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Case Report

# Severe anemia on the treatment of a Lepra patient with a history of long-term steroid consumption suspect of Cushing syndrome

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## ABSTRACT

Anemia is a clinical symptom caused by the disruption of erythrocyte formation, bleeding, and premature blood hemolysis. Severe anemia can occur in patients taking dapsone for the treatment of leprosy. Long-term use of steroids is also a predisposing factor for the occurrence of hematological changes and raises the suspicion of Cushing's syndrome. Reportedly a 20-year-old woman with the main complaint of sudden shortness of breath, accompanied by a cough with phlegm. The patient has had a history of multibacillary type leprosy since a month ago. There was a history of steroid consumption for about two years and only stopped a couple of months ago. Physical examination showed the oxygen saturation was 93%, conjunctival anemia, hyperpigmented plaques, tenderness in the abdominal, meteorism, and pitting edema in the upper and lower extremities. Laboratory examination revealed hemoglobin (Hb) level 2.4 mg/dl, erythrocytes 0.8x10$^6$/ul, and albumin 3.2g/dl. Peripheral blood smear results suggest refractory anemia and myelodysplasia syndrome. After being treated for seven days, the patient was re-evaluated and controlled at the Internal Medicine outpatient clinic, Syekh Yusuf Hospital. Complex symptoms and limited investigations make it difficult to establish the exact cause. Immediate blood transfusion and management of the underlying disease causing anemia, such as discontinuation of dapsone, are the primary management of this case.

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## INTRODUCTION

Anemia is a clinical finding often found in leprosy, especially in patients who have not received adequate treatment. In leprosy, two types of anemia can occur hemolytic anemia due to dapsone and anemia of chronic disease, anemia due to impaired iron utilization in the formation of erythrocytes (Wiryo, 2018). Dapsone is a multiple drug therapy (MDT) drug that is bacteriostatic by inhibiting the enzyme dihydrofolate synthetase. This main hydroxylation pathway is responsible for hematological disorders (Muhaira, Darmi, & Lubis, 2018).

Morbus Hansen is a chronic infectious disease caused by *Mycobacterium leprae*, an obligate intracellular rod-shaped bacteria (Gupta et al., 2020; Tamara et al., 2018). Mycobacterium requires iron that is obtained from its host. The iron will be used in various metabolic processes and as an energy co-factor in mitochondrial respiration and the proliferation of B lymphocytes and T lymphocytes, and the activation of both lymphocytes (Amalia, Tabri, Vitayani, & Petellongi, 2017; Tamara et al., 2018). In 1981, the World Health Organization (WHO) established a treatment regimen with multiple drug therapy, a combination of two or more anti-leprosy drugs known as MDT-WHO. The MDT includes rifampin, clofazimine, and dapsone in the treatment of leprosy (Palimbong & Kandou, 2019). However, there have been side effects from the dapsone (Deviana, 2019).

Cushing syndrome is a clinical syndrome caused by a chronic excess of glucocorticoids as a result of long-term exposure to exogenous glucocorticoids (Cushingoid phenotype) or adrenocorticotropic hormone (ACTH), or endogenously due to hypersecretion of cortisol, ACTH, or *corticotropin-releasing hormone* (CRH) (Tarigan, 2014). This article provides insight into the rare case of severe anemia in leprosy treatment, which is suspected to be caused by Cushing syndrome due to long-term steroid consumption within a limited setting. An adjunct examination area could also be done to achieve patient recovery.

## CASE REPORT

A 20-year-old female patient was brought to the Emergency Room with a chief complaint of shortness of breath. Shortness of breath suddenly appeared a day before and worsened in the morning. It was the first time this had happened.

The patient has had a cough since three days ago. Cough with whitish sputum, slightly thick, odorless, and did not appear bloody. Complaints of abdominal pain were also felt in the upper abdomen, in the solar plexus to the upper left. The pain was felt for two days before admission, and the pain worsened. The patient also complained of muscle pain throughout the body, nausea, vomiting, dizziness, weakness, and fever since the day before she was admitted to the hospital. The patient complained of edema on the face (Figure 1) and hands and feet that had been felt two months ago.

The patient has had a history of multibacillary type leprosy since a month ago and is currently being treated. The patient also had a history of gastric disease, asthma, diabetes, and hypertension. The patient had a history of Methylprednisolone 3x8 mg for ± 2 years post tympanomastoidectomy and septoplasty surgery and stopped since 2 months ago when she complaint of face edema. Currently, the patient is taking multiple drug therapy (Rifampicin, Dapsone, Clofazimine) as a treatment regimen for multibacillary type leprosy.

The general condition was severe on physical examination but still compos mentis with GCS E4V5M6. The patient vital signs were as follows: blood pressure 110/70 mmHg, pulse 109 beats/min, respiration rate 33 breaths/

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min, temperature 37.2°C, $O_2$ saturation 93% in room air, and 99% saturation when given $O_2$ with nasal cannula 3 liters per minute (lpm). The conjunctivas were anemic. The abdomen was round and soefl, and there was tenderness in the epigastric region and right hypochondria region, tympani, and meteorism, with increased peristalsis. There were generalized hyperpigmented and well-demarcated plaques (Figure 2) and pitting edema in the upper and lower extremities (Figure 3).

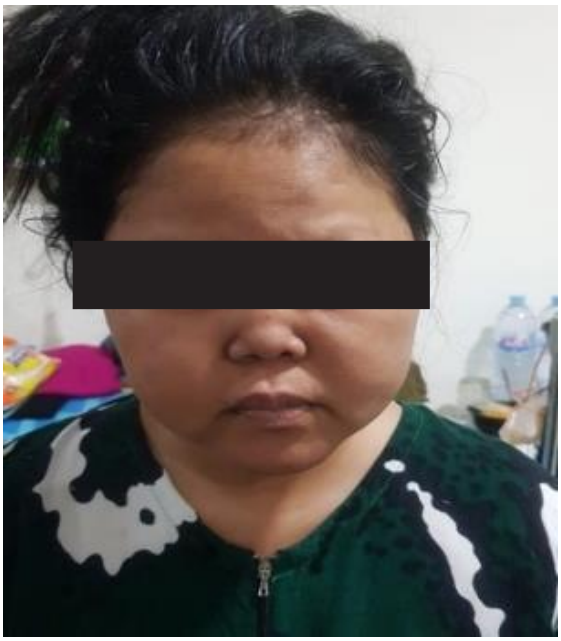

**Figure 1.** Moon face after prolonged steroid use

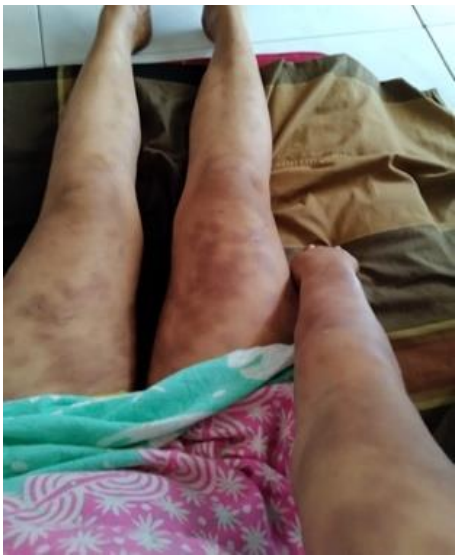

**Figure 2.** Generalized hyperpigmentation of the extremities

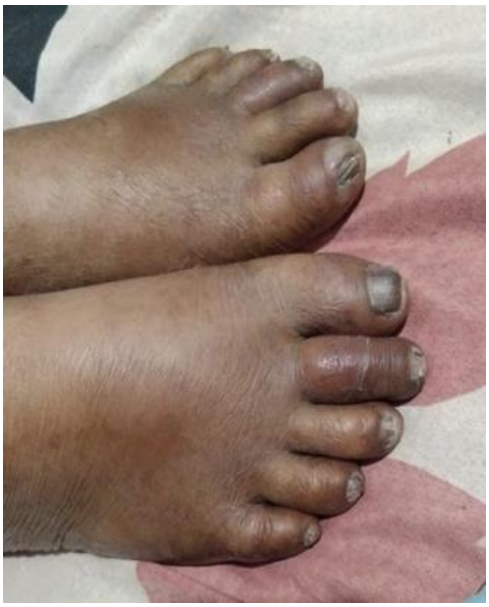

**Figure 3.** Pitting edema in lower extremities

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**Table 1.** Laboratory results

| Day | Day 1 | Day 3 | Day 5 | Day 7 |
|---|---|---|---|---|
| Leukocytes (x103/ul) | 13.1 | | 5.5 | 5.7 |
| Erythrocytes (x106/ul) | 0.87 | | 2.12 | 2.96 |
| Hemoglobin (g/dl) | 2.4 | | 6.2 | 8.5 |
| Hematocrit (%) | 8.8 | | 19.3 | 26.3 |
| MCV (fl) | 90 | | 91.0 | 88.9 |
| MCH (pg) | 27.6 | | 29.2 | 28.7 |
| MCHC (g/dl) | 27.3 | | 32.1 | 32.3 |
| PLT (x103/ul) | 210 | | 179 | 174 |
| Lymph % | 7.1 | | 11.4 | 13.4 |
| Mxd % | | | | 3.7 |
| net % | | | | 82.9 |
| Lymph # (x103/ul) | 0.9 | | 0.6 | 0.8 |
| Mxd # (x103/ul) | | | | 0.2 |
| Neut # (x103/ul) | | | | 4.7 |
| RDW (fl) | 92.4 | | 57.9 | 54.3 |
| PDW(fl) | 11.0 | | 11.6 | 11.2 |
| MPV (fl) | 9.3 | | 9.9 | 9.7 |
| P-LCR (%) | 20.7 | | 24.5 | 23.8 |
| Ureum (mg/dl) | 34 | | | |
| Creatinine (mg/dl) | 0.2 | | | |
| SGOT (µ/L) | | 30 | | |
| SGPT (µ/L) | | 22 | | |
| RBG (mg/dl) | 141 | 244 | 228 | |
| FBG (mg/dl) | | | 108 | |
| Serum albumin (gr/dl) | 3.2 | | | |
| Total Cholesterol (mg/dl) | 92 | | | |
| Triglycerides (mg/dl) | 153 | | | |

**Table 2.** Evaluation of Peripheral Blood Smear

| Peripheral Blood Smear | Result |
|---|---|
| ***Erythrocytes*** | |
| Distribution | Normal |
| Size | Normocytic + Normocytic dominant microcytic |
| Color | Normochrome |
| Morphology | Normoblast (+), Bilobed normoblast (+) , inclusion objects (-) |
| Normoblast | Found |
| ***Leukocytes*** | |
| Amount | Enough |
| Count Type | PMN > Lymphocytes, young cells (-) |
| Morphology | Normal |
| ***Platelets*** | |
| Amount | Enough |
| Morphology | Normal + Megaplatelet (+) |
| **Conclusion** | Suspect Refractory Anemia Myelodysplasia Syndrome |

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**Table 3.** Urinalysis

| Urinalysis | Result |
|---|---|
| Leukocytes (cell/ul) | 15 |
| Ketones (mg/dl) | - |
| Nitrate (mg/dl) | - |
| Urobilinogen (mg/dl) | 0.2 |
| Bilirubin (mg/dl) | - |
| Protein (mg/dl) | - |
| Glucose (mg/dl) | - |
| Erythrocytes (cell/µl) | 1.020 |
| Specific gravity | - |
| pH | 7.0 |
| Clarity (mg/dl) | 10 |

The laboratory examination showed some abnormal results. It revealed severe anemia with Hb 2.4 mg/dl, erythrocytes 0.8 x$10^6$/ ul, and albumin 3.2 g/dl. Peripheral blood smear results suggested refractory anemia and myelodysplasia syndrome.

The patient was diagnosed with severe anemia on leprosy treatment due to suspect Cushing syndrome caused by long-term steroid consumption.

Pharmacologically therapy, in this case, was given oxygen via nasal cannula at 3 lpm, ringer's lactate infusion fluid 28 drops per minute, evaluation of fluid balance every 24 hours, pantoprazole 40 mg/12 hours/IV for six days to reduce nausea and vomiting, spironolactone 100 mg/24 hourly/IV for two days, furosemide 40 mg/24 hours/IV for five days, transfusion of packed red cell 250 cc/ day for four days, premedication of transfusion with dexamethasone 5 mg/24 hours/IV for four days, and consult to Dermato-Venerology Department giving blood supplement tablets (ferrous fumarate - folic acid) 1 tablet for three times a day at the time of outpatient. The patient continued leprosy treatment with clofazimine and rifampicin, 2 caps MDT once daily without dapsone. As a result, the patient's hemoglobin has increased, and the patient's anemia symptoms have improved. Non-pharmacological therapy gave in the form of a high-calorie diet and protein.

## DISCUSSION

Shortness of breath is one of the many common symptoms that can arise due to anemia in which the hemoglobin level in the patient has decreased far below the normal value (2.4 mg/dl). Other symptoms that can arise due to a lack of hemoglobin in the body can be classified according to the organ affected. The cardiovascular system gives symptoms of lethargy, fatigue, palpitations, tachycardia, shortness of breath, on exertion, and heart failure. The nervous system gives symptoms of headache, dizziness, ringing in the ears, dizzy eyes, muscle weakness, irritability, and lethargy. The epithelium gives signs of pale skin and mucosa and decreased skin elasticity (Supandiman, Iman, & Fadjari, 2014). This is consistent with what was found in patients where the patient complained of shortness of breath with a respiratory rate of 33 breaths/ min, tachycardia with a heart rate of 109 beats/ min, accompanied by complaints of dizziness, difficulty walking due to feeling weak muscle strength, and pale skin and conjunctiva.

Shortness of breath due to lack of hemoglobin can be caused by various types of anemia depending on the type of anemia from the underlying disease. Morphologically, anemia can be classified according to the size of the cells and the hemoglobin they contain, such as macrocytic, microcytic, and normocytic anemia. It should be noted that there are various forms of normocytic anemia, namely anemia due to bleeding, anemia of chronic disease, anemia due to impaired iron absorption, and anemia due to parasitic infection (Manchanda, 2016). One of the most prominent symptoms of the patients, based on a history of leprosy suffered and history of dapsone treatment, was anemia of chronic disease and the patient's MCV and MCH levels were normal on laboratory examination. Anemia due to chronic disease is a decrease in Hb levels secondary to an underlying chronic disease (chronic

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inflammation, infection, or malignancy). It is the most common comorbidity in chronic disease. The pathogenesis of anemia in chronic disease involves various immune systems, namely cytokines and the reticuloendothelial system (Hawkins et al., 2013).

In anemia of chronic disease, uptake and retention of iron in reticuloendothelial cells increase which then causes the available iron to be limited for use by progenitor cells and erythropoiesis. This condition results in iron being easily stored in cells and not circulating freely (Yiannikourides & Latunde-Dada, 2019). Disruption of iron plays a significant role in the pathogenesis of anemia in chronic disease due to the effects of pro-inflammatory cytokines, TNF-a, IL-1, and IL-6, causing increased hypoferremia accompanied by increased ferritin synthesis (Tamara et al., 2018; Yacoub, Ferwiz, & Said, 2020). Heptidine, which is an acute-phase protein, will be produced by the liver, which plays a role in inhibiting the absorption of iron in the duodenum and inhibiting the release of iron by macrophages by inhibiting ferroportin. In anemia of chronic disease, low reticulocyte count indicates a failure of reticulocyte production to compensate for the decreased erythrocyte count (Hawkins et al., 2013; Oliveira et al., 2017; Yacoub et al., 2020). In this case, the patient was not tested for serum iron and reticulocyte levels in the blood because of the limited ability of the laboratory to carry out these tests.

The shortness of breath experienced by the patient is a sign of oxygen deficiency in the tissues and also an effort by the lungs to increase the respiratory rate so that oxygen in the tissues can be met (Muhaira et al., 2018; Supandiman et al., 2014). Anemia that occurs in the patient is also related to the patient's history of treatment using Dapsone (Muhaira et al., 2018; Pante, Coelho, Carelli, Avancini, & Trindade, 2018). Dapsone (4, 4-diamino-diphenyl sulfone) is a sulfonamide group that is slowly but almost completely absorbed from the gastrointestinal tract, and its central metabolism occurs in the liver (Vinod, Arun, & Dutta, 2013). Methemoglobinemia generally occurs when dapsone is administered at a dose of 200-300 mg/day, and severe methemoglobinemia results from a genetic disorder with deficiency of the enzyme NADH-dependent methemoglobin reductase (Kusumastanto, 2015; Muhaira et al., 2018; Tang et al., 2021). On laboratory examination, it was found that the Hb level was very low when the patient came with shortness of breath in the emergency room. The patient also had a history of leprosy and was currently on leprosy treatment.

Complaints of edema in the face and extremities can be caused by long-term steroid use, causing symptoms of Cushing syndrome in patients. Cushing syndrome is a collection of clinical signs and symptoms due to elevated glucocorticoids (cortisol) levels in the blood. Hyperglucocorticoid state in chusing syndrome causes excessive protein catabolism, which means the body lacks protein. The skin and subcutaneous tissue become thin, and blood vessels become fragile so that they appear as purple striae in the abdomen, thighs, buttocks, and upper arms. Muscles become weak and difficult to develop, bruise easily; wounds are difficult to heal, and thin and dry hair (Dow, Yu, & Carmichael, 2013; Nieman, 2015). On examination, not all can be found symptoms of Cushing syndrome in the patient. On examination, only found edema on the face and both extremities, hyperpigmentation of the skin, thin skin, weakness, and muscle pain when pressed. However, on physical examination, purple striae were not found, and there were no signs of bleeding. On laboratory examination, low albumin levels were found in the patient. The decrease in serum albumin is not proportional to the clinical symptoms of edema in the patient. Therefore, it is necessary

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to think about other causes that cause edema, such as a long history of steroid consumption in the patient.

Hyperglucocorticoid state in the liver will increase gluconeogenesis and aminotransferase enzymes. Amino acids resulting from protein catabolism are converted into glucose and cause hyperglycemia and decreased peripheral glucose utilization, leading to insulin-resistant diabetes. In Cushing syndrome, there is a characteristic redistribution of fat. Symptoms that can be found are obesity with redistribution of centripetal fat. Fat accumulates in the abdominal wall, upper back which forms a buffalo hump, and the face so that it looks round like a moon with a double chin (Dow et al., 2013; Nieman, 2015). On the third and fourth days, random blood sugar was found to be high but fasting blood sugar was still normal. This can occur due to the administration of dexamethasone as a premedication for transfusion or an increase in gluconeogenesis due to hyperglucocorticoids. However, in this case, the HbA1c test was not carried out because, at that time, the examination could not be carried out in the laboratory.

Standard adjuctional examination to determine the cause of the symptoms of suspect Cushing syndrome is laboratory examination (reticulocytes, ferritin, *Total Iron-Binding Capacity* (TIBC), serum Fe, liver function, and renal function) to determine the cause of anemia in patients. In addition, we also have to check the cortisol levels in the blood by performing the overnight 1-mg dexamethasone suppression test (DST) or late-night salivary cortisol test on the patient. A bone marrow puncture examination is also needed to confirm further the results obtained on the peripheral blood smear examination and assess the bone marrow's condition (Supandiman et al., 2014; Tarigan, 2014). In this case, the examination was not carried out due to the absence of standard examination facilities. As a result, it is difficult to diagnose Cushing syndrome and the specific cause of anemia.

General therapy when it is proven that the patient is anemic due to dapsone, in the form of discontinuation of dapsone as a suspected trigger drug, systemic steroids prednisone oral 1 mg/kg/day or equivalent dose of methylprednisolone, and supportive therapy while minimizing the use of other drugs (Kusumastanto, 2015). The administration of dapsone is started with a low dose of 25 mg twice daily for a week; if the hemolysis does not get worse, the dose can be increased at 3-4 weeks to 5-10 mg/day (Muhaira et al., 2018). In this patient, leprosy therapy was continued using only two drugs, rifampin and clofazimine. The use of steroids will also be minimized in the treatment selection in this case.

Treatment of anemia has different approaches in its treatment based on the cause of anemia. In anemia of chronic disease, namely treatment of underlying disease, high calorie-high protein diet, giving blood transfusion-packed red blood cell if hemoglobin <7 g/dl (125 cc packed red blood cell will increase hemoglobin in adults by an average of 1 g/dl), if accompanied by iron deficiency anemia, ferrous sulfate 300 mg twice daily can be added. In hemolytic anemia due to dapsone, if the hemoglobin is <7 g/dl, dapsone administration is discontinued. The patient had received a packed red cell transfusion of 250 cc/day or 2 bags/day for four days and was continued with blood supplement tablets (ferrous sulfate-folic acid) 3x1 at the time and consulted to Dermato-Venereology Department about leprosy treatment. As seen in the laboratory results (Table 1), the follow-up laboratory examination was carried out on day 5 after receiving a red blood cell transfusion of 500 cc/4 bags. There was an increase in hemoglobin to 6.2 g/dl.

The prognosis is generally better, although there have been reports of death in patients

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with dapsone syndrome. In this case, the patient's prognosis is good because of the early diagnosis and treatment, and there were improvements in the patient's condition. Therefore, the patient can be discharged, and the treatment could be continued at the Internal Medicine outpatient clinic.

## CONCLUSION

We report a case of severe anemia in a 20-year-old woman being treated for leprosy using this regimen of multiple drugs therapy with complaints of shortness of breath, cough with phlegm, edema of the face and both extremities, and abdominal pain. The patient has a history of prolonged steroid consumption, which has been discontinued two months ago. The patient was treated in the hospital for seven days and improved after being given therapy. Furthermore, the patient was evaluated by undergoing outpatient and control at clinical of internal medicine Syekh Yusuf Hospital.

The complexity of the symptoms and limited investigations makes it challenging to establish the exact cause of diagnosis in patients. Examining the condition of the bone marrow with bone marrow puncture is essential to see the response of the bone marrow. In addition, it is necessary to examine cortisol levels to help direct the association of symptoms with a patient's history of prolonged steroid consumption.

Prompt blood transfusion and management of the underlying disease-causing anemia, such as discontinuation of Dapsone, are the primary management of this case. Iron supplementation to prevent hypochromic microcytic anemia due to chronic disease and consuming foods high in iron are also essential.

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