CASE REPORT
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Thymic hyperplasia as a rare etiology of pure red cell aplasia

Hiperplazija timusa kao retka etiologija čiste aplazije eritroidne loze

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Abstract

Introduction. Thymic hyperplasia is a rare condition caused by an increase in cellular thymic mass and, in some cases, is associated with autoimmune diseases, such as pure red cell aplasia (PRCA). Thymectomy is considered the most effective therapy for PRCA associated with thymoma, with a 31.5% complete remission rate. Other treatments may induce partial remissions, but complete remission remains elusive. A case of PRCA attributed to thymic hyperplasia is presented, highlighting the effectiveness of thymectomy. **Case report.** A previously healthy 18-year-old woman presented with severe anemia and after hematological evaluation, including bone marrow biopsy confirmation, a diagnosis of PRCA was made. Immunological and virological analyses were unremarkable. Given the history of thymoma in the family and the known association between thymoma and PRCA, a chest magnetic resonance imaging was performed, which proved the existence of thymic hyperplasia. The patient underwent the least invasive surgical procedure – total thymectomy using video-assisted thoracic surgery approach. Pathohistological examination of the operative material confirmed the presence of thymic hyperplasia with a simple intrathymic cyst. Following thymectomy, the patient's hematological values significantly improved. **Conclusion.** The course and outcome of the patient's treatment support the role of thymectomy in PRCA associated with thymic hyperplasia. However, further research and follow-up are needed to optimize management strategies for this rare condition.

Key words:
anemia; diagnosis; histological techniques; red-cell aplasia, pure; thoracic surgery, video-assisted; thymoma; thymus hyperplasia.

Apstrakt

Uvod. Hiperplazija timusa je retko stanje koje nastaje kao posledica povećanog broja ćelija timusa, koje se u nekim slučajevima može dovesti u vezu sa autoimunskim bolestima kao što je čista aplazija eritroidne loze (*pure red cell aplasia* – PRCA). Timektomija se smatra najefikasnijim terapijskim modalitetom za lečenje PRCA povezane sa timomom, sa stopom potpune remisije od 31,5%. Ostali načini lečenja mogu dovesti do parcijalne ali ne i kompletne remisije. Prikazana je bolesnica kod koje je PRCA bila povezana sa hiperplazijom timusa, sa naglaskom na efikasnosti timektomije kao incijalnog terapijskog pristupa. **Prikaz bolesnika.** Prikazana je, prethodno zdrava, žena stara 18 godina, sa teškom anemijom kod koje je nakon hematoloških ispitivanja, uključujući i potvrdu biopsijom koštane srži, postavljena dijagnoza PRCA. Vrednosti imunoloških i virusoloških analiza bile su u granicama referentnih vrednosti. Zbog pojave timoma u porodičnoj anamnezi i poznate veze između timoma i PRCA, urađena je magnetna rezonanca grudnog koša kojom je dokazano postojanje hiperplazije timusa. Kod bolesnice je sprovedena najmanje invazivna hirurška procedura – totalna timektomija primenom video-asistirane torakoskopske hirurgije. Patohistološki pregled operativnog materijala potvrdio je prisustvo hiperplazije tkiva timusa, sa prisutnom „jednostavnom" cistom unutar timusa. Nakon timektomije, hematološki parametri bolesnice su se značajno poboljšali. **Zaključak.** Tok i ishod lečenja bolesnice podržavaju primenu timektomije u lečenju PRCA koja je povezana sa hiperplazijom timusa. Ipak, potrebna su dalja istraživanja i praćenja kako bi se optimizovao terapijski pristup za to retko stanje.

Ključne reči:
anemija; dijagnoza; histološke tehnike; aplazija crvene loze, čista; hirurgija, torakalna, video-asistirana; timom; timus, hiperplazija.

Introduction

Pure red cell aplasia (PRCA) is an exceptionally rare disorder characterized by the failure of erythropoiesis, resulting in anemia. This condition is characterized by normocytic, normochromic anemia, associated with severe reticulocytopenia and notable absence or severe decrease in erythroblasts from an otherwise normal bone marrow [1]. PRCA can mani-

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fest either as a congenital disorder, known as Diamond-Blackfan syndrome, or as an acquired disease resulting from various causes, including autoimmune disorders, some leukemias, lymphoproliferative disorders, ABO incompatible stem cell transplant, viral infections, medications, and notably, solid tumors. Among the last, thymoma is a prominent example strongly linked to PRCA [2].

Thymic hyperplasia (TH) refers to the enlargement of the thymus gland caused by an increase in the number of cells. During puberty, TH hyperplasia is not always a pathological condition – when the thymus grows beyond the expected size for a person's age, it warrants further investigation. In the pediatric population, TH is the most prevalent benign tumor found in the anterior mediastinum [3]. We present a case in which PRCA was attributed to TH, an exceptionally rare association. Notably, PRCA is presented as the primary feature of thymic enlargement in particular cases.

Case report

In July 2018, a previously healthy 18-year-old female was referred to hematology due to progressively worsening fatigue and malaise over the past two months. Moreover, she was also suffering from heavy menstrual bleeding. Physical examination revealed pallor of the skin but no enlarged lymph nodes or hepatosplenomegaly. Laboratory evaluation showed severe normocytic anemia [hemoglobin 56 g/L, reference range (RR) for female: 120–140 g/L; MCV 82 fL, RR: 80–100 fL] with normal white blood cell count (4×10^9/L, RR: 4–10×10^9/L) and normal platelet count (482×10^9/L, RR: 150–450×10^9/L).

Ferritin, total iron binding capacity, and iron levels were within the RR, even with a history of heavy menstrual bleeding. Due to the severity of the anemia, the patient received a packed red cell transfusion and was advised to take iron supplements for the following month. Regardless of that, her hemoglobin level declined further. The bone marrow aspirate was mildly hypocellular with a marked decrease in erythroid lineage, without signs of dysplasia. Cytogenetic analysis revealed a normal female karyotype. A bone marrow trephine biopsy demonstrated sparse erythroid lineage, with erythroblasts in various maturation stages lacking well-formed erythroid islets. With the present morphological features of PRCA, an immunology workup for connective tissue disease was performed and showed a complete absence of any immunological marker abnormalities. Antinuclear antibodies – ANA (Hep-2), antineutrophilic cytoplasmic antibody - ANCA, anti-transglutaminase antibodies - ATA, and anti-cardiolipin antibodies - ACA were negative; levels of complement (C) component 3 (C3), C4, and rheumatoid factor - RF were also within the RR. Virological analyses excluded cytomegalovirus, Epstein-Barr virus, parvovirus B19, human immunodeficiency virus, hepatitis C virus, and hepatitis B virus infections as possible causes. To evaluate further the mechanism responsible for the presence of PRCA, an in vitro hematopoietic progenitor culture assay was performed, showing preserved normal in vitro erythropoietic growth with an even more increased response of colony-forming unit (CFU)-E on erythropoietin stimulation (finding not consistent with typical PRCA). Erythropoietin level was 95.9 IU/mL (RR: 3.3–16.6 IU/mL), which is five times elevated.

Afterward, the co-cultivation cross-match assay was performed with the healthy bone marrow. This testing revealed that the patient's serum caused a dose-dependent humoral inhibition of erythroid colony growth at the level of CFU-E precursors in culture. Considering the patient's family history, especially the presence of thymoma in her aunt having myasthenia gravis (MG), it was decided to do a complete chest magnetic resonance imaging examination with a focus on the thymus due to the established association between thymoma and PRCA. The magnetic resonance imaging revealed an abnormal formation in the anterior mediastinum, measuring 41 × 11 mm, suggesting TH (Figure 1). After referral to the Thoracic Surgery Board, a decision was made to proceed with a total thymectomy, which was successfully performed by the video-assisted thoracoscopic sur-

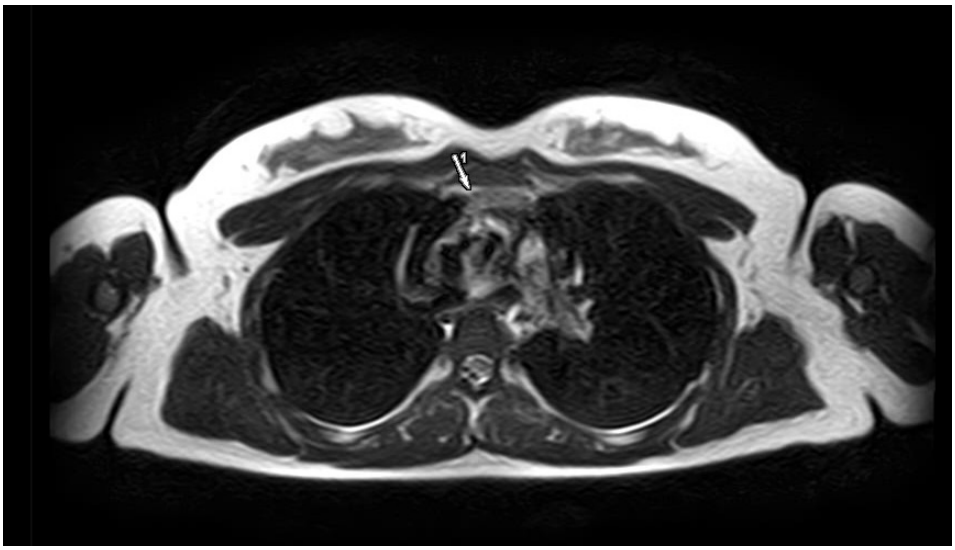

Fig. 1 – Chest magnetic resonance imaging demonstrating abnormal formation in the anterior mediastinum (arrow).

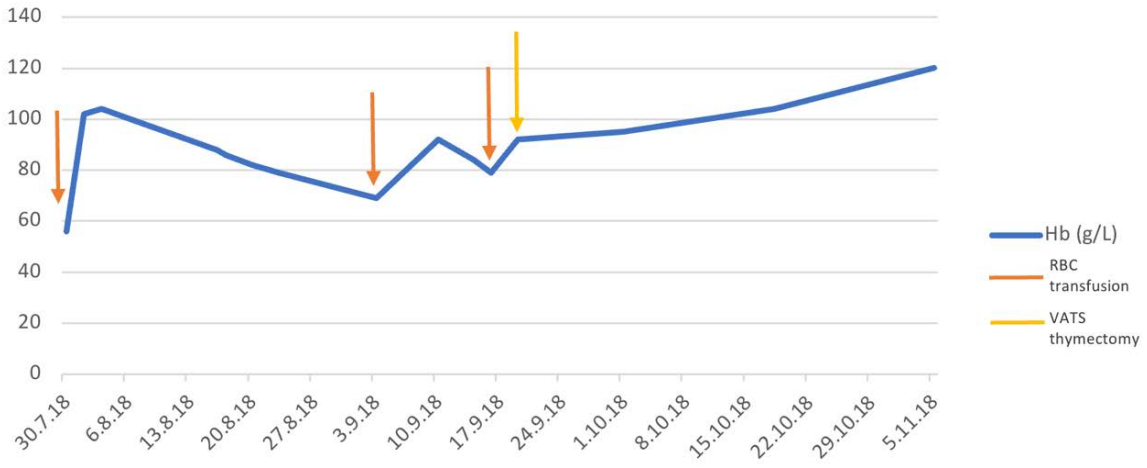

Fig. 2 – Effect of different treatment modalities on the patient's hemoglobin levels. Hb – hemoglobin; RBC – red blood cells; VATS – video-assisted thoracoscopic surgery.

gery (VATS) technique. The pathohistological examination of the excised thymus revealed morphological features consistent with thymus tissue containing an intrathymic simple cyst. Following the surgical intervention, the hematological parameters were stabilized with a subsequent rise toward normal values, indicating a positive outcome (Figure 2). During the five-year follow-up, her blood counts remained normal.

Discussion

The thymus is a crucial organ for the development of T-cells and for forming the adaptive immune system. It consists of various types of stromal cells and maturing T lymphocytes working together to build a strong cellular immune response [4].

Distinguishing between a normal and hyperplastic thymus can be challenging, but certain guidelines can help in this distinction, including the absence of rounded soft-tissue masses larger than 7 mm, the absence of a convex contour of the thymus in individuals above 19 years of age, the absence of soft-tissue lobulation, and absence of excessive thymic thickness (should be ≤ 1.3 cm in individuals above 20 years of age). Additionally, the absence of conditions associated with TH, like MG, is also important to consider [5]. In our patient, the thymus measured 41 × 11 mm, and it was presented as a convex formation in the anterior mediastinum. Moreover, the association with PRCA provided evidence that we were indeed dealing with TH.

TH itself is a benign condition characterized by an increase in the number of cells within the thymus gland. While TH and thymoma are separate entities, they can sometimes have similar clinical and radiological features, making it challenging to differentiate them based on imaging alone [6]. A definitive diagnosis usually requires a combination of clinical evaluation, imaging studies, and histopathological examination of a tissue sample obtained through biopsy or surgery. TH is associated with various autoimmune diseases, including MG, Graves' disease, systemic lupus erythematosus, ulcerative colitis, rheumatoid arthritis, and others [7]. The most common diseases associated with thymic function are MG and Grave's disease. MG is a neurological autoimmune disease characterized by autoantibodies targeting components of the neuromuscular junction, leading to disabling fatigability. Most MG patients have anti-acetylcholine receptor (AChR) antibodies. Histological abnormalities in MG are frequently found in the thymus, which can exhibit either TH or thymoma. TH is particularly associated with elevated levels of the anti-AChR antibody titer, which decreases after thymectomy. The hyperplastic thymus includes all components involved in the anti-AChR response: AChR, B-cells producing anti-AChR antibodies, and anti-AChR auto-reactive T-cells [8]. Graves' disease is an autoimmune disease characterized by the development of antibodies directed against the thyrotropin receptor. The relationship between TH and Graves' disease was first described in 1912, highlighting the importance of thorough thymus evaluation in patients with Graves' disease. The exact pathogenesis involves complex hormonal and immunological mechanisms, which remain to be fully elucidated [7]. In addition to these autoimmune diseases, there are certain hematological autoimmune conditions associated with thymic diseases, including aplastic anemia (AA) and PRCA. AA, as the worst manifestation of bone marrow failure, is characterized by low levels of blood cells in circulation and severely reduced marrow cellularity [9]. AA is a rare complication of thymoma and is even less common after surgical removal of a thymic tumor. The pathogenesis of AA associated with thymoma seems to be explained by bone marrow suppression related to unbalanced T-cell regulation and inverted $CD4^+/CD8^+$ T-cells ratio due to an increase in cytotoxic T-cells [9].

TH causing PRCA is very rare, with a limited number of published cases so far confirming this relationship [10–13] (Table 1).

The precise pathophysiology mechanism underlying PRCA associated with TH is yet to be determined. However,

Table 1

Other cases of pure red cell aplasia (PRCA) associated with thymic hyperplasia (TH)

Author (year)	Age at diagnosis (years)	Time of TH diagnosis	Time of PRCA diagnosis	Treatment	Follow-up (months)
Mohammad et al. (2021) [10]	25	2019	2019	thymectomy + prednisolone	21
Wong et al. (1995) [13]	28	1992	1992	thymectomy	24
Konstantopoulos et al. (1995) [11]	35	N/A	N/A	thymectomy	1
Suto et al. (2004) [12]	31	1975	2001	thymectomy + cyclosporine A	312

N/A – not available.

there is some understanding of the mechanisms contributing to PRCA in patients with thymoma. The published data suggests that multiple pathways may be involved in this clinical syndrome, including the presence of a humoral factor that suppresses the erythroid lineage, antibodies targeting erythropoietin, but also cell-mediated suppression involving T-cells, large granular lymphocytes, and natural killer cells [14]. In our case, we have demonstrated that TH induced an unbalanced immune response with humoral erythroid suppression even with high levels of endogenous erythropoietin. While TH is commonly associated with one autoimmune disease, there was a case in which TH was connected to both MG and PRCA [12]. Investigation of the pathogenesis in this case revealed increased $CD8^+$ T-cells and a decrease in $CD19^+$ B-cells. Interestingly, the $CD8^+$ T-cells were found to impede the maturation of early erythroid cells despite elevated erythropoietin levels. These results suggest that PRCA might be induced by a T-cell clonal disorder [15]. Similarly, in other reports in complex patients with polyglandular autoimmune syndrome, PRCA was associated with rearranged T-cell receptors (TCR) in response to calcineurin inhibitors. Due to the good response to VATS thymectomy, we have decided not to perform a TCR rearrangement study, as this might be a diagnostic step towards a decision for immunomodulatory treatment [16].

Moreover, some research has suggested that a thymoma or the thymus itself might, in some cases, share antigens with erythroblastic cells [17]. In a unique case, a patient with end-stage renal failure developed PRCA. The investigation revealed that the chronic antigenic stimulation of the thymus, caused by repeated blood transfusions and hemodialysis, resulted in lymphoid hyperplasia, ultimately leading to the development of PRCA [13].

Thymectomy stands out as the most potent anti-tumor therapy for PRCA associated with thymoma, yielding a 31.5% complete remission (CR) rate when performed alone or in conjunction with other treatment modalities [17]. While alternative anti-tumor interventions may induce partial remissions, the attainment of CR remains elusive based on available reports. It is worth noting that in some cases, PRCA can still occur after thymectomy. This finding suggests that immunological alterations of T- and B-cells may persist and continue to impact the maturation of erythroid precursors even after the surgical removal of the thymus [12]. Therefore, in instances where PRCA persists post-thymectomy, considering immuno-modulatory therapies, particularly cyclosporine, becomes crucial, as it has shown the most promising CR rates [18]. When it comes to treating PRCA associated with TH, there is a lack of official guidelines. However, there have been cases indicating that CR was achieved through thymectomy either alone or in combination with immunomodulatory therapy [10–13]. In one of these cases, thoracotomy was utilized to access the anterior mediastinum, while in the other case, a median sternotomy was chosen to allow for optimal exposure and complete clearance of mediastinal tissue [10, 11]. In our specific case, we opted for the VATS method, which has evolved over time to become a time-efficient, effective, and well-tolerated procedure with a low conversion rate and minimal complications [19]. As a result, the significant improvement in erythropoiesis and the subsequent normalization of laboratory values strongly support the compelling evidence that TH, operating through one of the previously discussed mechanisms, was indeed a causative factor behind PRCA.

Conclusion

Considering the previously discussed case, where PRCA was attributed to TH, our findings further support the effectiveness of thymectomy as a basic therapeutic approach for PRCA associated with this particular etiology. However, it is important to note that this is a rare condition that accounts for only a small subset of thymic masses associated with PRCA. Further research and exploration are warranted to deepen our understanding of this complex relationship and optimize management strategies for PRCA related to TH.

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