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Diagnostic Problems And Monitoring of Diabetes Mellitus In Patients With Aplastic Anemia and Hypoalbuminemia

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Diabetes mellitus, aplastic anemia, hypoalbuminemia, glycemic control

ABSTRACT
Aplastic anemia is a clinical syndrome that occurs due to bone marrow failure. One of the most common metabolic complications is diabetes mellitus (DM). The emergence of DM is allegedly caused by damage to pancreatic β cells due to accumulation of Fe post-transfusion as well as long-term steroid treatment during the patient's care. This case reports a 41-year-old male patient with steroid-resistant aplastic anemia since 8 years ago, elevated iron levels, and moderate malnutrition with hypoalbuminemia. He routinely received red blood cell transfusions and steroid therapy. Since 3 months ago, the patient has experienced classic DM symptoms. Initial laboratory examination revealed normochromic normocytic anemia and thrombocytopenia. Hyperglycemia, hypoalbuminemia, high glycated hemoglobin (HbA1c) levels, and normal glycated albumin (GA) levels were also obtained. The patient was diagnosed with DM. He was treated with medical nutrition therapy, red blood cell transfusion, human albumin transfusion, insulin, and regular blood glucose monitoring. Monitoring glycemic control in DM patients is essential since DM is a chronic disease. In this case, the patient's glycemic control was assessed using a combination of several methods and biomarkers, such as HbA1c, GA, and eAG (fasting glucose and postprandial glucose).

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INTRODUCTION

Aplastic anemia is a clinical syndrome that occurs due to malfunction of the bone marrow, both physiological and anatomical, characterized by a condition of hypohellularity in the bone marrow (Young, 2018). The disease is characterized by a reduced or absent presence of blood-forming precursor cells in the bone marrow, accompanied by pancytopenia in the peripheral blood, in the absence of hepatosplenomegaly or lymphadenopathy. Bone marrow examination results in patients with aplastic anemia generally show very little or no hematopoietic precursor cells, which are then replaced by fatty tissue. Bone marrow damage can result from exposure to toxic chemicals, certain viral infections, or hereditary factors (Young, 2018; Isyanto & Abdulsalam, 2016).

The incidence of aplastic anemia in Europe and North America is estimated to be about 2 cases per 1,000,000 population per year, while in the East Asian region, the rate is reported to be about two to three times higher (Siregar, 2018). To date, the management of aplastic anemia remains a significant clinical challenge because its pathophysiological mechanisms are not fully understood.

In general, aplastic anemia therapy strategies can be classified into four main groups, namely causal therapy, supportive therapy, therapy aimed at improving bone marrow function, and definitive therapy in the form of bone marrow transplantation (Siregar, 2018). Supportive management is provided to address conditions arising from pancytopenia, such as anemia, infection, and bleeding. Both supportive and curative therapies in aplastic anemia have the potential to cause new complications and may affect the patient's prognosis (Young, 2018; Siregar, 2018).

Aplastic anemia patients mostly require repeated transfusions to maintain the number of erythrocytes and other blood cells at levels adequate for the body's metabolism, this will lead to iron (Fe) buildup in the body. One packed red cell (PRC) unit contains 100 times more Fe than can be absorbed by the intestines normally. Excess Fe will cause iron accumulation in various organs, including in the pancreas. The buildup of Fe in body tissues in the form of ferritin or hemosiderin proteins can trigger damage to β cells of the pancreas, which in turn leads to diabetes mellitus (DM) (Devi et al., 2017; Indrasari et al., 2015). Patients who undergo routine PRC transfusions are 3.5 times more likely to suffer from DM if ferritin levels >2500 µg/L (Devi et al., 2017).

DM disease is a group of diseases related to certain metabolic disorders characterized by chronic hyperglycemia. Chronic high blood sugar (hyperglycemia) is caused by abnormal insulin secretion, its functioning, or both (Ake et al., 2017). The diagnosis of DM is established on the clinical basis of the patient and an examination of blood glucose levels. Monitoring glycemic control in DM patients is essential in patient management, this is because chronic hyperglycemia conditions or other DM complications including hypoglycemia play a role in increasing the morbidity and mortality of DM patients.

Currently, the common methods used in glycemic control are Adult Hemoglobin 1C (HbA1C), fasting glucose levels, and postprandial glucose levels (Young, 2018; Ake et al., 2017). Of the three tests, HbA1C is a test that can be used to monitor long-term glycemic control. HbA1C reflects blood glucose concentrations 3 months prior to screening and is not affected by diet prior to blood sampling (Ake et al., 2017). HbA1c screening cannot accurately describe glycemic control in some conditions or diseases that affect hemoglobin (Hb) levels, such as in patients with aplastic anemia due to low Hb levels and frequent red blood cell transfusions. In conditions like this, other biomarkers are used, one of which is glycated albumin (GA) which is ketoamin resulting from non-enzymatic glycation from serum albumin. GA levels are not affected by red blood cell transfusion and erythrocyte survival so they can be used in patients with anemia or hemoglobinopathy who also suffer from DM. GA levels cannot be used in patients with hypoalbuminemia and in patients receiving albumin transfusions (Devi et al., 2017).

In DM patients, in addition to diagnosis enforcement, blood sugar monitoring is also important. Biomarkers currently used to monitor long-term blood sugar control such as HbA1C and GA are strongly related to the condition of Hb or albumin protein in the body. In DM patients with anemia accompanied by hypoalbuminemia, conventional biomarker tests such as HbA1C and GA are less representative of the patient's glycemic control. In this case report, a patient with other types of DM was reported with aplastic anemia accompanied by excess iron, long-term steroid use, and moderate malnutrition with hypoalbuminemia.

This study aims to analyze diagnostic problems and monitoring strategies for Diabetes Mellitus in patients with aplastic anemia and hypoalbuminemia, considering that these conditions can affect the accuracy of standard diagnostic parameters such as HbA1c and blood glucose levels. The benefits of this study are to provide a more comprehensive clinical understanding of the limitations of conventional diagnostic methods, identify alternative indicators that are more reliable for glycemic monitoring, and become the basis for recommendations for health professionals in more appropriate clinical decision-making, so as to improve the accuracy of diagnosis, monitoring effectiveness, and quality of management of Diabetes Mellitus in patients with comorbid conditions complex.

METHOD

Case Illustration

One, a 41-year-old man, came to the Internal Medicine emergency department (ER) with the main complaint of drowning. The complaint of weakness was felt since 1 week ago and has been getting worse since 3 days before entering the hospital. Complaints of weakness are felt throughout the body. The weakness is felt so severe that the patient is unable to carry out normal activities. This complaint of weakness is often felt by patients and is usually recurring. Weakness complaints will feel better after the patient rests and receives a red blood cell transfusion. Other complaints were denied by patients.

The patient did have a history of aplastic anemia since 2011 and had routinely received red blood cell transfusions since then. In one year, patients usually get approximately 24 bags of red blood cell transfusions. Since 2015, the patient had stopped receiving red blood cell transfusions and began using steroid and iron chelation drugs for his aplastic anemia. For approximately 3 years of the patient's use of steroid drugs, the patient's blood cell levels are said to remain normal. In 2018, the patient's aplastic anemia disease worsened again, the patient's red blood cell levels often dropped and required the patient to transfuse red blood cells again until now.

In addition to aplastic anemia, the patient also has a history of diabetes. This disease is said to have been discovered by the patient only about 3 months ago. Initially, the patient felt weak, continued to feel thirsty, a lot of urination, and drastic weight loss. After a blood sugar check, it was found that at that time the patient's sugar level was above three hundred and the patient was immediately given insulin medication to control his blood sugar levels. History of other diseases such as hypertension, malignancy, and other chronic diseases is denied. In the patient's family, his father and mother also suffered from diabetes.

On physical examination, the patient was found to be in composing consciousness. Vital signs within normal limits. On the patient's physical examination, it was found that the patient was in a state of moderate malnutrition, the two conjunctiva appeared anemic, and all the patient's teeth had been removed. Other physical examinations were obtained within normal limits.

At the initial complete blood laboratory examination, the patient was found to have moderate normochronic anemia normositer and thrombocytopenia. Hyperglycemia, hypoalbuminemia, high HbA1C levels, normal GA levels, and high ferritin levels were also obtained. The patient's initial laboratory results can be seen in Table 1. Two months later, the

patient had time to repeat his laboratory examination at the time of control and at that time the results of normochromic mild anemia with thrombocytopenia were again obtained. Meanwhile, the HbA1C examination obtained normal results. In the span of 2 months, patients also routinely check their own blood sugar at home during fasting and after eating breakfast, from the results of their daily routine check-ups, the estimated average glucose (eAG) of fasting patients in the last 2 months is 179 mg/dL and eAG after eating 285. The results of the patient's laboratory during the 2-month follow-up can be seen in Table 1.

Based on the anamnesis, lab results, and supporting documents, the patient is known to suffer from steroid-resistant aplastic anemia, iron overload, moderate malnutrition with hypoalbuminemia, and other types of DM compared to type 2 DM. Patients are treated with medical nutrition therapy, PRC transfusion, human albumin transfusion, and insulin.

Table 1. Patient laboratory results

Laboratory (Unit)	Early Laboratory	Laboratory On-Control	Reference Value
WBC (103/µL)	9,19	6,61	4,1-11,0
RBC (106/µL)	2,61*	3,21*	4,5-5,9
HGB (g/dL)	6,52*	8,68*	13,5-17,5
HCT (%)	22,17*	27,83*	41,0-53,0
MCV (fL)	85,04	86,85	80,0-100,0
MCH (pg)	25,03*	27,10	26,0-34,0
MCHC (g/dL)	29,43*	31,20	31-36
RDW (%)	15,94*	11,24*	11,6-14,8
PLT (103/µL)	92,96*	39,39*	150-440
MPV (fL)	14,00*	13,48*	6,80-10,0
Albumin	2,00*	3,10	3,40-4,80
Blood sugar	305,00*	245,00*	70-140
HbA1C (%)	7,50*	5,50	4,8-5,9
GA (%)	13,5	-	11-16
fasting eAG (mg/dL)	-	179*	70-126
eAG post prandial (mg/dL)	-	285*	70-126
Serum Iron (g/dL)	213,44*	-	65-175
TIBC (g/dL)	243	-	261-478
Ferritin (ng/mL)	2678*	-	30-400

Description: * beyond reference value

RESULTS AND DISCUSSIONS

It has been reported that patients with aplastic anemia have been in the hospital for the past 8 years, and have routinely received about 24 bags of red blood cell transfusions per year and have received long-term steroid therapy. In the last 3 months, patients have also been known to suffer from DM. Currently patients are diagnosed with steroid-resistant aplastic anemia, iron overload, moderate malnutrition with hypoalbuminemia accompanied by DM.

The appearance of hyperglycemia in patients is suspected to occur due to several things, one of which is genetic factors passed down by the patient's parents who also suffer from type 2 DM disease. Patients also receive repeated transfusions that are given to meet the needs of

blood cells, especially erythrocytes, this can cause iron (Fe) buildup in the body (hemochromatosis). The buildup of Fe in body tissues in the form of ferritin or hemosiderin proteins can trigger damage to cells β pancreas, which in turn leads to DM (Devi et al., 2017; Indrasari et al., 2015). Patients who undergo routine PRC transfusions are 3.5 times more likely to suffer from DM if ferritin levels >2500 μg/L (Devi et al., 2017). Endocrinopathy is a common complication in patients with transfusion-related hemochromatosis, and the most common complication is DM.

Therefore, many studies have been conducted to show a positive association between DM and iron overload. In a meta-analysis of 4,366 participants with DM, the relative risk of developing DM when comparing the highest and lowest ferritin levels, was 1.66 (95% confidence interval [CI], 1.15-2.39) for the prospective study and 2.29 (95% CI, 1.48-3.54) for the cross-sectional study. Another recent prospective cohort study described an association between ferritin and DM concentrations in 1,613 Finnish men. Three hundred and thirty-one patients with an incidence of DM had significantly higher levels of ferritin than those in healthy (191 μg/L vs 151 μg/L, P≤0.001) (Kim et al., 2017).

Patients also received steroid therapy for approximately 3 years. Steroids are known to be one of the main causes of drug-induced hyperglycemia. Steroids not only worsen hyperglycemia conditions in patients with DM, but can also lead to the appearance of DM in patients who did not experience hyperglycemia before starting steroid therapy. The incidence of DM can reach 46% of total patients with GC therapy, and an increase in glucose levels of up to 68% compared to preliminary data (Tamez-Pérez et al., 2015). Glucocorticoids play a role in the emergence of oxidative stress metabolic substances that increase the occurrence of lipolysis, proteolysis, and hepatic glucose production.

The mechanism of glucose intolerance after GC administration is similar to that of type 2 DM, as steroids increase insulin resistance, which can be as high as 60%-80% depending on the dosage and type used. The mechanisms by which GC causes DM include: GC increases endogenous glucose production; increases gluconeogenesis, and inhibits the action of insulin metabolism; GC enhances the counterregulatory effects of hormones, such as glucagon and epinephrine, which increase endogenous glucose synthesis; GC reduces peripheral glucose uptake at the level of muscle and adipose tissue; and GC inhibit insulin production and secretion from pancreatic β cells and induce β cell damage indirectly due to lipotoxicity (Young, 2018; Tamez-Pérez et al., 2015).

In general, the diagnosis of Diabetes Mellitus (DM) is established based on the results of blood glucose level examination. The diagnosis cannot be established solely on the basis of the presence of glucosuria, since the presence of glucose in the urine does not always reflect the true blood glucose level. The recommended blood glucose test is an enzymatic glucose test using venous plasma samples, as this method has a high level of accuracy and is considered the standard in diagnosis enforcement.

Monitoring of the success of treatment or control of glucose levels can be done through capillary blood glucose examination using a glucometer device, which is practical and easy to use in daily monitoring of patients. Based on the criteria set by the Indonesian Endocrinology Association (PERKENI) in 2015, the diagnosis of Diabetes Mellitus can be established if there is one of the following conditions, namely fasting plasma glucose levels of more than 126

mg/dL after fasting without calorie intake for at least eight hours; plasma glucose levels two hours after the Oral Glucose Tolerance Test (TTGO) with a load of 75 grams reaching or exceeding 200 mg/dL; plasma glucose levels when reaching or exceeding 200 mg/dL accompanied by classic symptoms in the form of polyuria, polydipsia, polyphagia, and unexplained weight loss; or HbA1C levels of more than 6.5% which were checked by the High-Performance Liquid Chromatography (HPLC) method and have been standardized by the National Glycohaemoglobin Standardization Program (NGSP) (Perkeni, 2015).

Determining the specific type of DM is important to do, because by knowing the cause of the appearance of DM, the therapy given can be more specific. Therapeutic phlebotomy is the only treatment for hemochromatosis that is currently widely accepted. In previous studies, it was said that therapeutic phlebotomy can improve insulin secretion function but not significantly improve insulin sensitivity. Early initiation of therapeutic phlebotomy is said to increase insulin secretion and halt the progression of DM disease, although damage to β cells and insulin secretion defects may not be completely repairable in advanced conditions. The worldwide consensus recommends maintaining iron levels between 50 - 100 μg/L with regular monitoring. Alternative therapies with iron binding/chelation agents have also been widely used in patients with hemochromatosis. Iron binding/chelating agents can effectively remove excess iron and can quickly normalize ferritin levels in the blood (Kim et al., 2017). There is currently little clinical data examining the use of antidiabetic drugs in the management of other types of DM due to GC that can be used as a specific therapy recommendation in this population (American Diabetes Association, 2017).

In addition to a good anamnesis to distinguish other types of DM from type 2 DM that generally appears in adulthood, some additional checks also need to be done. To establish the diagnosis of other types of DM due to hemosiderosis can be done through quantitative phlebotomy, which is a standard method for assessing iron reserves in the body that can be used in the formation of hemoglobin. Measuring iron reserves in the liver with atomic absorption spectrometry can also be used to assess excess iron in the body. Another indicator that is also often used to describe iron reserves in the body is serum ferritin (Barton & Acton, 2017). Meanwhile, in patients suffering from DM after receiving long-term therapy, GC is categorized into other types of DM, especially drug-induced DM. An optimal diagnosis can only be made after the patient is stable at a certain maintenance dose and the patient is not accompanied by an acute infection (Tamez-Pérez et al., 2015; Perkeni, 2015).

All patients who start steroid treatment should have initial glucose screening data, as well as education on independent daily glucose monitoring prior to therapy, as the absence of initial glucose screening data and insulin administration before diagnosis is established may complicate subsequent diagnosis enforcement. Daily monitoring should be started when blood sugar levels are above 180 mg/dL after more than one check-up with or without symptoms associated with hyperglycemia. The criteria for diagnosing steroid-induced hyperglycemia are the same as the criteria for type 2 DM established by the American Association of Diabetes and Perkeni in 2015 (Tamez-Pérez et al., 2015; Perkeni, 2015).

Based on the pathophysiology and patterns of steroid-induced hyperglycemia, it appears that some of the current criteria for the diagnosis of DM rule out this. Because GC-induced diabetes is mostly detected in the postprandial state, some studies do not recommend the use of

fasting glucose as well as glucose tolerance curves as reliable diagnostic methods, as there is a high probability of missing some patients with postprandial hyperglycemic conditions. The Oral Glucose Tolerance Test (TTGO) is considered the gold standard test for the diagnosis of DM due to GC (Tamez-Pérez et al., 2015; American Diabetes Association, 2017). In cases, the diagnosis of DM is established through an anamnesis that finds that since the last 3 months the patient has felt weakness, continued to feel thirsty, urinating a lot, and drastic weight loss. Laboratory examination found conditions of hyperglycemia, hypoalbuminemia, high glycated hemoglobin (HbA1C), and normal glycated albumin (GA) levels. Based on this, the patient is diagnosed with another type of diabetes mellitus with a comparative diagnosis of type 2 DM.

DM disease cannot be cured but blood sugar levels can be controlled. Monitoring glycemic levels is essential in the management and control of diabetes. Currently, monitoring glycemic levels in DM cases is usually carried out by checking HbA1C and/or GA levels. However, in the case of the patient, the patient has aplastic anemia and hypoalbumin which can affect the results of the HbA1C and/or GA test so that it cannot be used as a reference for the patient's glycemic control. This is proven by the results of the examination of HbA1C and GA levels that are not in line. When HbA1C is high, GA values are normal, and when eAG is high, HbA1C levels are normal. Glycated hemogobin is a substance formed from a chemical reaction between glucose and hemoglobin, through a nonenzymatic reaction between glucose and N-terminal valine on the beta chain of hemoglobin A.

Glycated hemoglobin is not always reliable in describing average circulating glucose levels. HbA1c has a life span related to the half-life of red blood cells which is about 90 - 120 days. Changes in the production rate or life span of circulating red blood cells will affect HbA1c levels; for example, reduced production leads to a greater percentage of old erythrocyte cells, while faster turnover reduces the average time of exposure of red blood cells to hyperglycemia (Diwaker et al., 2019; Yazdanpanah et al., 2017; Dorcely et al., 2017). HbA1c testing cannot accurately describe glycemic control in some conditions that affect hemoglobin levels, such as in patients with aplastic anemia due to low Hb levels as well as interference in patients who have recently had a transfusion.

Changes in the production rate or life span of circulating red blood cells will affect HbA1c levels. Some clinical conditions can cause HbA1c levels to be too high or too low. Conditions that can cause falsely elevated HbA1c results include iron-deficiency anemia, asplenia, folate and vitamin B-12 deficiency, severe hypertriglyceridemia, and uremia (Dorcely et al., 2017). Falsely low HbA1c levels usually occur in hemolytic anemia, blood loss, splenomegaly, and end-stage kidney disease (Diwaker et al., 2019). So in cases, glycemic control tests are not enough with HbA1c alone, confirmation with other biomarkers is required.

Glycated albumin (GA) has long been found as an alternative biomarker for a glycemic control index that is superior to HbA1c in patients with renal failure, hemolytic anemia, and patients receiving blood transfusions. Glycated albumin is a non-enzymatic glycation ketoamin of serum albumin, not affected by transfusion and erythrocyte survival so it can be used in patients with anemia or hemoglobinopathy who also suffer from DM (Devi et al., 2017; Dorcely et al., 2017). Studies show serum GA levels of 15-16% in the Asian population are associated with diabetes. Glycated albumin has a medium sensitivity and specificity for diagnosing prediabetes and diabetes. Combining GDP <100 mg/dL (5.56 mmol/L) with serum GA <15%

for diabetes exclusion, and GDP ≥126 mg/dL (7.0 mmol/L) or serum GA ≥17% to diagnose diabetes, increases GA sensitivity (Yazdanpanah et al., 2017; Dorcely et al., 2017). The combination of GA with HbA1c shows greater sensitivity than HbA1c alone (Dorcely et al., 2017). There are some conditions in which GA may not be accurate due to changes in albumin turnover.

Lower-than-normal GA levels are found in patients with obesity, this is due to increased albumin catabolism and decreased albumin synthesis levels due to inflammation. Other conditions that can cause false low GA levels are individuals with increased BMI, high body fat mass, buildup of visceral adipose tissue, and hypoalbumin conditions. Proteinuria and albumin loss can also affect GA levels due to reduced serum albumin exposure to glucose (Dorcely et al., 2017; Divani et al., 2018). Currently several new biomarkers have been identified and developed to provide an overview of glycemic control, including adiponectin, metabolites fetuin-A, α-Hydroxybutyrate (α-HB), lipoprotein(a), triglycerides, high density lipopotrein, ceramides, ferritin and transferin, mannose binding lectin serine peptidase, thrombospondin 1, acyl-carnitine, microRNA, various inflammatory markers, and fibrinogen.

However, studies comparing its specificity and sensitivity compared to HbA1C have not been widely found (Diwaker et al., 2019; Dorcely et al., 2017). Another method that can be used to monitor patients' glycemic control is to conduct routine blood sugar checks every day at a specified time (e.g., during an 8-hour fast and after meals) and then assess the estimated average glucose (eAG) in the last 2 to 3 months. This procedure is usually performed by the patient or family alone (self-monitoring blood glucose (SMBG), requires a glucometer device and requires a fingertip prick with a lancet to access capillary blood. These methods have drawbacks including lack of practicality, inconvenience to routine, and accuracy and reliability depending on the patient's self-care situation and self-assessment (Villena Gonzales et al., 2019).

In this case, the assessment of the patient's glycemic control uses a combination of several methods and biomarkers, namely HbA1C, GA, and eAG (fasting and post prandial). This is in accordance with the recommendations of several literature which show that combining multiple tests and biomarkers can provide better sensitivity and specificity. Further studies on the comparison of biomarkers are urgently needed to ascertain the clinical capabilities of these biomarkers in a wide range of patients' clinical conditions.

CONCLUSION

This case reports a 41-year-old male patient with steroid-resistant aplastic anemia diagnosed 8 years prior, complicated by iron overload from approximately 24 bags of annual red blood cell transfusions, long-term steroid therapy, moderate malnutrition, and hypoalbuminemia. Over the past 3 months, he experienced classic diabetes mellitus (DM) symptoms including weakness, polydipsia, polyuria, and significant weight loss. Initial laboratory findings revealed moderate normochromic anemia, thrombocytopenia, hyperglycemia, hypoalbuminemia, elevated glycated hemoglobin (HbA1c) levels, and normal glycated albumin (GA) levels, leading to a DM diagnosis potentially triggered by genetic factors, iron accumulation, and steroid use. Treatment involved medical nutrition therapy, packed red cell transfusions, human albumin transfusions, insulin, and periodic glycemic

monitoring using HbA1c, GA, and estimated average glucose (eAG) via fasting and postprandial methods. Future research should investigate the long-term efficacy and safety of novel iron chelators combined with glycemic biomarkers in similar patients to prevent DM onset and improve outcomes in transfusion-dependent aplastic anemia.

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