

# Occurrence of acute pulmonary embolism induced by recombinant erythropoietin during treatment of pure red cell aplasia associated with thymoma

## A case report

Xiangli Cui, PhD<sup>a</sup>, Zirui Wan, MS<sup>a</sup>, Zhuo Ma, MS<sup>a</sup>, Lihong Liu, PhD<sup>a,\*</sup>, Yuanhua Yang, MD<sup>b,\*</sup>

### Abstract

**Rationale:** Thymoma is a type of rare tumor in the thymus gland, and among patients with thymoma, less than 10% will develop pure red cell aplasia (PRCA), whereas less than 5% of patients with PRCA have a thymoma. The optimal approach for PRCA in thymoma is immunosuppressive therapy, such as steroids, cyclosporine, and human antithymocyte globulin.

**Patient concerns:** A sixty-one-year-old male was diagnosed with thymoma with PRCA after he complained fatigue, tinnitus, and weakness for 1 month, he received therapy with recombinant erythropoietin (rhEPO) for 1 month after the tumor was totally resected and readmitted with pulmonary embolism and received anticoagulation therapy with enoxaparin for 3 months.

**Diagnoses:** Thymoma, pure red cell aplasia, pulmonary embolism.

**Intervention:** He received cyclosporine A, prednisone and rhEPO treatment. Two months after the thymectomy and postoperative radiation, he was readmitted with pulmonary embolism.

**Outcomes:** Thymoma and pulmonary embolism become complete response (CR), PRCA become partial response (PR).

**Lessons:** Clinicians should be alert to the possibility of the increased risk of thrombosis induced by rhEPO when it used to treat PRCA associated with thymoma. If other medication is effective for managing PRCA, rhEPO should be avoided.

**Abbreviations:** CR = complete response, CsA = cyclosporine, CTPA = computed tomographic pulmonary angiography, CTX = cyclophosphamide, PR = partial response, PRCA = pure red cell aplasia, PT = prothrombin time, PTT = partial thromboplastin time, rhEPO = recombinant erythropoietin, VTE = venous thromboembolism.

**Keywords:** erythropoietin, pulmonary embolism, pure red cell aplasia (PRCA), thymoma

## 1. Introduction

Thymomas are most frequently seen in people in their forties or fifties. In the United States, they have an overall incidence of 0.13 cases per 100,000 person-year.<sup>[1]</sup> Surgery is the primary medical treatment for thymoma, and if tumors can be completely

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Hospital. Informed consent was obtained from the patient for publication of this case report and accompanying images.

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<sup>a</sup> Department of Pharmacy, <sup>b</sup> Department of Respiratory and Critical Care Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China.

\* Correspondence: Lihong Liu, Department of Pharmacy, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China (e-mail: liulihong@bjcyh.com); Yuanhua Yang, Department of Respiratory and Critical Care Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China (e-mail: yyh1031@sina.com).

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removed, patients will have a higher cure rate. The hallmark of PRCA is reticulocytopenic, malproductive anemia, and the absolute reticulocyte count is always less than 10,000/mL (reticulocyte percentage, 1%), but essentially with normal granulopoiesis and megakaryopoiesis.<sup>[2,3]</sup> The therapeutic approach to PRCA typically involves immunosuppression medication, but specific pathogenic subtypes are associated with specific therapeutic approaches. The most common treatment used in idiopathic PRCA was cyclosporine (CsA) or cyclophosphamide (CTX) combined with a steroid taper. The other salvage treatment options include rituximab, danazol, mycophenolate mofetil, bortezomib, erythropoietin, abatacept, tofacitinib.<sup>[4,5]</sup> We report a case of a 61-year-old male who readmitted to our hospital with pulmonary embolism 1 month after total resection of thymoma.

## 2. Case report

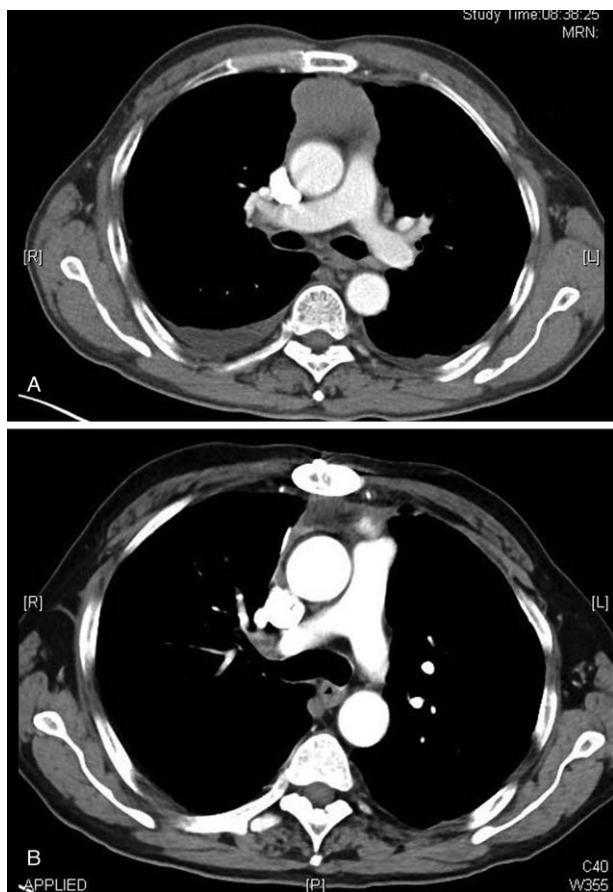
We present the case of a 61-year-old male who was admitted to our hospital on December 5, 2016 reporting fatigue, tinnitus, and weakness for 1 month. The patient had no history of illness or surgical intervention and did not take any medication at home. He was a smoker (20 cigarettes every day) for 36 years. His complaint started approximately 1 month before admission and worsened until he decided to go to hospital. Blood test showed persistent anemia, and the laboratory tests results were as follows: red blood cells (RBC),  $1.54 \times 10^{12}$  cells/L; reticulocytes, 0.0153 cells/ $\mu$ L; hemoglobin (Hb), 3.4 g/dL; white blood cells (WBC),  $5.72 \times 10^9$  cells/L; blood platelets (PLT),  $371 \times 10^9$  cells/L; immunoglobulin A (IgA), 92 mg/dL; immunoglobulin G (IgG),

945 mg/dL; immunoglobulin M (IgM), 96 mg/dL;  $\beta$ 2-microglobulin, 3.0 mg/L; CD4<sup>+</sup> T cells, 20.13%; CD8<sup>+</sup> T cells, 72%; CD4<sup>+</sup>/CD8<sup>+</sup> T cell ratio, 0.28; Fe, 47.1  $\mu$ mol/L; folic acid, 4.19 ng/mL; vitamin B12, 320 pg/mL; homocysteine (Hcy), 23.7  $\mu$ mol/L; erythrocyte sedimentation rate, 37 mm/h; D-dimer, 0.37 mg/L. The coagulative profile prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and antithrombin III) were within the reference range. Bone marrow aspiration revealed pure red cell aplasia (PRCA): the myeloid/erythroid ratio was 121:1, and the percentages of myeloid and erythroid precursors were 60.5% and 0.5% respectively, with lymphocytes accounting for the remaining 33%. A chest X-ray showed a mass in the upper lung field proximal to the mediastinum and adjacent to the diaphragm (Fig. 1). A chest computed tomography showed a 5 cm mass with spotty calcifications in the right anterior mediastinum (Fig. 1A) that disseminated to the right thoracic cavity. Venous ultrasound of the lower extremities showed no thrombosis in the veins of the lower extremities. Complete tumor resection was performed in 3 hours by thoracic surgeons on December 9, 2016 (Fig. 1B). The tumor volume was 5 × 5 × 6 cm, and the tissue pathology indicated type B3 epithelial thymoma (Fig. 2). Immunohistochemical analysis showed a Ki-67 level of 40% to 50%, and was positive for cytokeratin (CK)19, CK5/6, and CK7 in the neoplastic epithelial cells and for leucocyte common antigen, CD3, CD5, CD20, CD99, CD1a, and terminal

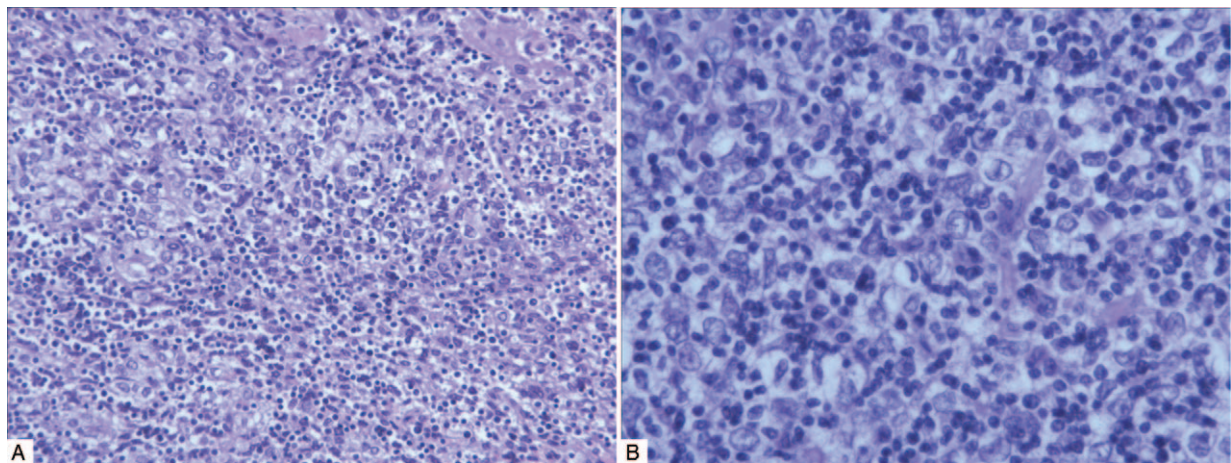
deoxynucleotidyl transferase in the lymphocytes. RBC and Hb increased after thymectomy 10 days later to RBC of  $3.09 \times 10^{12}$  cells/L, Hb of 91 g/L, and WBC of  $8.84 \times 10^9$  cells/L. After total resection of the tumor, the patient underwent external beam radiation therapy for 5 weeks, and took prednisone acetate tablets (15 mg bid) and cyclosporine A (75 mg bid) after discharge, and received recombinant erythropoietin (rhEPO; 8000 IU) subcutaneously every other day in the outpatient department for 1 month from January 6 to February 5, 2017. On February 23, 2017, he was readmitted to hospital with chest tightness and shortness of breath with progressive aggravation for about 20 days. On admission, venous ultrasound of the lower extremities showed bilateral calf vein thrombosis. A CT pulmonary angiograph (CTPA) showed an intravascular filling defect of the posterior basal segment of the right inferior pulmonary artery (Fig. 3). The laboratory results were as follows: RBC,  $5.07 \times 10^{12}$  cells/L; Hb, 16.9 g/dL; WBC,  $12.02 \times 10^9$  cells/L; PLT,  $241 \times 10^9$  cells/L; protein C, 145.5%; protein S, 81.6%; D-dimer, 4.5 mg/L; N-terminal pro-brain natriuretic peptide, 470.9 pg/mL; cardiac troponin I, 0.13 ng/mL; C-reactive protein, 0.51 mg/dL; Hcy, 13  $\mu$ mol/L; IgA, 56.1 mg/dL; IgG, 592 mg/dL; IgM, 77.8 mg/dL. The coagulative profile (PT, PTT, fibrinogen, and antithrombin III) was within the reference range. The patient received enoxaparin (6000 IU, q12 hours) for 8 days after admission to hospital, and his symptoms of chest tightness and shortness of breath were greatly improved and he was discharged. He continued to receive anticoagulation therapy with enoxaparin for 3 months. A further CTPA and venous ultrasound of the lower extremities showed no pulmonary embolism or deep vein thrombosis, his blood test was within the reference range, and he had no other symptoms of shortness of breath. The patient was followed up every 3 months for 1 year.

### 3. Discussion

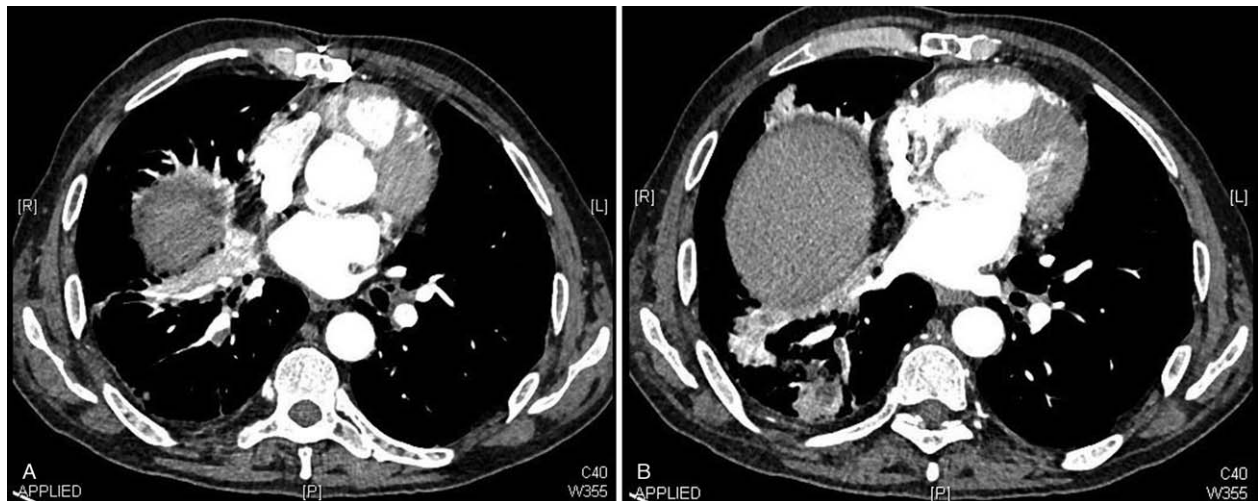
PRCA is characterized by erythropoietic failure with preserved granulopoiesis and megakaryopoiesis. The diagnosis should be suspected in a patient with isolated anemia and absent reticulocytes. Evaluation should include a peripheral reticulocyte count, and if there is reticulocytopenia, a bone marrow biopsy is prudent, which classically shows a selective decrease in erythroid precursors.<sup>[2,3]</sup> The pathophysiology of PRCA and thymoma is not entirely understood, but it may be related to dysfunction of the autoimmune system. This patient had a new diagnosis of anemia in conjunction with a thymoma, PRCA should be considered. There are only National Comprehensive Cancer Network guidelines for thymoma management by surgery, radiation, and chemotherapy. PRCA and thymoma are rarely simultaneous, so there are still no guidelines for treating PRCA in thymoma patients. Progress in the management of this rare disease relies on accumulating empirical experience, integrative analyses of several cases, and rare clinical trials.<sup>[4,5]</sup> Thompson and Steensma<sup>[6]</sup> reported that surgical resection of thymoma was insufficient for normalization of erythropoiesis, but immunosuppressive therapy was effective as an adjuvant treatment. The therapeutic approach to PRCA typically involves immunosuppression, but specific pathogenic subtypes are associated with specific therapeutic approaches. Cyclosporine A, with or without concurrent corticosteroids, appears to be the single most effective immunosuppressive agent, compared with other therapeutic options like intravenous immunoglobulin, rituximab, alemtuzumab, and bortezomib.<sup>[7,8]</sup> PRCA in thymoma is likely to respond to immunosuppressive therapy (steroids, cyclosporine A, and



**Figure 1.** CT scans showing preoperative and postoperative thymoma. A, Irregular anterior mediastinal mass with axial dimensions of approximately 52 × 49 mm situated between the ascendant aorta and the trunk of the pulmonary artery. B, CT scan after total resection of the thymoma. CT = computed tomography.



**Figure 2.** Pathology of type B3 thymoma. Hematoxylin and eosin stains at magnifications of (A)  $\times 100$  and (B)  $\times 400$ .



**Figure 3.** CTPA showing filling defects in the segmental branch of the posterior basal segment of the right lower lobe. CTPA = computed tomographic pulmonary angiography.

ATG) combined with thymectomy rather than to thymectomy alone. rhEPO is used in few cases, but its efficacy in treating PRCA is still controversial.<sup>[9]</sup> Some studies have reported that antierythropoietin antibody-mediated PRCA induced by rhEPO can be considered a specific form of autoimmune PRCA.<sup>[10,11]</sup>

This patient got pulmonary embolism which began 1 month after initiating postoperative treatment with rhEPO for PRCA associated with thymoma. The patient also received prednisone and CsA, which is common in treating PRCA. In this case, PRCA had not been resolved after thymectomy alone, but cyclosporine A and prednisone treatment subsequent to thymectomy was safe and effective. Additional treatment with rhEPO increased the effects of cyclosporine A and restored the patient's Hb and RBC to normal level. This patient achieved complete remission after a total thymectomy, radiation, and medication, but 2 months after the thymectomy, he was readmitted with a pulmonary embolism. CTPA suggested that the pulmonary embolism occurred in the segmental branch of the *posterior basal segment* of the *right lower lobe*. We assumed that the pulmonary embolism was

induced by rhEPO, and the rhEPO treatment was stopped. The patient received anticoagulation therapy with enoxaparin for 3 months and made a full recovery.

rhEPO is a standard treatment for anemia due to end-stage renal failure. It is also used in treating anemia in other chronic conditions, such as rheumatoid arthritis and acquired immune deficiency syndrome. The patients with anti-EPO antibody can also induce PRCA through inhibiting the growth of erythroid progenitor cells. So EPO is not a routine recommendation for treating of PRCA in most researches.<sup>[11]</sup> There are some reports of rhEPO-induced venous thromboembolism (VTE) when rhEPO is used in combination with thalidomide for treating multiple myeloma.<sup>[6,12,13]</sup> However, there are no reports of VTE induced by PRCA treatment with rhEPO, which is seldom used to treat PRCA.

This is the first report describing the occurrence of pulmonary embolism induced by rhEPO during treatment of PRCA associated with thymoma. Some thymoma patients can be cured by thymectomy,<sup>[14]</sup> but PRCA still requires additional therapy

with cyclosporine A, prednisone, or other salvage therapies, which include rituximab, antithymocyte globulin, and bortezomib. However, these issues around treating PRCA associated with thymoma should be addressed in future clinical trials. We are optimistic that after anticoagulation therapy with enoxaparin, the patient recovered well.

#### 4. Conclusions

Clinicians should be alert to the possibility of the increased risk of thrombosis induced by rhEPO when it used to treat PRCA associated with thymoma. If other medication is effective for managing PRCA, rhEPO should be avoided. If rhEPO must be used, it may increase the risk of VTE, and thus anticoagulation therapy may be even more prudent when the VTE risk is high.

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#### Author contributions

**Formal analysis:** Zirui Wan.

**Investigation:** Lihong Liu.

**Resources:** Zhuo Ma.

**Supervision:** Yuanhua Yang.

**Writing – original draft:** Xiangli Cui.

#### References

- [1] Thompson CA. Pure red cell aplasia and thymoma. *J Thorac Oncol* 2007;2:263–4.
- [2] Balasubramanian SK, Sadaps M, Thota S, et al. Rational management approach to pure red cell aplasia. *Haematol* 2018;103:221–30.
- [3] Robert T, Means Jr. Pure red cell aplasia. *Blood* 2016;128:2504–9.
- [4] Djaldetti M, Blay A, Bergman M, et al. Pure red cell aplasia—a rare disease with multiple causes. *Biomed Pharmacother* 2003;57:326–32.
- [5] Thompson CA, Steensma DP. Pure red cell aplasia associated with thymoma: clinical insights from a 50-year single-institution experience. *Br J Haematol* 2006;135:405–7.
- [6] Galli M, Elice F, Crippa C, et al. Recombinant human erythropoietin and the risk of thrombosis in patients receiving thalidomide for multiple myeloma. *Haematologica* 2004;89:1141–2.
- [7] Mochizuki H, Okada T, Yoshizawa H, et al. Cyclosporin improved pure red cell aplasia associated with thymoma and tended to decrease thymoma size: a case report. *Nihon Kokyuki Gakkai Zasshi* 2003;41:755–9.
- [8] Auner HW, Wöfler A, Beham-Schmid C, et al. Restoration of erythropoiesis by rituximab in an adult patient with primary acquired pure red cell aplasia refractory to conventional treatment. *Br J Haematol* 2002;116:727–8.
- [9] Maeda T, Shiokawa S, Yoshikawa Y, et al. Successful treatment of pure red cell aplasia with cyclosporin A and erythropoietin after thymectomy in a 88-year old woman. *Haematologica* 2004;89(6 suppl):ECR17.
- [10] Casadevall N, Nataf J, Viron B, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med* 2002;346:469–75.
- [11] Casadevall N, Eckardt KU, Rossert J. Epoetin-induced autoimmune pure red cell aplasia. *J Am Soc Neph* 2005;16(suppl 1):S67–9.
- [12] Maccougall IC. Adverse event issue management: what have we learnt from pure red cell aplasia (PRCA)? *Nephrol Dial Transplant* 2005;20 (suppl 8):viii18–21.
- [13] Zonder JA. Thrombotic complications of malignancy. *Hematology Am Soc Hematol Educ Program* 2006;1:348–55.
- [14] Bhargava R, Dolai TK, Singhal D, et al. Pure red cell aplasia associated with thymoma: is thymectomy the cure? *Leuk Res* 2009;33:e17–8.