Case Report

CARDIOGENIC SHOCK DUE TO NONISCHEMIC CARDIOMYOPATHY INDUCED BY SEVERE ANTERIOR HYPOPITUITARISM

Nicolas Kissell, MD[1]; James O. Mudd, MD[2]; Jill M. Gelow, MD[2]; Lindsay E. Chong, MD[1]; Kevin C. J. Yuen, MBChB, MD, FRCP (UK)[1,3]

ABSTRACT

Objective: To review a case of life-threatening cardiogenic shock due to nonischemic cardiomyopathy associated with anterior hypopituitarism and to compare this case with previous reports in the literature.

Methods: We describe the clinical presentation, biochemistry, imaging, treatment, and outcome of a patient with cardiogenic shock. We conducted an English language literature search of nonischemic cardiomyopathy associated with hypopituitarism secondary to Sheehan syndrome.

Results: Cardiogenic shock due to nonischemic cardiomyopathy associated with anterior hypopituitarism is rare and has been attributed to thyroid-stimulating hormone, cortisol, and growth hormone (GH) deficiencies. A 40-year-old female with no previous cardiac history presented with cardiogenic shock due to nonischemic cardiomyopathy. An chocardiograph (ECG) revealed global hypokinesia with severely decreased left ventricular ejection fraction. She was treated with inotropes and an intra-aortic balloon pump. The patient volunteered a history of severe postpartum hemorrhage 20 years ago during childbirth with subsequent failure to lactate. Further workup confirmed central hypothyroidism, hypoadrenalism, hypogonadism, and GH deficiency, and magnetic resonance imaging (MRI) of her pituitary demonstrated an empty sella. She was treated with levothyroxine (LT4) and hydrocortisone replacement therapy. After 18 months, ECG revealed partial improvement of her low ejection fraction.

Conclusion: We report an unusual case of persistent nonischemic cardiomyopathy and highlight the importance of considering hypopituitarism secondary to Sheehan syndrome as an etiology of cardiomyopathy in young female patients presenting with cardiogenic shock. The continued presence of persistent nonischemic cardiomyopathy is likely to be due to the effects of prolonged untreated anterior hypopituitarism. Instituting appropriate hormone replacement therapy may improve the overall cardiac function of these patients. **(AACE Clinical Case Rep. 2015;1:e147-e151)**

Abbreviations:
ECG = echocardiograph; **GH** = growth hormone; **L4** = levothyroxine; **MRI** = magnetic resonance imaging

INTRODUCTION

Sheehan syndrome, or postpartum hypopituitarism, is an uncommon complication following postpartum hemorrhage (1). While some women may have very few symptoms, rarely Sheehan syndrome can lead to life-threatening adrenal crisis (2). The more subtle manifestations of this syndrome include failure to lactate, oligo-/amenorrhea, involution of breast tissue, and loss of axillary and public hair (3). The cause of panhypopituitarism is thought to result from ischemic necrosis of the anterior pituitary secondary to postpartum hemorrhage (4), hence diabetes insipidus rarely occurs (5,6), even though Sheehan and Whitehead demonstrated lesions in the neurohypophysis and hypothalamic nuclei in over 90% of their patients (7).

Although extremely rare, cardiac abnormalities have been reported in patients with hypopituitarism, and most are associated with growth hormone (GH) deficiency (8,9).

Submitted for publication May 4, 2014
Accepted for publication July 24, 2014
From the [1]Division of Endocrinology, Diabetes and Clinical Nutrition; [2]Knight Cardiovascular Institute, Department of Medicine, Oregon Health and Science University, Portland, Oregon; [3]Swedish Pituitary Center, Swedish Neuroscience Institute, Seattle, Washington.
Address correspondence to Dr. Kevin C. J. Yuen; Swedish Pituitary Center, Swedish Neuroscience Institute; 550 17th Avenue, Suite 400; Seattle, WA 98122.
E-mail: kevin.yuen@swedish.org
DOI:10.4158/EP14207.CR

However, detailed studies on cardiac function in patients with Sheehan syndrome are scarce due to the rarity of the condition. We report a unique case of severe anterior hypopituitarism in a female patient with undiagnosed Sheehan syndrome for 20 years who presented with cardiogenic shock due to nonischemic cardiomyopathy. Her symptoms partially improved with 18 months of medical therapy for chronic heart failure and glucocorticoid and thyroid hormone replacement therapy. We believe this is the first such case to be reported in the literature.

CASE REPORT

A 40-year-old Filipino female with no known previous medical history presented to the emergency department with profound dyspnea at rest, nausea, and vomiting. She reported the dyspnea had been gradually worsening over the preceding 2 weeks to the point where it was constant even at rest. She began vomiting 1 day prior to her presentation with progressive fatigue and lethargy. However, she denied polydipsia or polyuria. On examination in the emergency department, she was severely tachypneic, her pulse rate was 115 beats per minute, blood pressure 90/60 mm Hg, bilateral crackles up to the midzones of her lungs were noted on auscultation, elevated jugular venous pressure, and cool extremities with marked bilateral lower extremity pitting edema. Her serum troponin levels were negative, but B-type natriuretic peptide levels were significantly raised at 1,400 pg/mL (reference range <101 pg/mL). A chest X-ray demonstrated cardiomegaly and increased pulmonary vascular congestion (Fig. 1 *A*), and echocardiography (ECG) revealed sinus tachycardia without ischemic changes, globally decreased left ventricular function with an ejection fraction of 10%, and small pericardial effusion, all supporting the diagnosis of acute systolic heart failure resulting in cardiogenic shock. Coronary angiography revealed nonobstructive coronary artery disease, and right heart catheterization confirmed a severely reduced cardiac index of 0.8 L/min/m^2. Because of her severely decreased ejection fraction and low cardiac index, she was started on intravenous inotropic support with dobutamine and milrinone, and an intra-aortic balloon pump was placed.

During her hospitalization, extensive work up was performed to exclude familial, inflammatory, and infectious causes of cardiomyopathy. The majority of her biochemical laboratory results were unremarkable except for a serum creatinine level of 1.4 mg/dL and a hematocrit of 32%. An endomyocardial biopsy revealed interstitial edema, myocyte hypertrophy, and mild interstitial lymphocytic infiltrate consistent with nonspecific inflammation of the myocytes that did not provide any further information to the etiology of her cardiomyopathy. When she was more awake and alert, she reported that during the birth of her second child approximately 20 years ago, she experienced a severe postpartum hemorrhage that required a hysterectomy. She subsequently failed to lactate, raising the likelihood that she had undiagnosed Sheehan syndrome. A 250 μg adrenocorticotropic hormone (ACTH) stimulation test confirmed underlying central hypoadrenalism, with peak serum cortisol levels of 7.3 μg/dL (Table 1). She was immediately started on hydrocortisone 50 mg every 8 hours. Further basal pituitary hormone evaluation revealed the presence of central hypothyroidism, hypogonadism, and GH deficiency (Table 1). At that point, she was also empirically started on a low dose levothyroxine (LT4, 25 μg/day). Magnetic resonance imaging (MRI) of the

Table 1
Hormone Levels at Initial Hospital Admission

Hormone	Patient's hormone level	Reference range
TSH (mIU/L)	6.88	0.4-4
Free T4 (ng/dL)	0.3	0.6-1.2
250 μg ACTH stimulation test - basal cortisol (μg/dL) - 30-min cortisol (μg/dL) - 60-min cortisol (μg/dL)	 3.2 6.7 7.3	5-21
IGF-1 (ng/mL)	<25	101-267
Prolactin (ng/mL)	3	3-20
FSH (IU/L)	5	26.7–133.41
LH (IU/L)	2	5.0–52.3
Estradiol (pg/mL)	<20	Postmenopausal <48

Abbreviations: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; T4 = thyroxine; TSH = thyroid-stimulating hormone.

pituitary gland was consistent with an empty sella (Fig. 2 *A* and *B*), and bone densitometry testing confirmed the presence of osteopenia. She continued to improve clinically but was unable to be fully weaned off dobutamine. She was therefore discharged on this medication with the hope that medical therapy for heart failure and hormone replacement therapy would allow weaning from her cardiac medications in the near future. The dose of hydrocortisone was then tapered down to 10 mg in the morning, 5 mg at midday and 5 mg at 4 PM just before discharge.

At 3-, 10-, and 18-month follow-up visits, ECG revealed improvements in her ejection fraction from 15% to 35% to 45%, respectively, and her pericardial effusion resolved. A chest X-ray taken 18 months after hospitalization showed marked improvement of cardiomegaly and pulmonary edema resolution (Fig. 1 *B*). Her cardiac symptoms continued to improve, and she was weaned off dobutamine after 3 months. Presently, she has reasonable functional status with New York Heart Association Class I to II symptoms, and she is currently on maintenance doses of LT4 (75 μg/day) and hydrocortisone (20 mg/day in divided doses). We discussed the option of considering GH and estrogen replacement therapy with our patient, but she declined due to a fear of daily GH injections and her concern of the possible link between estrogen and breast cancer.

DISCUSSION

Our patient exhibited clinical and hormonal evidence of undiagnosed anterior hypopituitarism following postpartum hemorrhage in the clinical setting of postpartum pituitary necrosis for approximately 20 years after the birth of her second child. She presented with severe cardiogenic shock with no obvious precipitating cause. The diagnosis of Sheehan syndrome was substantiated with biochemical evidence of anterior hypopituitarism, a distant history of obstetric-related bleeding, and MRI findings of an empty sella. Her cardiac parameters gradually improved with thyroid hormone and glucocorticoid replacement therapy, but they remained suboptimal despite achieving euthyroid and eucortisolemic states. To the best of our knowledge, this is the first report of cardiogenic shock secondary to nonischemic cardiomyopathy induced by severe anterior hypopituitarism with substantial yet persistent suboptimal reversal of ejection fraction despite adequate glucocorticoid and thyroid hormone replacement up to 18 months after presentation. Our observations in this patient suggest that glucocorticoid and thyroid hormones play major permissive roles in maintaining cardiac performance.

Cardiac abnormalities have been studied extensively in patients with primary hypothyroidism, with almost one-third of patients having pericardial effusion that resolves when euthyroidism is achieved. Various types of cardiomyopathies, dilated or hypertrophic, have been reported and can be reversed with LT4 replacement (10,11). Cardiac abnormalities have also been reported in patients with hypopituitarism. Some of these abnormalities have been attributed to glucocorticoid, thyroid and GH deficiencies, as reports have demonstrated reversibility of cardiac function when these hormones are adequately replaced (8,9,12,13). Oki et al described a case of cardiomyopathy in a 74-year-old male with adrenal insufficiency and hypothyroidism secondary to pituitary adenoma, and administration of hydrocortisone and LT4 normalized the left ventricular wall motion abnormalities in 2 weeks (12). Shah et al reported a 46-year-old female with type 1 diabetes, congestive heart failure, and neurological signs, and subsequent hormonal investigations revealed central hypothyroidism. ECG demonstrated thickened myocardium, while cardiac MRI showed no evidence myocardial infiltration, and coronary angiography was normal. Complete

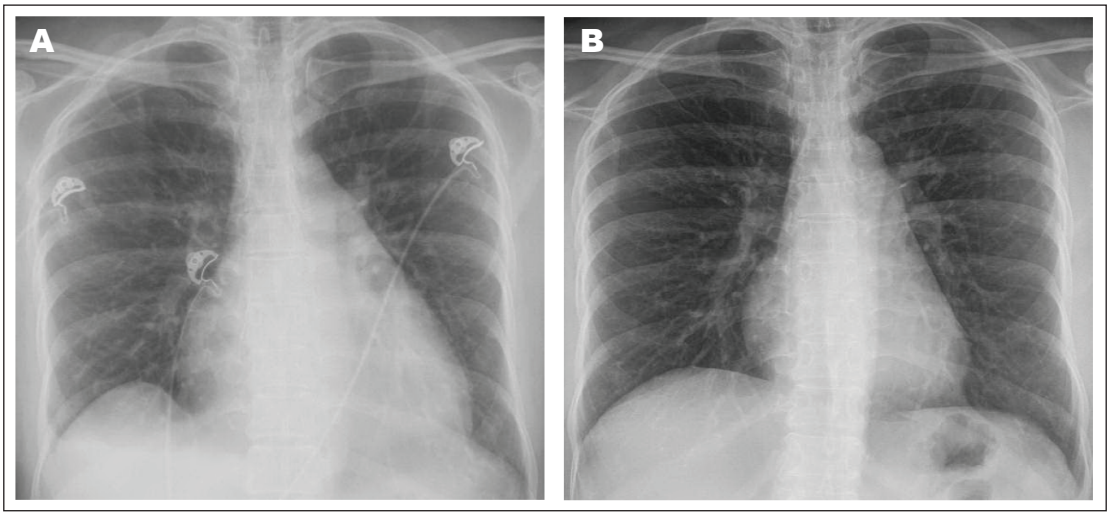

Fig. 1. Posterior-anterior view of chest X-rays at (*A*) initial presentation and (*B*) 18 months later.

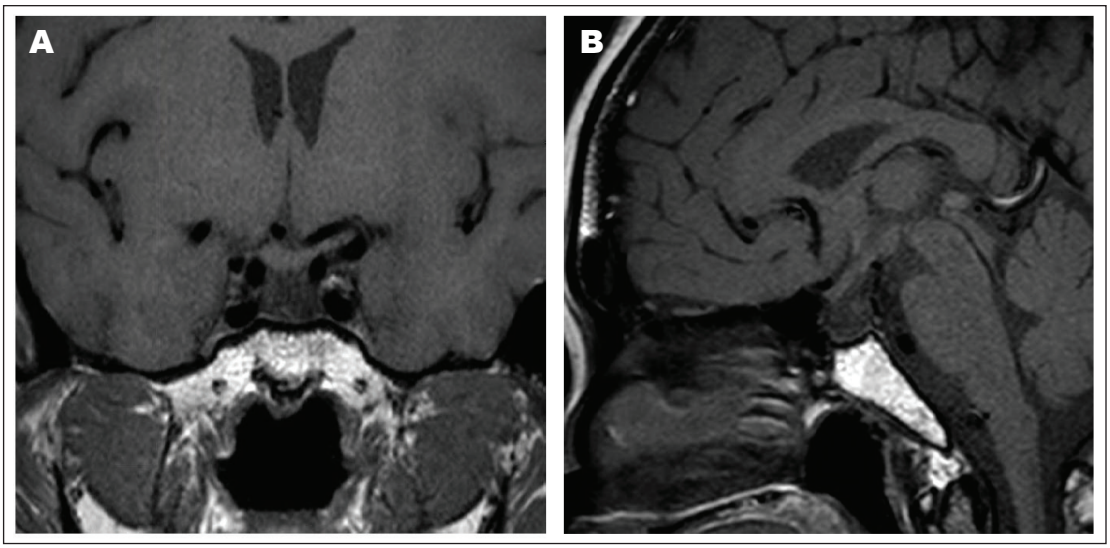

Fig. 2. T1-weighted magnetic resonance images in the (*A*) coronal and (*B*) sagittal planes showing the patient's empty sella turcica.

resolution of cardiomyopathy was noted following LT4 treatment. Cardiomyopathy was presumed to be due to hypopituitarism, although the levels of other pituitary hormones were not available, and her pituitary MRI was normal (13). Parikh et al described a 37-year-old female with lymphocytic hypophysitis, panhypopituitarism, postpartum cardiomyopathy, and pneumonitis who was initially treated with high doses of prednisolone, LT4, angiotensin-converting enzyme inhibitors, and beta blockers. Over 2 years, the patient responded clinically and was maintained on replacement doses of prednisolone and other medications. The patient was also found to have GH deficiency, but this was not treated (14). More recently, Laway et al described a 22-year-old female presenting with adrenal crisis following antitubercular therapy. She had a 2-year history of failure to lactate and secondary amenorrhea following her fourth pregnancy. Further evaluation revealed ECG evidence of dilated cardiomyopathy, but unlike our case, this patient's cardiac function fully reversed after 7 months following glucocorticoid and LT4 replacement therapy (15). The observations by Parikh et al (14) and other investigators (16,17) have prompted the hypothesis that Sheehan syndrome and its association with cardiomyopathy might have an autoimmune basis, and it is postulated that tissue necrosis may release sequestered antigens, triggering pituitary autoimmunity and delayed hypopituitarism and cardiomyopathy (18).

Our patient's cardiomyopathy and heart failure were likely the result of her anterior hypopituitarism. Her history of severe postpartum hemorrhage resulting in a hysterectomy caused pituitary necrosis that is consistent with the MRI finding of an empty sella. During pregnancy, the anterior pituitary gland typically grows out of proportion to its blood supply, rendering it vulnerable to hypoxemia and hypotension (19). When a sudden hemorrhagic event occurs, blood is shunted away from the hypophyseal arteries, which can lead to infarction of the gland. Normally, the first manifestation that suggests this diagnosis is a failure to lactate, which our patient reported. Failure to resume normal menses is another clue. However, our patient's postpartum hemorrhage resulted in a hysterectomy, which may have clouded the underlying clinical situation. Furthermore, she did not display any manifestations of diabetes insipidus, suggesting that her neurohypophysis was spared from infarction following the postpartum hemorrhage.

Sheehan syndrome may not manifest as a deficiency of all anterior pituitary hormones for many years. Although rare, there have been reports of late onset hypopituitarism presenting with new cardiomyopathy. Doshi et al reported a 42-year-old female with new onset cardiomyopathy secondary to hypopituitarism that occurred 14 years after a postpartum hemorrhage (20). In contrast to the present case, their patient's cardiomyopathy completely reversed with replacement hormones. Despite being treated with appropriate doses of LT4 and hydrocortisone but not estrogen replacement therapy, our patient had persistent ECG evidence of supoptimal ejection fraction 18 months after her initial presentation. The fact that near reversal of cardiomyopathy was observed without estrogen replacement suggests that estrogen may not play a major role in cardiac function. To the best of our knowledge, no other case with persistent decreased ejection fraction despite improvement in functional class has been described this long after the primary insult. The exact reason why her cardiomyopathy did not completely reverse is unclear. One hypothesis is that there was a direct effect of longstanding untreated panhypopituitarism. Another possible explanation is that

GH deficiency may have contributed to the cardiomyopathy based on the patient's low insulin-like growth factor-1 IGF-I level. However, we do not think that GH played a significant role in our patient as her cardiomyopathy substantially improved with only LT4 and glucocorticoid replacement. Nevertheless, the exact mechanism(s) of how hypothyroidism, hypocortisolism, and GH deficiency induce cardiomyopathy remains unclear.

CONCLUSION

This case highlights the importance of diligent history taking in the diagnosis of cardiomyopathy secondary to hypopituitarism in young female patients. Sheehan syndrome may present much later in life, and the induction of nonischemic cardiomyopathy is likely to be due to the effects of prolonged untreated anterior hypopituitarism, particularly hypothyroidism and hypocortisolism. Therefore, it is important to consider the possibility of undiagnosed hypopituitarism when cardiomyopathy develops in females because instituting appropriate hormone replacement therapy may improve their overall cardiac function.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Feinberg EC, Molitch ME, Endres LK, Peaceman AM.** The incidence of Sheehan's syndrome after obstetric hemorrhage. *Ferti Steril*. 2005;84:975-979.
2. **Burman P, Mattsson AF, Johannsson G, et al.** Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. *J Clin Endocrinol Metab*. 2013;98:1466-1475.
3. **Zargar AH, Singh B, Laway BA, Masoodi SR, Wani AI, Bashir MI.** Epidemiologic aspects of postpartum pituitary hypofunction (Sheehan's syndrome). *Fertil Steril*. 2005; 84:523-528.
4. **Kelestimur F.** Sheehan's syndrome. Pituitary. 2003;6: 181-188.
5. **Kan AK, Calligerous D.** A case report of Sheehan syndrome presenting with diabetes insipidus. *Aust N Z J Obstet Gynaecol*. 1998;38:224-226.
6. **Laway BA, Mir SA, Dar MI, Zargar AH.** Sheehan's syndrome with central diabetes insipidus. *Arq Bras Endocrinol Metab*. 2011;55:171-174.
7. **Sheehan HL, Whitehead R.** The neurohypophysis in post-partum hypopituitarism. *J Pathol Bacteriol*. 1963;85: 145-169.
8. **Frustaci A, Gentiloni N, Corsello SM, Caldarulo M, Russo MA.** Reversible dilated cardiomyopathy due to growth hormone deficiency. *Chest*. 1992;102:326-327.
9. **Lombardi G, Di Somma C, Grasso LF, Savanelli MC, Colao A, Pivonello R.** The cardiovascular system in growth hormone excess and growth hormone deficiency. *J Endocrinol Invest*. 2012;35:1021-1029.
10. **Klein I, Ojamaa K.** Thyroid hormone and the cardiovascular system. *New Engl J Med*. 2001;344:501-509.
11. **Ladenson PW.** Recognition and management of cardiovascular disease related to thyroid dysfunction. *Am J Med*. 1990;88:638-641.
12. **Oki K, Matsuura W, Koide J, et al.** Ampulla cardiomyopathy associated with adrenal insufficiency and hypothyroidism. *Int J Cardiol*. 2006;108:391-392.
13. **Shah AN, Dubrey SW, Thomas D.** Hypothyroid cardiomyopathy due to hypopituitarism: a diagnostic dilemma. *Clin Med*. 2007;7:639-640.
14. **Parikh A, Ezzat S.** Complete anterior pituitary failure and postpartum cardiomyopathy. *Endocr Pract*. 2006;12: 284-287.
15. **Laway BA, Alai MS, Gojwari T, Ganie MA, Zargar AH.** Sheehan syndrome with reversible dilated cardiomyopathy. *Ann Saudi Med*. 2010;30:321-324.
16. **Goswami R, Kochupillai N, Crock PA, Jaleel A, Gupta N.** Pituitary autoimmunity in patients with Sheehan's syndrome. *J Clinc Endocrinol Metab*. 2002;87:4137-4141.
17. **Sundstrom JB, Fett JD, Carraway RD, Ansari AA.** Is peripartum cardiomyopathy an organ-specific autoimmune disease? *Autoimmun Rev*. 2002;1:73-77.
18. **Sheehan HL.** The incidence of postpartum hypopituitarism. *Am J Obstet Gynecol*. 1954;68:202-223.
19. **Karaca Z, Kelestimur F.** Pregnancy and other pituitary disorders (including GH deficiency). *Best Pract Res Clin Endocrinol Metab*. 2011;25:897-910.
20. **Doshi S, Roy A, Ramamoorthy A, Kothari SS, Bahl VK.** Dilated cardiomyopathy: a ghost from the past. *Circ Heart Fail*. 2013;6:e19-e21.