Postpartum Granulomatous Hypophysitis with Sphenoid Sinus Involvement: A Case Study

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Disclosure  
The authors have no conflicts of interest to disclose.

Abbreviations  
ACTH, adrenocorticotropic hormone; ANA, antinuclear antibody; ANCA, antineutrophilic cytoplasmic antibody; IGF-1, insulin-like growth factor 1  
MRI, magnetic resonance imaging; TSH, thyroid stimulating hormone; T4, thyroxine

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ABSTRACT

Objective: To report an unusual case of granulomatous hypophysitis with sphenoid sinus involvement in a woman presenting with headaches and visual field deficits 2 weeks after a normal delivery.

Methods: We present the history, physical findings, hormonal assay results, imaging, surgical findings and pathology at presentation, and then at several times, covering 1 year of observation. We also performed a literature review on granulomatous hypophysitis.

Results: A 29 year old female presented with headache and visual disturbances 11 days postpartum. MRI revealed a sellar mass with suprasellar extension, invasion of cavernous sinuses and optic chiasm, along with sinus mucosal thickening. A subtotal resection was performed via transphenoidal route. Histology demonstrated extensive non vasculitic granulomatous tissue in pituitary and sphenoid mucosa samples. Investigation for known causes of granulomatous hypophysitis was negative. She required desmopressin and thyroxine replacement after surgery. Sequential follow up revealed spontaneous resolution of the residual mass in 5 months.

Conclusions: Unique features of this case include the simultaneous presence of granulomatous lesions in the pituitary and sphenoid sinus, its presentation in early postpartum period, as well as the spontaneous resolution of the residual granulomatous lesions in both the sphenoid sinus and sella turcica.

INTRODUCTION

Hypophysitis is an inflammatory condition of the pituitary gland that can be difficult to distinguish from other pituitary lesions. There are 3 histopathological categories of hypophysitis, namely granulomatous, lymphocytic, and xanthomatous. Granulomatous hypophysitis can be secondary to systemic inflammatory conditions, infection or extension from a neighboring
foreign body reaction. The granulomatous form has been described in the setting of tuberculosis, syphilis, Takayasu’s disease (1), Crohn’s disease (2), Wegener’s granulomatosis (3), sarcoidosis, Langerhans’ histiocytosis, rheumatoid arthritis (4) and Rathke’s cleft cyst rupture (5). The term primary granulomatous hypophysitis is reserved to those cases where the investigation fails to reveal a cause. We describe a case of granulomatous hypophysitis presenting in the early postpartum period in a 29-year-old female.

CASE REPORT

History and Physical Exam. A 29-year-old Caucasian female, presented to the hospital 11 days postpartum with worsening headaches and progressive visual loss. Labor had been induced at 37 weeks because of preeclampsia. She developed headache 3 weeks before delivery thought to be her usual migraine. The pain was persistent, severe, and not relieved by acetaminophen or non-steroidal anti-inflammatory drugs. She noted “blurry spots” obstructing her temporal visual fields. Despite multiple attempts at breastfeeding, she was unable to lactate. She denied fever, fatigue, symptoms of thyroid or adrenal insufficiency, polydipsia or polyuria. She had a history of migraine and chronic sinusitis since adolescence and had 3-4 presumptive episodes of acute sinusitis per year but had no formal investigation. There was family history of endocrine autoimmunity.

She was afebrile and normotensive. Her visual fields on confrontation revealed bitemporal hemianopsia more pronounced on the left. The optic discs were sharp on fundoscopic exam. Cranial nerve function was intact with normal extra-ocular motions and she had no neurological deficits.

Preoperative Pituitary Function. Serum prolactin was 8.8 ng/dl. She had no evidence of adrenal insufficiency, but TSH was slightly reduced at 0.33 μIU/ml (reference range 0.4-4) and free thyroxine was 0.89 ng/dl (0.7-1.8 ng/dl) (Table 1).
**Pituitary Imaging.** MRI revealed a 2 x 1.5 x 2.8 cm heterogenously enhancing sellar and suprasellar mass compressing the optic chiasm with possible invasion of the cavernous sinus (Fig. 1). There was enhancement of the adjacent dura mater as seen in meningiomas (6). There was mucosal thickening and dense material seen within the sphenoid sinus suggesting chronic sinusitis.

**Operative findings.** She underwent urgent transsphenoidal resection of the pituitary mass for the purpose of decompression of the optic chiasm. The sphenoid sinus was filled with a thick amorphous, mucoid substance which was aspirated and sent for microbiology and pathology studies. No evident defect on the sellar floor or communication between the sella and sphenoidal sinus was detected during surgery. The intrasellar lesion was fibrous and adherent to the dura mater. Frozen section examination revealed a granulomatous process. A subtotal resection was performed.

**Pathology.** The intrasellar material consisted of granulomatous inflammatory tissue (Fig. 2 A, B) with abundant necrosis. The sphenoid sinus mucosa was thickened displaying the same granulomatous process with less extensive findings (Fig. 2 C). There was no evidence of vasculitis.

**Microbiology and Infectious Disease Markers.** Staining and culture of the surgical specimens for fungi, tuberculosis and bacteria were negative. A tuberculin skin test was negative. Serology for bartonella, histoplasmosis, blastomyccosis, syphilis, and HIV were also negative.

**Markers of Inflammation and Autoimmunity.** Thyroid peroxidase antibodies were undetectable. Pituitary antibodies and serum IgE were not measured given the histological diagnosis of a non-eosinophilic, non-vasculitic granulomatous process. Serum levels of angiotensin converting enzyme were normal, whereas cytoplasmic ANCA, perinuclear ANCA, and ANA panel were negative as well. Histone antibody, SSA and SSB antibodies, RNP antibody, myeloperoxidase antibody, and anti PR3 were all undetectable. Complement C3 was
166 (71-171 mg/dl); complement C4 was 39 (13-39 mg/dl); and double stranded DNA antibody titer was 1(0-9).

**Clinical Course.** One day postoperatively, the MRI showed a reduction in the size of the intrasellar mass with significant decompression of the optic chiasm and a substantial amount of abnormal tissue occupying the sella (Fig. 3 A). She developed postoperative diabetes insipidus that required desmopressin. She received hydrocortisone pre- intra- and postoperatively with a rapid taper and was discharged 6 days postoperatively on 15 mg of hydrocortisone daily. The TSH level fell further and she was begun on levothyroxine.

Her visual fields normalized completely after surgery. The headaches decreased in intensity and frequency. Three months postoperatively hydrocortisone was held for 48 hours and an early AM serum cortisol and simultaneous ACTH were measured at 14 µg/dl and 16 pg/ml respectively (Table 1), suggesting recovery of her adrenal axis. Hydrocortisone was discontinued and adrenal function remained normal (Table 1). At her last visit, 14 months postoperatively, levothyroxine was discontinued but she still needed desmopressin, while IGF-1 levels continued to decrease. Menses remain regular.

Five months postpartum, MRI showed resolution of the residual lesion (Fig 3 B). One year postpartum, MRI remained unchanged without evidence of disease progression.

**DISCUSSION**

Primary granulomatous hypophysitis was first described by Simmonds in 1917 who reviewed 2000 pituitary glands at autopsy. He reported 4 cases with granulomatous pituitary infiltration unrelated to tuberculosis, syphilis, or other forms of granulomatous disease. The first biopsy in a living case was reported in 1980 in a 50 year old man with unilateral ophthalmoplegia (7). Approximately 45 cases have since been reported. The estimated annual
incidence is 1 in 10 million (8), but this may be an underestimation as more cases are likely to be incidentally described with increase use of imaging.

We feel our case represents a primary granulomatous process given the absence of any associated systemic or infectious granulomatosis. We cannot determine whether the lesion was primarily hypophyseal or due to local extension from the adjoining sphenoidal sinusitis.

Headache, nausea, and vomiting are commonly reported in granulomatous hypophysitis (9). Other typical findings include diabetes insipidus, hyperprolactinemia, anterior pituitary dysfunction, visual impairment, cranial nerve palsy, and aseptic meningitis with CSF lymphocytosis (10,11).

There are no pathognomonic MRI findings specific for hypophysitis. Suprasellar or hypothalamic extension, loss of posterior pituitary bright spot, and a thickened stalk have all been reported. The presence of dural enhancement or a “dural tail” as seen in our case (Fig. 1A) was thought to be specific to meningiomas (12), but has since been reported in pituitary adenomas, hypophysitis (13), and other mass intracranial lesions. Sphenoid sinus mucosal thickening (fig 1-A) has been described on imaging in both granulomatous and lymphocytic hypophysitis (14,15), but to the best of our knowledge, concomitant primary granulomatous hypophysitis and sinusitis have not been documented histologically. The coexistence of both conditions, with identical histology in our case suggests they are expression of the same process.

Asymptomatic physiologic pituitary hypertrophy can occur during female adolescence (16) and pregnancy (17) and must be considered when an individual presents with features suggesting a pituitary mass to avoid unnecessary surgery (18). If “physiologic pituitary hyperplasia of pregnancy” becomes symptomatic, one must consider the possibility of an underlying pituitary mass.

Our literature review revealed only 5 cases of granulomatous hypophysitis associated with pregnancy. De Bruin et al. (2) reported a case of granulomatous hypophysitis associated
with active Crohn’s disease; Mehndiratta et al. (19) reported a woman with visual disturbances at 6 months gestation but the case was diagnosed two years postpartum; and Tashiro et al. (20) reported 3 cases in a review of histologic samples.

The etiology of primary hypophysitis appears to be autoimmune but the exact pathophysiology remains unknown. An autoimmune basis has been demonstrated in lymphocytic hypophysitis, but this is not as clear in the granulomatous type. Novel autoantigens such as chorionic somatomamotrophin and c14orf166 (14) appear as candidates but their validation awaits confirmation.

Histopathology in granulomatous hypophysitis usually reveals multinucleated giant cells, fibrosis, non-caseating granulomas, and varying degrees of lymphocytic and plasma cell infiltration. Some cases demonstrate findings consistent with both granulomatous and lymphocytic hypophysitis, suggesting that these two conditions might represent different stages of the same disease (11,20).

The diagnosis of primary hypophysitis is difficult to make given the lack of specific clinical and radiologic findings, except for lymphocytic hypophysitis which occurs commonly in association with pregnancy and other autoimmune disease. Inflammatory lesions may be responsive to medical management or observation (11,13). Therapy with glucocorticoids may be considered in presumptive cases of primary hypophysitis, especially those demonstrating progression. In our case, glucocorticoid therapy was not considered in view of the rapid postoperative regression of the granulomatous process.

CONCLUSION

Granulomatous hypophysitis is a rare condition difficult to diagnose on clinical grounds alone. Histopathology remains the only means of obtaining a definitive diagnosis. Sphenoid sinus thickening has been reported in the past but we have determined that a non-vasculitic granulomatous lesion within the sinus mucosa can occur in the setting of primary
granulomatous hypophysitis. Whether the sinus lesion extended superiorly into the pituitary or the pituitary lesion traversed inferiorly into the sphenoid sinus is open to speculation. Our workup did not demonstrate any autoimmune or systemic cause which may explain the spontaneous regression of the lesions. Whether the surgical decompression played a role in the rapid resolution is matter of speculation. Restoration of pituitary function after surgery has been described in both, lymphocytic and granulomatous types (1,2). Most reported cases received pharmacologic dose corticosteroids, complete surgical resection, or both. Regression of inflammatory tissue and improvement of pituitary function with glucocorticoids is well described in lymphocytic hypophysitis. The role of the either of the above treatment modalities in improvement of pituitary function in granulomatous hypophysitis is controversial. Our patient had spontaneous regression of the lesion and improvement in pituitary function with surgical decompression alone. This case demonstrates that complete resolution of granulomatous hypophysitis can occur in a postpartum patient without the use of glucocorticoids.
Table 1 Pituitary Hormone Functional Measurements

<table>
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<tr>
<th>Measurement</th>
<th>Preop</th>
<th>3 months postop</th>
<th>5 months postop</th>
<th>11 months postop</th>
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<tr>
<td>TSH (0.4-4 mlU/ml)</td>
<td>0.33</td>
<td>0.65</td>
<td>0.16</td>
<td>0.30</td>
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<tr>
<td>Free T4 (0.7-1.8 ng/dl)</td>
<td>0.89</td>
<td>0.51</td>
<td>0.99</td>
<td>0.95</td>
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<td>Prolactin (4.8-23.3 ng/ml)</td>
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<td>14.3</td>
<td></td>
<td>6.8</td>
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<tr>
<td>A.M. Cortisol (6.2-19.4 µg/dl)</td>
<td>14.1</td>
<td>8.8</td>
<td>10</td>
<td>7.9</td>
</tr>
<tr>
<td>ACTH (6-48 pg/ml)</td>
<td>22</td>
<td>16</td>
<td>28</td>
<td>24</td>
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<tr>
<td>IGF-1 (117-329 ng/ml)</td>
<td>190</td>
<td>88</td>
<td></td>
<td>85</td>
</tr>
</tbody>
</table>

Anterior pituitary functional testing. A.M. Cortisol and ACTH levels were measured without glucocorticoid replacement. Levothyroxine replacement was initiated 3 months postoperatively.

Abbreviations: TSH, thyroid stimulating hormone; T4, thyroxine; ACTH, adrenocorticotropic hormone; IGF-1, insulin-like growth factor-1.
Fig 1. Preoperative gadolinium enhanced magnetic resonance imaging. Invasive heterogeneously enhancing sellar lesion with optic chiasm compression and cavernous sinus invasion. Note the enhancing adjacent duramater with dural tail (short arrow). Of particular note, is the presence extensive sinus disease (long arrow).
**Fig 2. Pituitary and Sinus Histology.**

(A) Pituitary lesion under low power light microscopy displaying dense lymphocytic aggregation around an area of necrosis (original magnification 4X).

(B) Pituitary lesion displaying necrotizing granulomatous tissue with abundant fibrosis, and plasma cells (arrow) (original magnification 20X).

(C) Sphenoid sinus mucosa displaying giant cell granuloma (original magnification 40X).

All of the above were stained using hematoxylin-eosin.
Fig. 3 Magnetic resonance imaging following transsphenoidal decompression.

(A) After transsphenoidal debulking, there is resolution of optic chiasm compression (short arrow). Dense material persists adhered to cavernous sinuses. Sphenoid sinus is distorted by surgery but there appears to be residual mucoid material and thickening of the mucosa.

(B) Five months after surgery, without further specific treatment, the sella is free of the residual material suggesting virtual resolution.
REFERENCE LIST


