Sheehan's syndrome in a patient presenting with organizing hematoma of the maxillary sinus*

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ABSTRACT

Sheehan's syndrome is a rare complication of post-partum hemorrhage that has decreased in incidence in the past decade due to better obstetrical practices, although still seen in developing countries. This is a case of a 31-year-old Gravida 1 Para 1 (1-0-0-0) with a 1-year history of enlarging maxillary sinus mass, where an incidental finding of an empty sella in an MRI with contrast was noted. The patient had amenorrhea of 15 years and received no medications for her undiagnosed Sheehan's syndrome incurred during her first and only pregnancy. The patient's cardiomyopathy and organizing hematoma may be rare complications of Sheehan's syndrome. Patients, laymen, health practitioners, and traditional birth attendants should be informed of these complications. Treatment should be individualized and administered after diagnosing a patient with Sheehan's syndrome to prevent complications such as adrenal insufficiency, hypothyroidism, infertility, and seen in this case, acute heart failure and possibly organizing hematoma.

Keywords: Sheehan's syndrome, post-partum hemorrhage, oraganizing hematoma, dilated cardiomyopathy

CASE REPORT

A 31-year-old Gravida 1 Para 1 (0-1-0-0) was admitted due to a 1-year history of enlarging maxillary sinus mass, for surgical management. The patient was admitted under the service of Otorhinolaryngology and was referred to the service of Obstetrics and Gynecology for amenorrhea of 15 years. The patient has no known co-morbidities, and she previously underwent appendectomy last 1990 in Quezon City. She is a 2-pack year smoker, stopped 1 year prior to admission, and is an occasional alcoholic beverage drinker.

The patient had one pregnancy in 2003 at 16 years of age. She had her prenatal consults in a local lying-in center. The pregnancy was unremarkable, until day of delivery, when decreased fetal movement and labor pains prompted consult at the lying-in center. Fetal demise was noted, and she delivered after 6 hours of labor. She could not recall if any uterotonic agents or if any other medications were administered. The patient recalled heavy vaginal bleeding post-partum, with two episodes of loss of consciousness. She claims that she was not transfused with any blood products and was discharged after 7 days. The patient noted continuous vaginal bleeding, 2 pads per day, for 3 months. Cyclic menstruation ceased since then. The patient had no other symptoms such as weight gain, reduced height, weakness, decreased libido, decrease in facial or pubic hair, nocturia, polyuria, polydipsia, heat intolerance, palpitations, or diarrhea. She remained amenorrheic but did not consult due to financial constraints. She had regular, unprotected sexual intercourse in order to conceive, but the patient did not have any successful pregnancies since then. She remained asymptomatic.

Fourteen months prior to admission, the patient experienced unilateral nose bleeding, left, occurring 2-3 times a week, managed with direct pressure. The patient eventually noted a 1.0 x 1.0 cm mass on the left nostril, which gradually enlarged. The patient did not seek consult due to financial constraints, until 7 months prior to admission, when the patient sought consult in a tertiary hospital, and a maxillary & nasal mass biopsy, left, was done, revealing: acute necrotizing inflammation with abscess tissue formation. She was given unrecalled antibiotics, with no effect. Six months prior to admission, the mass was still enlarging, now around 6.0 x 6.0 cm, and opted to seek second opinion in this institution, where Computed Tomography scan (Figure 1) was done, with an impression of: Expansile mass involving the left maxillary sinus, with submental lymphadenopathies, reactive sinusitis of left frontal, left sphenoid, bilateral ethmoid sinusitis. Another biopsy was done through a gingivobuccal approach, revealing an organizing hematoma. On review of the imaging done, an incidental finding of an "empty sella" (cerebrospinal fluid filled), (+) bright spot corresponding

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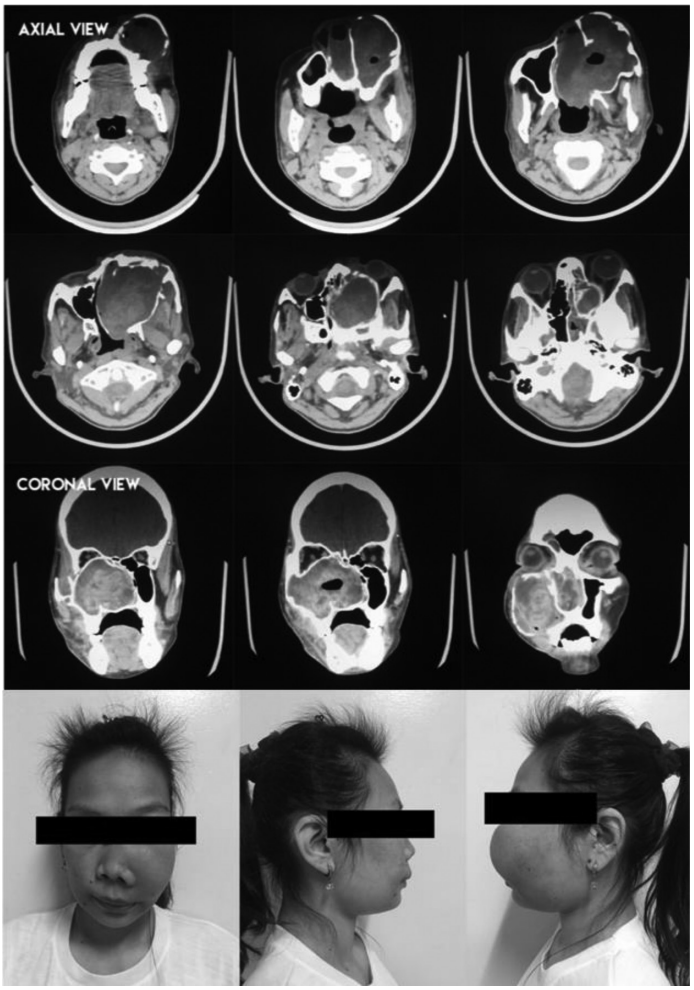

Figure 1. Computed Tomography Scan of the Maxillary mass, and patient status post excision of organizing hematoma, left maxillary sinus, via gingivobuccal Caldwell Luc approach

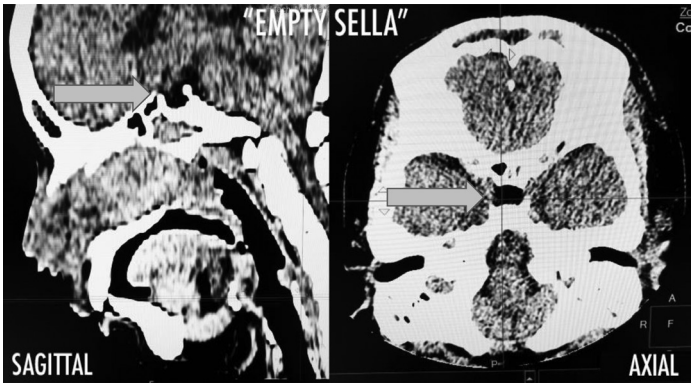

Figure 2. Computed Tomography Scan with incidental finding of "Empty Sella" (yellow arrow)

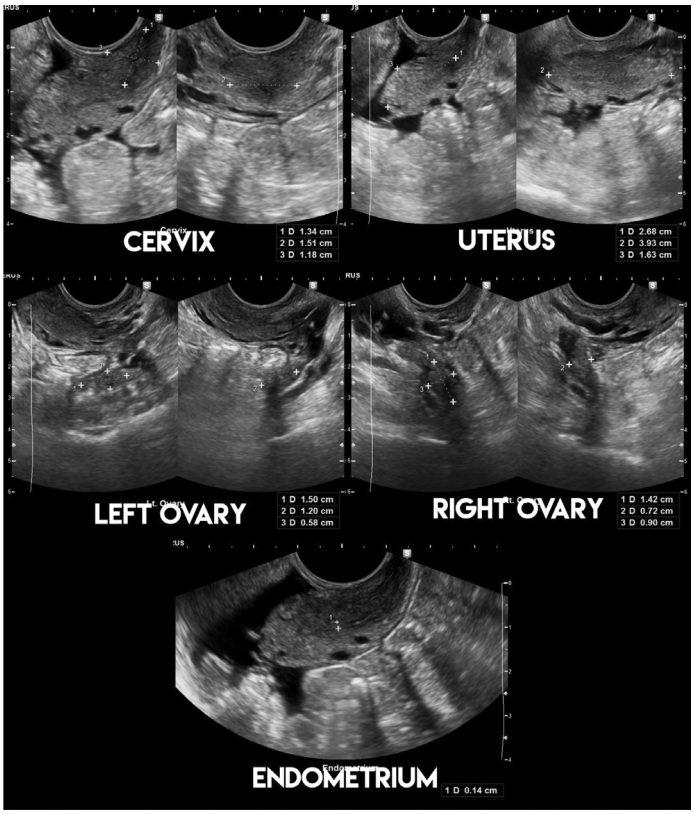

Figure 3. Transvaginal Ultrasound findings

to the posterior pituitary gland and cannot ascertain anterior pituitary gland, was seen in the Paranasal MRI with contrast (Figure 2).

Along with the history of post-partum hemorrhage and the incidental finding of an empty sella in the MRI, amenorrhea secondary to Sheehan's Syndrome was considered. The patient had essentially normal breast examination, with no masses or discharge noted. She also had Tanner stage III pubic hair distribution. On internal examination, she had normal external genitalia, smooth parous vagina, smooth cervix around 2.0 x 2.0 cm on palpation, corpus was small, with no adnexal masses or tenderness. On rectovaginal examination, the patient had good sphincter tone, intact rectal vault, no intraluminal masses, bilateral parametria smooth and pliable. A transvaginal ultrasound (Figure 3) was done initially, revealing a small uterus measuring 4.0 x 3.9 x 1.6 cm, cervix measuring 1.3 x 1.5 x 1.2 cm with homogenous stroma and distinct endocervical canal, endometrium measuring 0.1cm, and atrophic ovaries, with the right ovary measuring 1.4 x 0.7 x 0.9 cm and the left ovary measuring 1.5 x 1.2 x 0.6cm, with no follicles seen in both ovaries. Further workup was done by obtaining levels of anterior pituitary hormones, where Thyroid Stimulating Hormone was seen to be normal, while Prolactin, Serum Cortisol, Insulin Growth Factor-1, Follicle Stimulating hormone, and Luteinizing hormone levels (Table 1) were all below normal, confirming panhypopituitarism. The initial gynecologic plan is to start the patient on Hormonal Replacement Therapy after resolution of the other medical problems.

The patient underwent excision of organizing hematoma, left maxillary sinus via gingivobuccal Caldwell

Luc approach (Figure 1). She tolerated the procedure well and was discharged on her 4th post-operative day with the following medications: Cefuroxime 500mg/tablet 1 tablet to complete 7 days, Tranexamic acid 500mg/tablet 1 tablet thrice a day, Celecoxib 200mg/capsule, 1 capsule twice a day, and Levothyroxine 75mcg/tablet, 1 tablet daily.

The patient was admitted for epigastric pain two months after discharge. This was associated with vomiting, abdominal distention, orthopnea, bipedal edema, and jaundice. One week prior to admission, the patient had dyspnea, exacerbated after walking short distances. Ancillary tests were done (Table 2), pointing to a diagnosis of Heart Failure Functional Class II-III secondary to dilated cardiomyopathy, probably secondary to long-standing hypothyroidism, in acute decompensation, with secondary chronic passive congestion of the liver. She was started on Hydrocortisone 10mg/tab in the morning and 5mg/tab in the afternoon, Spironolactone 25mg/tab, ½ tab once a day, Enalapril 5mg/tab 1 tab twice a day. She was eventually discharged upon resolution of the dyspnea and jaundice. The patient expired a month after discharge at her home.

Table 1. Anterior Pituitary Hormone levels results

	Result	Normal Values
TSH	1.2421	0.35-4.94 ulu/mL
FT4	<5.15	9.01-19.05 pmol/L
Prolactin	1.31	5.18-26.53 ng/mL
Serum cortisol	14.3	138-690 mmol/L
IGF-1	4.86	73-244 IU/mL
Follicle Stimulating Hormone	1.44	Ovulatory – 4.0-13.5 Pre & Post Ovulatory – 0.6-9.5 Post menopausal – 30-135
Luteinizing Hormone	0.47	Ovulatory – 25-94 Pre & Post Ovulatory – 0.7-9.0 Post menopausal – 13-80
Estradiol	23.33	<40pg/mL
Adrenocortico-tropic Hormone	38.24	Middle follicular phase – 57-227 Pre-ovulatory phase – 127-476 Middle luteal phase – 77-277 Post-menopausal – <82

Table 2. Work-up for Heart Failure

12-Lead ECG 7/31/18	Regular Sinus Rhythm Normal Axis Prolonged QT (hypothyroidism) Non-specific ST-T wave changes Poor R wave progression
2D Echocardiogram	Ejection fraction = 25% Global hypokinesia Minimal pericardial effusion

CASE DISCUSSION

Severe post-partum hemorrhage may lead to several complications- thromboembolism, hemodynamic instability, organ failure, abdominal compartment syndrome, severe postpartum anemia, intrauterine adhesions, and post-partum hypopituitarism. According to the Department of Health, around 16% of maternal deaths in the Philippines may be accountable to post-partum hemorrhage.[1] Efforts to improve maternal healthcare has targeted to lessen mortalities and morbidities associated with post-partum hemorrhage. It is critical to recognize post-partum hemorrhage because maternal death is not the only devastating outcome of such a catastrophic event.

The true prevalence of post-partum hypopituitarism, or Sheehan's syndrome, is not known. In 1965, Prof. Harold Sheehan, estimated that the worldwide prevalence was 100–200 per 100,000 women[2], although this was postulated to have decreased in rate as obstetric care improved throughout the years.

In a study done in the Philippines, analysis of 82 female patients with hypopituitarism revealed that in 14% of patients the underlying etiology was Sheehan's Syndrome.[3] There may be increased incidence of Sheehan's Syndrome in the Philippines, a developing country where home births are very common. Despite this, information about the complications of post-partum hemorrhage, is still not widely available, especially among people in the lower socioeconomic status.

The diagnosis of Sheehan's Syndrome is often delayed due to non-specific signs and symptoms. The mean period between delivery and diagnosis was found to be from 7-19.7 years among several retrospective studies from different countries. The classical criteria for the diagnosis of Sheehan's Syndrome[4] are: (1) typical obstetrical history of severe PPH; (2) severe hypotension or shock, for which blood transfusion or fluid replacement is necessary; (3) failure of postpartum lactation; (4) failure to resume regular menses after delivery; (5) varying degree of anterior pituitary insufficiency; partial or complete hypopituitarism; and (6) a partially or completely empty sella on a computed tomography (CT) scan or MRI. This patient was able to fulfill five out of six of the criteria, as the patient did not report any signs and symptoms of hypopituitarism, although the patient's laboratory work-up revealed decreased values for all anterior pituitary hormones, as well as an empty sella on MRI. Stimulation tests such as the adrenocorticotropic hormone (ACTH) stimulation test, glucagon stimulation test (GST), TRH stimulation test, or insulin tolerance test (ITT), can be used to ascertain the diagnosis. The best single test to confirm the diagnosis of Sheehan syndrome

is administration of intravenous TRH (100 mg) and measuring serum prolactin levels at 0 and 30 minutes. The ratio of prolactin measured at 30 minutes to that before TRH treatment (time 0) should be greater than 3.0, if normal.

The pathogenesis of post-partum pituitary hemorrhage is not completely understood, but there are two main conditions that may contribute: 1) a physiologic enlargement (approximately 120–136% towards the end of pregnancy) and increased vascularity of the pituitary gland in pregnancy, and 2) an interruption of the arterial blood supply to the gland. Massive bleeding in a non-pregnant patient does not cause hypopituitarism, and pituitary enlargement due to the lactotroph hyperplasia induced by pregnancy is required to cause hypopituitarism secondary to post-partum hemorrhage. There are two main arteries from the internal carotid artery that provide blood supply to the gland: the superior artery which supplies blood to the adenohypophysis and inferior artery supplying blood to the stalk and neurohypophysis. Sheehan has described several hypotheses about the development of hypopituitarism after massive hemorrhage: that arrest of blood flow from the arterial vasospasm due to severe hypotension or release of vasoconstrictor cytokines due to hypovolemic shock resulting from post-partum hemorrhage, arterial compression because of larger pituitary enlargement and/or smaller sella turcica size, or thrombosis in the pituitary arteries due to hypercoagulation.

The pathophysiology of organizing hematoma is unknown, although believed to develop initially from the accumulation of blood in the maxillary sinus resulting from various causes, such as trauma, surgery, bleeding diatheses, hemorrhagic lesion within the sinus, and the loss of mechanical integrity of an arterial branch. Histologically, it is described as a combination of dilated vessels, hemorrhage, fibrin exudation, fibrosis, hyalinization, and neovascularization.[5] Ozaki et al. has provided the "Negative Spiral Theory" that may explain the formation of an organizing hematoma: a blood clot accumulates in the closed space due to various causes of bleeding. Necrosis, fibrosis, and hyalinization occur. Neovascularization develops as part of these processes, but blood flow becomes sluggish at the lead of new vessels. As a result, the new vessels become dilated, and rebleeding occurs.[6]

It is postulated in this case that the patient's long-standing panhypopituitarism secondary to Sheehan's syndrome, particularly, untreated hypothyroidism, may have been the primary cause of dilated cardiomyopathy. Several case reports have shown Sheehan's syndrome in relation to cardiomyopathies of variable types, dilated or hypertrophic. Most patients treated with hormone replacement have demonstrated reversibility of the cardiac function if they are adequately treated. A case report by Kisell et. al[7] showed a 40-year-old Filipino female presenting with profound dyspnea at rest, nausea, and vomiting. On 2D echocardiogram, a globally decreased left ventricular function with an ejection fraction of 10% and small pericardial effusion was seen, supporting the diagnosis of acute systolic heart failure resulting in cardiogenic shock. History revealed that she had severe post-partum hemorrhage that required a hysterectomy during the birth of her second child 20 years ago, with failure of lactation after. ACTH stimulation test confirmed central hypoadrenalism. Results showed central hypothyroidism, hypogonadism, and GH deficiency, as well as findings of an empty sella on MRI of the pituitary gland. She was immediately started on hydrocortisone 50 mg every 8 hours and a low dose levothyroxine (LT4, 25 mg/day). After 18 months, ejection fraction improved to 45%. Another case report by Laway et. al[8] have shown complete resolution of dilated cardiomyopathy after therapy with levothyroxine 100 mg/day and prednisolone 7.5 mg/day. She initially presented with lactation failure, secondary amenorrhea, features of hypothyroidism and a hypocortisol state following severe postpartum hemorrhage two years prior.

Right-sided heart failure may then cause hepatic congestion, as seen in our patient. Laboratory work-up (Table 3) showed that the initial liver enzymes showed that the AST was elevated 82.5 times and ALT 46.6 times elevated. Bilirubins were also elevated, with the total bilirubin elevated 5.67 times, direct bilirubin elevated 8.88 times, and indirect bilirubin elevated 3.3 times normal values. Coagulation tests showed that protime, prothrombin time, and INR were all elevated, showing an increased risk for bleeding. Furthermore, a Hepatitis profile revealed only the Anti-HBC to be reactive, which may indicate either Hepatitis B infection in the remote past or that she may be a low-level carrier.

In retrospect, the patient's initial condition led to deleterious consequences. The postpartum hemorrhage caused Sheehan's syndrome, causing undiagnosed, long-standing hypothyroidism, which led to dilated cardiomyopathy, then causing chronic passive congestion of the liver. Hepatic damage then caused an increased risk for bleeding, which may have contributed to the formation of an organizing hematoma.

Excellent history-taking precedes any laboratory exam in being able to diagnose the condition. Several rare complications may be indirectly caused by Sheehan's syndrome, and timely diagnosis and replacement of hormones may improve outcomes. Prevention of post-partum hemorrhage is still the most important intervention to decrease the incidence of Sheehan's

Table 3. Laboratory work-up

	7/31/18	**8/1/18**	**8/4/18**	**8/7/18**
AST	2971	2592	1233	376
ALT	1631	1638	1638	502
	7/31/18	**8/1/18**	**8/4/18**	
Total bilirubin	124.9	79.4	31.5	
Direct bilirubin	62.2	44.1	17.1	
Indirect bilirubin	62.7	35.3	14.4	
	8/3/18			
PT-REFERENCE	12.90			
PT-TIME	21.6 H			
PT-%	41			
PT-INR	1.91 H			
APTT-REFERENCE	30.38			

Syndrome. The use of uterotonics to actively manage the third stage of labor is an important intervention that has been developed throughout the years to decrease the incidence of post-partum hemorrhage. The primary goal of treatment is to replace the deficient hormones.[9] Replacement of thyroid and glucocorticoids are deemed to be the hormones that need to be replaced urgently, in cases where Sheehan's Syndrome presents acutely. Glucocorticoid therapy should be initiated prior to the administration of thyroid hormones to prevent adrenal crisis. Free T4 and free T3 are used rather than TSH in monitoring response of treatment and titrating doses of levothyroxine, while clinical signs and symptoms of hypocortisolism are considered more advantageous compared to laboratory results in monitoring response. The treatment of choice for patients who present with diabetes insipidus is desmopressin. Growth Hormone should be started on a low-dose regimen (0.1–0.3 mg/d) and titrated upward by 0.1 mg/d per month with careful monitoring, maintaining the insulin-like growth factor-1 levels within the age-appropriate range for the patient.[10] Gonadotropin deficiency may be treated by hormone replacement therapy, which is also individualized. Gonadal and growth hormone replacement therapies are not as vital therapies but may be started and tailored to the needs of the patient. Patients who are desirous of pregnancy may be assisted by the fertility service for ovulation induction. Cases of successful pregnancy after acute Sheehan's Syndrome have been reported. The patient was maintained on Levothyroxine 75mcg daily, Hydrocortisone 15mg daily, Spironolactone 12.5mg daily, Enalapril 5mg/tab 1 tab twice a day until her demise.

Initiatives to further educate local health centers, lying-in centers, birth attendants, and midwives about the possible consequences of massive blood loss intra- and post-partum should be instigated by Obstetrician-Gynecologists. Training programs designed by physicians to help train birth attendants to use uterotonics may also be a public health measure to help decrease the incidence of post-partum hemorrhage especially in areas where Obstetrician-Gynecologists are out of reach.

SUMMARY

Sheehan's Syndrome is a preventable complication of post-partum hemorrhage. Cardiomyopathy and organizing hematoma may be rare complications of Sheehan's syndrome, as presented in this case. Dissemination of information about Sheehan's Syndrome among laymen, health workers, and traditional birth attendants is necessary, as prevention is still the most effective way to avoid these complications. While signs and symptoms could be non-specific, clinicians should keep a high index of suspicion should a woman have a history of excessive bleeding during child birth. Treatment should be administered as soon as the patient is worked up for Sheehan's Syndrome to prevent further complications brought about by hypopituitarism. ■

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