rate of approximately 40%. Prednisone is tapered once a response is achieved and may be combined with other agents if remission is not accomplished. Other immunosuppressive therapies, like azathioprine, cyclophosphamide, and tacrolimus, have been used in patients unresponsive to corticosteroids alone or in patients who do not respond to or tolerate cyclosporine A; the response rate in this context is approximately 40%. Additionally, antithymocyte globulin, in the doses used for treating aplastic anemia, has a 50% response rate in primary autoimmune PRCA. Other modalities used in refractory primary PRCA with relatively low response rates include intravenous immunoglobulin, plasma exchange, splenectomy, and bone marrow transplantation [6, 10, 15, 17–20].

Rituximab, an anti-CD20 monoclonal antibody, has shown varying results in treating PRCA in patients who have not responded to multiple immunosuppressive therapies (IST). Several reports indicate successful treatment of PRCA with rituximab, particularly in patients diagnosed with B-cell lymphoproliferative disorders, mainly chronic lymphocytic leukemia [11, 12]. However, few studies report effective erythropoiesis restoration in adults with primary PRCA resistant to IST with a notable rapid increase in reticulocyte counts observed within a few days following the initial rituximab infusion. The exact mechanism of this effect is unclear, but it may indicate a role for B cells and humeral immunity in the pathogenesis of some PRCA cases, similar to cases of PRBCA associated with myasthenia graves and Good's syndrome [8, 9, 21]. In our case, cyclosporine was not preferred due to its potential side effects, including nephrotoxicity, hyperglycemia, and an elevated risk of secondary malignancies. Additionally, avoiding long-term corticosteroid use was essential, as the patient had autoimmune insulin-dependent D. Therefore, rituximab was the safest alternative therapy. This option proved to be both effective and well-tolerated.

Conclusion

This case report highlights the risk of PRCA occurrence following thymectomy and suggests the potential efficacy of rituximab in its treatment. Furthermore, the availability of multiple medical treatment options for PRCA, along with the limitations and invasiveness of thymectomy, raises questions about the suitability of thymectomy as a first-line therapy for PRCA when associated with Thymoma.

Statement of Ethics

This case was approved by the Hamad Medical Corporation's Medical Research Center, and the approval No. is MRC-04-24156. Written informed consent was obtained from the patient to publish this case report and any accompanying images. The authors have completed the CARE Checklist for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000542915>).

Conflict of Interest Statement

The authors have no conflicts of interest.

Funding Sources

Case report publication charge will be covered by Qatar National Library.

Author Contributions

M.A.: conceptualization, writing – original draft, and writing – review and editing. I.G. and F.A.: writing – review and editing. H.S. and U.A.-H.: review and editing. H.C.: supervision, validation, and writing – review and editing.

Data Availability Statement

The data supporting this study's findings are not publicly available for privacy reasons but are available upon reasonable request from the corresponding author (M.A.).

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