Radiation-induced pure red cell aplasia combined with acquired amegakaryocytic thrombocytopenia in a thymoma after rapid response to radiotherapy: A case report and literature review

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Received July 21, 2022; Accepted February 16, 2023

DOI: 10.3892/etm.2023.11936

Abstract. Thymoma combined with pure red cell aplasia (PRCA) and acquired amegakaryocytic thrombocytopenia (AAMT) has been rarely reported, often occurring in the initial stage of treatment and after chemotherapy or thymectomy, while PRCA and AAMT occurring after radiotherapy for thymoma has not been reported. The present study describes the case of a 42-year-old female patient with thymoma complicated by radiation-induced PRCA and AAMT after a rapid response to radiotherapy, who was in complete remission without recurrence after adjustment of initial symptomatic therapy to cyclosporine combined with prednisone. After 1 month, the patient underwent complete resection of mediastinal tumor. Next-generation sequencing revealed that the DNA damage repair pathway-related gene MSH3 was mutated, with p.A57P in abundance of 9.21%. To the best of our knowledge, the present study is the first to report that PRCA and AAMT secondary to thymoma after radiotherapy may be associated with increased sensitivity to radiotherapy caused by a mutation in the MSH3 gene.

Introduction

Thymomas are epithelial tumors originating from the thymus gland and the most common tumors of the anterior mediastinum (1). It is known that approximately 2-5% of patients with thymoma develop pure red cell aplasia (PRCA) (2,3), but the concurrent combination of acquired amegakaryocytic thrombocytopenia (AAMT) is rarely reported. The most common treatment used in PRCA complicated with AAMT included cyclosporine, alone or in combination with corticosteroid therapy (4-9). The other salvage treatment strategies include antithymocyte globulin, bone marrow transplantation, erythropoietin, iterative transfusions, platelet transfusion and eltrombopag (4-7,9-11). Here, this novel report details the course of our clinical treatment of PRCA and AAMT induced by thymoma radiotherapy. The patient underwent a complete resection of mediastinal tumor after healing from AAMT and PRCA. Postoperative NGS testing revealed mutation in the MSH3 variant, which was thought to enhance the sensitivity of radiotherapy and promote apoptosis of tumor cells and normal cells as one of the mechanisms leading to the development of PRCA and AAMT, hitherto absent from prior reports.

Case report

A 42-year-old female patient was diagnosed with thymoma via mediastinal mass puncture biopsy on April 13, 2019, at Shanghai Jiao Tong University Chest Hospital and received two cycles of chemotherapy (paclitaxel and carboplatin). After chemotherapy, a chest CT showed stable disease according to RECIST. For further treatment, the patient sent pathological sections from this hospital to ours (West China Hospital of Sichuan University in Chengdu) for consultation and was also diagnosed with thymoma on August 2, 2019. The patient's pre-radiotherapy CT chest enhancement suggested a soft tissue mass in the left anterior mediastinum, with a size of approximately 7.4x8.2 cm, and the mass was poorly demarcated from the left border of the pericardium and adjacent large vessels. In order to improve the success rate of complete surgical resection, preoperative neoadjuvant radiotherapy was used to shrink the size of the mass to achieve better radical surgical resection. Prior to chest radiotherapy, her complete blood count (CBC) test was normal. Her hemoglobin was 133 g/l (range, 115-150 g/l), platelet count $261x10^9$ cells/l (range, 100-$300x10^9$ cells/l, and white blood cell (WBC) count $7.59x10^9$ cells/l (range, 3.5-$9.5x10^9$ cells/l). After 36 Gy in 12 fractions (Fig. 1), chest CT scan showed that left anterior mediastinal mass had greatly shrunken with the formation of calcification (Fig. 2).

One month after the end of radiotherapy, the patient was admitted to our hospital because of the appearance of bleeding spots on the skin and gum bleeding. The CBC test showed normocytic anemia at 69 g/l, WBC count $6.44x10^9$ cells/l, reticulocyte count $0.0027x10^{12}$ cells/l (range, 0.024-$0.084x10^{12}$ cells/l), percentage of reticulocytes was 0.12% (range, 0.5-2.5%) and concomitant thrombocytopenia of $2x10^9$ cells/l. There was

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Key words: pure red cell aplasia, acquired amegakaryocytic thrombocytopenia, thymoma, radiotherapy, surgery

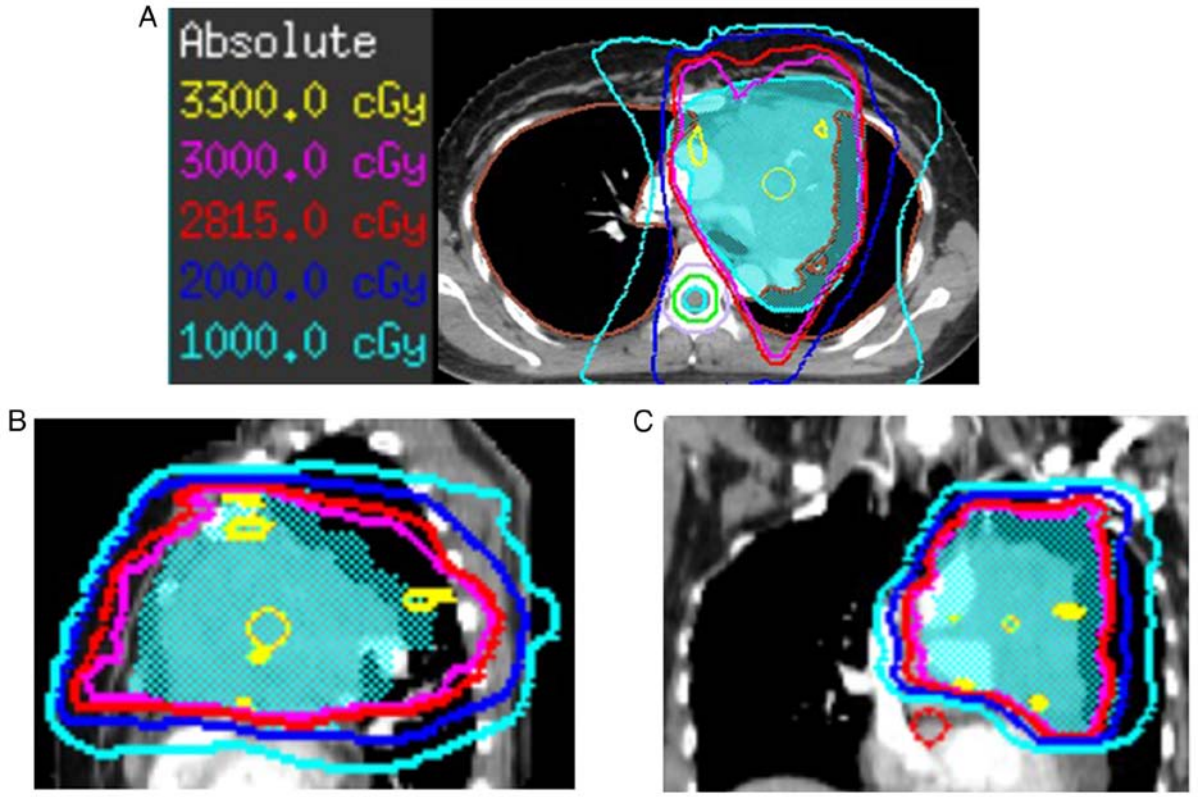

Figure 1. (A) Transverse radiation field. (B) Sagittal radiation field. (C) Coronal radiation field.

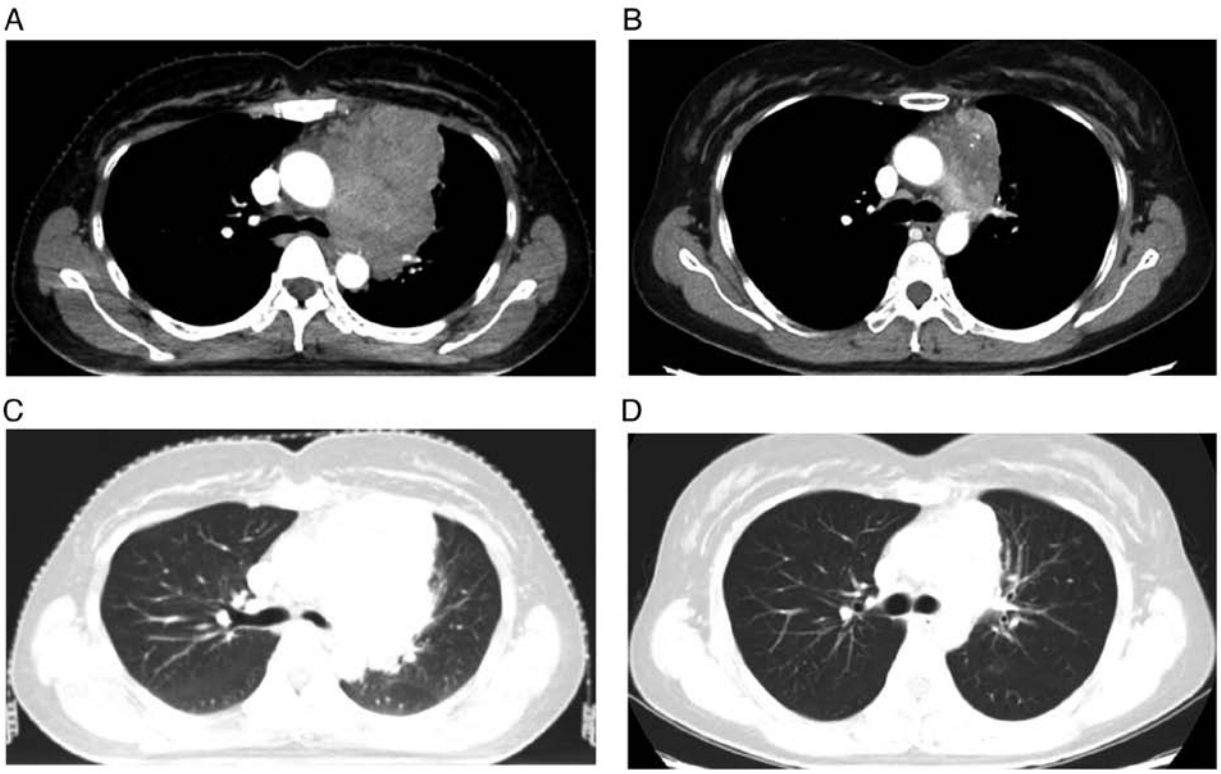

Figure 2. (A) Chest CT of the mediastinal window before radiotherapy. (B) Chest CT of the mediastinal window after radiotherapy. (C) Chest CT of the lung window before radiotherapy. (D) Chest CT of the lung window after radiotherapy.

no folic acid and vitamin B19 deficiency, while anti-internal factor antibodies were reduced. The coagulation function was basically normal. The erythropoietin level was high and the direct Coombs test yielded a positive for 2+.

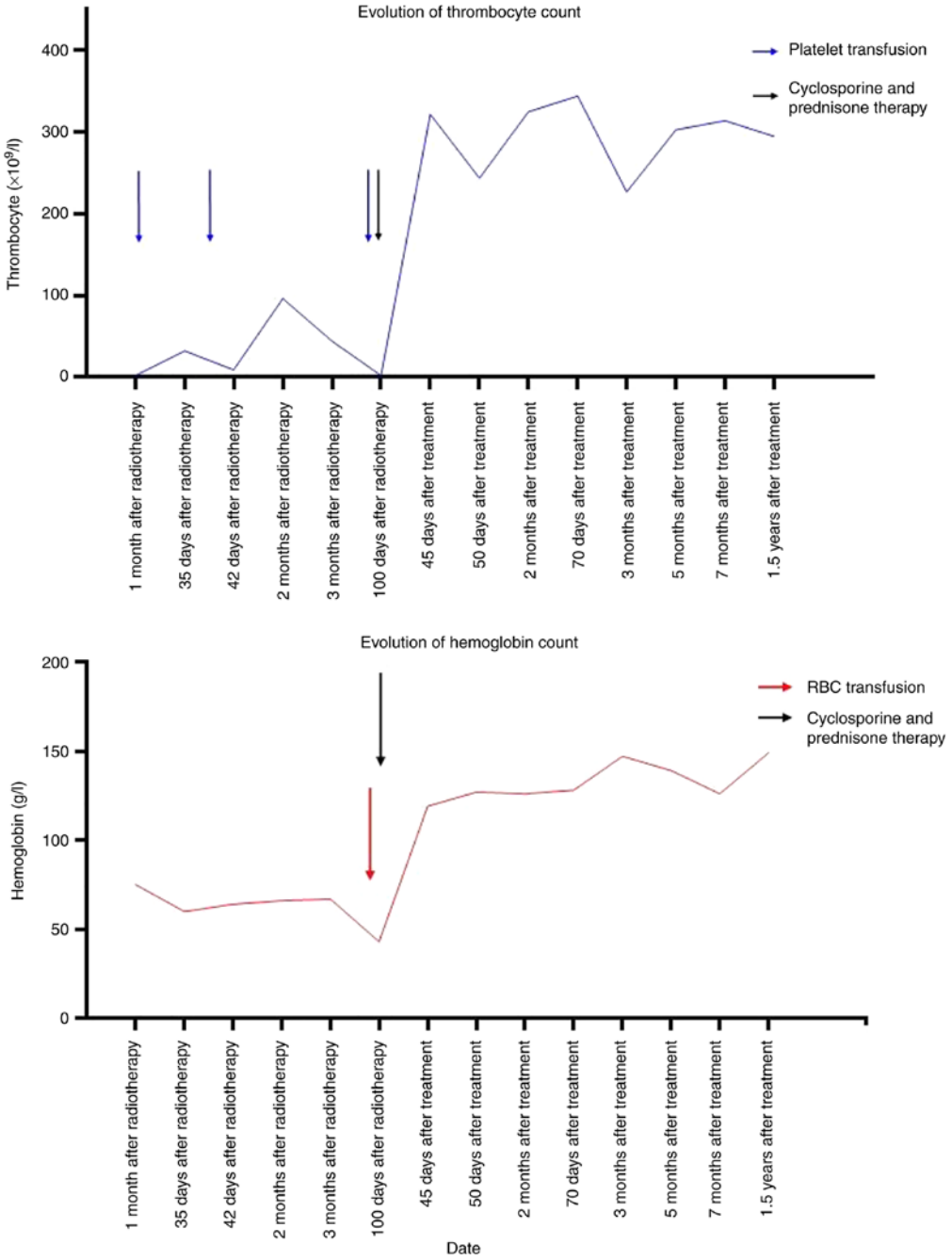

Figure 3. Clinical case diagram on the evolution of platelet (x10^9/l) and hemoglobin (g/l) counts over time (including the process of the platelet and hemoglobin changes in the pre-radiotherapy, post-radiotherapy and post-surgery). The blue arrows indicate platelet transfusion, the red arrow indicates the blood transfusion of red cell concentrate and the black arrows indicate cyclosporine in combination with prednisone therapy. RBC, red blood cell.

Bone marrow aspiration suggested that myeloid cells were normal, while granulocytic hyperplasia with toxic-like changes, with no red or megakaryocytic lineage detected. Fluorescence *in situ* hybridization (FISH) test, leukemia fusion gene WT1 test and flow-through immunophenotyping were all negative. Therefore, the combination of all the patient's findings led to a diagnosis of acquired PRCA and AAMT. We regret that the lack of hematological images was a limitation of our study because the patient's bone marrow aspiration was performed at The Affiliated Hospital of Guizhou Medical University and its hematological images were not available for loan, so we did not obtain the hematological images.

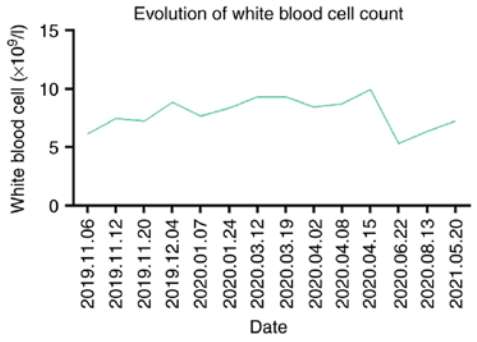

Figure 4. Clinical course diagram on the evolution of white blood cell (x10^9/l) counts over time.

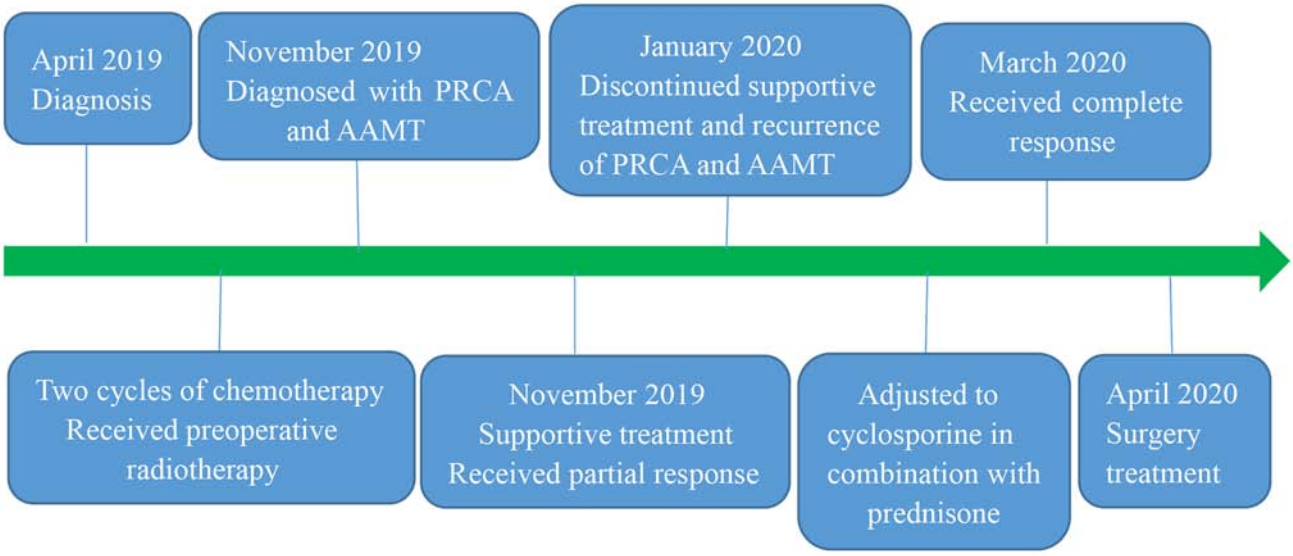

Figure 5. Timeline of disease status and corresponding treatment regiments.

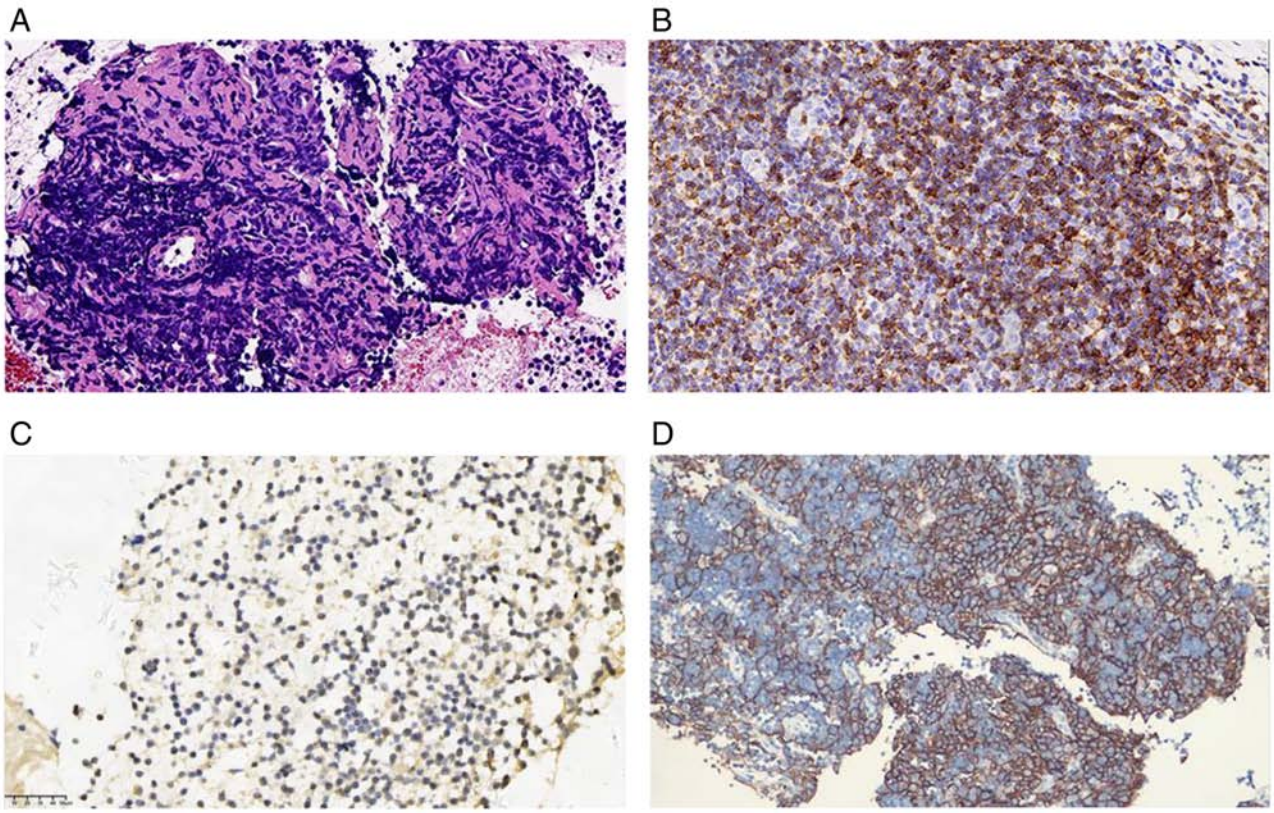

Figure 6. (A) Type AB thymoma (H&E, x400). (B) Background lymphocytes were positive for CD5 (immunohistochemistry, x400); (C) Background lymphocytes were positive for TdT (immunohistochemistry, x400); (D) Expression of PD-L1 was high (immunohistochemistry, x200).

Initially, the patient received supportive therapy such as hemostasis, Recombinant Human Erythropoietin Injection to relieve anemia, recombinant human platelet thrombopoietin, Eltrombopag Olamine Tablets and platelet transfusion to raise platelets, which led to partial alleviation of symptoms. However, PRCA and AAMT recurred after the patient stopped the above treatment on her own. The CBC results were shown below: hemoglobin 43 g/l, WBC 7.82x10^9 cells/l, and platelets 2x10^9 cells/l. The treatment regimen was then adjusted to cyclosporine in combination with prednisone therapy. After more than one month, the CBC results indicated that the patient's indicators had returned to the normal range and there was no recurrence (Fig. 3). Due to low hemoglobin and platelets, the patient was transfused with 6 units of platelet and 2 units of red blood cell suspension during the whole treatment (Fig. 3). Throughout the course of treatment, the patient's white blood cell count was normal (Fig. 4).

One month later, she underwent a complete resection of mediastinal tumor on April 14, 2020 (Fig. 5). On the first

postoperative day, the patient's CBC results were as follows: hemoglobin 141 g/l, WBC $10.99x10^9$ cells/l and platelets $205x10^9$ cells/l. The tissue pathology indicated type AB thymoma, with a predominance of B2 type, about 70-80% (Fig. 6A). Immunohistochemical analysis showed the epithelial cells to be positive for PCK, CK19, P63, EMA, but negative for CD117, CgA, Syn, while background lymphocytes were positive for CD5 and TdT, and the MIB-1 positivity rate was approximately 80% (Fig. 6B and C). Next-generation sequencing (NGS) was performed. The NGS was performed by a company (Shanghai Siludi Medical Laboratory) separate to the study, and the results obtained by the company are reported in the present study. Expression of PD-L1 was high with TPS=40% and CPS=40 (Fig. 6D), and immune status was in favor of immunotherapy. Notably, NGS indicated that MSH3 variants in DNA damage repair pathway-related genes was mutated with p.A57P in abundance of 9.21%. Other than that, the patient's PRCA and AAMT did not recur after the surgery. The CBC was performed on 2022-01-19 with the following results: hemoglobin 113 g/l, WBC $9.10x10^9$ cells/l and platelets $268x10^9$ cells/l. By telephone follow-up on October 20, 2022, we were informed that the patient had no tumor recurrence, no recurrence of PRCA and AAMT, and the CBC results in the normal range.

Discussion

Thymoma has a strong correlation with paraneoplastic immune disorders, and PRCA is the most common hematologic paraneoplastic manifestation of thymoma (12). Thymoma is rarely associated with AAMT, with only 8 cases reported in the literature (4-11). From the available reported literature, thymoma in combination with AAMT was always accompanied by PRCA, and in three of these cases the patients eventually developed aplastic anemia (AA) despite immunotherapy (6,9,10). Therefore, we support the theory that PRCA and AAMT may be early manifestations of aplastic anemia (10), and early intervention is needed for patients with combined PRCA and AAMT to avoid further progression to AA.

AAMT and PRCA secondary to thymoma frequently occur before or after chemotherapy and thymectomy (9). However, in our case, the simultaneous appearance of AAMT and PRCA after a favorable response to radiotherapy for thymoma is the first to be reported. Single nucleotide polymorphisms (SNPs) in genes associated with biological responses to radiation damage may affect the radiosensitivity of clinically normal tissues (13). MSH3, a member of DNA mismatch repair-related genes, while its genetic variant was found to be associated with the development of radiosensitivity in breast cancer patient (14), increasing the risk of acute skin toxicity after radiotherapy in breast cancer patients (14,15). In addition, MSH3 variant genotype has been reported to alter the toxicity of cisplatin-based chemotherapy and response to radiotherapy in patients with squamous cell carcinoma of the head and neck (16). Thus mismatch repair mechanisms may be involved in the cellular response to radiation therapy, and genetic polymorphisms may be valid candidates for predicting radiosensitivity (14). In this case, NGS detection revealed MSH3 gene variants, so we speculate that the pathogenesis may be related to the enhanced radiosensitivity caused by MSH3 variants, which may involve increased apoptosis of tumor cells and normal cells through an endogenous pathway, leading to a prolonged response and causing severe side effects (17).

Patients with AAMT in combination with PRCA may present with anemia, such as weakness, fatigue, pallor or dyspnea, or with bleeding due to thrombocytopenia, such as mucocutaneous or skin bleeding (9). The CBC test showed markedly reduced hemoglobin and platelets, as well as markedly reduced reticulocytes; bone marrow biopsy shows severe depletion of megakaryocytes and red lineage precursor cells, while myeloid cells are normal (4-11,18). In this case, the patient was presented with weakness, bleeding gums and bleeding spots on the skin, while her CBC tests and bone marrow aspiration were consistent with previous reports. Unfortunately, we did not obtain hematological images because the patients' bone marrow aspiration was not performed at our hospital, which is a limitation of the present study.

The treatment options for patients with thymoma combined with AAMT and PRCA remain unclear, but most patients achieve remission on cyclosporine-based therapy, combined or not with corticosteroid (4,7,8). After failure of first-line cyclosporine combined with corticosteroids, the addition of antithymocyte globulin may be effective (4). Allogenic stem cell transplantation may be considered if the patient fails to respond to these treatments or eventually progresses to Aplastic anemia (6). Successful immunotherapy with azathioprine or rituximab in patients with AAMT has also been reported (19,20). Corticosteroids alone may be ineffective, and one patient with unresolved thrombocytopenia after prednisolone treatment eventually died of intracranial hemorrhage (11). Iterative transfusions and platelet transfusions seems may not be effective (5,6,9,10). However, this patient achieved partial remission with symptomatic supportive therapy, AAMT and PRCA recurred after cessation of therapy and complete remission after treatment with cyclosporine combined with prednisone.

Acknowledgements

Not applicable.

Funding

This study was supported by the Youth Project of Sichuan Natural Science Foundation (reference no. 2023NSFSC1892).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL designed the study, edited and approved the manuscript. YX drafted the manuscript. YX and QW were involved in the process of diagnosis, treatment, follow-up of the patient, and revised the article. QW, FX and DP collected and analyzed the data. All authors were involved in writing the manuscript. YX,

QW and YL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the subject for the publication of any potentially identifiable images or data included in this article.

Competing interests

The authors declare that they have no competing interests.

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