ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Pure Red Cell Aplasia in Follicular Lymphoma with Bone Marrow Involvement and Isoniazid Exposure

Aplasia Eritroide Pura em Linfoma Folicular com Envolvimento de Medula Óssea e Exposição a Isoniazida

Leonardo MAIA MOÇO [1,2], Inês RAMOS [1], Gil BRÁS [1], José Mário MARIZ [1]
Acta Med Port 2026 Feb;39(2):137-141 ▪ https://doi.org/10.20344/amp.23222

ABSTRACT

Pure red cell aplasia is a rare bone marrow failure syndrome that is often overlooked, as it is potentially associated with other more common diseases. This report describes a 79-year-old man who was referred due to red cell transfusion-dependent anemia, severe reticulocytopenia, and generalized lymphadenopathies. An excisional lymph node biopsy suggested a diagnosis of follicular lymphoma. Trephine biopsy identified areas of lymphoma infiltration and a significant reduction of erythroid precursor cells. The patient was treated with four-weekly doses of rituximab; however, only after suspension of isoniazid treatment for latent tuberculosis was a complete and persistent hematologic recovery achieved. This case highlights the rarely described association between pure red cell aplasia and isoniazid in a patient with simultaneous follicular lymphoma with bone marrow involvement. Recognition of such connections is crucial for accurate diagnosis and appropriate management, as the treatment of lymphoma might not be sufficient as a sole strategy for clinical improvement.

Keywords: Isoniazid/adverse effects; Latent Tuberculosis/drug therapy; Lymphoma, Follicular; Red-Cell Aplasia, Pure/chemically induced; Rituximab/therapeutic use

RESUMO

A aplasia eritroide pura é uma síndrome rara de falência medular muitas vezes subdiagnosticada, visto que pode ser secundária a outras doenças mais comuns. Este caso retrata um homem de 79 anos encaminhado por anemia dependente de transfusões, reticulocitopenia severa e linfadenopatias generalizadas. A biópsia excisional de gânglio foi sugestiva de linfoma não-Hodgkin folicular. A biópsia de medula óssea foi concordante, mas revelou ainda uma redução significativa de precursores eritroides. O doente foi tratado com rituximab em monoterapia; no entanto, somente após a suspensão do tratamento com isoniazida para tuberculose latente é que se obteve uma recuperação hematológica completa e persistente. Este caso destaca, assim, a associação raramente descrita entre aplasia eritroide pura e isoniazida, num doente com linfoma folicular concomitante com envolvimento medular. O reconhecimento destes casos é crucial para um diagnóstico e gestão adequados, uma vez que o tratamento do linfoma poderá não ser suficiente.

Palavras-chave: Aplasia Eritroide Pura/induzida quimicamente; Isoniazida/efeitos adversos; Linfoma Folicular; Rituximab/uso terapêutico; Tuberculose Latente/tratamento farmacológico

INTRODUCTION

Pure red cell aplasia (PRCA) is a rare bone marrow failure syndrome characterized by normocytic, normochromic anemia, severe reticulocytopenia (< 10 000/µL), and a marked reduction or absence of erythroid precursors, while leukocyte and platelet lines remain unaffected.[1]

Acquired PRCA is classified as either primary or secondary. Primary PRCA, in turn, can be autoimmune or myelodysplastic, the latter often associated with marrow hypercellularity, dysplasia, and cytogenetic abnormalities. For instance, mutations in N-RAS and RPS-14 gene loss are occasionally found in PRCA with myelodysplastic neoplasms.[2] Secondary PRCA may result from autoimmune or collagen vascular diseases, lymphoproliferative disorders, infections (e.g., parvovirus B19, HIV, CMV, EBV, HHV-6), solid tumors like thymomas, or drug exposure.[1,3] Drug-induced PRCA accounts for less than five percent of PRCA cases, although the number of reported cases for each drug remains limited and this proportion might thus be underestimated. The literature reports over 30 drugs possibly associated with PRCA, such as chloramphenicol, trimethoprim-sulfamethoxazole, phenytoin, azathioprine, ticlopidine, allopurinol, procainamide, penicillamine, ribavirin and isoniazid.[1]

CASE REPORT

A 79-year-old man with dyslipidemia, hypertension, peripheral artery disease, and latent tuberculosis under isoniazid (started approximately three months prior) presented with a two-month history of fatigue and anorexia, and no B symptoms. The physical examination was unremarkable. Blood tests showed severe normocytic anemia (hemoglobin 4.8 g/dL), reticulocytopenia (5700/µL; reticulocyte index 0.06), normal WBC (6720/µL) and platelets (326 000/µL), and an unremarkable smear. Extensive laboratory investigations showed normal results for iron kinetics, folate, vitamin B12, thyroid-stimulating hormone, antinuclear antibodies, serum protein electrophoresis, and lactate dehydrogenase. Screening for viral agents, including HIV, hepatitis B and hepatitis C virus, CMV, EBV, HHV-6 and B19 parvovirus,

1. Department of Hematology and Bone Marrow Transplantation. Instituto Português de Oncologia do Porto Francisco Gentil. Porto. Portugal.
2. Laboratory of Histology and Embryology. Department of Microscopy. School of Medicine and Biomedical Sciences. Universidade do Porto. Porto. Portugal.
✉ **Autor correspondente:** Leonardo Maia Moço. lfmoco@gmail.com
Recebido/*Received*: 10/04/2025 - **Aceite/*Accepted*:** 19/08/2025 - **Publicado *Online*/*Published Online*:** 27/10/2025 - **Publicado/*Published*:** 02/02/2026

also yielded negative results. Erythropoietin (179 mU/mL) and β2-microglobulin (5.47 mg/L) were elevated.

An 18F-FDG PET/CT scan revealed suspicious generalized lymphadenopathy, with nodes measuring less than 30 mm and a maximal standardized uptake value (SUV) of 5.0 (benign lesions usually present a SUV inferior to 2.0 - 2.5), as well as splenic and marrow uptake (Fig. 1). Lymph node biopsy showed nodular proliferation of CD10+, CD20+, CD23+, Bcl6+, variably Bcl2, and CD5- small lymphocytes, consistent with a grade 1 follicular non-Hodgkin lymphoma (NHL). Bone marrow biopsy revealed hypercellularity, reticulin fibrosis (MF-2), erythroid hypoplasia with dysplasia, mild megakaryocytic changes, and a predominance of myeloid cells, with CD34+ cells mildly elevated (< 2%). Interstitial and nodular infiltrates of CD20+/PAX5+ B cells was also compatible with the above-mentioned diagnosis (Fig. 2). The disease was staged IV with a follicular lymphoma international prognostic index score of 3 (high-risk disease), and rituximab monotherapy (375 mg/m^2 weekly for four weeks) was initiated. Post-treatment PET/CT showed a partial response, now without bone marrow involvement. Although a temporary clinical recovery was observed, it was soon, followed again by persistent low reticulocyte counts and transfusion-dependency. Repeat trephine biopsy showed similar findings to the previous one, and cytogenetics was unremarkable.

Two months later, isoniazid was discontinued after six months of use, given suspected drug-induced PRCA. Reticulocyte counts rose significantly (from 7500/μL to 119 000/μL; RI from 0.07 to 1.83) within a month. Sustained hematologic recovery and transfusion independence were achieved (see Table 1).

DISCUSSION

This case posed diagnostic challenges because even though follicular NHL explained the systemic and marrow findings, the degree of reticulocytopenia and erythroid suppression raised suspicion of an additional process, suggesting a concurrent PRCA secondary to the lymphoproliferative disease. The association between lymphoproliferative and autoimmune disorders is well-documented. A recent cohort study found that, among 85 701 hospitalizations for lymphoma, 3.3% had a concurrent diagnosed autoimmune disorder.[4] Nonetheless, the coexistence of PRCA and follicular NHL is seldom reported and apparently very rare. In a separate cohort study of 185 PRCA patients, only one case involved concomitant follicular NHL.[5] Proposed mechanisms explaining this association include humoral responses against erythroid precursors or erythropoietin, and cytotoxic effects by CD8+ T-cells or NK-cells. An antibody-dependent cellular cytotoxicity pathway may also be involved, highlighting the complexity of immune interactions in PRCA.[6-8]

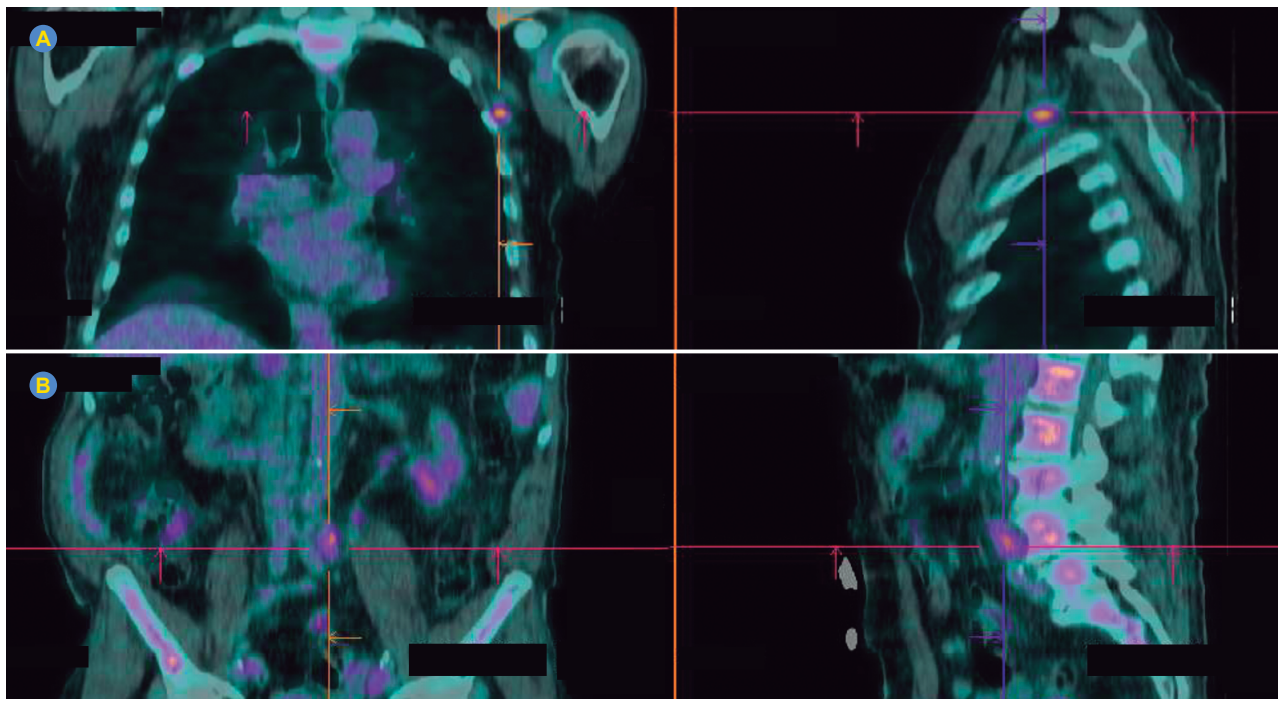

Figure 1 – 18F-FDG PET/CT scan, coronal (on the left) and sagittal (on the right) views, displaying metabolic hypercaptation (A) in left axillar lymph nodes (maximum standardized uptake value (SUVmax) of 4.8), (B) left common iliac and ilio-obturator chains (SUVmax 5.0) and also diffusely throughout the axial skeleton.

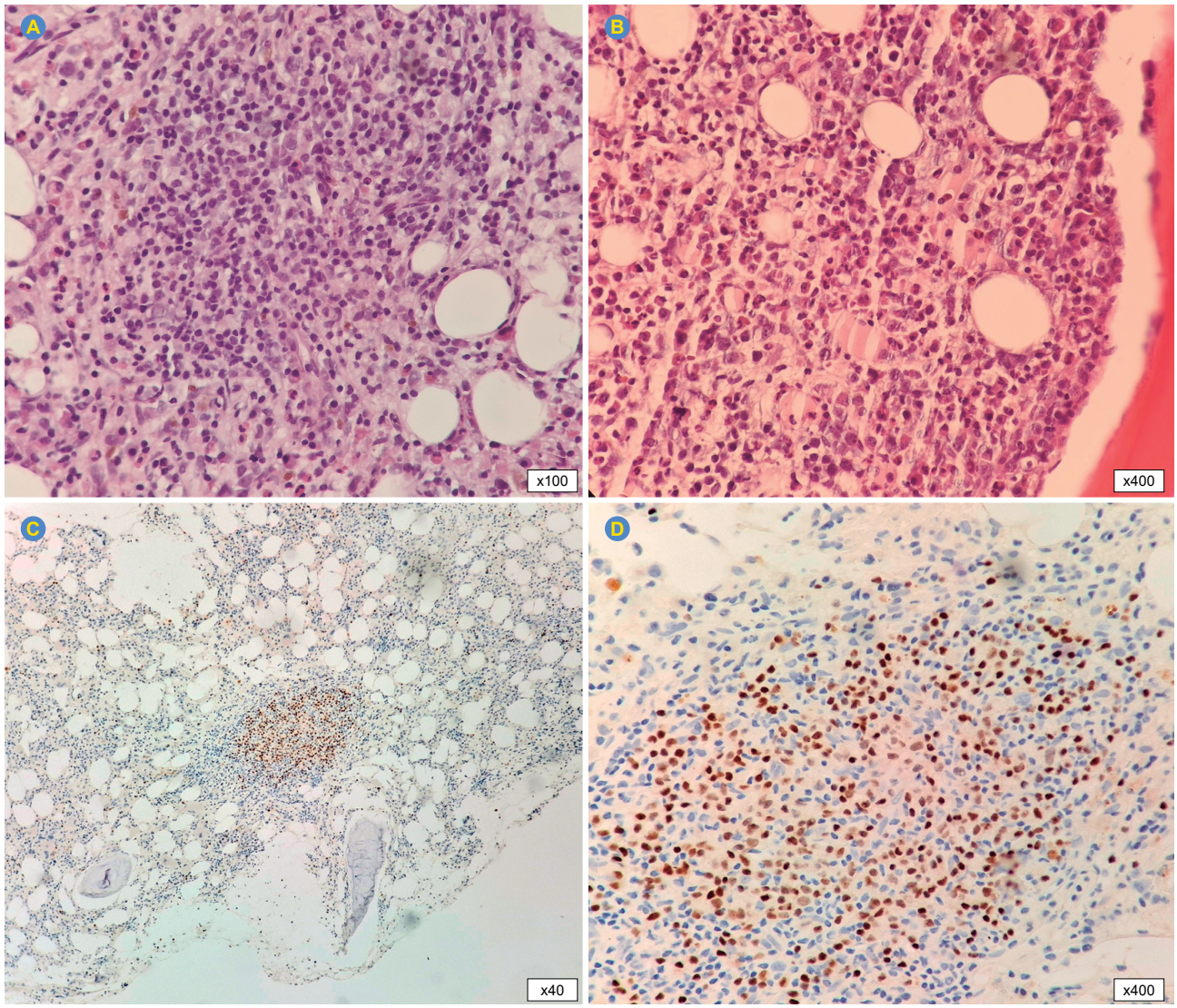

Figure 2 – Trephine biopsy displaying markedly diminished erythroid lineage and a relative predominance of myeloid lineage (A and B, hematoxylin and eosin staining), as well as a population of small B lymphocytes PAX5(+), organized in a nodular pattern (C and D).

Table 1 – Evolution of the patient's hemogram. Hemoglobin, reticulocyte count and reticulocyte index (RI) values variation show an initial temporary analytical recovery after treatment with rituximab. However, it was only sustained following isoniazid suspension.

Timing	**Hemoglobin** (g/dL)	**Reticulocyte count** (/µL)	**RI**
Admission	4.8	5700	0.06
Month one (after treatment with rituximab)	7.6	43 000	0.46
Month three (isoniazid withdrawal)	7.7	7500	0.07
Month four	10.8	119 000	1.83
Month six	12.6	89 600	2.2

Later, isoniazid was also considered a likely contributor, and in fact a few case reports describe this very rare phenomenon of isoniazid-induced PRCA. Loulergue *et al* reported marrow-confirmed PRCA resolving within 10 days of isoniazid withdrawal.[9] Azhar *et al* and Shukla *et al* also reported recovery after stopping isoniazid.[10,11] Usually, symptoms manifest around one to two months after the introduction of isoniazid, as it was observed in this case. Even though mechanisms remain unclear, an autoimmune response may be involved, as some cases were Coombs positive.[12]

Treatment of PRCA is primarily directed at addressing its underlying etiology. In autoimmune PRCA, corticosteroids and cyclosporine A are first-line options.[1] Rituximab, effective for B-cell NHL in general, has also shown benefit in PRCA related to lymphoproliferative diseases,[13-15] and occasionally in primary acquired autoimmune PRCA.[1,15] Given this body of evidence, we hypothesized that the immunosuppressive role of rituximab could address both underlying pathophysiological mechanisms. A case report of PRCA secondary to follicular NHL illustrates a close temporal alignment between the progression and treatment response of both conditions.[16] However, in this patient, although rituximab may have contributed partially to recovery, a sustained hematologic response coincided more directly with isoniazid withdrawal.

A limitation is the close timing between rituximab treatment and isoniazid suspension, making it difficult to definitively attribute recovery to one of these factors. Still, the marked and sustained reticulocyte rise post-isoniazid cessation strongly supports a drug-induced etiology, and in that case, the diagnosis of follicular NHL was just an incidental, synchronous finding.

This case illustrates a very rare and complex presentation of PRCA in a patient with follicular NHL and concurrent isoniazid exposure. Both the lymphoma and the drug may have contributed to PRCA, and both situations are scarcely documented. Clinicians should maintain high suspicion for PRCA in patients with anemia, especially when erythropoiesis is suppressed and reticulocyte counts are low. Because secondary PRCA often resolves with the treatment of the underlying disease, many such cases of PRCA might remain underreported. Therefore, prompt recognition and timely investigation are crucial for the thorough exclusion of alternative differential diagnoses and for ensuring optimal management.

ACKNOWLEDGMENTS

The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

LMM: Conceptualization, data curation, writing – original draft, writing – review & editing.

IR: Data curation, writing – review & editing.

GB: Conceptualization, data curation, supervision, validation.

JMM: Supervision, validation.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Sawada K, Fujishima N, Hirokawa M. Acquired pure red cell aplasia: updated review of treatment. Br J Haematol. 2008;142:505-14.
2. Vlachos A, Farrar JE, Atsidaftos E, Muir E, Narla A, Markello TC, et al. Diminutive somatic deletions in the 5q region lead to a phenotype atypical of classical 5q- syndrome. Blood. 2013;122:2487-90.
3. Visco C, Barcellini W, Maura F, Neri A, Cortelezzi A, Rodeghiero F. Autoimmune cytopenias in chronic lymphocytic leukemia. Am J Hematol. 2014;89:1055-62.
4. Sukhera AB, Rodriguez Vazquez J, Erazo G, Ogedegbe OJ, Ntukidem OL, Sanchez A, et al. Association of autoimmune disorders and lymphoma: a population-based cohort study. Blood. 2024;144:6429.
5. Hirokawa M, Sawada K, Fujishima N, Kawano F, Kimura A, Watanabe T, et al. Acquired pure red cell aplasia associated with malignant lymphomas: a nationwide cohort study in Japan for the PRCA collaborative study group. Am J Hematol. 2009;84:144-8.
6. Fisch P, Handgretinger R, Schaefer HE. Pure red cell aplasia. Br J Haematol. 2000;111:1010-22.
7. Handgretinger R, Geiselhart A, Moris A, Grau R, Teuffel O, Bethge W, et al. Pure red-cell aplasia associated with clonal expansion of granular lymphocytes expressing killer-cell inhibitory receptors. N Engl J Med. 1999;340:278-84.
8. Vlachaki E, Diamantidis MD, Klonizakis P, Haralambidou-Vranitsa S, Ioannidou-Papagiannaki E, Klonizakis I. Pure red cell aplasia and lymphoproliferative disorders: an infrequent association. Sci World J.

2012;2012:475313.
9. Loulergue P, Mir O, Dhote R. Pure red blood cell aplasia and isoniazid use. Emerg Infect Dis. 2007;13:1427-8.
10. Azhar W, Zaidi F, Hannan A. Isoniazid induced pure red blood cell aplasia. Cureus. 2020;12:e7112.
11. Shukla A, Mishra S, Jain M, Tripathi AK. Pure red cell aplasia: a rare complication of isoniazid therapy. Indian J Hematol Blood Transfus. 2014;30:36-7.
12. Goodman SB, Block MH. A case of red cell aplasia occurring as a result of antituberculous therapy. Blood. 1964;24:616-23.
13. Kahl BS, Hong F, Williams ME, Gascoyne RD, Wagner LI, Krauss JC, et al. Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: eastern cooperative oncology group protocol e4402. J Clin Oncol. 2014;32:3096-102.
14. Ghazal H. Successful treatment of pure red cell aplasia with rituximab in patients with chronic lymphocytic leukemia. Blood. 2002;99:1092-4.
15. Auner HW, Wolfler A, Beham-Schmid C, Strunk D, Linkesch W, Sill H. 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.
16. Yamamoto G, Maki H, Ichikawa M, Kurokawa M. Pure red cell aplasia with follicular lymphoma showing regression and progression parallel to lymphoma. Int J Hematol. 2011;94:576-7.