CASE REPORT

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

Qing Zhou[1,2,*], Li-Yong Zhang[3], Qing-Xian Fu[2], Chao-Chun Zou[4,*], Hui Liu[1,2]

[1]Fujian Maternity and Child Health Hospital, Clinic of Endocrinology, Fuzhou, China
[2]Fujian Children's Hospital, Clinic of Endocrinology, Fuzhou, China
[3]Fujian Medical University Union Hospital, Minimal Invasive Center, Clinic of Thyroid and Vascular Surgery, Fuzhou, China
[4]Children's Hospital of Zhejiang University School of Medicine, Clinic of Endocrinology, Hangzhou, China

**They contributed equally as corresponding authors.*

What is already known on this topic?

Thyroid storm is a rare but life-threatening acute complication of hyperthyroidism. 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^3. Therefore, management of thyroid storm in the setting of pancytopenia is challenging.

What this study adds?

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

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 (CBC) 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 CBC 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 drugs

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Address for Correspondence: Hui Liu MD, Fujian Maternity and Child Health Hospital; Fujian Children's Hospital, Clinic of Endocrinology, Fuzhou, China
E-mail: zmjia2019@163.com **ORCID:** orcid.org/0000-0001-9126-5917

Address for Correspondence: Chao-Chun Zou MD, Children's Hospital of Zhejiang University School of Medicine, Clinic of Endocrinology, Hangzhou, China
E-mail: zcc14@zju.edu.cn **ORCID:** orcid.org/0000-0002-4667-3636

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Introduction

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 (1). Moreover, pancytopenia has also been reported in some patients on antithyroid drug therapy, but its incidence is much lower than that of agranulocytosis (2). 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 Report

A 13-year-old girl was diagnosed with Graves' disease and started methimazole (7.5 mg twice daily) five weeks earlier (day -35). Thyroid function showed improvement after two weeks of methimazole therapy. 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 five days later, and a review of laboratory results revealed improved thyroid function, 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 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 at the PICU, the patient was febrile (temperature 38.5 °C), tachycardic (heart rate 140 beats/min), tachypneic (respiratory 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, a 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

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 × 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 × 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 × 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 × 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	-	6.68	2.49
Free T4 (12.6-21 ρmol/L)	64.1	41.9	-	33.2	52	55.1	24	-	8.99	14.4
Free T3 (3.93-7.7 ρmol/L)	42.0	18.7	-	11.4	5.7	8.19	3.96	-	4.92	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	-	-

Reference ranges are given in brackets.
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, TSH: thyroid-stimulating hormone

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 (0.55×10^9/L, normal range 4.1-11 $\times 10^9$/L) with only 0.02×10^9/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 (34×10^9/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 (thyroid-stimulating hormone < 0.01 mIU/L, normal range 0.51-4.3 mIU/L; fT3 8.19 ρmol/L, normal range 3.93-7.7 ρmol/L; and fT4 55.1 ρmol/L, normal range 12.6-21 ρmol/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 μmol/L, normal range 0-21 μmol/L), in which direct bilirubin corresponded to 124.1 μmol/L (normal range 0-8 μmol/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. Magnetic resonance imaging of the neck revealed suppurative cervical lymphadenitis with abscess formation (measuring 34 × 23 × 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 (0.6 g every 8 hours), oral metoprolol (10 mg every 8 hours), oral acetaminophen (0.3 g when body temperature higher than 38.5 degrees Celsius), 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 restarted (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 three days of methimazole therapy in the PICU, CBC was monitored daily. The clinical status of the patient improved rapidly, she became afebrile as early 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 were drained from the right side and 10 mL from the left. Bone marrow tests revealed decreased granulocytes with maturation disorder and clearly showed histiocytes and phagocytes with occasional haemophagocytic cells. Further immunophenotyping was performed with normal results. Both granulocyte and platelet counts were normal after five days of therapy (Figure 1). Figure 1 depicts variation of CBC before and after thyroid storm. Methylprednisolone therapy was tapered over the course of one week. Bone marrow aspiration was reviewed two 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 four weeks of hospitalization and prescribed 7.5 mg methimazole per day. Thyroid function, CBC, and liver function tests were checked 10 days after discharge, and methimazole was weaned to 6.6 mg daily. These indicators were then rechecked every 2 weeks thereafter, and methimazole was weaned to 5 mg daily about 1 month after discharge, CBC and liver function tests were all within the normal range.

Discussion

Thyroid storm is a rare but life-threatening endocrine emergency with a mortality rate of up to 22% (3), which is mainly triggered by precipitating factors such as discontinuation of antithyroid drug therapy for Graves' disease and infection (4). In the presented case, uncontrolled thyrotoxicosis appears to have been 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 the associated 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

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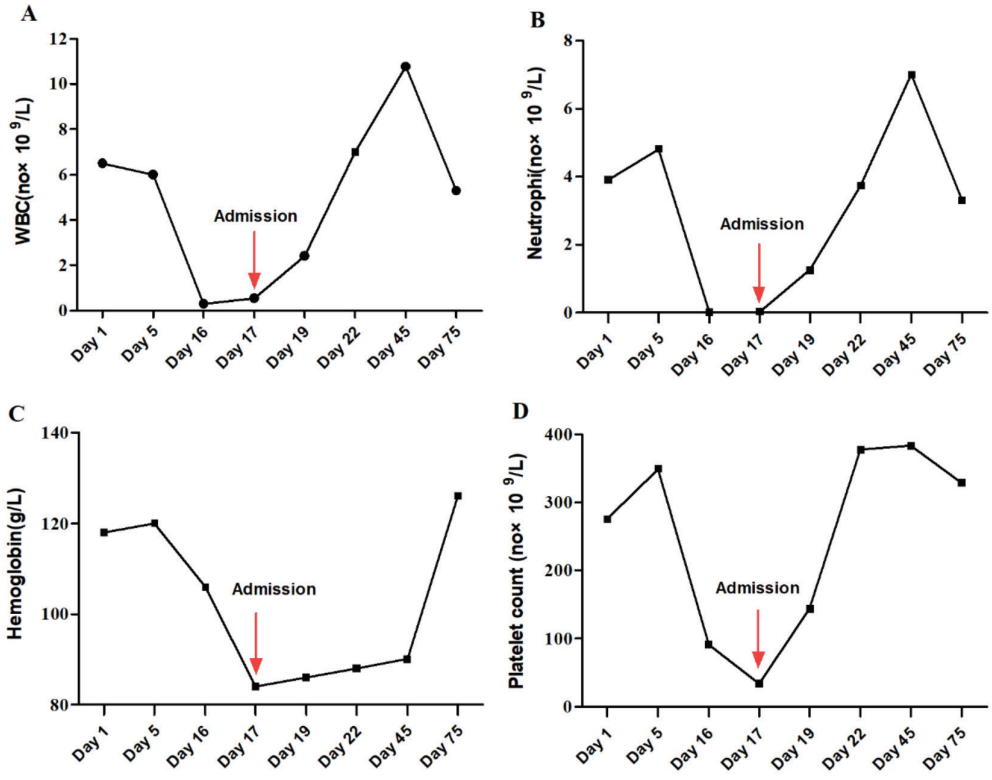

Figure 1. Chronological variation of CBC count during the period of fever. White blood cells (A), neutrophils (B), haemoglobin (C), and platelets (D)

CBC: complete blood count, WBC: white blood cells

a score of 45 or more is highly suggestive of thyroid storm. New peer-reviewed diagnostic criteria for thyroid storm were proposed by the Japan Thyroid Association (JTA) in 2012 (5), 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 (6). The presented patient met the criterion for definite thyroid storm under both diagnostic schemes. The BWPS score was 90 (temperature ≥39.5 °C, agitation, jaundice, heart rate ≥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 ≥3.0 mg/dL).

Pancytopenia is a rare but severe complication of Graves' disease (7) and is an extremely rare adverse reaction to antithyroid drug therapy (2). 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 (7,8,9,10), but the therapeutic principles are totally different. If patients with Graves' disease have pancytopenia before methimazole treatment, then pancytopenia is considered to be due to 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 due to the antithyroid drugs, and methimazole treatment must be discontinued immediately because sepsis induced by methimazole therapy with pancytopenia is often 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 presented 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^3 (13). Therefore, the question of whether to start therapy with methimazole was debatable. 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 was the diagnosis, the neutrophil count must have been 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.

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.

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Ethics

Informed Consent: Written informed consent was obtained from the patient and her parents.

Authorship Contributions

Surgical and Medical Practices: Qing-Xian Fu, Chao-Chun Zou, Hui Liu, Concept: Qing Zhou, Design: Qing Zhou, Qing-Xian Fu, Chao-Chun Zou, Hui Liu, Data Collection or Processing: Qing Zhou, Li-Yong Zhang, Analysis or Interpretation: Qing Zhou, Li-Yong Zhang, Literature Search: Qing Zhou, Hui Liu, Writing: Qing Zhou, Qing Zhou, Qing-Xian Fu, Chao-Chun Zou, Hui Liu.

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References

1. Nakamura H, Miyauchi A, Miyawaki N, Imagawa J. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. J Clin Endocrinol Metab. 2013;98:4776-4783. Epub 2013 Sep 20
2. Watanabe N, Narimatsu H, Noh JY, Yamaguchi T, Kobayashi K, Kami M, Kunii Y, Mukasa K, Ito K, Ito K. Antithyroid drug-induced hematopoietic damage: a retrospective cohort study of agranulocytosis and pancytopenia involving 50,385 patients with Graves' disease. J Clin Endocrinol Metab. 2012;97:49-53. Epub 2011 Nov 2
3. Bourcier S, Coutrot M, Kimmoun A, Sonneville R, de Montmollin E, Persichini R, Schnell D, Charpentier J, Aubron C, Morawiec E, Bigé N, Nseir S, Terzi N, Razazi K, Azoulay E, Ferré A, Tandjaoui-Lambiotte Y, Ellrodt O, Hraiech S, Delmas C, Barbier F, Lautrette A, Aissaoui N, Repessé X, Pichereau C, Zerbib Y, Lascarrou JB, Carreira S, Reuter D, Frérou A, Peigne V, Fillatre P, Megarbane B, Voiriot G, Combes A, Schmidt M. Thyroid Storm in the ICU: A Retrospective Multicenter Study. Crit Care Med. 2020;48:83-90.
4. Feldt-Rasmussen U, Emerson CH, Ross DS, Kopp PA, Pearce EN. Thoughts on the Japanese and American Perspectives on Thyroid Storm. Thyroid. 2019;29:1033-1035. Epub 2019 Jul 1
5. Akamizu T. Thyroid Storm: A Japanese Perspective. Thyroid. 2018;28:32-40. Epub 2017 Oct 5
6. Ladd JM, Sabsabi B, von Oettingen JE. Thyroid Storm in a Toddler Presenting as a Febrile Seizure. Pediatrics. 2020;145:e20191920.
7. Lima CS, Zantut Wittmann DE, Castro V, Tambascia MA, Lorand-Metze I, Saad ST, Costa FF. Pancytopenia in untreated patients with Graves' disease. Thyroid. 2006;16:403-409.
8. Nagarajan VD, Morales A, Pleasant L, Shenoi A. Sepsis and thyroid storm in a patient with methimazole-induced agranulocytosis. BMJ Case Rep. 2020;13:e235536.
9. Stumpf MAM, Schrut GCA, Ramthun M, Onuma S, Osternack HECG. Methimazole-Induced Agranulocytosis And Sepsis: Was Thyroid Storm Present Or Just Being Mimicked? Acta Endocrinol (Buchar). 2019;15:522-525.
10. Rayner SG, Hosseini F, Adedipe AA. Sepsis mimicking thyroid storm in a patient with methimazole-induced agranulocytosis. BMJ Case Rep. 2013;2013:bcr2013200145.
11. Scappaticcio L, Bellastella G, Maiorino MI, Longo M, Catalano C, Esposito K, Paolisso G, Rizzo MR. Graves' hyperthyroidism-related pancytopenia: a case report with literature review. Hormones (Athens). 2021;20:93-100. Epub 2020 Jul 8
12. Léger J, Carel JC. Diagnosis and management of hyperthyroidism from prenatal life to adolescence. Best Pract Res Clin Endocrinol Metab. 2018;32:373-386. Epub 2018 Apr 5
13. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388:906-918. Epub 2016 Mar 30
14. Gnanaraj J, Parnes A, Francis CW, Go RS, Takemoto CM, Hashmi SK. Approach to pancytopenia: Diagnostic algorithm for clinical hematologists. Blood Rev. 2018;32:361-367. Epub 2018 Mar 5