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CASE REPORT

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Delayed Sheehan's syndrome diagnosed during the evaluation of secondary infertility: A case report

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Key Clinical Message

Sheehan's syndrome may present with postpartum lactation failure and amenorrhea or with features of isolated hypopituitarism to panhypopituitarism. A high index of suspicion is required in a relevant clinical setting of postpartum hemorrhage.

KEYWORDS

anterior pituitary hormones, hypopituitarism, infertility, postpartum hemorrhage, postural hypotension

1 | BACKGROUND

Sheehan's syndrome, also known as postpartum hypopituitarism, is a condition that occurs when there is significant bleeding and tissue damage to the pituitary gland during childbirth, leading to its impaired function.[1,2] It typically presents shortly after delivery, but in some cases, the symptoms may not manifest until months or even years later. This delayed presentation is called the late-onset or late presentation of Sheehan's syndrome.[3] Late presentation of Sheehan's syndrome can occur for various reasons, including the slow and progressive nature of pituitary gland damage, partial damage that may have been compensated for initially, or delayed postpartum symptoms mistakenly attributed to other causes.

The diagnosis is often challenging, as the symptoms may be subtle or mistaken for other conditions. Individuals with a history of postpartum hemorrhage and persistent or unexplained symptoms must consult a healthcare professional who can conduct appropriate tests and evaluations. Infertility presentation of Sheehan's syndrome is a rare occurrence. Damage to the pituitary gland can disrupt the production and release of hormones necessary for ovulation, follicular development, and maintaining a healthy menstrual cycle. As a result, women with Sheehan's syndrome may experience difficulties conceiving and achieving a successful pregnancy. Fertility treatment for Sheehan's syndrome may not always result in successful conception, as other factors such as age, overall health, and any additional fertility issues can influence the chances of pregnancy. Therefore, a high index of suspicion is required for early diagnosis of these patients and to attain good clinical outcomes.

We present a case of secondary infertility with features of hypopituitarism in a woman with a history of severe postpartum hemorrhage. We focus on the profile of pituitary hormones, establishment of diagnosis, and management to improve the quality of life of the individual.

2 | CASE PRESENTATION

A 30-year-old woman presented to our center to be evaluated for secondary infertility. She had a spontaneous

pregnancy about 9 years back with appropriate antenatal follow-up at a local hospital. During delivery, she required an emergency cesarean section due to a cord around the neck of the fetus and fetal distress. The postpartum period was complicated, with severe postpartum hemorrhage requiring blood component support. She presented with severe headaches post-pregnancy, which were attributed to a lumbar puncture given during a spinal block. She had breast congestion and was treated with Bromocriptine to stop lactation. However, she failed to regain lactation. She was evaluated at many centers for assisted reproduction but could not conceive.

During an evaluation at our center, she gave a history of progressive gain of weight of 9 kg with decreased appetite over the past 5–6 years, postural giddiness, slurring of speech, cold intolerance, dryness of skin, thinning of hair with decreased secondary sexual characteristics in the form of breast atrophy, and loss of axillary and pubic hair.

A physical examination of the patient revealed facial puffiness, pallor, enlarged tongue, loss of eyebrows, skin dryness, and postural fall of blood pressure. There was no sign of insulin resistance or metabolic syndrome. On nervous system examination, she had a delayed relaxation of ankle jerk (Woltman's sign), suggesting hypothyroidism (Video S1). There was no goiter.

2.1 | Investigations

Her laboratory results revealed macrocytic hypochromic anemia with Hb of 8.4 g/dL and normal biochemical parameters (Table 1).

The thyrotropic axis evaluation revealed a low total T_4 and TSH, which was suggestive of central hypothyroidism in the clinical context. Her basal and stimulated cortisol levels were low. She had a low IGF-1 and low LH/FSH. The abdomen ultrasound revealed a small uterus with an endometrial thickness of 1 mm. These values and the clinical characteristics revealed panhypopituitarism; therefore, a contrast-enhanced MRI of sella was done. She had low bone mass, as revealed by a DEXA scan. The MRI brain showed a partially empty sella with a thin rim of the pituitary gland and a pituitary stalk (Figure 1).

2.2 | Differential diagnosis

This patient presented with amenorrhea for approximately 9-year duration with a history of severe postpartum hemorrhage following a lower segment cesarean section. This clinical context sets up a possibility of pituitary necrosis. The hormonal evaluation later confirmed this, revealing

TABLE 1 Investigations at the time of the first review of a female with postpartum hypopituitarism.

Parameters	Value	Normal values
Hemoglobin	8.4	8.7–11.2 g/dL
White blood cells	5300	4000–11,000/mm^3
Platelets	268,000	150,000–400,000/mm^3
Peripheral blood smear	Macrocytic hypochromic anemia	–
Plasma glucose fasting	5	3.9–5.6 mmol/L
Plasma glucose post-prandial	5.2	
Serum creatinine	68	53–106 μmol/L
Plasma sodium	132	137–142 mEq/L
Serum calcium	2.5	2.2–2.6 mmol/L
Serum phosphorus	1.24	1.12–1.45 mmol/L
Serum protein	72	64–83 g/L
Serum albumin	38	34–54 g/L
IGF-1	<2.6	11–40 nmol/L
Serum prolactin	1.16	<25 μg/L
Serum total T_4	32	57–148 nmol/L
Serum TSH	0.1	0.3–5 U/mL
Serum LH	1.2 mIU/mL	–
Serum FSH	1.1 mIU/mL	
Serum cortisol	63	275–550 nmol/L
Post-ACTH stimulation serum cortisol	22.9	>500 nmol/L

Abbreviations: ACTH, adrenocorticotrophic hormone; FSH, follicle stimulating hormone; IGF-1, Insulin-like growth factor 1; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

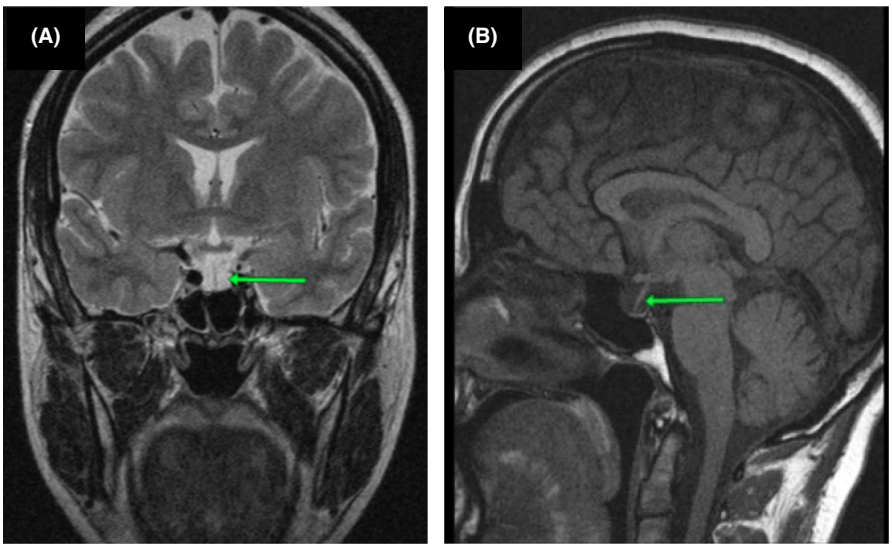

FIGURE 1 Magnetic resonance imaging of sella—The arrow shows a CSF-filled sella with a thin rim of pituitary tissue and pituitary stalk, indicating an empty sella. (A) T2 coronal section, (B) T1 sagittal section. CSF, cerebrospinal fluid.

multiple pituitary hormone deficiencies. Putting these together, a delayed diagnosis of Sheehan's syndrome was considered. The late presentation of the syndrome may have been due to the subtle and non-specific clinical signs and symptoms and only came to light when she was being evaluated for infertility.

The patient was counseled regarding the need for hormone replacement. She was also made to understand that infertility would require management at a specialty center; however, the priority was to make her metabolic and eucortisolemic. She received hydrocortisone replacement of 200 mg per day, tapered off over a week to a maintenance dose of 10 mg at 6 a.m. and 5 mg at 4 p.m. Her symptoms improved, and the postural fall recovered. She was subsequently started on l-thyroxine, which was adjusted to 75 µg per day over a few months based on the T_4 response. She was started on estrogen replacement, and after she had achieved a breakthrough bleed, she was switched to a combined oral contraceptive pill. Growth hormone was started on an adult growth hormone replacement dose of 1 IU/day at bedtime. She was given vitamin D and calcium replacement for low bone mass, and we expected the condition to further improve on estrogen replacement.

2.3 | Outcome and follow-up

She responded well to her treatment. On initial follow-up, her postural symptoms and fatigue improved on hydrocortisone replacement. Her hypometabolic symptoms improved as thyroid hormone replacement was started after she was eucortosleimic, and the clinical signs of adrenal insufficiency improved. She noticed an improvement in her voice, and the generalized swelling decreased. The delayed relaxation of reflexes took about 5 months after she had been rendered euthyroid. On combined oral contraceptive pills, she had a regular menstrual cycle of 4–5 days every 28 days with a regular flow. She was worked up for assisted reproduction, as this was her primary concern and why she had sought medical attention.

3 | DISCUSSION

The incidence of Sheehan's syndrome has declined over the years, primarily because of improved obstetric care and skilled birth attendance, but underdiagnosis may also contribute to the lower incidence.[1] Sheehan syndrome is far less common in developed countries than in places with limited obstetric care access. During pregnancy, the pituitary gland enlarges by 120%, therefore highly vulnerable to ischemia in hypotension and hemorrhage during delivery. This may be associated with the release of antigens into circulation resulting in autoimmune destruction of the pituitary gland mediated through the antipituitary antibodies.[4] However, the role of autoimmunity and genetic predisposition in the pathophysiology of Sheehan's syndrome requires further investigation.[1]

The criteria used for diagnosis of Sheehan's syndrome are based on an obstetric history of severe postpartum hemorrhage, severe hypotension or shock, failure of postpartum lactation, failure to resume regular menses after delivery, clinical features of hypopituitarism and an empty sella on CT or MRI.[5,6] Patients can have deficiencies in some or all anterior pituitary hormones and even posterior pituitary hormones, causing diabetes insipidus. Hemorrhagic shock during pregnancy is a crucial leading point in diagnosis. Failure to lactate is often a common initial complaint in patients with Sheehan's syndrome. Many of them report amenorrhea after delivery. The diagnosis of Sheehan's syndrome is not made until several years later in some instances when the features of

hypopituitarism become apparent in a woman who had postpartum bleeding.[3,7]

Sheehan's syndrome can also present with varied symptoms depending on the specific anterior pituitary hormone deficiencies. Prolactin deficiency can cause lactation failure. Gonadotropin deficiency will often cause amenorrhea or genital hair loss. Corticotrophin deficiency can result in generalized fatigue, weakness, hypoglycemia, or dizziness. Growth hormone deficiency causes fatigue and decreased quality of life. Symptoms of central hypothyroidism are clinically like primary hypothyroidism, but patients with central hypothyroidism have low triiodothyronine and thyroxine levels, with normal or even inappropriately low thyroid-stimulating hormone levels. The diagnosis of panhypopituitarism is straightforward, but partial deficiencies are often difficult to determine. A diagnosis may not be made for years because of vague symptoms, including fatigue and mild cognitive impairment. A study of 60 cases estimated an average time to diagnosis of 13 years from delivery, while another study in France estimated an average of 9 years.[7]

Our patient had both acute and chronic presentations. She acutely presented with postpartum hemorrhage and failure to regain her menstrual cycle, which were overlooked initially. She subsequently reported amenorrhea, for which she was evaluated and detected multiple pituitary hormone deficiencies. MRI study of the pituitary gland may reveal different features depending on the stage of the disease. While early scans are not usually helpful for diagnosis, they demonstrate a non-hemorrhagic enlargement of the pituitary gland, leading to its subsequent involution, and late scans typically show an empty sella. A secondary empty sella is considered a characteristic finding in the classical form of Sheehan's syndrome.[8]

Treatment of young women with hypopituitarism usually includes the replacement of hydrocortisone first and then replacing thyroid hormone and estrogen with or without progesterone.[9] Growth hormone replacement is required to improve the quality of life, and growth hormone may have some role in follicular growth.[10]

The prevention of Sheehan's syndrome is strongly related to improving obstetric care including institutional delivery, skilled birth attendance, and prevention and management of postpartum hemorrhage. All these interventions are also directly related to achieving Sustainable Development Goals related to the reduction in maternal mortality.

4 | CONCLUSION

The diagnosis of Sheehan's syndrome is often difficult due to the non-specific nature of symptoms. The recognition of features of hypopituitarism, the evaluation of hormone levels, and imaging of the sella help in establishing the diagnosis. The management includes hormone replacement therapy with a target of ensuring improved quality of life. The prevention of Sheehan's syndrome is closely related to the broader interventions of improving obstetric care and reducing maternal mortality through the prevention and management of postpartum hemorrhages.

AUTHOR CONTRIBUTIONS

Surbhi Saxena: Conceptualization; data curation; formal analysis; resources; writing – original draft; writing – review and editing. **Vishesh Verma:** Conceptualization; data curation; formal analysis; resources; visualization; writing – original draft; writing – review and editing. **Samir Samadarshi:** Conceptualization; data curation; methodology; supervision; writing – original draft; writing – review and editing. **Thinley Dorji:** Conceptualization; data curation; resources; validation; visualization; writing – original draft; writing – review and editing. **Jayaraman Muthukrishnan:** Conceptualization; formal analysis; resources; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

All relevant data sources are cited in this article.

ETHICS STATEMENT

Our institution does not require ethics approval for individual case reports.

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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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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