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Case Report

A Case of Pure Red Cell Aplasia as a Possible Complication of Pulmonary Tuberculosis Treatment

Kasus *Pure Red Cell Aplasia* sebagai Komplikasi Terapi Tuberkulosis Pulmonal

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Abstract

Pure red cell aplasia (PRCA) is a rare disorder caused by failure or abnormalities in erythropoiesis only, among all cell lines of the bone marrow. Patients with PRCA usually present with no specific clinical presentation, thus its recognition depends on a clinician's high index of suspicion, to facilitate early diagnosis and treatment to provide a better prognosis. Tuberculosis (TB) is the infectious disease with the highest casualty rate worldwide and is still a problem in many countries, including Indonesia. This study is a case report of a pulmonary TB patient with PRCA as a complication. PRCA was confirmed by the bone marrow puncture (BMP) examination as the gold standard. In this case, PRCA was inferred to occur due to the use of Isoniazid in the TB treatment regimen. The discontinuation of Isoniazid administration subsequently results in the normalization of Hb levels. In this paper we would highlight PRCA as a differential diagnosis that should be taken into consideration in symptomatic anemia in patients with tuberculosis under standard treatment.

***Keywords** : Pure red cell aplasia; tuberculosis; isoniazid; anemia; tuberculosis treatment*

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Abstrak

Pure red cell aplasia (PRCA) merupakan kelainan langka yang hanya disebabkan oleh kegagalan atau kelainan pada eritropoiesis, di antara semua galur sel sumsum tulang. Pasien dengan PRCA biasanya datang tanpa presentasi klinis yang spesifik, sehingga rekognisinya bergantung dari indeks kecurigaan yang tinggi dari klinisi, untuk memfasilitasi diagnosis dan terapi awal untuk memberikan prognosis yang lebih baik. Tuberkulosis (TB) merupakan penyakit menular dengan angka kematian tertinggi di dunia dan masih menjadi masalah di banyak negara, termasuk Indonesia. Studi ini adalah laporan kasus pasien TB paru dengan PRCA sebagai komplikasi. PRCA dikonfirmasi dengan pemeriksaan punksi sumsum tulang sebagai standar emas. Dalam kasus khusus ini, PRCA diduga terjadi karena penggunaan isoniazid dalam rejimen pengobatan TB. Penghentian pemberian isoniazid selanjutnya menghasilkan normalisasi kadar Hb. Melalui laporan kasus ini, kami hendak menyorot PRCA sebagai salah satu diagnosis banding yang harus dipertimbangkan apabila ditemukan anemia simtomatik pada pasien tuberkulosis dalam terapi standar.

Kata kunci: *pure red cell aplasia*; tuberkulosis; anemia; terapi tuberkulosis

Introduction

Pure Red Cell Aplasia (PRCA) is a syndrome defined by normocytic normochromic anemia with severe reticulocytopenia and marked reduction or absence of erythroid precursors from the bone marrow.[1–3] Pure red cell aplasia is a rare disorder.[2] Based on etiology, PRCA is classified into two distinct forms, with no definitive incidence or prevalence of the disease in the general population except for some estimates, and a report from Japan.[4]

Clinical presentation of PRCA is the same as that of anemia.[1,5] PRCA patients usually have a stable hemodynamic system, and rarely need hospitalizations.[4,6] For acquired PRCA, the main concern is how to find the underlying cause of the anemia and the appropriate treatment according to its cause.[6]

In this study, we will present a case report of a PRCA patient as a complication of pulmonary TB therapy. In this paper we would highlight PRCA as a differential diagnosis that should be taken into consideration in symptomatic anemia in patients with tuberculosis under standard treatment.

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This case report has received an Ethical Clearance from Immanuel Hospital Health Research Ethics Committee, No. 58/A01/EC/XII/2021.

First Hospitalization

A 16-year-old female was brought into the ER with the chief complaint of sudden loss of consciousness accompanied by seizures. On the way from a clinic to the hospital, the patient was

unconscious, with generalized stiffening of the body, and upward gaze of the eyes. The patient previously complained about shortness of breath, without cough or fever. About a week earlier, the patient had complaints of yellow eyes, epigastric pain, swollen face, but not swollen feet. No urinary complaints. The patient also had a history of irregular menstruation.

Initial physical examination showed blood pressure of 97/52 mmHg, heart rate 147x/minute, respiratory rate 46x/minute, with 100% SpO2 level. The sclera was icteric, but the conjunctiva was not anemic. Blood sugar examination while in the ER showed hypoglycemia with a level of 37 mg/dL. The patient has been previously diagnosed with pulmonary tuberculosis (TB) and has been taking anti-TB medications since one month prior. Further laboratory findings revealed normochromic normocytic anemia, with decreased hemoglobin level (10.7 g/dL), decreased hematocrit and erythrocyte count, leukocytosis with neutrophil predominance, elevated liver enzymes, decreased eGFR, and metabolic acidosis.

The patient was diagnosed with urosepsis with hypoglycemia-induced seizure, drug induced liver injury (DILI) due to TB medications, congestive heart failure (CHF), with AKI and post-convulsive metabolic acidosis.

Patients were treated with broad-spectrum antibiotic therapy for urosepsis, anticonvulsants for seizure control, along with nutritional, fluid, and electrolyte support. TB 4FDC (RHZE) was contemplated to be shifted to 2RHES – $6RH^{4,5}$, however due to streptomycin's known renal toxicity, due to AKI, the regimen $9RHE^{4,5}$ was chosen. Once the condition was stable, the patient was discharged.

Second Hospitalization

Two weeks afterwards, the patient was brought back to the ER with the chief complaint of shortness of breath that has been worsening since the previous two days, felt especially when doing activities, without wheezing. One week ago, the patient had a seizure that lasted less than five minutes, presumably due to recurrence of hypoglycemia. No fever or cough. There were complaints of difficulty eating.

Physical examination showed tachycardia, tachypnea, elevated JVP, and positive signs of acute pulmonary edema. The patient was diagnosed with acute pulmonary edema due to CHF. Laboratory findings revealed anemia with Hb 10.0 g/dL. Echocardiography showed global hypokinesia with decreased left ventricular ejection fraction (LVEF) of 33.77% which supported the diagnosis of heart failure with reduced ejection fraction. The patient received the following additional therapy: furosemide 2 x 40 mg, bisoprolol 1 x 2.5 mg, and MRA spironolactone 1 x 25 mg. After 5 days of treatment, the patient's condition was stable, and the patient was discharged.

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Third Hospitalization

Three months afterwards, the patient was brought back to the ER, this time with complaints of nausea, vomiting and lack of appetite since one day ago, accompanied by generalized body weakness and irregular menstruation, the last one was six months ago. History of bleeding and fever was denied. The patient also complained about infrequent coughs, denies purulent sputum, denies hemoptysis, denies pink frothy sputum. The patient admitted that she had been taking all her medications regularly according to the doctor's advice.

On physical examination, hypotension was found to be 80/45 mmHg, with an initial diagnosis of shock. On further investigation, it turned out that the patient had anemia gravis with an initial Hb of 2.6 g/dL. After peripheral blood smear was acquired, PRC transfusion therapy was administered. After a total of 3 units PRC transfusion, the Hb level increased to 8.9 g/dL (see Tables 1 and 2).

After the patient's conditions are stable, the patient was discharged with dietary advice, Fe+ and folic acid supplementations. Other previous medical therapies including TB and CHF medications were continued.

Table 1. Hematology Findings (28/01/2021 - 01/02/2021 Hospitalization)

	28/01/2021	29/01/2021	01/02/2021
Hematology			
HGB (g/dL)	2.6	7.2	8.9
HCT (%)	8	22	27
WBC (10^3/mm^3)	6.72	8.35	7.22
PLT (10^3/mm^3)	247	164	179
RBC (10^6/mm^3)	1.1	2.6	3.3
RBC Indices			
MCV (fL)	76	83	84
MCH (pg/mL)	24	28	27
MCHC (g/dL)	31	33	33

(HGB, Haemoglobin; HCT, Haematocrit; WBC, Leukocyte Count; PLT, Platelet Count; RBC, Erythrocyte Count; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Haemoglobin; MCHC, Mean Corpuscular Haemoglobin Concentration)

Table 2. Peripheral Blood Smear (28/01/2021)

Component	Interpretation
Erythrocyte	Hypochromic, anisopoikilositosis (microcytic, ovalocytes, pencil shape), normoblast (-), reticulocytes (+)
Leukocyte	Adequate count, normal morphology
Thrombocyte	Adequate count, giant thrombocytes (+)
Impression	Hypochromic anemia with the impression of iron deficiency dd/ chronic inflammation in origin

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Fourth Hospitalization

After two months, the patient returned to the ER with the same symptoms as before. On physical examinations, blood pressure showed 107/59 mmHg, heart rate 133x/minute, temperature 37.1ºC, respiratory rate 24x/minute, SpO2 91%. Laboratory findings showed that the Hb dropped to 2.8 g/dL. Blood transfusion was given again accordingly.

Due to recurrent anemia even though the patient's nutritional intake was deemed adequate, and the focus of infection (TB) was controlled, bone marrow puncture (BMP), antinuclear antibody (ANA) test, G6PD enzyme levels, and direct and indirect Coombs tests were requested. Results were obtained (Tables 3-6) which supported the diagnosis of PRCA.

Table 3. Hematology Findings (17/03/2021 - 25/03/2021 Hospitalization)

	17/03/2021	20/03/2021	22/03/2021
Hematology			
(HGB) (g/dL)	2.8	7.4	7.5
(HCT) (%)	8	22	22.2
(WBC) (10^3/mm^3)	4.40	6.48	5.16
(PLT) (10^3/mm^3)	359	154	178
(RBC) (mil/mm^3)	1	2.7	
RBC Indices			
MCV (fL)	79	82	-
MCH (pg/mL)	28	28	-
MCHC (g/dL)	36	34	-

(HGB, Haemoglobin; HCT, Haematocrit; WBC, Leukocyte Count; PLT, Platelet Count; RBC, Erythrocyte Count; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Haemoglobin; MCHC, Mean Corpuscular Haemoglobin Concentration)

Table 4. BMP Readings (17/03/2021)

Parameter	Interpretation
Smear	Adequate
Cellularity	Hypocellular
Erythrocyte Series Activity	Very low activity, erythroblast <1%, dyserythropoiesis (+)
Granolucyte Series Activity	Good activity, eosinophilia, dysgranulopoiesis (-)
Thrombocyte Series Activity	Good activity, dysthrombopoiesis (-)
Impression	Marked decrease in erythropoiesis activity. PRCA + eosinophilia.

Table 5. Peripheral Blood Smear (17/03/2021)

Component	Interpretation
Erythrocyte	Normochromic, anisopoikilositosis (microcytic, ovalocytes, acanthocytes), normoblast not found, low count of reticulocytes (+)
Leukocyte	Adequate numbers, shift to the left, band cells 8%, relative eosinophilia
Thrombocyte	Adequate numbers, giant thrombocytes (+)

Table 6. ANA, G6PD, Coombs' Test (17/03/2021)

Tests	Results
Serum ANA total	17,3 U/ml (normal)
G6PD	10,8 IU /g Hb
Direct Coombs' Test	Negative
Indirect Coombs' Test	Negative

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Based on medical history, results of physical examination, and supporting laboratory examinations, the patient was diagnosed with Acquired Pure Red Cell Aplasia, with isoniazid (INH) being the suspected precipitating factor. Due to TB therapy now being at continuation phase, INH therapy was discontinued, and the regimen was shifted to Rifampicin and Ethambutol administration for a total of 10 months (10RE). To ensure the effectiveness of the ongoing TB therapy (currently at 7th month), a chest X-ray was repeated and compared to previous X-rays. Radiological findings showed no active pulmonary TB, along with cardiomegaly with no signs of pulmonary congestion.

The patient was referred to the Hematology-Oncology subspecialty service, and she subsequently received additional therapy of cyclosporine 2x 25 mg and prednison 0.5 mg/kgBW/day (20 mg/day in total), with tapering off dose per week to a minimum dose of 5 mg/day, then stopped. After the patient's condition was stable, the patient was discharged.

Subsequent follow ups

The patient was regularly monitored every 2 weeks at the OPD. TB medications were discontinued after a total of 10 months continuation phase. Cyclosporine and prednison were discontinued after tapering off for approximately 3 weeks. The patient was programmed for regular follow-up at the Cardiology OPD for continuation of CHF therapy.

In the figure 1, we can see the trend of Hb levels in concordance with TB medications. Initially, the Hb decreases over time, attributed to chronic disease, requiring multiple transfusions. It is noted subsequently that discontinuation of INH prompted a sustained increase in Hb levels without further episodes of anemia.

Discussion

Based on etiology, PRCA is classified into two distinct forms[1,2]. In our case, we will focus more on secondary subtype of acquired PRCA. Secondary acquired PRCA may be associated with autoimmune/collagen vascular disorders; lymphoproliferative disorders, particularly chronic lymphocytic leukemia; infections, especially B19 parvovirus; pregnancy; hematologic malignancies; nonhematologic neoplasms, of which the association with thymoma is the best known; and drugs and toxic agents.[2,3,6] Many of the mechanisms underlying secondary acquired PRCA are immunologic, although not always antibody-mediated.[3,6]

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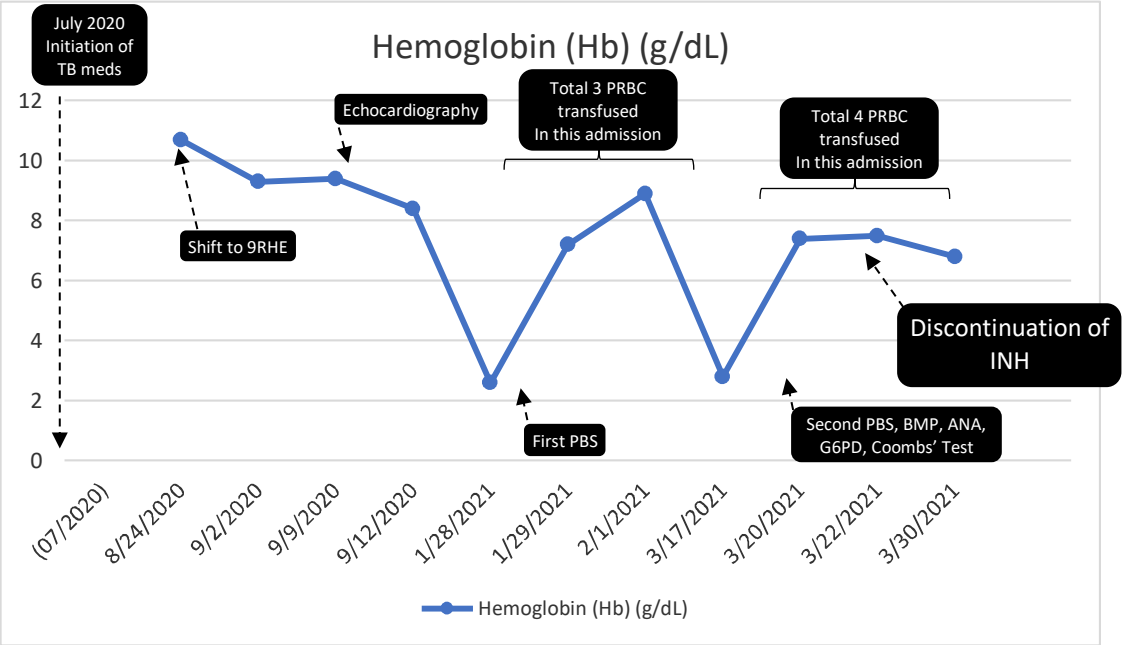

Figure 1. History of The Patient's Hemoglobin Levels
X axis indicates time of examination, Y axis indicates haemoglobin levels

In Japan, the average annual incidence of acquired PRCA was 1.06% per million with 69% of its cause being idiopathic, and the ratio for female:male was found 1.5:1.[4] The cardinal findings of PRCA are a low hemoglobin level combined with reticulocytopenia and absent or extremely infrequent marrow erythroid precursor[2,3]. These findings are also present in our case.

Clinical presentation is the same as that of anemia: generalized fatigue, decreased exercise tolerance, palpitations, and in extreme cases, presyncope or syncope (when associated with cardiac stress due to increased work of function).[5] The physical exam is also non-specific, with pallor found in all patients upon hospital visit.[1,2,5] PRCA patients usually have a stable hemodynamic system, and only 0.98% need hospitalization for PRCA treatment.[4,6] As we can see, in this particular case, the patient were admitted multiple times with significant time gap between admissions, of which the patient's Hb reached levels as low as 2,6 and 2,8 at the time of admissions, supporting the theories above.

For acquired PRCA, the main concern is how to find the underlying cause of the anemia and the appropriate treatment according to its cause.[6] The cause of PRCA could be divided into primary (autoimmune) or secondary (B19 parvovirus infections, hematologic malignancies, nonhematologic neoplasms/thymoma, and drugs).[3,6] One of the drugs that cause secondary PRCA is isoniazid,[7] which is part of the treatment regimen for pulmonary tuberculosis (TB).[8]

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* (MTB).[12] MTB generally favors a person's lungs as its main site of infection,

however extra-pulmonary organ involvement is not uncommon.[13] Cardinal symptoms of TB are chronic cough (more than two weeks), accompanied by fever, night sweats, and weight loss.[8,14–16] World Health Organization (WHO) 2020 data showed that TB is the second leading cause of death due to infectious diseases worldwide.[17] Indonesia is ranked 3rd highest worldwide in TB incidence rate, [17] with prevalence rate of 759 per 100.0000 and mortality rate of 34 per 100.000.[9–11] The success of TB treatment is highly dependent on the patient's adherence to medications.[18] TB treatment requires a minimum of 6 months therapy of a specialized regimen, which contains a fixed dose combination of several types of antibiotics, among which the commonly used are Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, and Steptomycin, the use of which in some people may induce adverse drug reactions.[8,12] Abbas (2017) compiled the following list of symptoms that are commonly reported by patients taking TB FDCs as follows: joint pain, nausea, itching, lack of appetite, dizziness, tingling, vomiting, stomach pain, visual disturbances, headaches and hearing loss.[19]

Of the first-line anti-TB drugs, isoniazid, pyrazinamide and rifampicin can all cause liver damage (drug-induced hepatitis).[20] In addition, rifampicin can cause asymptomatic jaundice without evidence of hepatitis.[8,20] Anti-TB drugs is the most common cause of drug-induced liver injury (DILI).[21] Besides hepatotoxicity, a very rare complication of anti-TB drugs is the occurrence of Pure Red Cell Aplasia.[7,22]

In this particular case, the anemia was resolved after withdrawal of isoniazid, supporting the diagnosis of isoniazid-induced secondary PRCA, in line with prior literatures that describe haematological disorders as adverse effect of isoniazid treatment besides hepatotoxicity, including hemolytic anemia, agranulocytosis, sideroblastic anemia, and PRCA.[6,7,20,21]

The exact mechanism of secondary PRCA is not known, but many of the diverse clinical associations are consistent with an immune-mediated pathophysiology.[1,2] PRCA shares with aplastic anemia an immune pathophysiology and responsiveness to immunosuppressive therapies, however, the absence of involvement of neutrophils, monocytes, and platelets makes the diagnostic distinction evident.[1] Several case reports have linked PRCA with idiosyncratic reactions to drugs, including diphenylhydantoin, sulfa/sulfonamide, azathioprine, allopurinol, isoniazid, procainamide, ticlopidine, ribavirin, and penicillamine.[1]

In this case, there were common features compared with the previous cases as reported by Azhar et.al. and Shukla et.al., namely: an increase in Hb levels within a short period ranging from two to six weeks since the offending agent was discontinued, with the diagnosis of PRCA itself confirmed through BMP.[7,24] Several immunologic phenomena that may be induced by isoniazid, includes: targeted cytotoxicity mediated by lymphocytes, impaired DNA synthesis,

antibodies that attack red blood cell precursor cells or erythropoietin, or direct toxicity of isoniazid to bone marrow, causing PRCA.[7,23–25]

Conclusion

Early detection of PRCA is very important so that the right medical intervention can be given earlier to the patient. Because of its rarity and nonspecific clinical findings, clinicians' awareness and clinical suspicion are paramount in the early diagnosis of the disease, especially in adult patients. The diagnosis of PRCA can be considered in cases of anemia in TB patients receiving isoniazid in their TB regimen, after ruling out other possible causes of anemia. BMP, as the gold standard for etiologic diagnosis of anemia, should be performed early in cases of anemia that are persistent or unresponsive to medical intervention. Early discontinuation of the precipitating agent in cases of drug induced secondary PRCA is expected to result in a better prognosis. Further research in isoniazid toxicity to immune mechanism, including IgG mediated and T-cell mediated mechanisms, may further shed some light in this matter.

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