

Case report

**Sepsis-induced Pancytopenia in an Adolescent Girl with Thyroid Storm: A Case Report**

**Zhou Q et al. Thyroid Storm with Pancytopenia**

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**Abstract**

Thyroid storm is a rare but life-threatening condition mainly triggered by infection and abrupt discontinuation of antithyroid drug therapy for Graves' disease. Pancytopenia is a rare adverse reaction to antithyroid drugs. We present a 13-year-old girl with thyroid storm and pancytopenia with symptoms similar to those of methimazole-induced pancytopenia. Although in this context the use of methimazole is still under debate, due to multiple normal complete blood counts monitored during fever, sepsis-induced pancytopenia with thyroid storm was considered, and methimazole treatment combined with methylprednisolone and meropenem was able to resolve both pancytopenia and thyroid storm. During the period of infection and antithyroid drug therapy, close monitoring of complete blood count may help differentiate the aetiology of pancytopenia. This is the first paediatric case report that outlines the use of methimazole in the management of thyroid storm with pancytopenia.

**Keywords:** Thyroid Storm; Pancytopenia; Sepsis; Antithyroid Drug

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**Background**

Thyroid storm is a rare, acute complication of hyperthyroidism characterized by extreme manifestation of

thyrotoxicosis, and it occurs in 1% to 2% of patients with hyperthyroidism. Methimazole has been used as a first-line therapy for Graves' disease in children. Agranulocytosis is a rare adverse reaction of antithyroid drugs and can be life-threatening, occurring in 0.2%–0.5% of patients generally within 90 days after initiation of antithyroid drug therapy<sup>[1]</sup>. Moreover, pancytopenia has also been reported in some patients on antithyroid drug therapy, but its incidence is much lower than that of agranulocytosis<sup>[2]</sup>. Therefore, it is challenging to differentiate whether patients with pancytopenia and thyroid storm is due to sepsis or methimazole. Herein, we present a case report of a 13-year-old girl with thyroid storm accompanied by sepsis-induced pancytopenia.

### Case presentation

A 13-year-old girl was diagnosed with Graves' disease and started methimazole (7.5 mg twice daily) 5 weeks prior (Day -35). Thyroid function showed improvement after 2 weeks of methimazole therapy (see Table 1). Table 1 shows laboratory results at the different evaluation points.

The patient developed fever 17 days after methimazole therapy, and complete blood cell count (CBC) and C-reactive protein (CRP) were normal on the first day of fever, so methimazole treatment was continued. The patient still had a fever 5 days later, and a review of laboratory profiles revealed improved thyroid function and normal CBC and liver function, but CRP was elevated. Therefore, methimazole therapy was continued and oral antibiotics were prescribed. However, the patient had a recurrent and intermittent fever, and she discontinued the use of methimazole on her own on the day 11 of fever. Two days after methimazole withdrawal, she developed recurrent high fever, accompanied by sore throat and hoarseness. She was hospitalized with sepsis and pancytopenia in the local hospital. Due to no improvement in her symptoms, she was transferred to our paediatric intensive care unit (PICU) for suspected thyroid storm.

On arrival to the PICU, the patient was febrile (temperature 38.5 °C), tachycardic (heart rate 140 beats/min), tachypneic (respirator rate 30/min), had a blood pressure of 126/72 mmHg and oxygen saturation of 98% on room air. Her weight was 30 kg. On physical examination, the neck mass or swelling was obvious, tender to palpation with multiple palpable lymph nodes, making it difficult to distinguish the thyroid from other structures, such as lymphatic tissue. On examination of the oropharynx, retropharyngeal abscess and tonsillar abscess were significant. The respiratory examination indicated transmitted rhonchi from the upper airways. The abdomen and neurological examination were normal.

Further initial laboratory assessment revealed a decrease in white blood cell count ( $0.55 \times 10^9/L$ , normal range  $4.1-11 \times 10^9/L$ ) with only  $0.02 \times 10^9/L$  (normal range  $1.8-8.3 \times 10^9/L$ ) neutrophil count, as well as decreased haemoglobin concentration (84 g/L, normal range 115-150 g/L) and platelet count ( $34 \times 10^9/L$ , normal range  $125-350 \times 10^9/L$ ). A peripheral blood smear confirmed pancytopenia with lymphocytosis (lymphocytes 80%). Thyroid function evaluation showed severe thyrotoxicosis (TSH  $<0.01$  mIU/L, normal range 0.51-4.3 mIU/L; FT3 8.19 pmol/l, normal range 3.93-7.7 pmol/l; and FT4 55.1 pmol/l, normal range 12.6-21 pmol/l). Liver function evaluation showed normal alanine aminotransferase and aspartate aminotransferase but hypoalbuminemia (23 g/L, normal range 40-55 g/L) and markedly increased total bilirubin (138.1  $\mu\text{mol/L}$ , normal range 0-21  $\mu\text{mol/L}$ ), in which direct bilirubin corresponded to 124.1  $\mu\text{mol/L}$  (normal range 0-8  $\mu\text{mol/L}$ ). The infection index indicated significant increases in CRP (156.7 mg/L, normal range 0-10 mg/L) and procalcitonin (70.55 ng/ml, normal range  $<0.046$  ng/ml). Renal function tests, coagulation function, and electrolytes were normal. A pharyngeal throat swab was positive for *Aeromonas caviae*. Blood culture, serum cytomegalovirus DNA, Epstein-Barr virus DNA, mycoplasma pneumoniae antibody, and antibody profiles for autoimmune diseases were negative. An electrocardiogram revealed sinus tachycardia. Normal echocardiographic values were recorded with an ejection fraction of 64%. Chest x-ray was normal. MR imaging of the neck revealed suppurative cervical lymphadenitis with abscess formation (measuring 34 mm $\times$ 23 mm $\times$ 38

mm), accompanied by inflammatory infiltrates in the bilateral parapharyngeal, retropharyngeal and cervical fascial space.

Following transfer to the PICU, the patient was treated with intravenous meropenem, oral metoprolol, oral acetaminophen, and supportive care in the form of fluid and electrolyte replacement. In addition, an evaluation by a multidisciplinary team involving endocrinology, haematology, infectious diseases, and surgery was requested. The initial diagnosis was thyroid storm. Pancytopenia due to sepsis was first considered and discussed from a multidisciplinary standpoint, as a result methimazole treatment was initiated again (7.5 mg twice daily). To rule out haematological system diseases, bone marrow aspiration was performed and a high-dose corticosteroid was used (methylprednisolone 50 mg intravenous every 8 hours). During the first 3 days of methimazole therapy in the PICU, CBC was serially monitored daily. The clinical status of the patient improved rapidly, she became afebrile as soon as 24 hours after initial therapy, and her CBC count elevated after 48 hours. Neck abscess was operated on for incision and drainage, and approximately 50 ml of purulent blood material from the right and 10 ml from the left were drained. Bone marrow tests revealed decreased granulocytes with maturation disorder and easily showed histiocytes and phagocytes with occasional haemophagocytic cells. Further immunophenotyping was performed with normal results. Both granulocyte and platelet counts were normal after 5 days of therapy (Fig 1). Fig 1 depicts variation of CBC before and after thyroid storm. Methylprednisolone therapy was tapered over the course of 1 week. Bone marrow aspiration was reviewed 2 weeks later and showed obvious hypercellular marrow and granulocytes, of which 64% had toxic granulations. The patient remained afebrile throughout her hospital stay, and she was discharged after 4 weeks of hospitalization and prescribed 7.5mg methimazole per day. At a 1-month outpatient visit, methimazole was weaned to 5 mg daily, and thyroid function, CBC, and liver function tests were within the normal range.

## Discussion and Conclusions

Thyroid storm is a rare but life-threatening endocrine emergency with a mortality rate up to 22%<sup>[3]</sup>, which is mainly triggered by precipitating factors such as discontinuation of antithyroid drug therapy for Graves' disease and infection<sup>[4]</sup>. In our patient, uncontrolled thyrotoxicosis was first precipitated by infection characterized by intermittent fever and elevated CRP, subsequently followed by abrupt withdrawal of methimazole therapy. Therefore, the onset of thyroid storm was not a surprise. Similarly, in the case of thyroid storm with extreme metabolic disorder, the infection cannot be controlled and progresses to sepsis. Early diagnosis of thyroid storm is challenging due to the lack of a global "gold standard" diagnostic test and because its multisystem involvement can mimic many other conditions. The diagnosis is largely based on clinical assessment. In the last 20 years, the most commonly used diagnostic criterion has been the Burch-Wartofsky Point Scale (BWPS), in which a score of 45 or more is highly suggestive of thyroid storm. New peer-reviewed diagnostic criterion for thyroid storm were proposed by the JTA in 2012<sup>[5]</sup>, in which the grade of TS1 indicates definite thyroid storm. Although it is not specific to paediatrics, the BWPS or the JTA criteria for thyroid storm can be used<sup>[6]</sup>. Our patient met the criterion for definite thyroid storm under both diagnostic schemes. The BWPS was 90 (temperature  $\geq 39.5$  °C, agitation, jaundice, heart rate  $\geq 140$  bpm, positive precipitant history), and the grade of TS1 was determined by the JTA criteria (thyrotoxicosis, central nervous system manifestation of agitation, fever, tachycardia, total bilirubin level  $\geq 3.0$  mg/dL).

Pancytopenia is a rare but severe complication of Graves' disease<sup>[7]</sup> and is an extremely rare adverse reaction to antithyroid drug therapy<sup>[2]</sup>. Based on the results of previous studies, pancytopenia in patients with Graves' disease has been reported to be caused either by Graves' disease itself or by methimazole therapy<sup>[7-10]</sup>, but the therapeutic principles are totally different. If patients with Graves' disease have pancytopenia before methimazole treatment, then pancytopenia is considered to be correlated with Graves' disease itself, and

antithyroid drugs can be used to treat both pancytopenia and Graves' hyperthyroidism with close monitoring of CBC counts [7, 11]. In contrast, if patients with Graves' disease present with pancytopenia during methimazole treatment, then pancytopenia is highly suspected to be correlated with antithyroid drugs, and methimazole treatment must be discontinued immediately because sepsis induced by methimazole therapy with pancytopenia is fatal. Alternatively, treatments such as total thyroidectomy or radioactive iodine therapy should be considered as first-line therapy [12].

Similar to the symptoms in a previously reported case [8], the patient was diagnosed with methimazole-induced agranulocytosis and had neck abscess. Therefore, methimazole-induced pancytopenia is a possible diagnosis in our case as well, and the diagnosis of sepsis-induced pancytopenia in our patient can be challenged. Moreover, according to the American Thyroid Association guidelines, antithyroid drugs should be immediately discontinued if the granulocyte count is less than 1000 cells/mm<sup>3</sup> [13]. Therefore, the question of whether to start therapy with methimazole was a subject of debate. Pancytopenia is a relatively common phenomenon encountered in clinical practice, and numerous aetiologies may determine pancytopenia [14]. Identifying the true pathogenesis is crucial for implementing an appropriate therapy. By reviewing the entire case, we found that the CBC level in our patient was checked multiple times before pancytopenia occurred, with two normal CBC results during the period of fever before the thyroid storm. If methimazole-induced pancytopenia is the diagnosis, the neutrophil count must be decreased whenever fever occurs. Consequently, combined with a healthy past medical history and normal bone marrow results, the diagnosis of sepsis-induced pancytopenia with thyroid storm can be confirmed.

In conclusion, our case serves to remind physicians that close monitoring of CBC counts may help avoid mistaking sepsis-induced pancytopenia for the side effects of antithyroid drugs. This is the first paediatric case report that outlines the use of methimazole in the management of thyroid storm with pancytopenia.

#### **What is already known on this topic?**

Thyroid storm is a rare but life-threatening acute complication of hyperthyroidism, and methimazole has been used as a first-line therapy for hyperthyroidism. Pancytopenia can be an extremely rare but serious side effect of antithyroid drugs, which should be immediately discontinued if the granulocyte count is less than 1000 cells/mm<sup>3</sup>. Therefore, management of thyroid storm with pancytopenia is challenging.

#### **What this study adds?**

We present a 13-year-old girl with thyroid storm and pancytopenia, presenting symptoms similar to those of methimazole-induced pancytopenia. Due to close monitoring of complete blood cell count during fever, sepsis-induced pancytopenia with thyroid storm was considered, and methimazole treatment combined with methylprednisolone and meropenem was able to resolve both pancytopenia and thyroid storm. This is the first paediatric case report that outlines the use of methimazole in the management of thyroid storm with pancytopenia.

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**Author's Contributions:** ZQ wrote the main manuscript text, LYZ and FQX prepared the clinical data. LH and ZCC reviewed and revised the manuscript text. All authors have read and approved the final manuscript.

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#### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### **Declarations**

**Ethics approval and consent to participate:** All study procedures were performed in accordance with the

ethical standards as laid down in the Declaration of Helsinki and its later amendments, and were approved by the Ethical Committee of Fujian Maternity and Child Health Hospital. Written informed consent was obtained from the patient and her parents.

#### **Competing interests**

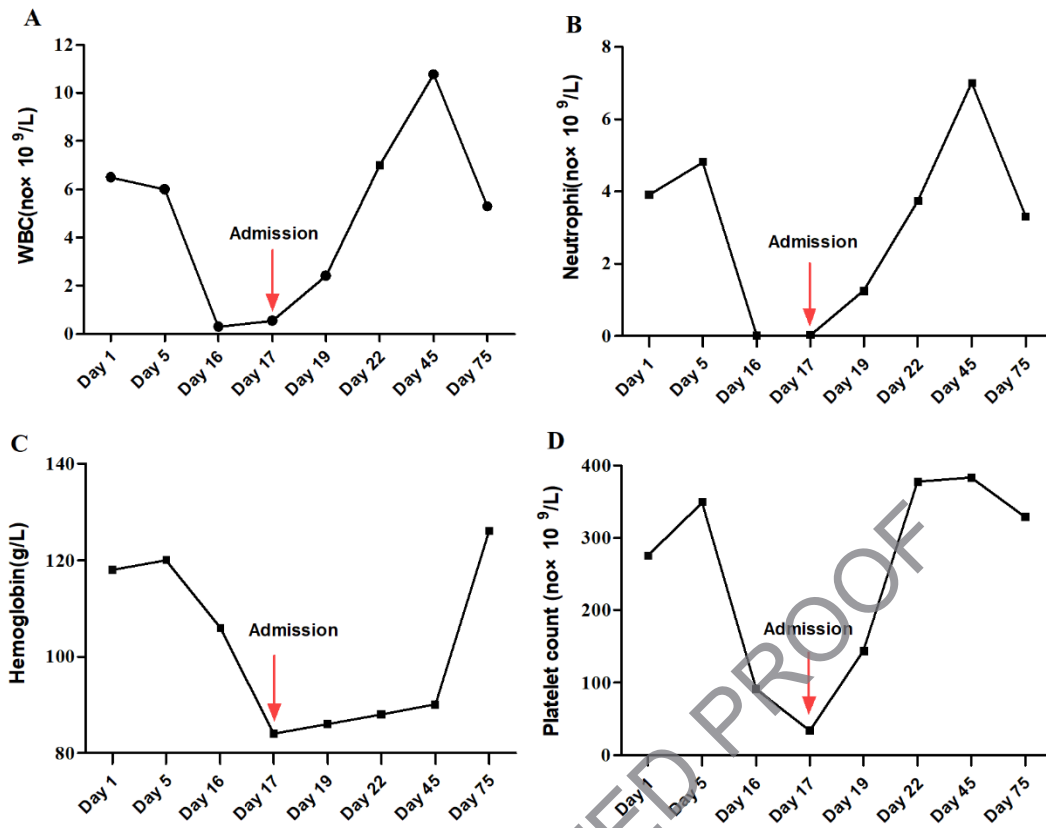
The authors declare no competing interests.

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**Fig.1** Over time variation of CBC count during the period of fever. White blood cells (A), neutrophils (B), haemoglobin (C), and platelets (D).

Table 1. Laboratory profile from the patient at the different evaluation points

Test	Day -35	Day -21	Day 1	Day 5	Day 16	Day 17 (on admission)	Day 19	Day 22	Day 45 (On Discharge)	Day 75
CBC										
WBC ( $4.1-11 \times 10^9/L$ )	5.5	-	6.5	6.0	0.3	0.55	2.43	6.99	10.77	5.3
Neutrophils ( $1.8-8.3 \times 10^9/L$ )	6.1	-	3.9	4.8	0.0	0.02	1.25	3.72	7	3.3
RBC ( $3.8-5.1 \times 10^{12}/L$ )	4.7	-	4.38	4.44	4.28	3.42	3.39	3.52	3.37	4.13
Hemoglobin (115-150 g/L)	125	-	118	120	106	84	86	88	90	126
Platelets ( $125-350 \times 10^9/L$ )	318	-	276	349	91	34	144	378	384	329
Liver function										

ALT (7-40 U/L)	26	-		17	31	11	44	35	13	10
AST (13-35 U/L)	19	-		22	23	8	16	13	16	16
Albumin (40-55 g/L)	51	-	-	47.4	23.6	23	28	39	38	50
Total bilirubin (0-21 µmol/L)	11.7	-	-	17.6	70	138.1	53.4	33.2	20.6	12.3
Direct bilirubin (0-8 µmol/L)	4.2	-	-	6.4	31	124.1	43.4	21.8	12.7	5.1
Thyroid function										
TSH (0.51-4.3 mIU/L)	<0.01	<0.01	-	<0.01	<0.01	<0.01	<0.01	-	0.02	2.49
Free T4 (12.6-21 pmol/l)	64.1	41.9	-	33.2	52	55.1	24	-	7.64	14.4
Free T3 (3.93-7.7 pmol/l)	42.0	18.7	-	11.4	5.7	8.19	3.96	-	2.06	6.31
TRAb (0-1.75 IU/ml)	17.24	-		-	13.1	-	-	-	-	-
Infection index										
CRP (0-10 mg/L)	-	-	8.49	67.9	>200	156.7	54	13.5	6.89	0.58
PCT (<0.046 ng/ml)	-	-	-	-	87.9	70.55	17.41	0.18	-	-

CBC, complete blood count; WBC, white blood cells; RBC, red blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAb, thyrotropin receptor antibodies. CRP, C-reactive protein; PCT, procalcitonin; Reference ranges are given in brackets.