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CASE REPORT

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A rare case of pancytopenia causing- Sheehan's syndrome: Case report and literature review

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Abstract

We describe the case of a 58-year-old woman who was presented with pancytopenia and hypofibrinogenemia. Treatment with iron supplementation was not satisfactory. Physical findings and a history of a massive postpartum hemorrhage suggested Sheehan's syndrome(SS). After thyroxine and glucocorticoid replacement therapy, the blood cell count improved. SS is a rare etiology of hemocytopenia, of which hematologists need to be aware. We conclude that hormonal therapy can produce full hematological recovery.

KEYWORDS

glucocorticoid, gum bleeding, pancytopenia, Sheehan's syndrome, thyroxine

1 | INTRODUCTION

Sheehan's syndrome (SS) develops due to pituitary hormone insufficiency caused by postpartum hemorrhage. Clinical manifestations include fatigue, asitia, hypotension, hypoglycemia, hypopigmentation, dry skin, chills, anemia, postpartum lack of lactation, amenorrhea, and loss of libido. In addition to the typical clinical manifestations and medical history of postpartum hemorrhage and amenorrhea. The diagnosis should be combined with laboratory endocrine assays, sellar computed tomography scans, anterior pituitary reserve function assays, and immunoradiometric assays to detect triiodothyronine, thyroid-stimulating hormone, pituitary hormone, follicle-stimulating hormone, and prolactin. Most of the above hormones are low in SS, but some remain in the normal range.

Sheehan's syndrome is preventable, and timely treatment of postpartum hemorrhage and prolonged shock prevention are key measures to prevent the disease. For patients with severe pituitary involvement or delayed diagnosis, hormone replacement should be performed. It is recommended to take 15–25 mg of prednisone per day, of which two-third are taken in the morning and one-third in the afternoon. If there are special circumstances such as trauma and surgery, the dosage may be increased as appropriate. If the patient suffers from hypothyroidism, thyroxine supplementation should be given, starting at 15–30 mg/day and gradually increasing to 60–120 mg/day. Thyroxine supplementation should not be administered earlier than prednisone.

Over the last 20 years, more than 80 cases of SS have been reported in the literature, among which more than 40 presented with anemia and only 6 showed pancytopenia. Pancytopenia due to hormone deficiency is rare and is easily misdiagnosed, although hormonal therapy can produce full hematological recovery. Therefore, accurate diagnosis is essential.

2 | CASE PRESENTATION

A 58-year-old woman, who was a college graduate of Chinese origin, was admitted to our hospital with repeated gum bleeding, which did not stop by the application of pressure. The patient visited a hospital 4 years previously for the same reason but was not successfully diagnosed. At that time, laboratory tests had showed the white blood cell(WBC) count of 4.2 $\times 10^9$/L(3.5–9.5 $\times 10^9$/L), hemoglobin(HGB) of 96 g/L(115–150 g/L), and platelet (PLT) count of 60×10^9/L($125–350 \times 10^9$/L). Additionally, fibrinogen was 1.3 g/L(2–4 g/L). Testing of bone marrow cytology showed that intracellular iron was decreased, therefore, the patient was diagnosed with iron deficiency anemia and hypofibrinogenemia. The patient was treated with iron supplementation and cryoprecipitate infusion. Subsequently, the bleeding gums showed slight improvement. However, without cryoprecipitate infusion, repeated gum bleeding persisted, and blood cell counts did not significantly improve. The patient then visited our hospital for further diagnosis and treatment. Upon investigation, a history of postpartum hemorrhage after her second pregnancy, >20 years ago, when she was 38 years old, was revealed which required a total abdominal hysterectomy to control the bleeding, This was followed by amenorrhea and weakness. Her pregnancy-labor history was G2P2A0, with both deliveries being in the hospital. Upon physical examination, there were no petechiae in the skin and axillary hair was sparse. Laboratory examination showed hyponatremia of -118 mmol/L (137–147 mmol/L), pancytopenia, and hypofibrinogenemia. Her WBC count was 3.39×10^9/L, HGB was 105.00 g/L, PLT count was 68.00×10^9/ L. The prothrombin time was 14.8 seconds and fibrinogen content was 1.18 g/L. A bone marrow aspiration smear showed 131 megakaryocytes, 92% of which were granular megakaryocyte(10–27%, Figure 1). The laboratory test results were as follow: prolactin 1.810 ng/ml (4.79–23.3 ng/m); trinary cortisol, 13.85 ng/ml; urinary-free cortisol, 34.62 μg/24 h (30–350μg/24 h). Other laboratory tests results are presented in Table 1. Additionally, pituitary magnetic resonance imaging showed an empty sella (Figure 2). The differential diagnosis included megaloblastic anemia and acute leukemia. Vitamin B12 and folate deficiencies are major causes of megaloblastic anemia, and clinical features include anemia, cytopenia, jaundice, and megaloblastic marrow morphology. By replenishing vitamin B12 or folate parenterally, blood counts should return to normal. However, this patient did not have vitamin B12 or folate deficiencies. Acute leukemias are characterized by greater than 20% blasts in the peripheral blood smear or bone marrow. They may also be accompanied by specific genetic alterations, such as PML/RARα, etc. In this patient, no blasts were seen, and

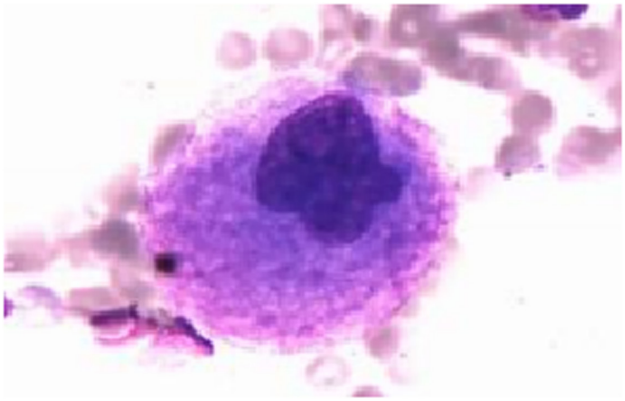


FIGURE 1 Megakaryocyte morphology

PML/RARα was negative. The final diagnosis was syndromes as her anterior pituitary function was almost zero. Levothyroxine sodium (25μg/day) and prednisone acetate (7.5 mg/day) were administrated orally as replacement therapy. After 1 month, the WBC and PLT levels returned to normal.

3 | DISCUSSION

Sheehan's syndrome refers to the deficiency of pituitary hormones caused by anterior pituitary ischemia due to postpartum hemorrhage,[1] leading to premature dysfunction of the target organs of various pituitary hormones. Hormone replacement is necessary, but, thyroxine alone cannot be used. This is due to, thyroxine causing more vigorous metabolism, resulting in a sudden increase in the need for glucocorticoids, aggravating adrenal cortical insufficiency, which can cause serious ill patients with adrenal crisis.

The incidence of SS in developing countries is higher than in developed countries, with SS accounting for 5.1% of hypopituitarism cases.[2] In 2001, a Spanish study of hypopituitarism reported that the prevalence rate of SS was 2.6 cases per 100,000 women.[3] Additionally, SS is more common in older women than in young women, and the mean age of diagnosis is 41.1 years.[1]

Physiological enlargement of the pituitary during pregnancy may lead to pituitary tamponade and ischemia, consequently leading to impaired function, which may be the cause of SS. Additionally, postpartum hemorrhage may lead to an interruption in blood flow in the anterior pituitary artery and cause pituitary embolism or avascular necrosis.[4]

The specific pathogenesis of SS remains unclear. Studies have shown that abnormal coagulation function may be related to the onset of SS, and that protein S deficiency and hereditary hypercoagulability may be risk

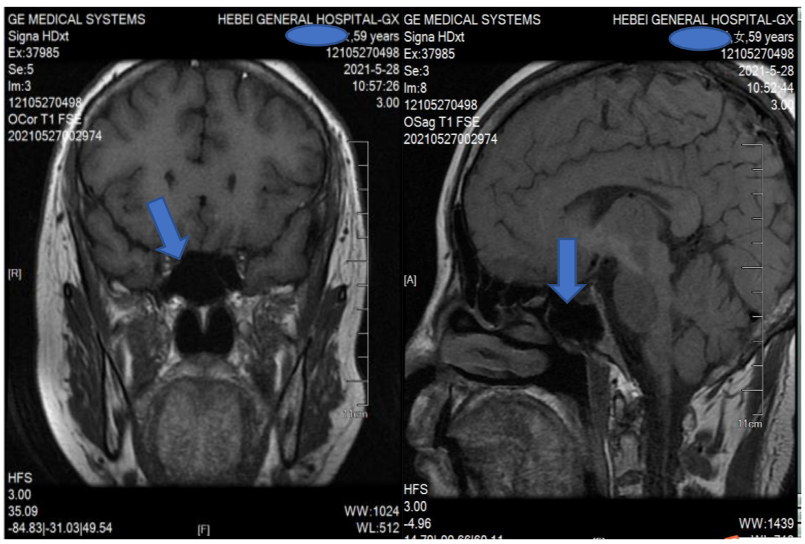
TABLE 1 Blood and endocrine laboratory test results

Test name		Before treatment	1 month after treatment	Reference range
Blood count	WBC ($\times 10^9$/L)	3.39	4.25	3.5–9.5
	HGB (g/L)	105	108	115–150
	PLT ($\times 10^9$/L)	68	92*	125–350
Blood coagulation	PT (s)	14.2	13.2	9.8–12.1
	APTT (s)	24.5	32.8	23.2–32.5
	FIB (g/L)	1.18	2.06	2–4
Electrolyte	Na (mmol/L)	120	136	137–147
	Cl (mmol/L)	94	97	99–110
	Ca (mmol/L)	1.92	2.32	2.11–2.52
Endocrine test results	TT3 (nmol/L)	0.845	1.43*	1.3–3.1
	TT4 (nmol/L)	53.63	76.24	66–181
	FT3 (pmol/L)	2.27	3.58	3.1–6.8
	FT4 (pmol/L)	5.96	11.05	12–22
	TSH (uIU/ml)	2.53	1.65	0.27–4.2
	GH (ng/ml)	0.21	1.20	0.06–5.0
	FSH (IU/L)	1.65	30.16*	25.8–134.8
	LH (IU/L)	0.649	10.21*	7.7–63.3

Abbreviations: APTT, activated partial thrombin time; Ca, calcium; Cl, chloride; FIB, fibrinogen; FSH, follicle-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; HGB, hemoglobin; LH, luteinizing hormone; Na, sodium; PLT, platelet; PT, prothrombin time; TSH, thyroid-stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine; WBC, white blood cell.

*After treatment, some hormone levels were significantly improved compared with those before treatment, and the diagnosis was also confirmed by the curative effect.

FIGURE 2 Pituitary magnetic resonance imaging showing empty sella



factors for SS.[5,6] Another study found that methylenetetrahydrofolate(MTHFR), C677T and A1298C polymorphisms had significantly higher frequencies in SS patients.[7] In addition, factor II (G20210A), factor V (G1691A), and PAI-1 4G/5G mutations are also more common in SS patients. Platelet dysfunction is also one of the causes of SS, as it may cause postpartum hemorrhage, leading to the occurrence of SS.

Most patients with SS have only slightly impaired pituitary function. Insufficient lactation, postpartum amenorrhea,[8] and severe postpartum hemorrhage are important symptoms for the diagnosis of SS. In addition to the typical pituitary deficiency, SS may have non-specific symptoms such as weakness, fatigue,[9] osteoporosis,[10] cognitive dysfunction, and diabetes insipidus. Abnormalities in hematology can cause anemia,[11]

pancytopenia,[12] coagulopathy, and thrombosis tendencies; however, because they are relatively rare, they are often overlooked.

Anemia associated with hypopituitarism has rarely been investigated and is often overlooked. However, anemia is a manifestation of hypopituitary function, normocytic normochromic anemia is part of the course of SS, and some SS manifests as hypochromic microcytic anemia.[11,13] Many hormonal deficiencies may explain the pancytopenia in SS. Early studies showed that the pituitary gland can produce some erythropoietic factors; however, the removal of the posterior lobe of the rat pituitary does not cause anemia, suggesting that, anemia caused by hypopituitary function is caused by the anterior pituitary hormone.[14,15] Active thyroid hormone stimulates the formation of red blood cell colonies and growth hormone increases the secretion of erythropoietin. Therefore, anemia can occur when these hormones are deficient.[16] In addition, experimental studies have shown that some growth factors can affect the stem progenitor cells in the bone marrow to cause anemia.[17] Anterior pituitary insufficiency also leads to complete bone marrow hypoplasia and hematological abnormalities.

Due to a lack of knowledge regarding menstrual and birth history, overlooking physical signs, such as sparse eyebrows and body hair loss often leads to missed diagnosis or misdiagnosis. In the process of diagnosing SS, it is important to concentrate on a history of postpartum hemorrhage; clinical manifestations including postpartum and amenorrhea, body hair loss, indifference, unresponsiveness, dry and dull skin, fatigue, and dizziness; and decreased HGB, blood sodium, LH, and FSH in laboratory examinations.

In conclusion, we presented a patient who manifested with pancytopenia which was finally diagnosed as SS. The abnormal manifestations of the hematological system resulted in a misdiagnosis over the period of years. Physicians should be aware that SS could be a rare cause of pancytopenia; thus, they should carefully conduct medical history inquiries and physical examinations to avoid the omission of important examinations and delay the diagnosis and treatment of this disease. In this case, glucocorticoid replacement was more significant than thyroxine replacement in hematological recovery.

AUTHOR CONTRIBUTIONS

Xiaohan Gao: Conceptualization; data curation; funding acquisition; investigation; methodology; writing – original draft; writing – review and editing. **Yuan Wang:** Writing – original draft. **Rui-Cang Wang:** Writing – original draft. **Jun Yuan:** Writing – original draft. **Jie Yang:** Writing – original draft. **Xiao-Xia Zhang:** Writing – original draft. **Jie Li:** Funding acquisition; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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