Case Report

Post-partum pituitary insufficiency and livedo reticularis presenting a diagnostic challenge in a resource limited setting in Tanzania: a case report, clinical discussion and brief review of existing literature

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Abstract

Background: Pituitary disorders following pregnancy are an important yet under reported clinical entity in the developing world. Conversely, post partum panhypopituitarism has a more devastating impact on women in such settings due to high fertility rates, poor obstetric care and scarcity of diagnostic and therapeutic resources available.

Case presentation: A 37 year old African female presented ten years post partum with features of multiple endocrine deficiencies including hypothyroidism, hypoadrenalism, lactation failure and secondary amenorrhea. In addition she had clinical features of an underlying autoimmune condition. These included a history of post-partum thyroiditis, alopecia areata, livedo reticularis and deranged coagulation indices. A remarkable clinical response followed appropriate hormone replacement therapy including steroids. This constellation has never been reported before; we therefore present an interesting clinical discussion including a brief review of existing literature.

Conclusion: Post partum pituitary insufficiency is an under-reported condition of immense clinical importance especially in the developing world. A high clinical index of suspicion is vital to ensure an early and correct diagnosis which will have a direct bearing on management and patient outcome.

Keywords: Post partum panhypopituitarism, Lymphocytic hypophysitis, Sheehan’s syndrome, Livedo reticularis, Africa

Background

The pituitary gland undergoes major anatomic, physiologic and immunologic changes during pregnancy. Its enlargement is chiefly attributed to lactotroph hyperplasia [1]. These changes then predispose the pregnant woman to a spectrum of pituitary disorders in the intra-partum and post-partum periods. These include Sheehan’s syndrome which is by far the commonest, lymphocytic hypophysitis and rarely, apoplexy of pituitary adenomas [1,2].

Sheehan’s syndrome (SS) is becoming increasingly rare in the developed world due to improved standards of obstetric care; the same is not yet true for the developing world. The prevalence of women of reproductive age with suspected SS in the Kashmir valley (Indian subcontinent) was estimated at 3.2% [3]. Similar cross-sectional studies are virtually non-existent for Africa but a couple of case series have appeared in the literature. Cénac et al reported 40 cases of SS within a 5-year period at a hospital in Niger. All their patients were black African women living in rural areas and had no medical assistance during the last delivery [4]. Another group of researchers from Senegal noted that the main risk factors were traditions of home delivery and lack of obstetric care [5]. In addition, they observed a long latency period before the disease manifestations became overt [5]. Not surprisingly, lymphocytic adenohypophysitis with an estimated annual incidence in the UK of one case per 9 million [6], is even less commonly reported in sub-Saharan Africa with only a couple of isolated case reports till date from South Africa [7,8].

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Case presentation

History
ZM, a 37 year old multiparous woman from Northern Tanzania, presented with complaints of generalized body swelling associated with progressive weight gain for ten years. The onset coincided with her last child birth which was complicated by mild post-partum haemorrhage following which she failed to lactate. She also experienced cold intolerance, loss of libido and a complete cessation of her menses. Four years prior admission she had had a serious febrile illness following which she experienced a brief period of altered level of consciousness and transient aphasia; since then she noted slowing of speech. As part of her systems review, she reported an anterior neck swelling which increased during her last pregnancy then gradually subsided a few months later. She also reported headaches of moderate intensity but no gross visual changes; she suffered from occasional rashes in sunlight gradually subsided a few months later. She also reported swelling which increased during her last pregnancy then gradually subsided a few months later. She also reported headaches of moderate intensity but no gross visual changes; she suffered from occasional rashes in sunlight associated risk of osmotic demyelination syndrome. During her stay in the wards the patient's condition deteriorated abruptly due to an adrenal crisis probably precipitated by the vigorous thyroid hormone replacement. The dose of thyroxine was lowered to 25 mcg daily and the patient kept on normal saline and IV hydrocortisone 100 mg 6hourly. In addition, severe hyponatraemia should be managed with water restriction and hypertonic saline infusion; the latter was avoided because of the difficulty monitoring Na⁺ levels and the associated risk of osmotic demyelination syndrome. Upon discharge three weeks later her rate of speech, mentation and exercise tolerance was significantly better compared to admission. On a two-month follow-up visit, there was a marked reduction in the generalised edema. The thyroxine dosage was subsequently increased gradually to 100 mcg daily. Her hair pattern had normalized in three months. At her five-month follow up visit, it

Table 1 Relevant laboratory results

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|-----------------------------------|
| CBC/ESR                           |
| Hb = 96.6 g/L (121–153), MCV = 83.3 fl (82–103), ESR = 60 mm/hr (0–10) |
| Coagulation panel                 |
| International Normalized Ratio (INR): 2.06 (1.0–1.5), Activated Partial Thromboplastin Time(APTT): 31.15 sec (20–35) |
| Chemistry panel                   |
| Fasting blood glucose: 3.2 mmol/L (3.6 – 6.3), Na⁺: 113.9 mmol/L (137–147), K⁺: 3.4 mmol/L (3.4-5.3), aspartate aminotransferase (AST): 83.6 U/L (11–47); creatinine: 67 mcmol/L (44–150) |
| Dipstick urinalysis               |
| proteinuria 2+, specific gravity: 1.030 (1.010-1.025) |
| Endocrine panel                  |
| T4: 38 ng/ml (60–160), T3: 0.8 ng/ml (1.0-3.1), TSH: 0.0 ulU/ml (0.4-6.2); LH, FSH, ACTH, GH, prolactin and cortisol could not be tested due to lack of reagents |
| Autoimmune panel                 |
| ANA (anti-nuclear antibody) tities less than 1:40; Anti-cardiolipin and anti-B2-glycoprotein IgM / IgG were all within normal limits. Thyroid auto-antibodies and angiotensin converting enzyme (ACE) levels could not be tested. |

Computerized visual perimetry
Minor field defects were noted in both temporal fields.

Radiology
Chest X-ray: cardiomegaly, small left sided pleural effusion; Echo: 15 mm pericardial effusion, normal left ventricular function; X-ray of Sella: no evidence of mass lesion, symmetric floor (Figure 1); Non-contrast axial head CT scan: possible asymmetric density within the sella turcica (but no ‘empty sella’ sign); dorum sellae poorly visualized (Figure 2).

Management and progress in wards
The patient was started on hormone replacement therapy including thyroxine 50 mcg daily, prednisone 5 mg AM and 2.5 mg PM and a combined oral contraceptive. During her stay in the wards the patient’s condition deteriorated abruptly due to an adrenal crisis probably precipitated by the vigorous thyroid hormone replacement. The dose of thyroxine was lowered to 25 mcg daily and the patient kept on normal saline and IV hydrocortisone 100 mg 6hourly. In addition, severe hyponatraemia should be managed with water restriction and hypertonic saline infusion; the latter was avoided because of the difficulty monitoring Na⁺ levels and the associated risk of osmotic demyelination syndrome. Upon discharge three weeks later her rate of speech, mentation and exercise tolerance was significantly better compared to admission. On a two-month follow-up visit, there was a marked reduction in the generalised edema. The thyroxine dosage was subsequently increased gradually to 100 mcg daily. Her hair pattern had normalized in three months. At her five-month follow up visit, it

Investigations

Labs
Please see Table 1.

Physical examination

Vitals: Pulse: 70/min; BP: 102/68 mm Hg; Temp: 36.2 degrees C; Respiratory rate 14/min. Orthostatics: Supine BP 110/80 mm Hg, standing BP 95/60 mm Hg. General/endocrine: overweight woman (BMI 29.1 kg/m²), looking younger than her stated age. She was pale with generalized, non-pitting edema involving face and extremities. Of note she had no oral ulcers and her thyroid gland was not palpable. She had “alabaster” skin with patchy hair loss over scalp; sparse axillary and pubic hair. Cardiovascular: Regular rate and rhythm with distant heart sounds. Respiratory/Abdominal exams were unremarkable. Neurologic Exam: Higher centres: Fully oriented to time, place and person but with marked slowing of speech and mentation. Cranial nerves: Optic nerve- Visual acuity 20/30 both eyes; gross visual fields normal at bedside. Fundoscopy: no papilledema noted. Extra-ocular movements were intact. Motor: Limbs hypotonic; power reduced to grade 4/5 MRC (Medical Research Council grade) with proximal weaker than distal muscle groups. Reflexes: Ankle jerks were delayed and plantar responses flexor. Sensation was normal for all modalities tested.
was noted that she had developed livedo reticularis over her lower extremities bilaterally. (Figure 3) She was subsequently started on anti platelet therapy (junior aspirin 75 mg daily) and the oral contraceptive stopped. The livedo reticularis had disappeared on a subsequent visit. At 16 months, the patient was in good general health except for a headache and occasional palpitations. At this juncture, the thyroxine dose was lowered to 75 mcg daily.

Differential diagnosis
This patient has anterior pituitary insufficiency beginning in the post partum period. Neurohypophyseal involvement is unlikely given the persistently elevated urine specific gravity even post steroid therapy which essentially rules out diabetes insipidus. The most likely differentials are lymphocytic hypophysitis (LyHy) and Sheehan’s syndrome. An underlying co-morbid autoimmune condition such as systemic lupus erythematosus (SLE) or anti-phospholipid syndrome is a relevant clinical consideration but is made less likely given her negative antibody screens. Neoplasms and other granulomatous disorders of the hypophysis (tuberculosis, syphilis, sarcoidosis and histiocytosis X) are also possibilities but would be lower on the list of

**Figure 1** Sella turcica X-ray (lateral view). Legend: No evidence of mass lesion seen, symmetric floor with no erosion or ‘double floor’ sign.

**Figure 2** Non-contrast axial head CT scan (at the level of sella). Legend: Possible asymmetric density within the pituitary gland on the left (but no ‘empty sella’ sign); dorsum sellae poorly visualized.
differentials in the absence of appropriate clinical and laboratory evidence.

Discussion
In this patient, the diagnosis of anterior pituitary insufficiency is evident from the constellation of secondary hypothyroidism, secondary amenorrhea and the clinical manifestations of secondary adrenocortical insufficiency (hypoglycaemia, orthostatic hypotension and marked hyponatremia with low normal K⁺ levels). Interestingly, her TSH levels were undetectable which is quite rare in panhypopituitarism but has been previously reported [9]. Also noteworthy in this case is the severe hyponatremia which is likely multifactorial. In secondary adrenal

Figure 3 Photograph of proximal left lower extremity at five-month follow up visit. Legend: appearance of diffuse reticular rash consistent with livedo reticularis.
insufficiency, one accepted explanation is that hypo-
cortisolism leads to failure of inhibition of vasopressin
secretion. In addition severe secondary hypothyroidism,
which this patient also had, leads to a syndrome of
inappropriate secretion of ADH (SIADH)-like picture
[10-12].

Arriving at an etiologic diagnosis is more challenging.
The history of post-partum hemorrhage albeit mild, and
lactation failure may favor Sheehan’s syndrome (SS)
over lymphocytic hypophysitis (LyHy) which is another
recognized, but less common cause of post-partum pitu-
itary insufficiency [1,2]. However in light of a history
suggestive of painless post-partum thyroiditis, a physical
exam which revealed signs of co-existing autoimmune
conditions such as alopecia areata and the elevated ESR,
the latter provides a better diagnostic fit [2,9,13,14].

While LyHy often presents with hyperprolactinemia
from stalk dysfunction leading to galactorrhoea in a
quarter to one-third of cases [1,6], agalactia has been
reported in 11% of patients [6].

Although, thyroid auto-antibodies could not be tested
and her antinuclear antibody and antiphospholipid anti-
bodies were negative, a comprehensive retrospective
analysis of 379 patients with lymphocytic hypophysitis
(LyHy) by Caturgeli et al found that the prevalence of
auto-antibodies for Hashimoto’s and SLE was only 7.4%
and 1.3% respectively [6]. Similarly, anti-pituitary anti-
bodies could not be assayed however these are consid-
ered of limited sensitivity and specificity in the diagnosis
of lymphocytic hypophysitis since they are present in
other autoimmune conditions and several non-immune
pituitary disorders (including Sheehan’s syndrome) [6].

In the latter, post partum hemorrhage may trigger pituita-
ary autoimmunity by the release of sequestered antigens
following necrosis of the gland [15].

Assessment of visual fields is a simple but very useful
diagnostic test. The minor defect in the patient’s tem-
poral visual fields detected bilaterally upon visual perim-
etry may signify an ischemic process secondary to a
mass effect at the optic chiasm – this could indicate a
pituitary macroadenoma or an infiltrative process such
as LyHy. The normal size sella on skull X-ray and CT
scan might argue against a large tumor.

MRI is the imaging study of choice for the pituitary
[16], the lack of which makes it difficult to accurately
diagnose pituitary disease in most hospitals in the de-
veloping world. In any case, up to 9% of patients suffering
from LyHy have normal imaging findings on CT/MRI.
More common presentations include symmetric enlarge-
ment of sellar content (66%), thickening of the pituitary
stalk (56%), homogenous enhancement (51%) and occa-
sionally asymmetry of the enlarged sellar content (18%)
[17]. This differs from the imaging findings in Sheehan’s
syndrome which almost always results in a partially or
completely empty sella that may be normal or reduced
in size [18,19].

A definitive diagnosis usually requires a tissue biopsy
often obtained via the endonasal transsphenoidal approach
which was not possible in this case. Molitch et al have
suggested criteria for making a strong presumptive clinical
diagnosis non-invasively. These are as follows: a history
of gestational / postpartum hypopituitarism, a contrast-
enhancing sellar mass with MRI features characteristic of
LyHy, a pattern of endocrine deficiency with early loss of
adrenocorticotropic hormone and thyroid-stimulating
hormone unlike that found with macroadenomas and
pituitary failure disproportionate to size of the mass [20].

Of note, livedo reticularis has never been reported
before in patients with a clinical or histopathologic diag-
nosis of lymphocytic hypophysitis and may be unrelated.
However, an association is not inconceivable particularly
if the patient were to have an underlying co-morbidity
such as SLE, since both LyHy and livedo reticularis have
independently been documented in lupus [21,22]. This
patient likely meets four (4) of the eleven (11) criteria
required for a diagnosis of lupus namely photosensitivity,
proteinuria, serositis (pleural and pericardial effusions)
and hematologic abnormalities (normocytic anemia) [23].
However her ANA was negative and more specific tests
such as anti-ds DNA or anti-Sm antibodies to rule out
antinuclear-antibody negative disease were not available.

Finally, does a definitive diagnosis necessarily influence
management in post-partum panhypopituitarism? The
simple answer is yes - while hormone replacement is
often all that is necessary for Sheehan’s syndrome, addi-
tional measures may be required for patients with LyHy
presenting with symptoms of sellar compression. While
surgery or pituitary radiotherapy may eventually be
needed, in the absence of urgent visual symptoms it is
reasonable to advocate using high dose glucocorticoids
as first line therapy for LyHy under imaging surveillance
if possible; decrease in volume of the pituitary mass and
improving hormone status helps to confirm the diagno-
sis retrospectively [6,17]. Methotrexate and azathioprine
can be used for poor responders [24-26]. Among the
320 patients with LyHy followed by Caturgeli, 73% required
long term hormone replacement therapy, 16%
recovered following mass-reduction without need for
hormone-replacement, 8% died probably from irrevers-
able adrenal insufficiency and 3% experienced spontan-
eous resolution without treatment [6].

Conclusion
In the developing world, post-partum pituitary insuffi-
ciency is not altogether a rare clinical entity. The differ-
ential diagnosis becomes more challenging if clinical
features suggestive of an auto-immune condition are
also present. An accurate history and a keen physical
exam become indispensable in correctly diagnosing and appropriately managing such patients especially in resource limited settings. A specific diagnosis may allow effective use of pharmacologic therapy before resorting to more invasive measures. There is a dire need for educating health care professionals and the general public since the disorder left undiagnosed has a devastating impact on maternal morbidity and mortality; properly designed epidemiologic studies to quantify the exact magnitude of the problem will be a necessary step towards the solution.

Consent
The patient has provided explicit informed consent for publication of this case report and all accompanying images in a scientific journal.

Abbreviations
ACTH: Adrenocorticotropic hormone; ANA: Anti-nuclear antibody; BMI: Body mass index; ESR: Erythrocyte sedimentation rate; FSH: Follicle stimulating hormone; GH: Growth hormone; LH: Luteinizing hormone. LyHy: Lymphocytic hypophysitis; MCV: Mean corpuscular volume; SLE: Systemic lupus erythematosus; SS: Sheehan's syndrome; TSH: Thyroid stimulating hormone.

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
FGS, WPH and KGK were involved in the initial case diagnosis. FGS and WPH were involved with revising the manuscript for publication. KGK continues with proof reading the manuscript and providing valuable insight into the diagnostic process. He is a consultant neurologist at Oregon Health and Science University, Portland OR. Prof Gibbs has completed a research fellowship in neuroendocrinology at UCSF and has over thirty publications in this area of research. We would also like to acknowledge the contributions of the following individuals: H Diefenthal, M.D., Ph.D. (Professor in Diagnostic Radiology Kilimanjaro Christian Medical Centre (KCMC), Tanzania); M Jaffer, M.D. (Physician, Nairobi Kenya); V Maro, M.D. (Head of department, Internal medicine KCMC, Tanzania) and Mr C Mataro (Lab technologist KCMC, Tanzania). Personal funds were utilized during the entire process of patient work up – no external funding was made use of.

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