Pancytopenia and Hypoglycemia – Atypical Presentations of Thyrotoxicosis
Pansitopenia dan Hipoglikemia – Presentasi Atipikal dari Tirotoksikosis

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Abstract

Pancytopenia and hypoglycemia are atypical presentations and potentially devastating complications of thyrotoxicosis which may lead to delayed diagnosis. This case report aims to describe atypical presentations of thyrotoxicosis. A case report of a 55-year-old man who was admitted with a history of epigastric pain for seven days, accompanied by malaise, weight loss, clammy hand, increase in appetite followed by a decrease in appetite, diarrhea, nausea, nervousness, and restlessness, palpitation, easy fatigability, and fever which happened for the past one month until the day he was admitted on 13 October 2020 to Sumedang General Hospital. He was treated accordingly. Laboratory examination showed pancytopenia, hypoglycemia, and low Thyroid Stimulating Hormone level. The Electrocardiogram showed atrial fibrillation and left ventricular strain. The patient was diagnosed with Thyroid Crisis. After four days of treatment, the clinical condition of the patient was getting better. Conclusion, history taking of previous symptoms and disease is becoming significant to establish a working diagnosis. A thorough history taking could help a physician to consider hyperthyroidism as a differential diagnosis not merely based on laboratory results. Recognition of unusual thyrotoxicosis presentations is important in early diagnosis and effective treatment of the disease to prevent further complication and morbidity.

Keywords: hypoglycemia; pancytopenia; thyrotoxicosis

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Abstrak


Kata kunci: hipoglikemia; pansitopenia; tirotoksikosis

Introduction

A thyroid storm or thyrotoxic crisis is a relatively rare, life-threatening endocrine emergency.1,2 The prevalence is 1-2% among patients admitted for thyrotoxicosis.1,2 It has a mortality of 10-20%.1 It results from decompensated thyrotoxicosis with increased activity of the thyroid hormones, exceeding the patient’s metabolic demands.2,3 Thyroid storm usually develops in a setting of a specific precipitating event such as surgery, infection, sepsis, trauma, cerebrovascular accident, drugs, an acute iodine load, or parturition.1,2,3 Clinical picture comprises an exaggerated feature of hyperthyroidism such as hyperthermia, tachycardia, hypertension, severe agitation, and altered mental status.1,2,3

The basis for diagnosis is formed by clinical presentation and laboratory findings. A semi-quantitative scale called Burch-Wartofsky Score was developed to help assess the presence and severity of the most common signs and symptoms and thereby create a more objective basis for establishing the diagnosis.2,3 The treatment of thyroid storm should be initiated as soon as the diagnosis is suspected.1

In recent years, there have been increasing reports of atypical presentation of thyrotoxicosis that includes haematological abnormalities such as pancytopenia and also metabolic disturbances such as hypoglycaemia.4,5 Pancytopenia is a rare entity of thyrotoxicosis...
clinical manifestation. The pathogenesis is poorly understood, but there are several postulates.\textsuperscript{6,7,8} The occurrence of thyroid storm in conjunction with hypoglycaemia is rare, but the literature does show that this condition can have a variety of causes.\textsuperscript{9,10,11}

We present a case report of a 55-year-old man who was admitted with a history of epigastric pain for seven days, accompanied by malaise, hiccup, weight loss, clammy hand, increase in appetite followed by a decrease in appetite, diarrhea, nausea, nervousness and restlessness, palpitation, easy fatigability, and fever which happened for the past one month until the day he was admitted on 13 October 2020 to Emergency Department of Sumedang General Hospital. Laboratory examination showed pancytopenia, hypoglycemia, and low Thyroid Stimulating Hormone (TSHs) level. The Electrocardiogram (ECG) showed atrial fibrillation and left ventricular (LV) strain showing left ventricular hypertrophy. The patient was diagnosed with Thyroid Crisis. This case report aims to describe pancytopenia and hypoglycemia as atypical presentations and potentially devastating complications of thyrotoxicosis, which may lead to delayed diagnosis.

Case Illustration

A 55-year-old man presented to the Emergency Department of Sumedang General Hospital with a chief complaint of epigastric pain for 7 days. The complaint was accompanied by nausea and diarrhea up to 10 times/day without mucus and blood for 7 days. One day before admission he had a fever. He complained of malaise one month before admission which worsened over the past 7 days. One week before admission he felt nervous and scared. His wife also felt that he became restless. It was accompanied by palpitation one week before admission. For the past 7 days, he also complained of easy fatigability even for light activities such as walking. He felt his hands clammy two weeks before. He had lost 12 kg in 2 weeks. The wife saw an increase in appetite 2 weeks before admission without an increase in body weight, yet one week before admission he lost his appetite due to nausea. He experienced hiccups for 3 weeks.

There was no history of heat or cold intolerance, vomit, excessive sweating, and warm hands. There was no history of episodic yellowish discolouration of eyes or body, dark-coloured urine, delirious, seizure, and loss of consciousness. He was not on any long-term medications. No history of congenital or chronic illness. History of hospital admission due to typhoid fever and dengue haemorrhagic fever when he was young. He ever experienced rash and pruritus after
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a drug injection, but he was not aware of the drug. There was no family history of the same complaints. The timeline of the complaints was summarized in Figure 1.

![Figure 1 Timeline of Complaints](image)

On admission, he was 160 cm tall and weighed 40 kg. On general examination, he was thinly built and looked weak, and nervous. His vital signs were as follows: temperature of 38°C, blood pressure of 180/120 mmHg, pulse rate of 114 beats per minute, which was irregularly irregular, and respiratory rate of 22x/minute. His conjunctiva was anaemic and anicteric. There were no eye signs of Graves’ disease such as exophthalmos, proptosis, or chemosis. Neck examination revealed palpable diffuse struma, firm in consistency, without tenderness. The heart sound was irregular, with no murmur or fine basal rales heard over both lungs. The cardiac apex was felt 2 cm lateral to the fifth intercostal space of the left midclavicular line. Epigastric tenderness was felt. There was no liver and spleen enlargement. There was a fine tremor on both hands without pretibial myxoedema. The hands were moist. An electrocardiogram showed atrial fibrillation and LV strain showing left ventricular hypertrophy (Figure 2).

The laboratory result during hospitalization was described in table 1. His laboratory result showed anaemia and thrombocytopenia on the first day of admission. He was also in a hypoglycaemic state. On the 3rd day, the laboratory result showed pancytopenia. He also had a low TSHs level which was possibly due to negative feedback from a high level of thyroid hormone and suggested a thyrotoxicosis state.
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Figure 2 Electrocardiogram Showing Atrial Fibrillation and LV Strain

Table 1 Laboratory Findings During Hospitalization

<table>
<thead>
<tr>
<th></th>
<th>13 October 2020</th>
<th>14 October 2020</th>
<th>15 October 2020</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
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<td>8.9 g/dL</td>
<td>9.2 g/dL</td>
<td>13.5-18.0</td>
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<tr>
<td>Leucocyte</td>
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<td>6,400/mm³</td>
<td>2,400/mm³</td>
<td>4500-10,000</td>
</tr>
<tr>
<td>Thrombocyte</td>
<td>49,000/mm³</td>
<td>50,000/mm³</td>
<td>45,000/mm³</td>
<td>150,000-450,000</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>25.2%</td>
<td>25.1%</td>
<td>25.1%</td>
<td>40-48</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>54 mg/dL</td>
<td>85 mg/dL</td>
<td>174 mg/dL</td>
<td>100-150</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.68 mg/dL</td>
<td></td>
<td></td>
<td>0.5-1.1</td>
</tr>
<tr>
<td>TSHs</td>
<td>&lt;0.05 UI/mL</td>
<td></td>
<td></td>
<td>0.27-4.70</td>
</tr>
</tbody>
</table>

TSH: thyroid-stimulating hormone
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The patient was initially diagnosed as 1st-degree Dengue Haemorrhagic Fever + Hypoglycemia + Hypertensive crisis + Epigastric pain et causa gastroesophageal reflux disease. He was given 2 flacons (50 ml) of D40% intravenous (IV) bolus, 500 ml of D10% IV 10 drops per minute, 1500 ml Ringer Lactate for 24 hours as maintenance fluid, amlodipine 10 mg, ranitidine 2x50 mg IV, and sucralfate 4 tablespoons a day. The blood glucose was checked 1-hour post-correction. The next day, after being examined thoroughly by an internist in the ward, he was diagnosed with Thyroid Crisis based on the Burch-Wartofsky score, with a total score of 50 (figure 3). He was treated accordingly. He was given 1000 ml of D10% IV for 24 hours, Propylthiouracil 3x200 mg per oral (after the blood was taken for TSHs level examination), Dexamethasone 3x5 mg IV, Propranolol 3x20 mg per oral, Omeprazole 1x40 mg IV, and Paracetamol 3x500 mg per oral. Iodine was not given because his clinical condition was not too severe. The next day, the maintenance fluid was changed into 1000 ml of D5% IV for 24 hours. He was getting better after four days of treatment. He no longer complained of fever, epigastric pain, palpitation, diarrhea, tremor, and moist hand. His heart rate had returned to sinus rhythm and was no longer tachycardia. He still felt malaise, but it was much better compared to the day of admission. He was discharged after four days and asked to control the internal medicine polyclinic.

Discussion

Our patient had a thyroid storm complicated by pancytopenia and hypoglycemia. The history or examination did not reveal any causes that may have attributed to the pancytopenia such as features of hematological malignancies, infection, autoimmune hemolysis, or use of any drugs. The possibility of thyrotoxicosis predisposing to pancytopenia was therefore considered. Single-cell lineage hematological abnormalities such as anemia, thrombocytopenia, or leukopenia can be associated with thyrotoxicosis with anemia as the most associated one (10-34%). Leukopenia is reported among 15-30% of untreated thyrotoxicosis, and thrombocytopenia is the least common (2-5%). Pancytopenia is a rare complication of thyrotoxicosis. It can also be a complication of antithyroid medication. A case report with literature review in 2020 says there were 19 case reports and two case series regarding the occurrence of pancytopenia in a hyperthyroidism scenario.
The pathogenesis of thyrotoxicosis-related pancytopenia is not fully elucidated. There are several suspected pathogenic mechanisms responsible for pancytopenia included: 8,13,15,16,17

1) Ineffective hematopoiesis due to excessive thyroid hormones (inhibition effect)
2) Reduced blood cell’s life span either by immune destruction or sequestration of mature hematopoietic cells caused by functional hypersplenism with or without splenomegaly
3) The autoimmune process that induces antineutrophil or antiplatelet antibodies, and
4) Direct toxicity of thyroid hormones to bone marrow stem cells

Two patients reported by Duquenne et al. exhibited signs of macrophage activation with eosinophilia in their bone marrow, which was consistent with an immune-allergy reaction. Moreover, antineutrophil antibodies and antiplatelet antibodies have been detected in the serum of patients with thyrotoxicosis.6 There was a case reported by Shaw and Mehta of post-bone marrow transplant pancytopenia which was related to hyperthyroidism. Therefore, they postulated that thyroid hormone may have a direct effect on hematopoiesis at a stage earlier than erythropoietic stem cell differentiation and disturb the maturation and differentiation of the pluripotent stem cells. A reduced marrow granulocyte reserve has also been observed in association with hyperthyroidism and ascribed to the direct toxicity of the thyroid hormones.6

Anemia has been reported in up to 10-34% of patients with hyperthyroidism and it could be normocytic, microcytic, or macrocytic and is usually mild.7 Interestingly, hyperthyroidism is correlated with the increased total number of erythrocytes, likely due to increased tissue oxygen demands resulting in increased erythropoietin secretion. Nevertheless, anemia could be seen in hyperthyroid patients due to simultaneous increase in plasma volume, shorter erythrocyte life span, ineffective erythropoiesis, abnormal iron utilization, or deficiency of iron, vitamin B12, or folate.4,15

Leukopenia is reported in 15% to 30% of untreated thyrotoxicosis but is usually associated with pancytopenia.4,7 Relative lymphocytosis with a normal or slightly low white blood cell count is the characteristic hematological finding of Graves’ Disease, called Kocher’s blood picture.5,7 The proposed mechanisms for leucopenia include a cross antigenicity between TSH receptors and polynuclear neutrophils, a decreased circulating time of granulocytes, and a reduced marrow granulocyte reserve. The hypothesis of immunologic destruction mechanisms has been suggested, as antineutrophil antibodies were detected in the serum of patients with thyrotoxicosis.4,7,12 It could also be because of arrested hematopoiesis or hypersplenism.14

Thrombocytopenia is rarely observed in 2% to 5% of thyrotoxicosis cases.12 Thyroid antibodies could react with protein on platelet and the thyrotoxicosis itself could increase the phagocytic activity of the reticuloendothelial system with or without splenomegaly. The immunologic and toxic effects of thyroid hormone are also presumed to disturb the maturation
and differentiation of pluripotent stem cells. A study by Kurata et al. regarding the effect of T3 on platelet kinetics showed that mice injected with T3 had a decreased platelet count and reduced platelet life span. Studies have also shown that thrombopoiesis is increased in hyperthyroidism to compensate for the decreased platelet lifespan and increased platelet turnover.5,6,7,8

The causes of hypoglycemia that have been reported include hormonal hyposecretion, sepsis, renal dysfunction, liver dysfunction, congestive heart failure, lactic acidosis, emaciation, shock, tumors, and pheochromatosis effect post-operation.9 Hypoglycemia occurs in the treatment of diabetes, anorexia nervosa, liver disease, and adrenal insufficiency. Hyperthyroidism usually induces impaired glucose tolerance. However, hyperthyroidism with congestive heart failure or liver dysfunction is thought to induce hypoglycemia, but this is extremely rare.10 Hypoglycemia is an uncommon presentation of hyperthyroidism.1,18,19 Normotension, normothermia, hypoglycemia, and lactic acidosis have been proven to be too atypical for a physician to diagnose a thyroid crisis accurately.9

Hypoglycemia in a thyroid crisis can have a variety of causes. For example, Kobayashi et al. described a case of thyroid crisis with hypoglycemia due to starvation. In that case, the common cold caused anorexia and the patient did not eat carefully because she had lived alone for 10 years. Starvation for more than 2 weeks could induce substrate deficiency for gluconeogenesis.2,3,9 In cases of prolonged thyrotoxicosis, glycogen deposits in the liver are completely depleted and may cause hypoglycemia. It particularly happens in the elderly, when aggravated by malnutrition secondary to emesis and abdominal pain.2 Severe malnutrition combined with thyrotoxicosis should induce hypoglycemia. Alternatively, hypoglycemia may precipitate a thyroid crisis.2,3,9

Hyperthyroidism with congestive heart failure or liver dysfunction is considered to induce hypoglycemia, though it is very rare. Congestive heart failure is associated with hypoglycemia due to decreased insulin clearance and severe liver dysfunction, which inhibits glucose release from liver cells. In the English literature, there are three case reports of hypoglycemia along with hyperthyroidism. The first case was due to anorexia, the second was due to liver dysfunction and lactic acidosis, and the cause of the third was unclear. Lactic acidosis might be caused by an increased anaerobic metabolism due to insufficient oxygen supply as a result of decreased cardiac output and respiratory failure. Furthermore, liver failure leads to a decreased lactate clearance, which cannot be converted into glucose in the hepatocyte, resulting in worsening of lactic acidosis and simultaneous development of hypoglycemia.9,10,18,20
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In this case report, the pancytopenia is not yet confirmed whether it was related to the thyrotoxicosis state due to the limitations of the supporting examinations performed such as differential count, erythrocyte index, and blood smear, specific evaluation of anemia, thyroid autoantibodies, and bone marrow aspiration and biopsy. Thus, other possible causes of pancytopenia could not be ruled out yet. However, this does not rule out the possibility that the pancytopenia, in this case, was related to thyrotoxicosis as reported in various case reports.

The hypoglycemia that occurred in this patient was probably caused by reduced glycogen deposits in the liver due to prolonged thyrotoxicosis and accompanied by starvation as the patient had decreased appetite for one week before admission. It was exaggerated by the conditions of the patient, who is quite old and presents with abdominal pain, diarrhea, nausea, and poor intake. The possibility of hypoglycemia due to heart failure and liver failure, lactic acidosis, or adrenal problems in this patient has not been ruled out due to limitations of the examination. Evaluation of liver function, chest X-ray, echocardiography, natriuretic peptide, adrenal evaluation, and examination of lactate levels was not performed in this patient.

The possibility of insulin injection as the cause of hypoglycemia can be ruled out because the patient does not use insulin. The patient also did not consume alcohol during this period. So, it is assumed that the hypoglycemia in this patient is not caused by iatrogenic hyperinsulinemia or alcoholism. Hypoglycemia can also be a precipitating factor in a thyroid crisis. In this case, it could not be concluded yet whether hypoglycemia is a precipitating factor of the thyroid crisis or the consequence of the thyroid crisis.

Conclusion

The possibility of hyperthyroidism should always be considered in patients with unexplained pancytopenia. The importance of history taking of previous symptoms and disease is becoming significant to establish a working diagnosis. A thorough history taking could help a physician to consider hyperthyroidism as a differential diagnosis not merely based on laboratory results. Studies suggest that hematologic parameters and thyroid function should be monitored monthly for the first 3 months. If improvement is not achieved within 3 months, therapy is considered ineffective and other treatment modalities should be sought. Proper hematologic examination before starting antithyroid medication is essential to prevent misdiagnosis, antithyroid drug-induced pancytopenia not pancytopenia inducing thyrotoxicosis. Likewise, in
patients with pancytopenia, evaluation of the thyroid can be helpful even in the absence of associated symptoms. Monitoring blood sugar and lactic acid levels can be necessary in complications of thyroid crisis. Blood sugar levels need to be checked in patients with thyroid crisis, especially if followed by heart and liver failure. It is important to consider the diagnosis of a thyroid crisis early, even if the presentation is very atypical, because of the importance of responding quickly to these situations.

References