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NEUROLOGY | CASE REPORT

Granulomatous hypophysitis in a postpartum patient: A case report

Alexey Youssef[1], Rahaf Ali[1] and Maya Marouf[1*]

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*Corresponding author: Maya Marouf, Faculty of Medicine, Tishreen University, MED Research Team, Lattakia, Syria
E-mail: maroudmaya96@gmail.com

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Abstract: Hypophysitis is a pituitary inflammatory disorder commonly misdiagnosed and treated as a pituitary macroadenoma. Occurring at an incidence of 1 case to 9 million people into lymphocytic, granulomatous, _histopathologically_ per year, it is further classified and xanthomatous hypophysitis. A recent report indicated that 85 cases of granulomatous hypophysitis have been reported in the literature. Mainly affecting females, the most common presenting symptoms are headaches and visual symptoms due to optical chiasm compression. Although histopathology is the sole method for definitive diagnosis, other diagnostic modalities like MRI can give some suggestive findings. Here, we present a case of a 30-year-old postpartum woman that presented to our institution for polyuria/polydispia, headaches, visual disturbances, and symptoms of hypothyroidism. Further evaluation led to the diagnosis of Lymphocytic hypophysitis that recrudesced despite treatment with corticosteroids. Consequently, she was treated with transsphenoidal surgical resection, and postoperative histopathological evaluation indicated that this is a case of granulomatous not lymphocytic hypophysitis. The patient recovered perfectly after surgery with no residual symptoms on follow-up. These findings stress on the profound similarities between both pathologies and supports the theory that they are .different phases of the same disease process rather than different diseases.

Subjects: Medicine; Endocrinology; Neurology; Obstetrics, Gynecology & Women's Health

Keywords: granulomatous hypophysitis; lymphocytic hypophysitis; pituitary mass; postpartum; autoimmune history

ABOUT THE AUTHORS

The authors are members of MED Research Team in Tishreen University. A team of medical students and residents who developed sheer interest in medical research. We started small by reporting the peculiar clinical cases that we encountered during our time at the hospital, one of which is this case report. Later on, we built upon that experience to take up bigger research projects like leishmaniasis epidemiology, and depression in the medical students. Our overall aim is to use research to investigate the potential of new medical technologies in Syria and to take part in creating an evidence-based approach to rebuilding the Syrian healthcare system.

PUBLIC INTEREST STATEMENT

Our case might be of interest to a non-specialist because it provides a quick overview of Primary Granulomatous Hypophysitis PGH, which is a rare (85 reported cases in the literature) and interesting pituitary disorder. Additionally, it sheds light on the diagnostic challenges and misdiagnosis risks that accompany the diseases of bodily structures that are hard to access or high risk for biopsy.

1. Introduction

Granulomatous hypophysitis GRH is a rare inflammatory disorder affecting the pituitary gland with a sum of 85 cases reported in the literature (Joneja, Hooper, Evans, & Curtis, 2016). It is a member of a family of disorders including lymphocytic and xanthomatous hypophysitis. GRH could be either primary granulomatous hypophysitis PGH or secondary. Systemic inflammatory disorders like sarcoidosis, Wegener granulomatosis, tuberculosis, and Langerhans cell histiocytosis are accused in the etiology of secondary GRH (Hunn, Martin, Simpson, & Mclean, 2014). The two most common presenting symptoms are headaches and visual disturbances, mainly due to the hypophysitis-induced sellar compression (Su, Zhang, Yue, & Zhang, 2011). GRH is commonly misdiagnosed as a pituitary adenoma, chiefly because the definitive diagnosis can only be obtained through histopathological evaluation. Although an armament of various treatments is present, GRH is typically treated either medically with corticosteroids after doing a pituitary biopsy or surgically with transsphenoidal resection (Hunn et al., 2014). In this report, we present a patient with PGH that was first misdiagnosed as lymphocytic hypophysitis.

2. Case presentation

Our patient is a 30-year-old Caucasian female that presented to our institution for symptoms of polyuria, polydipsia, excruciating frontal headaches, recent onset of fatigue, constant feeling of cold, and visual disturbances. She was in her postpartum period P30; she delivered a female neonate one month ago. Through detailed history taking, it was found that her symptoms started 5 months ago, that is to say in her 5th month of pregnancy and has been worsening ever since, without any noticeable improvement after pregnancy. Physical examination was unrevealing except for mildly dry skin. Her medical history proved positive for autoimmune disorders; it included both autoimmune thrombocytopenic purpura and Behcet's disease. Her family history was also positive for autoimmune disorders. Her workup included a complete laboratory study, available in (Table 1 and Figure 1); an MRI of the head; and a water deprivation test. Her laboratory results and her physical symptoms led to the diagnosis of Hypothyroidism while the prolactin values were normal considering that she is in her postpartum period. Her MRI showed pituitary enlargement, suprasellar expansion, compression of the optic chiasm, and a thickened infundibulum. Her water deprivation test indicated a central Diabetes Insipidus DI. We speculated that her DI was in the context of her pituitary disease rather than a pregnancy-associated DI because it did not improve postpartum. Taking all of this into consideration, the managing medical team along with a consulted neurosurgeon postulated that the most probable etiology is lymphocytic hypophysitis. Taking into consideration that surgical resection is associated with a high risk of postsurgical hypopituitarism and that the patient was in her child bearing age, the decision was to start her on a trial of glucocorticosteroid therapy, and to treat her surgically only if she does not improve. She was started on a high dose prednisolone regimen (50 mg daily), to which she reported a noticeable improvement in her clinical symptoms, and a decrease in the size of her pituitary mass. However, her symptoms and her pituitary mass recrudesced when we tapered her steroid dose. Thus, she was scheduled for transsphenoidal transnasal surgical resection. Interestingly, postsurgical histopathological evaluation revealed an inflammatory infiltrate of macrophages, and CD68+ histiocytes, lymphocytes with a 0.7 CD4/CD8 ratio, granulomas formed by multinucleated giant cells, and necrosis. This description fits the diagnosis of granulomatous hypophysitis. Ruling out all causes of a secondary disease, primary granulomatous hypophysitis was diagnosed. The patient recovered perfectly after the surgery, but it induced a permanent hypopituitary state for which she was started on hormonal replacement therapy (Dexamethasone, Desmopressin, and Levothyroxine).

Table 1. Laboratory values

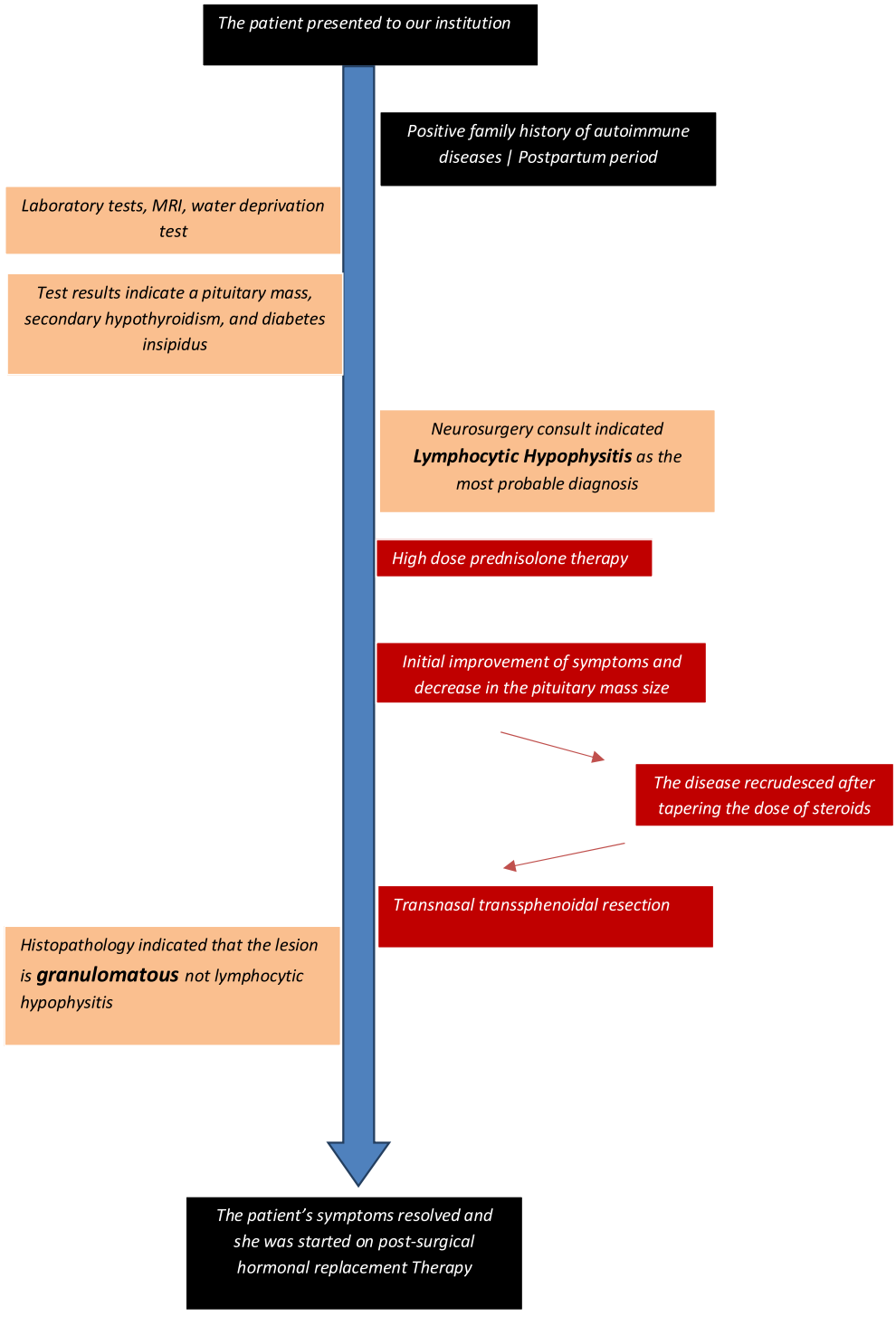
Test	Level	Reference range
Prolactin (ng/dL)	50	Up to 100
ACTH (pg/dL)	8	7–51
TSH (mU/L)	**0.09**	**0.2–4.5**
FT4 (pg/dL)	**340**	**700–1630**
Hematocrit (%)	41.5	35–45
Hemoglobin (g/dl)	14.3	M 13–18
		F 12–16
White-cell count (per mm^3)	7,600	4000–10000
Platelet count (per mm^3)	233,000	150,000–450000
Red-cell count (per mm^3)	5,060,000	M 4.5–6.2 million
		F 4–5.4 million
Mean corpuscular volume (fl)	82	78–98
Creatinine (mg/dl)	0.9	0.5–1.2
Urea (mg/dl)	23.5	5–45
C-reactive protein (mg/dl)	67	0.5–5
ALT (U/l)	29.8	5–40
Alkaline phosphatase (mg/dl)	73	40–125
Amylase (mg/dl)	77	Less than 100
Total bilirubin (mg/dl)	0.5	0.18–0.94
Erythrocyte sedimentation rate (mm/h)	15	M 0–10
		F 3–15
Glucose (mg/dl)	89	70–110
Gamma-glutamyl transferase (u/l)	23	M 10–55
		F 5–35
Cholesterol (mg/dl)	123	Less than 200
Triglycerides (mg/dl)	122	53–150

3. Discussion

Hypophysitis is a rare inflammatory disorder of the pituitary gland, with an approximate incidence of one case per 9 million people per year. Based on pathological findings, it is classified into lymphocytic, granulomatous and xanthomatous hypophysitis. While lymphocytic hypophysitis LH is the most common (397 reported cases in the literature), granulomatous hypophysitis PGH comes in the second place with 85 proven cases reported in the literature (Bhansali, Velayutham, Radotra, & Pathak, 2004; Hunn et al., 2014; Joneja et al., 2016; Su, Zhang, Yue, & Zhang, 2011). Furthermore, GRH is classified into primary and secondary disorders. Secondary causes include systemic inflammatory disorders such as sarcoidosis, Wegener granulomatosis, tuberculosis and Langerhans cell histiocytosis. Unlike LH, PGH is not associated with pregnancy nor with autoimmune diseases. However, both are similar in that they have a female predilection (Hunn et al., 2014).

Brissaud et al. first described PGH in 1908. Autoimmune diseases were reported only in 6% of the cases (Hunn et al., 2014). We present a peculiar case because our patient had a positive personal and family history of autoimmune disorders and her disease was associated with pregnancy, both of which are hallmarks of LH not PGH. There is an ongoing dispute about the caliber of differences between LH and PGH. Some authors consider that these disorders have different evolutionary mechanisms; that is to say an autoimmune mechanism in LH, and a type IV hypersensitivity mechanism in PGH (Rao et al., 2016). On the other hand, other authors consider them to be different phases of the same disease process rather than different diseases (Hunn et al., 2014; Su, et al., 2011). This is

Figure 1. Timeline.



mainly because of a myriad of clinical and radiological similarities between both diseases. This same myriad along with the association of the disease with pregnancy and the history of autoimmune diseases led to the misdiagnosis that happened at first in our case.

PGH usually presents with four sets of symptoms; hypopituitarism, hyperprolactinism, Diabetes Insipidus DI, and sellar compression symptoms. Headaches and visual changes are the most prevalent symptoms, while fever, galactorrhea and cold intolerance are the least prevalent (Su, et al., 2011). Sometimes it may present with peculiar findings such as Trigeminal Autonomic Neuralgia or Horner syndrome (Motte et al., 2017). Hyperprolactinemia is commonly associated with PGH, it could be attributed to stalk compression, or inhibition of prolactin regulation by the inflammatory process (Hunn et al., 2014; Su et al., 2011). Hypothyroidism is also reported as an accompanying finding (Hunn et al., 2014). Our patient presented initially with headaches, visual, and DI symptoms, and was later diagnosed with hypothyroidism.

PGH is a tricky diagnosis that may mimic pituitary nonfunctioning adenomas in up to 50% of the patients (Su et al., 2011). Despite some suggestive radiological and clinical features, the definitive diagnosis is histopathological (Shi et al., 2009). MRI is the most accurate radiological study for pituitary disorders and is the most used one to evaluate PGH (Su et al., 2011). Pituitary gland enlargement, marked enhancement by Gadolinium, pituitary stalk thickening and loss of posterior pituitary bright spots on T1-weighted MRI are the most common and suggestive findings. Other findings may include suprasellar extension of the pituitary gland and optic chiasm compression (Hunn et al., 2014; Su et al., 2011). Histologically, PGH is characterized by granulomas that are formed by a collection of multinucleated giant cells, histiocytes, and a number of lymphocytes and plasma cells. Lymphocytic infiltrate has been described in 62% of the cases, while necrosis has been described in 15%. The infiltrate is usually composed of somehow equal proportion of CD3+ T-cells and CD68+ histiocytes, and the CD4:CD8 ratio is <1 (Rao et al., 2016).

Autoantibodies for pituitary autoantigens APA have been described in both LH and PGH. The antigenic targets for those APAs include growth hormone, alpha-enolase, pituitary gland-specific factors 1a and 2, secretogranin II, C14orf166 and chorionic somatomammotropin. However, these APAs are not specific for hypophysitis, as an elevated level has been described in various pituitary and non-pituitary disorders like empty sella syndrome, panhypopituitarism, isolated pituitary hormone deficiencies, isolated hyperprolactinemia, eating disorders and cryptorchidism (Hunn et al., 2014; Rao et al., 2016).

Treatment of PGH is a controversial topic. Since a histopathological examination is needed for definitive diagnosis, pituitary biopsy and corticosteroid therapy should be tried as a first line, then excisional surgery–transnasal transsphenoidal–can be used in unresponsive cases, with no significant differences between both treatment modalities as shown by Hunn et al. (2014). However, pituitary biopsy is a markedly invasive procedure, which limits its practical use. Therefore, transsphenoidal transnasal surgery with intraoperative histology on frozen sections seems to provide a definitive diagnosis, eliminate the need for unnecessary glucocorticoid therapy, and treat other disorders that profoundly mimic LH and PGH like pituitary macroadenomas (Leung, Lopes, Thorner, Vance, & Laws, 2004; Su et al., 2011). On the other hand, different treatment options like immunosuppressive medication (cyclosporine, azathioprine, etc.) have been described. Moreover, Gamma Knife Surgery has been successfully used in LH and PGH and may thus present a promising alternative treatment modality. Despite the fact that the pituitary gland may recover its function after successful therapy, hypopituitarism ensues postoperatively in a large proportion of the patients. This risk can be reduced by less invasive surgeries that preserve the normal pituitary tissue (Su et al., 2011). Several reports indicate the need for long term hormone replacement therapies in more than 50% of the patients (Hunn et al., 2014; Leung et al., 2004).

4. Conclusion

The profound similarity between PGH and LH imposes a diagnostic dilemma that can only be solved by histopathological evaluation. In addition to that, the LH associated conditions like pregnancy and the history of autoimmune disorders that accompanied the disease make a contribution towards the aforementioned theory that LH and PGH are different phases of the same disease process rather than different diseases.

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Author details
Alexey Youssef[1]
E-mail: alexeyyousef1994@gmail.com
Rahaf Ali[1]
E-mail: rahaf_ahmad_ali@hotmail.com
Maya Marouf[1]
E-mail: maroudmaya96@gmail.com
[1] Faculty of Medicine, Tishreen University, MED Research Team, Lattakia, Syria.

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