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# Newly Diagnosed T1DM With Dka In Major β-Thalassemia Patient During Covid-19 Infection

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**ABSTRACT**

The COVID-19 pandemic has significantly impacted global public health, with diabetes mellitus (DM) being a key factor associated with adverse clinical outcomes. This case report discusses a 20-year-old male diagnosed with major β-thalassemia who developed newly diagnosed type 1 diabetes mellitus (T1DM) with diabetic ketoacidosis (DKA) during COVID-19 infection. Thalassemia patients are at increased risk for iron overload, which contributes to β-cell dysfunction and insulin resistance, leading to diabetes. This patient had persistent hyperglycemia, recurrent DKA, and was classified as idiopathic T1DM due to negative autoantibodies and low C-peptide levels. The case highlights the complex interplay between iron overload, β-cell dysfunction, and hyperglycemia in thalassemia patients, compounded by COVID-19 infection. Despite intensive management, including insulin therapy, fluid resuscitation, and iron chelation therapy, the patient succumbed to transfusion-related acute lung injury (TRALI). This case underscores the need for early detection of diabetes in thalassemia patients and emphasizes the importance of optimizing iron chelation therapy to reduce metabolic complications.

***Keywords:*** *COVID-19, Type 1 Diabetes Mellitus, Diabetic Ketoacidosis, β-Thalassemia Major, Iron Overload, Insulin Resistance, Transfusion-Related Acute Lung Injury (TRALI).*

## 1. INTRODUCTION

The COVID-19 pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a globally significant public health crisis. Data from WHO until June 2023, 767.984.989 confirmed cases of COVID-19 have been reported with 6.943.390 deaths (WHO, 2023). Diabetes mellitus (DM) is consistently associated with adverse clinical outcomes and high mortality in COVID-19 patients both independently and with co-morbidities (Shresta *et al.*, 2021). A study from Wuhan in elderly patients with COVID-19 reported newly diagnosed diabetes (GDP ≥ 126 mg/dL and/or HbA1C ≥ 6.5%) of 20.8% (Li *et al.*, 2020). The mechanism of newly diagnosed DM in COVID-19 patients is not known with certainty, but is thought to involve a series of complex interrelated processes, including previously undiagnosed diabetes, stress-related hyperglycemia, steroid-induced hyperglycemia and direct and indirect effects of SARS-CoV-2 on β cells (Khunti *et al.*, 2021).

Patients with thalassemia are at risk of being infected with COVID-19 with severe manifestations. Iron overload is a trigger factor for the development of DM in thalassemia patients (de Sanctis *et al.*, 2021). A study from an adult thalassemia unit in the UK showed that 41% of 92 transfusion-dependent thalassemia patients had DM associated with a mean ferritin > 2000 ng/mL (Ang *et al.*, 2014).

Diabetic ketoacidosis (DKA) is an acute complication of DM characterized by hyperglycemia, metabolic acidosis and ketosis (Alhumaid *et al.*, 2021). Based on a study of COVID-19 patients, the prevalence of DKA was found to be 70% of 30 children with newly diagnosed type 1 DM (T1D) (Unsworth *et al.*, 2020) and 31.4% of 42 patients with type 2 DM (T2D) (Armeni, Aziz and Kamal, 2020). DKA in thalassemia due to iron overload was reported 0.3% of 2500 patients (Karimi *et al.*, 2008). We reported a thalassemic patient who experienced DKA as an early manifestation of newly diagnosed T1D during COVID-19 infection.

**Case**

A 20-year-old man, was sent from the COVID outpatient clinic to the RSUD Dr. Soetomo ER on September 14, 2021 with shortness of breath as the chief of complaint. Shortness of breath was felt for the last four days continuously. He felt body weakness. There is a history of frequent drinking and urination. There were no complaints of cough, runny nose, anosmia, ageusia, sore throat, decreased appetite, fever, nausea, vomiting and diarrhea. The patient was diagnosed with β thalassemia major since 1 year old with complaints of frequent paleness and fatigue. The patient underwent splenectomy at the age of 5 years. There was a history of severe COVID-19 infection accompanied by KAD 50 days prior to readmission, he was treated at RSUD Dr. Soetomo isolation ward for 14 days and was sent home for independent isolation without any complaints but still with positive COVID-19 PCR results. He routinely undergoes 2-unit blood transfusions every month, but did not take deferasirox regularly. There is a history of treatment with remdesivir, dexamethasone, ceftriaxone, insulin, and deferoxamine.

On physical examination the condition was weak, GCS E4V5M6, blood pressure 92/55 mmHg, pulse 116 bpm regular, respiratory rate 29 breaths/min, axillary temperature 36.7°C and $O_2$ saturation 98% (nasal 3 lpm). Slightly anemic conjunctiva, slightly icteric sclerae, dyspnea and with no cyanosis. Symmetrical chest movement without retraction. Normal heart margin, single $S_1S_2$ heart sound, regular, no gallops, murmurs and extrasystoles. Resonant lung percussion, vesicular breath sounds in both lung fields, no rhonchi and wheezing. Normal bowel consistency and sounds, without palpable liver and spleen. Acral warm, dry, and capillary refill time <2 seconds. Weight: 50kg, height: 165cm, and BMI 18.37 kg/m$^2$. Urine output: bedpan ± 200ml, initial catheter ± 20ml followed by 1000ml in 6 hours. A comprehensive analysis of laboratory parameters is illustrated in Table 1. ECG: sinus rhythm, axis normal, heart rate 120 bpm, tall T in V1-V3. Normal chest X-ray. Monitoring of blood sugar and potassium in initial therapy is illustrated in Figure 2.

**Table 1: Laboratory findings**

| Parameters | Admission | Normal range | Parameters | Admission | Normal range |
|---|---|---|---|---|---|
| Hgb (g/dL) | 9,4 | 11.0–14.7 | AST (U/L) | 137 | 0–37 |
| WBC | 15580 | 3370–10,000 | ALT (U/L) | 21 | 0–55 |
| NEUT | 68,6% | 39.8%–70.5% | Alb (g/dL) | 2,9 | 3.4–5.0 |
| LYMPH | 21,8% | 23.1%–49.9% | TBIL (mg/dL) | 3,54 | 0,1-1,2 |
| PLT | 239.000 | 150–450x10$^3$/µL | BC (mg/dL) | 0,74 | <0,3 |
| CRP (mg/dL) | 0,1 | <0,9 | Ferritin(ng/ml) | 19034,5 | 24-336 |
| BUN (mg/dL) | 15 | 10–20 | pH | 7,24 | 7,35-7,45 |
| SCr (mg/dL) | 0,6 | 0.5–1.2 | $pO_2$ (mmHg) | 85 | 80-100 |
| HbSAg | negative | negative | $pCO_2$ (mmHg) | 19 | 35-45 |
| RBG (mg/dL) | 448 | <200 | HCO3 (mmoL/L) | 8,1 | 22-26 |
| Na (mmoL/L) | 113 | 135-145 | BE (mmoL/L) | -19,3 | -2 - +2 |
| K (mmoL/L) | 6,3 | 3,5-5 | $SaO_2$ (%) | 94 | ≥95 |
| Cl (mmoL/L) | 79 | 95-105 | COVID | Antigen (-) | negative |
| Urinalysis | Glucose +4 | negative | | PCR (-) | negative |
| | Ketones +3 | negative | | | |

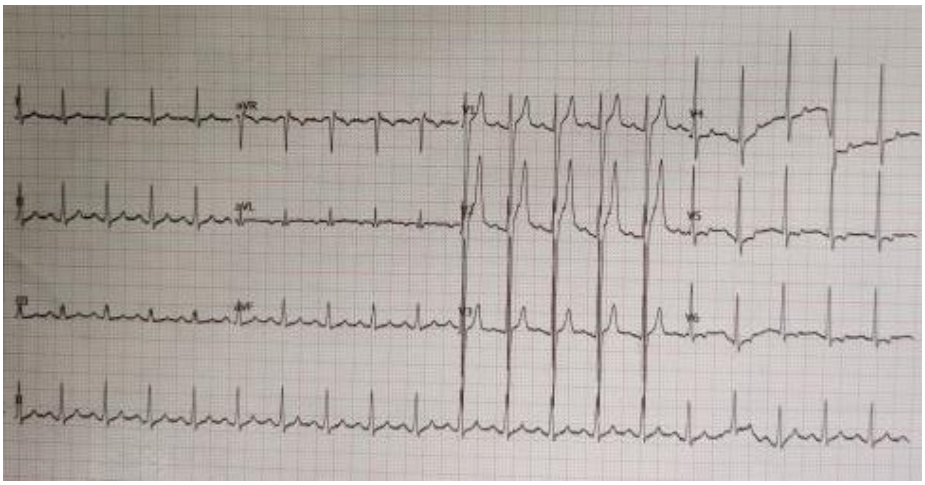

**Figure 1. ECG**

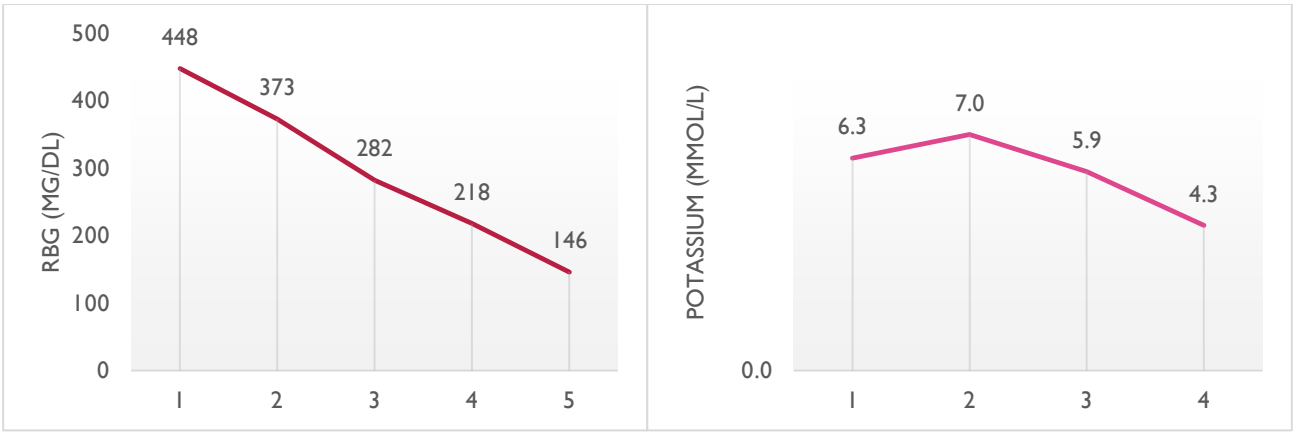


**Figure 2. Monitoring of RBG and potassium**

The patient was diagnosed with DKA, Hyperkalemia, Hypertonic hypovolemic hyponatremia, Elevated transaminase enzymes, Hyperbilirubinemia, Hyperchromic macrocytic anemia, DM, and Major β-thalassemia. Diagnostic plan: FPG, BG 2 hours post prandial, HbA1C, C-Peptide, HOMA-B, HOMA-IR, GAD-65, lipid profile, amylase, lipase, and anti-HCV. Treatment plan: diet 1900 kcal/day, nasal oxygen 3 lpm, rehydration with NaCl 0.9% 2000 ml IV in 2 hours, followed by NaCl 0.9% 80 drops/min in 4 hours, then NaCl 0.9% 30 drops/min in 18 hours and NaCl 0.9% 20 drops/min within 24 hours, rapid regulation of intravenous Aspart 4 units 1 hour interval (four times), Aspart 1 unit/hour IV continue, Ceftriaxone 1000mg every 12-hour IV, Deferasirox 500mg every 8-hour PO, NAC 600mg every 12-hour PO, Curcuma 1 tablet every 8-hour PO. Monitoring: CBC, electrolytes, RBG, BGA.

## 2. COURSE OF THE DISEASE

On the second day of treatment, he felt that the shortness of breath had reduced. GCS E4V5M6, blood pressure 90/55 mmHg, pulse 123 bpm, respiratory rate 22 breaths/min, axillary temperature 36.5°C and $O_2$ saturation 97%. Laboratory results, blood sugar: pre-breakfast 270 mg/dL, pre-dinner 108 mg/dl, HbA1C 15.3%, Sodium 117 mmol/L, Potassium 4 mmol/L, Chloride 91 mmol/L, and Anti-HCV 0.010 AU/mL. Diagnosis: Post DKA, Hyponatremia, Elevated transaminase enzymes, Hyperbilirubinemia, Macrocytic hyperchromic anemia, DM, Major β-thalassemia. Treatment: NaCl 0.9% 1500 ml IV in 24 hours, Aspart 8 IU every 8-hours SC pre-meals. He was transferred to high care unit.

On the third day of treatment, complaints of shortness of breath are decreasing, but he still felt body weakness. GCS E4V5M6, blood pressure 116/60 mmHg, pulse 96 bpm, respiratory rate 22 breaths/min, axillary temperature 36.5°C and $O_2$ saturation 98%. Laboratory results, Hb 6.6g/dL, Hct 20%, MCV 72.2 fL, MCH 23.8 pg, Leukocytes 13180/mm3, Platelets 471000/uL, Neutrophils 74.2%, Lymphocytes 17.1%, Sodium 128 mmol/L, Potassium 3.1 mmol/L, Chloride 96 mmol/L, Amylase 25U/L, Lipase 51U/L, Total cholesterol 151 mg/dL, HDL 16 mg/dL, LDL 128 mg/dL, Triglycerides 155 mg/dL. Blood sugar: Pre-breakfast 125 mg/dl, pre-dinner 172 mg/dl and bedtime 376 mg/dl. BGA: pH 7.25, pCO2 47 mmHg, pO2 83 mmHg, HCO3 20.6 mmol/l, BEecf -6.6 mmol/l, SaO2 94%. Chest X-ray showing pneumonia and cardiomegaly. Diagnosis: Confirmed COVID-19, Microcytic hypochromic anemia, Respiratory acidosis, Hyponatremia, Hypokalemia, Elevated

transaminase enzymes, Hyperbilirubinemia, Hypoalbuminemia, DM, and Major β-thalassemia. Treatment: PRBC transfusion 1 bag/day, Desferal 1000mg IV in 8 hours, kalium slow release (KSR) 600mg every 8-hours PO, and Aspart 2 IU/hour IV. He was transferred to isolation ward.

On the fourth day of treatment, he complained of body weakness. GCS E4V5M6, blood pressure 108/70 mmHg, pulse 90 bpm, respiratory rate 20 breaths/min, axillary temperature 36.5°C and $O_2$ saturation 98%. Laboratory results, FPG 261 mg/dL, GAD-65 <5 IU/mL. C-Peptide 0.69 ng/mL, HOMA-B 63, HOMA-IR 22.3 and Blood sugar: pre-breakfast 181 mg/dl, pre-lunch 435 mg/dl, and pre-dinner 268 mg/dl. Diagnosis: Confirmed COVID-19, Microcytic hypochromic anemia, Respiratory acidosis, Hyponatremia, Hypokalemia, Elevated transaminase enzymes, Hyperbilirubinemia, Hypoalbuminemia, Idiopathic T1DM, and Major β-thalassemia. Treatment: Aspart 2.5 IU/hour IV continue.

On the fifth day of treatment, he complained of body weakness. GCS E4V5M6, blood pressure 100/60 mmHg, pulse 88 bpm, respiratory rate 20 breaths/min, axillary temperature 36.5°C and O2 saturation 98%. Laboratory results, Hb 8.6g/dL, Hct 25.1%, MCV 74 fL, MCH 25.4 pg, Leukocytes 12800/mm3, Platelets 400000/uL, Neutrophils 62.1%, Lymphocytes 33.6%, Sodium 127 mmol/L, Potassium 3.7 mmol/L, Chloride 96 mmol/L, SGOT 212 U/L, SGPT 164 U/L, Albumin 3.3 g/dL, Total Bilirubin 4.29 mg/dL, Direct Bilirubin 2.08 mg/dL, blood sugar: pre-breakfast 153 mg/dl, pre-lunch 146 mg/dl, and pre-dinner: 240 mg/dl, INR 1.4, Ddimer 5640 ng/mL. BGA: pH 7.34, pCO2 34 mmHg, pO2 53 mmHg, HCO3 18.3 mmol/l, BEecf -7.5 mmol/l, SaO2 85%. Urinalysis: protein +2, ketones (-), erythrocytes +2. Diagnosis: Confirmed COVID-19, Microcytic hypochromic anemia, Metabolic acidosis, Hyponatremia, Hypokalemia, Elevated transaminase enzymes, Hyperbilirubinemia, Hypoalbuminemia, Idiopathic T1DM, and Major β-thalassemia. Treatment: Aspart 8-12-12 IU SC pre-meals.

On the sixth day of treatment, he felt better. GCS E4V5M6, blood pressure 100/60 mmHg, pulse 77 bpm, respiratory rate 20 breaths/min, axillary temperature 36.5 C and $O_2$ saturation 97%. Laboratory results, blood sugar: pre-breakfast from 13 to 285 mg/dl after treatment, pre-lunch 330 mg/dl, pre-dinner 178 mg/dl and bedtime 71 mg/dl. COVID-19 PCR swab negative. Chest X-ray: bilateral pneumonia, cardiomegaly with lung edema, right laminar pleural effusion. Diagnosis: Discarded COVID-19, Microcytic hypochromic anemia, Metabolic acidosis, Hyponatremia, Hypokalemia, Elevated transaminase enzymes, Hyperbilirubinemia, Hypoalbuminemia, Idiopathic T1DM, and Major β-thalassemia. Therapy: D40 100ml IV, rapid regulation of subcutaneous Aspart 6 IU, Aspart pump 0.5 IU/hour IV stop, Aspart 8 IU every 8-hour SC pre-meals, Detemir 16 IU SC every night, Fondaparinux 2.5 mg every 24-hour SC, and Vitamin D 1000 IU every 24-hour PO. He was transferred to non-isolation ward.

On the Seventh day of treatment, he felt weakness, nauseous, vomiting and shortness of breath. GCS E4V5M6, blood pressure 90/60 mmHg, pulse 70 bpm, respiratory rate 24 breaths/min, axillary temperature 36.5°C and $O_2$ saturation 97% free air. Laboratory results, Hb 8.4 g/dL, Hct 25.7 %, MCV 76.3 fL, MCH 24.9 pg, Leukocytes 23000/mm3, Platelets 345000/uL, Neutrophils 72.1%, Lymphocytes 20.4%, Sodium 126 mmol/L, Potassium 4.6 mmol/L, Chloride 90 mmol/L, SGOT 240 U/L, SGPT 202 U/L, Albumin 3.23 g/dL, Total Bilirubin 6.48 mg/dL, Direct Bilirubin 4.75 mg/dL. Blood sugar: pre-breakfast 309 mg/dL. BGA: pH 7.28, pCO2 26 mmHg, pO2 82 mmHg, HCO3 12.2 mmol/l, BEecf -14.5 mmol/l, SaO2 94%. Diagnosis: Microcytic hypochromic anemia, Metabolic acidosis, Hyponatremia, Elevated transaminase enzyme, Hyperbilirubinemia, Hypoalbuminemia, Idiopathic T1DM and Major β-thalassemia. Therapy: rapid regulation of subcutaneous Aspart 6 IU, Lansoprazole 40mg every 24-hour PO, and Domperidone 10mg every 8-hour PO.

On the Eighth day of treatment, the patient experienced severe shortness of breath accompanied by a high fever at the time of blood transfusion. GCS E4V5M6, Blood pressure 80/50 mmHg, pulse 120 bpm, respiratory rate 28 breaths/min, axillary temperature 37.8C and $O_2$ saturation 98% with simple mask. Thoracic examination was obtained by ronchi in the entire lung field. Steroids and diuretics have been given but that has not provided optimal results. The patient was declared dead with TRALI as the suspected cause of death.

## 3. DISCUSSION

β-thalassemia is a form of hemoglobinopathy due to mutations in the globin gene that result in reduced production of β-globin chains (thalassemia β+) or no production of β-globin chains at all (thalassemia β0) (Atmakusuma and Setyaningsih, 2014). β thalassemia is most often found in Mediterranean countries, Southeastern Europe, countries on the Arabian Peninsula, and Asia. β thalassemia has three main forms namely thalassemia major, intermedia and minor. Thalassemia β major belongs to the transfusion-dependent thalassemia (TDT) phenotype (Farmakis *et al*, 2022).

From the history taking, there are complaints of chronic pallor, yellow eyes, distended abdomen, delayed development, history of repeated transfusions, and family history of thalassemia. On physical examination, anemia, jaundice, Cooley's facies, hepatosplenomegaly, malnutrition, short stature, delayed puberty, and skin hyperpigmentation can be found. The results of hematological examination found severe anemia with Hb levels <7 g/dL, decreased hematocrit, decreased erythrocyte index, increased RDW accompanied by anisocytosis, and reticulocytosis (5-10%). Microcytic hypochromic anemia, anisopoikilocytosis, normoblasts, fragmentocytes and target cells were found on the peripheral blood smear. Hemoglobin electrophoresis shows an increase in hbF with a slight increase in HbA2. High performance liquid

chromatography (HPLC) found dominant HbF (> 90%) in almost all cases of severe β thalassemia with low or undetectable HbA. DNA analysis is performed when hematologic examination is unable to confirm hemoglobinopathy (Atmakusuma and Setyaningsih, 2014; Kemenkes, 2018; Farmakis *et al*, 2022).

*He felt body weakness, pale, and easily tired. On physical examination found anemic conjunctiva, slightly icteric sclerae, and asplenia. BMI 18.37 kg/m2. Laboratory results obtained: Hb 6.6g/dL, Hct 20%, MCV 72.2 fL, MCH 23.8 pg, Direct Bilirubin 1.23 mg/dL, Total Bilirubin 3.64 mg/dL. This situation describes a hemolytic process in beta thalassemia major patients. The patient has been diagnosed with β thalassemia major since 2007.*

TDT patients without adequate chelation therapy will cause iron overload in the pancreas starting at an early age, because the body does not have a mechanism to eliminate it. Iron overload causes transferrin saturation to become saturated, thus forming non-transferrin bound iron (NTBI). NTBI will cause direct toxic damage to pancreatic β cells by triggering the production of reactive oxygen species (ROS) which induces phospholipid peroxidation, oxidation of amino acid side chains, DNA strain termination, and protein fragmentation. This process causes damage to membrane lipids, organelles and DNA, with the end result of cell death and fibrogenesis mediated by transforming growth factor 1 (TGF β1). ROS directly activate caspase thereby accelerating apoptosis. Pancreatic β-cells are rich in mitochondria and are very sensitive to oxidant-producing substances, making them vulnerable to oxidative stress. Damage to pancreatic β-cells will cause a significant reduction in function which results in insulin deficiency with the end result developing DM. In hepatocytes, iron overload and chronic hepatitis infection will cause liver dysfunction which causes impaired ability of insulin to suppress hepatic glucose absorption, as well as decreased glucose absorption at the muscle level, so that the component of insulin resistance also plays a role as a cause of glucose toxicity (de Sanctis *et al.*, 2021).

The method for assessing iron overload can be done by examining serum ferritin and serum transferrin, both of which are representative for total cellular iron stores and extra hepatic risk. Accurate tests to assess the efficacy of chelation therapy and end-organ risk stratification are liver iron concentration (LIC) and cardiac T2 MRI. Serum ferritin level >1500 ng/dL has the potential to trigger DM. This parameter becomes unreliable in conditions, infections, malignancies, liver disease, and vitamin C deficiency. MRI-assisted LIC has replaced biopsy as the gold standard for monitoring chelation therapy efficacy or end organ risk stratification. In TDT patients, there was a hypointense MRI of the pancreas which was associated with the presence of fatty changes. Splenectomy will hasten the loss of signal intensity on pancreatic MRI Patients with impaired fasting glucose, impaired glucose tolerance, or diabetes showed lower global pancreatic T2* values. Liver siderosis occurs when LIC levels > 3 mg g dw which are classified as mild (< 7 mg/g dw), moderate (> 7 mg/g dw), and severe (> 15 mg/d dw) (de Sanctis *et al.*, 2021).

*He was routinely get 2 units blood transfusions every month. Ferritin levels were obtained at 19840.8 ng/ml thus reflecting the condition of iron overload which is a risk factor for DM in thalassemia.*

Risk factors for the development of DM in thalassemia are male sex, initiation of iron chelation therapy at advanced age, non-compliance with iron chelating drugs, inefficient iron chelating drug dosage, increased LIC (>7 mg/g dw), splenectomy, low insulin secretion after OGTT, liver cirrhosis or severe fibrosis. The strongest predictors were duration of transfusion therapy and inefficiency of chelation, where every decade of transfusion increases the risk of DM 2.5-fold (de Sanctis *et al.*, 2016).

*The patient is male, he did not take iron chelator regularly and has undergone splenectomy at the age of 5 years, these factors play a role in the development of DM.*

DM is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Based on the cause, DM can be classified into 4 groups, namely T1D, T2D, gestational DM (GDM), and other types of DM (PERKENI, 2021). T1D is characterized by immune-mediated destruction of beta cells resulting in insulin deficiency and hyperglycemia. T1D is divided into two categories based on the presence of serum autoantibodies, namely autoantibody-positive (immune mediated) and autoantibody-negative (idiopathic). Idiopathic T1D is only 10-15% of all cases of T1D (Holt *et al.*, 2021; Patel *et al.*, 2021).

There is a relationship between Human leukocyte antigen (HLA) and DR3-DQ2 and DR4-DQ8 genotypes in individuals with classic autoimmune T1D. Immune-mediated destruction of beta cells is initiated by antigen presenting cells (APCs) that present beta cell peptides to autoreactive CD4+ T cells. Activation of autoreactive CD8+ T cells in pancreatic lymph nodes leads to beta cell lysis and expression of immunogenic autoantigens. This process is compounded by dysfunctional T reg cells and the release of proinflammatory cytokines from innate immune cells. Autoantibody production is triggered by T cell activation which stimulates B cells to produce autoantibodies into beta cell peptides (Patel *et al.*, 2021).

The mechanism of B-cell destruction in idiopathic T1D is still unclear, but this form of diabetes is strongly inherited in certain ethnicities (Asian, African) and is not HLA-related (ElSayed *et al.*, 2022). Findings of higher BMI and C-peptide suggest that mechanisms such as insulin resistance may play an important role in disease pathogenesis. The underlying mechanism is thought to be through increased apoptosis of beta cells through glucotoxicity and lipotoxicity, thereby promoting the release of immunogenic autoantigens. Idiopathic T1D has a slower rate of pancreatic b-cell destruction (Patel

*et al.*, 2021).

Diagnosing T1D in adults has its own challenges where sometimes these individuals have a mixed clinical picture between T1D and T2D. The onset of T1D is more variable in adults, whereas the classic symptoms may not be present as in children. The classic triad of polydipsia, polyphagia and polyuria and weight loss are common symptoms in T1D. The most discriminatory clinical features for the diagnosis of T1D include age <35 years at diagnosis, BMI <25 kg/m2, unexplained weight loss, ketoacidosis, glucose >360 mg/dl at diagnosis and need for insulin therapy in less than 3 years after diagnosis (Holt *et al.*, 2021). Adults can maintain sufficient b-cell function to prevent DKA for many years before becoming insulin dependent for survival and developing DKA (ElSayed *et al.*, 2022). Idiopathic T1D individuals have a higher BMI, onset milder symptoms, older age, male gender, non-European ethnicity, lower insulin requirements, and higher C-peptide values Diagnostic criteria for diabetes in general according to the American Diabetes Association, namely FPG ≥ 126 mg/dL or 2-hG ≥ 200 mg/dL during OGTT or HbA1c ≥ 6.5% or RBG ≥ 200 mg/dL plus symptoms of hyperglycemia or hyperglycemic crisis (Patel *et al.*, 2021; ElSayed *et al.*, 2022).

An assessment of islet autoantibodies is recommended as a primary investigation in adults with suspected T1D. Glutamic acid decarboxylase-65 (GAD-65) is the primary antibody that is measured, if negative, then proceed with islet tyrosine phosphatase 2 (IA2) and or zinc transporter 8 (ZNT8) when available. The majority of individuals with immune-mediated T1D have one or more detectable islet cell autoantibodies. The absence of autoantibodies does not exclude T1D, as approximately 5–10% of white Europeans with new-onset T1D are islet antibody negative. In adults under 35 years of age, idiopathic T1D is still the most likely diagnosis, especially in the absence of clinical features of T2D or monogenic diabetes. Explanations for negative autoantibodies include true negatives, persistent negatives, autoantibody reversion, presence of autoantibodies at concentrations too low to be detected in the peripheral blood, defects in antibody formation, or the possibility that a new autoantigen has not been discovered (Holt *et al.*, 2021; Patel *et al.*, 2021).

C-Peptide is an insulin peptide residue that links between the A chain and the B chain of insulin comparable to the insulin produced by pancreatic β cells. The C-peptide value will not be affected by exogenous insulin administration. A decrease in C-Peptide levels indicates pancreatic cell damage. A random C-peptide value of >600 pmol/l strongly suggests type 2 diabetes, whereas a C-peptide value of <200 pmol/l or undetectable confirms the diagnosis of T1D. Molecular genetic testing should only be considered if the antibody is negative and the non-fasting C-peptide is >200 pmol/l (Holt *et al.*, 2021; ElSayed *et al.*, 2022). Flow chart for investigation of suspected T1DM in newly diagnosed adult is shown in Figure 3.

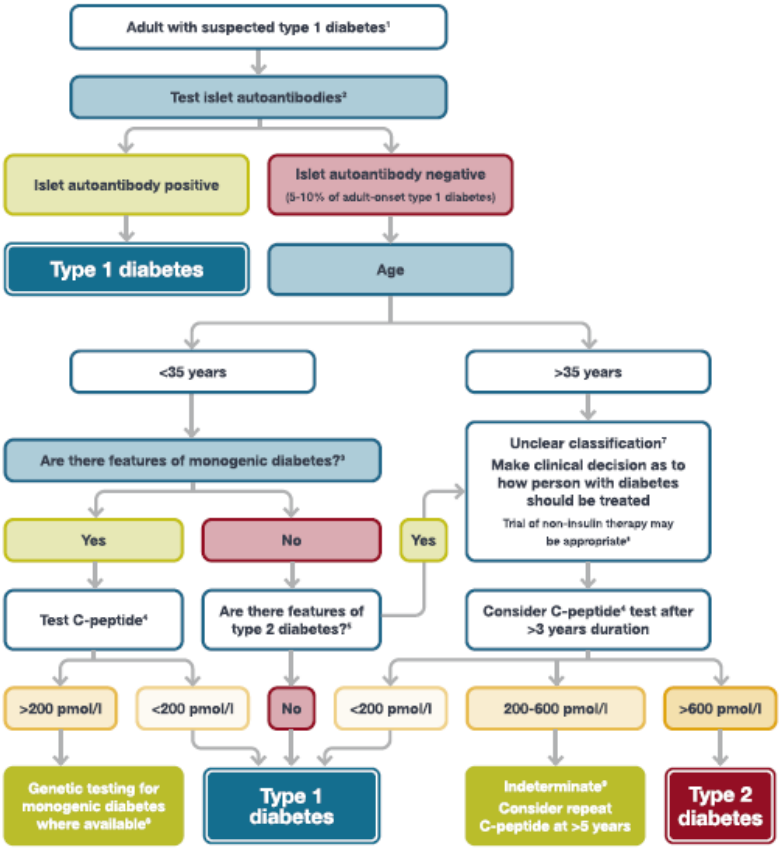


**Figure 3. Flow chart for investigation of suspected T1DM in newly diagnosed adult (Holt *et al.*, 2021)**

*The patient is a 20-year-old male, Asian ethnicity, has complaints of polydipsia, polyuria. BMI 18.37 kg/m2, RBG 448 mg/dl, FPG 261 mg/dl, HbA1C 15.3%, C-peptide 0.69 ng/ml, GAD-65 <5 IU ml and received insulin therapy. Based on these data, the patient is included in idiopathic type 1 DM.*

DKA belongs to the spectrum of hyperglycemic crisis which is a serious acute metabolic complication of DM. Its main manifestations are insulin deficiency and severe hyperglycemia resulting in severe dehydration, increased ketone production and acidosis (PERKENI, 2021). Factors that can trigger DKA include infection, inadequate or discontinued insulin therapy, pancreatitis, myocardial infarction, CVA, and drugs (Kitabchi *et al.*, 2009). Iron overload in TDT patient is also a risk factor for DKA (Karimi *et al.*, 2008). There are several factors that can cause recurrent DKA, including young age, male gender, patient comorbidities (psychiatric illness, alcohol abuse, chronic medical illness), low socioeconomic status, noncompliance with medical treatment, technical issue related to insulin, poor glycemic control and elevated HbA1C (Brandstaetter *et al.*, 2019).

*Factors that cause recurrent DKA in patients are male gender, young age, non-adherence to therapy, hyperglycemia, high HbA1C, iron overload and pneumonia.*

The diagnosis of DKA is made if there is a triad of DKA which includes hyperglycemia (>250 mg/dl), ketonemia and/or ketonuria, and metabolic acidosis (pH <7.3 and Kussmaul respirations). Additional findings that support the criteria for DKA are blood sugar >250mg/dl, arterial pH <7.30, serum bicarbonate <18meq/l, anion gap >10, and mild increases in blood and urine ketones. Classic clinical symptoms include polyuria, polydipsia, nausea, vomiting, weakness, dehydration, hypotension to shock, and decreased consciousness (Kitabchi *et al.*, 2009; Tjokroprawiro, 2017).

*The patient came with complaints of shortness of breath with Kussmaul pattern, weakness, polyuria and polydipsia. There are signs of dehydration based on presence of hypotension and tachycardia. From laboratory examination, RBG 428 mg/dl, arterial pH 7.24, HCO3 8.1 mmol/L, ketonuria +3, and anion gap 25.9 mEq/L. Based on these data, the patient was diagnosed as DKA.*

DKA is classified into three degrees, namely mild, moderate and severe which can be seen in table 2 below.

**Table 1. DKA severity classification (Kitabchi *et al.*, 2009)**

| | Mild (plasma glucose >250 mg/dl) | Moderate (plasma glucose >250 mg/dl) | Severe (plasma glucose >250 mg/dl) |
|---|---|---|---|
| Arterial pH | 7.25–7.30 | 7.00 to <7.24 | <7.00 |
| Serum bicarbonate (mEq/l) | 15–18 | 10 to <15 | <10 |

*Based on above classification, the patient met in the criteria for moderate DKA.*

Based on the 2022 COVID-19 management guidelines in Indonesia, a confirmed case of COVID-19 is a person who meets one of the following criteria: a). someone with a positive RT-PCR laboratory test. b). meet the criteria for a suspected case or close contact and a positive RDT-Ag test result in moderate-high risk zone c). A person with positive RDT-Ag test results high risk zone. Positive persistence in COVID-19 is found in patients who have experienced an improvement in their condition after being diagnosed with COVID-19 but the RT-PCR examination results did not convert to negative, or in other words, RT-PCR tools can still detect inactivated viral components from patient specimens. Several studies have shown that RT-PCR is still detectable for a duration of 8-12 weeks, although the detectable viral load is decreasing. Patients with persistent positives with low viral loads are still advised to self-isolate and carry out health protocols until the negative conversion of RT-PCR (Burhan e*t al.*, 2022).

*The patient was confirmed Covid-19 based on a positive RT-PCR result Clinically the patient classified as a mild disease with complaints of shortness of breath and fatigue. A positive RT-PCR result on day 50 from the initial test indicated a positive persistence, so the patient was moved to the isolation room until negative seroconversion of RT-PCR.*

One form of new-onset diabetes is COVID-19 patients who may have previously undetected DM as a consequence of insulin resistance due to obesity and hyperglycemia associated with lifestyle changes. Stress hyperglycemia in acute illness is a sign of insulin resistance associated with increased lipolysis and circulating free fatty acids, as well as increased gluconeogenesis. Acute inflammation in cytokine storm will exacerbate insulin resistance. Acute hyperglycemia in COVID-19 is associated with binding of SARS-CoV-2 to the ACE-2 receptor on pancreatic islet cells. Proinflammatory cytokines and acute phase reactants associated with COVID-19 can directly cause inflammation and damage to pancreatic beta cells, including transdifferentiation and degranulation, resulting in decreased insulin secretion. SARS-Cov-2 can also trigger an autoimmune process against pancreatic beta cells. Steroid use in COVID-19 is associated with increased glycogenolysis and decreased insulin sensitivity in liver, skeletal muscle, adipose tissue (Khunti *et al.*, 2021; Yonekawa and Shimono, 2022).

Hyperglycemic crisis therapy aims to correct the underlying pathophysiological abnormalities, namely fluid and electrolyte balance disorders, blood glucose levels, acid-base disorders, and overcome precipitating factors. The main goal of DKA

treatment is to stop the process of ketosis. The main components of DKA management include fluid administration, electrolyte and acid-base correction and insulin therapy. Fluid resuscitation aims to correct fluid depletion in the body. Rehydration using 2000 ml 0.9% NaCl or RL in 2 hours, followed by 80 drops/minute for 4 hours, then 30 drops/minute for 18 hours, and 20 drops/minute for 24 hours. It is necessary to limit rehydration if there is a condition of heart failure or kidney failure by monitoring via central venous pressure (CVP). Intravenous low-dose insulin was started at 4 units/hour and blood sugar was checked every hour. In general, intravenous insulin infusion of 5-7 units/hour can reduce blood glucose levels 50-75 mg/dL/hour and can inhibit lipolysis, stop ketogenesis, and suppress gluconeogenesis in the liver. The rate of insulin infusion needs to be adjusted based on blood glucose levels, if it has fallen <250 mg/dL, the insulin dose should be reduced by 50% from the previous dose. The insulin infusion is continued until the ketosis is resolved and the patient is able to eat and drink. Potassium supplementation should be given before starting insulin therapy if the potassium level is <3.3 mEq/L at baseline and is maintained above 3.5 mEq/L. Acid-base disorders that are quite severe also require special handling. Bicarbonate infusion is given if pH 7.2 or serum bicarbonate <12 mEq/L, using 50-100meq sodium bicarbonate in 24 hours. Administration of antibiotics must be rational and in adequate doses in DKA patients (Tjokroprawiro, 2017; PERKENI, 2021). The DKA protocol consists of two phases, namely the emergency phase and the rehabilitation phase with the limit of blood glucose levels between the two phases is 250 mg/dL (Tjokroprawiro and Murtiwi, 2015). In the maintenance phase, 0.9% NaCl or 10% Maltose was given alternately at a rate of 20 drops/minute with the principle of start slow go slow. Potassium levels are still monitored, if <4 mEq/L can be supplemented parenterally or orally with either tomato water or broth. The transition from continuous IV insulin to subcutaneous insulin is carried out when the patient can eat normal food or moves to the usual ward. The subcutaneous insulin dose was administered between 75-80% of the total daily dose of continuous IV insulin, which was then divided proportionally into the basal and prandial components. Subcutaneous insulin should be given 2 hours before the IV insulin infusion is discontinued to prevent hyperglycemia. Oral nutrition is given soft foods containing complex carbohydrates. (Tjokroprawiro, 2017; PERKENI, 2021) The criteria for resolution of DKA include a RBG of 200 mg/dl and the following two criteria, namely a serum bicarbonate level of 15 mEq/l, venous pH 7.3, and an anion gap of 12 mEq/l (Kitabchi *et al.*, 2009).

*When in the emergency room he was given nasal oxygen therapy 3lpm, rehydration with 2000cc NaCl 0.9% in 2 hours, followed by NaCl 0.9% 80 drops/min for 4 hours, then NaCl 0.9% 30 drops/min for 18 hours, and NaCl 0.9% 20 drops/min for 24 hours. Given rapid regulation of intravenous Aspart 4 units 1 hour interval, followed by Aspart 1 unit/hour IV continue. Empirical antibiotics were given ceftriaxone 1 gram every 12 hours on the basis of pneumonia. The patient refused CVC insertion for continuity of therapy and monitoring of central venous fluids. The transition from continuous intravenous insulin to basal-bolus subcutaneous insulin was performed on the sixth day of treatment, Aspart 8 IU every 8-hour SC pre-meals, Detemir 16 IU SC every night. He also received KSR 600 mg every 8-hours PO.*

Specific management of thalassemia with DM is intensification of iron chelation therapy to achieve a negative iron balance. Iron chelation therapy is initiated after transfusion of 5-10 units of blood or SF >1000 g/l. There are three approved iron chelators, namely deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX). Iron chelators can be used as monotherapy if the iron load is still within acceptable levels, while combination therapy is indicated in patients with severe iron load, iron-related organ damage and experiencing side effects (de Sanctis *et al.*, 2021).

*The patient received iron chelation therapy using Deferasirox (DFX) 3x500mg PO in combination with Desferal (DFO) 1000mg IV every 8 hours.*

Complications from transfusions that can occur in thalassemia patients can be divided into: 1. Blood Transfusion-Associated Infections: Hepatitis B and Hepatitis C, HIV, Syphilis; 2. Immune - mediated blood transfusion reactions (occurring <24 hours): Acute haemolytic transfusion reactions (AHTRs, Febrile nonhemolytic transfusion reactions (FNHTRs), Transfusion related acute lung injury (TRALI), Urticaria, Anaphylactic reactions; 3. Non immune-mediated blood transfusion reactions (occurring <24 hours): sepsis-related transfusion reactions, transfusion reactions related to fluid overload, pulmonary embolism 4. Immune - mediated blood transfusion reactions (occurring >24 hours): Delayed haemolytic transfusion reactions (DHTRs), Transfusion associated immunomodulation (TRIM), Transfusion-associated graft versus host disease (TA-GVHD), Post-transfusion purpura; 5. Non immune-mediated blood transfusion reactions (occurring >24 hours): Iron Overload (Sahu, Hemlata and Verma, 2014).

*On the eighth day the patient experienced shortness of breath, fever, tachycardia, and hypotension at the time of blood transfusion. Chest examination revealed crackles over all lung fields. Oxygenation therapy, steroids and diuretics have been given but it did not provide optimal results. The patient was declared dead with TRALI as the suspected cause of death.*

The management of patients with confirmed COVID-19 at mild degrees is based on the Indonesian guidelines for the management of COVID-19 3rd edition, namely independent or centralized isolation for a maximum of 10 days from the appearance of symptoms plus 3 days without symptoms of fever and respiratory problems; Antivirals: Favipiravir, Molnupiravir, Nirmatrelvir/Ritonavir Vitamins C and D; symptomatic therapy; Supportive medicine, both traditional (Fitofarmaka) and Modern Original Indonesian Medicine (OMAI) (Burhan *et al.*, 2022).

*The patient received therapy according to the guidelines for the management of mild COVID-19, however, the patient was*

*treated at the hospital due to the need for DKA management and blood transfusions.*

**Summary**

We have reported a case of a 20-year-old β thalassemia major man with idiopathic T1DM accompanied by moderate DKA complications. There was evidence of pancreatic beta cell dysfunction and insulin resistance that are consistent with the pathophysiology of idiopathic T1DM. Patient had recurrent DKA with the main cause of non-adherence to insulin therapy that contribute to poor glycemic control, besides another non-modifiable factor such as young age and male gender. He was given therapy according to the DKA protocol which included fluid rehydration, insulin, potassium, and antibiotic. It is important to manage other risk factors such as infection and iron overload as found in this patient to prevent another episode of DKA which can contribute to poor prognosis.

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