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Xanthomatous hypophysitis associated with autoimmune disease in an elderly patient: A rare case report

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Abstract

Background: Xanthomatous hypophysitis (XH) is an extremely rare form of primary hypophysitis characterized by infiltration of the pituitary gland by mixed types of inflammatory cells, including foamy cells, plasma cells, and small mature lymphocytes. XH manifests as varying degrees of hypopituitarism. Although several previous reports have denied a possible contribution of autoimmune mechanism, the exact pathogenesis of XH remains unclear.

Case Description: We describe the case of a 72-year-old woman with a history of rheumatoid arthritis and Sjögren's syndrome who presented with panhypopituitarism and diabetes insipidus. At the time of her visit, she also experienced relapsed rheumatoid arthritis and Sjögren's syndrome, manifesting as arthralgia. Magnetic resonance imaging (MRI) showed a multicystic mass in the sellar and suprasellar regions. In the course of steroid replacement therapy for hypocortisolism, the patient's arthralgia diminished, and MRI revealed shrinkage of the mass. XH was diagnosed histologically following a transsphenoidal endoscopic biopsy, and it was the oldest case of XH.

Conclusion: To the best of our knowledge, this patient is the oldest of reported patients diagnosed with XH. Steroid therapy may be effective to XH temporarily. XH should be considered when diagnosing pituitary cystic lesions in elderly patients with autoimmune disease.

Key Words: Autoimmune disease, hypopituitarism, xanthomatous hypophysitis

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INTRODUCTION

Primary hypophysitis is an inflammation of the pituitary gland that is histologically characterized by the focal or diffuse infiltration of inflammatory cells and destruction of the pituitary gland, resulting in varying degrees of hypopituitarism. Primary hypophysitis has been classified into three distinct histological subtypes: Lymphocytic, granulomatous, and xanthomatous hypophysitis (XH).[6,7] Although XH has been recently described in several studies, it is the rarest of these three subtypes. Folkerth *et al.* first reported three cases of XH in 1998, and a review of previous reports of XH shows that this disease has a high prevalence in young women; however, its pathogenesis, etiology, epidemiology, natural history, and prognosis remain unexplored.

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We describe the case of an elderly woman with a history of rheumatoid arthritis and Sjögren's syndrome who presented with hypopituitarism and diabetes insipidus (DI) and was histologically diagnosed with XH.

CASE REPORT

A 72-year-old woman had experienced polydipsia, polyuria, fatigue, low-grade fever, and arthralgia for several months before visiting our department. Her medical history included rheumatoid arthritis and Sjögren's syndrome. Six years prior to her visit, she was treated for 6 months with 5 mg of prednisolone per day, and her arthralgia diminished. Her family history was unremarkable. Results of a physical examination were normal except for the presence of arthralgia. Endocrine laboratory testing revealed a moderately elevated serum prolactin (PRL) level of 95.2 ng/mL (normal range: 6.1–30.5 ng/mL), suggesting a compression of the pituitary stalk. Test results of other hormones secreted from the anterior lobe of the pituitary gland were as follows: Thyroid-stimulating hormone (TSH): 0.54 μU/mL (normal range: 0.35–4.94 μU/mL); free T4: 1.25 ng/dL (normal range: 0.70–1.48 ng/dL); adrenocorticotrophic hormone (ACTH): 15.2 pg/mL (normal range: 7.2–63.3 pg/mL); cortisol: 3.6 μg/dL (normal range: 3.8–18.4 μg/dL); growth hormone (GH): 0.30 ng/mL (normal range: 0.28–1.64 ng/mL); luteinizing hormone: 0.42 mIU/mL; and follicle stimulating hormone: 3.28 mIU/mL. Thyrotropin-releasing hormone stimulation resulted in an appropriate increase in PRL level to 132.6 ng/mL after 15 min and in TSH level to 10.11 μU/mL as peak values. An insulin-induced hypoglycemia test resulted in poor responses of both GH and cortisol levels (peak values: 0.79 ng/mL and 3.2 μg/dL, respectively). These results indicated hypopituitarism affecting ACTH, gonadotropin, and GH axes. Based on the results of hypertonic saline infusion test, the patient was diagnosed with the central type of DI. Hypocortisolism was treated with 20 mg of hydrocortisone for 2 months. The dose was then gradually decreased to 5 mg. About 0.5 μg of 1-deamino-8-D-arginine vasopressin (DDAVP) per day was taken for DI as hormone replacement therapy. The patient showed prompt recovery from her symptoms, including arthralgia.

Magnetic resonance imaging (MRI) showed a thickened pituitary stalk with a multicystic lesion extending toward the hypothalamus and no evidence of posterior lobe hyperintensity on T1-weighted imaging [Figure 1a-c and e]. A series of MRI recorded during the following 2 months revealed a gradual decrease in the lesion size without diminishment [Figure 1d-f]. To make a definitive diagnosis for further treatment, neurosurgical exploration was performed via transsphenoidal and tuberculum sellae approach with an endoscope.

Endoscopic exploration clearly displayed a soft yellowish lesion along with the pituitary stalk [Figure 2], and subtotal resection was performed. Histological analysis

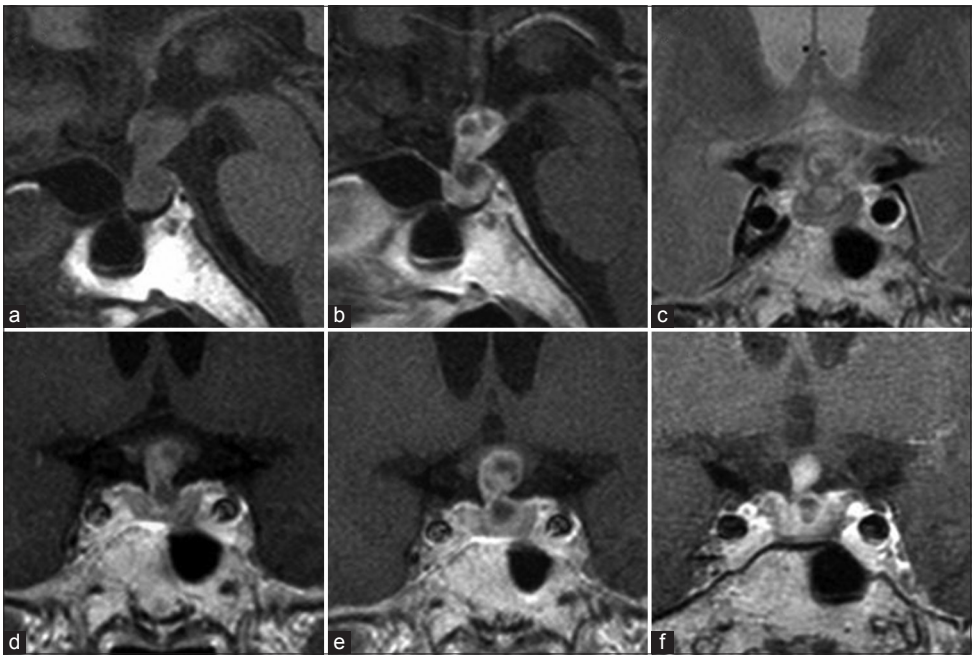

Figure 1: Magnetic resonance imaging from onset to surgery. Sagittal section of T1-weighted images on admission showed thickened pituitary and stalk extending toward the hypothalamus and no evidence of posterior lobe hyperintensity (a). Sagittal and coronal section of gadolinium-enhanced T1-weighted image (b and e) and coronal section of T2-weighted image (c) at the time of her visit showed the intrasellar and suprasellar multicystic lesion with heterogeneous contrast. Coronal section of gadolinium-enhanced T1-weighted image showed the lesion shrinking (f) after transient expanding on admission (e) compared to 1 month ago (d)

of the surgical specimen showed infiltration by foamy histiocytes, plasma cells, and mature lymphocytes. The infiltrating foamy cells were immunopositive for the macrophage marker CD68 and were immunonegative for CD1a and S-100 protein [Figure 3]. The majority of mature lymphocytes were immunopositive for CD3. There was no histological evidence of a pituitary adenoma, Rathke's cleft cyst, or germinoma.

The patient was discharged without any neurological complications. Postoperative pituitary function was unchanged compared to the preoperative state. The patient continued to take 5 mg of hydrocortisone and 0.5 μg of DDAVP per day. Postoperative MRI showed no progression of the lesion [Figure 4].

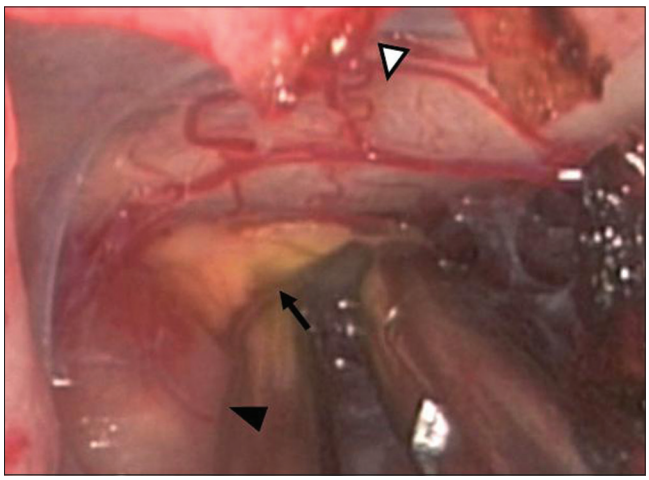

Figure 2: Intraoperative picture of the transsphenoidal and tuberculum sellae endoscopic surgery. Intraoperative findings revealed a soft yellowish cystic lesion (→) along the pituitary stalk (▲) and the optic chiasma (Δ)

DISCUSSION

XH is the rarest form of primary hypophysitis and is histologically characterized by the diffuse infiltration of the pituitary gland by mixed inflammatory cells, including foamy cells, plasma cells, small mature lymphocytes, and multi-nucleated giant cells.[5] The foamy cells are strongly immunoreactive for the macrophage marker CD68 and nonimmunoreactive for S-100 protein and CD1a. Histological analysis is considered the sole method for distinguishing between several different potential diagnoses, including lymphocytic and granulomatous hypophysitis, Erdheim–Chester disease, Langerhans cell histiocytosis, Rosai–Dorfman disease, and plasma cell granuloma.[3,4,11] In the present case, a final diagnosis of XH was made following a transsphenoidal biopsy. Histological analysis ruled out lymphocytic and granulomatous hypophysitis, as well as other brain tumors arising at the sellar and suprasellar regions such as craniopharyngioma, malignant lymphoma, germinoma, and metastatic tumors.

Transsphenoidal surgery is a useful diagnostic and therapeutic tool for the clinical entities discussed here and should be performed in patients whose lesions show progression of clinical or neuroradiological findings. Indeed, surgical intervention and histological verification have been performed in all of the 19 previously reported cases of XH.[1-5,7-13] Although the etiology of XH and effects of medical treatment remain unclear, patients with XH typically show acceptable outcomes. Intraoperative pathological examination can be helpful in confirming diagnosis and preventing unnecessary damage to the potentially viable pituitary gland and stalk.

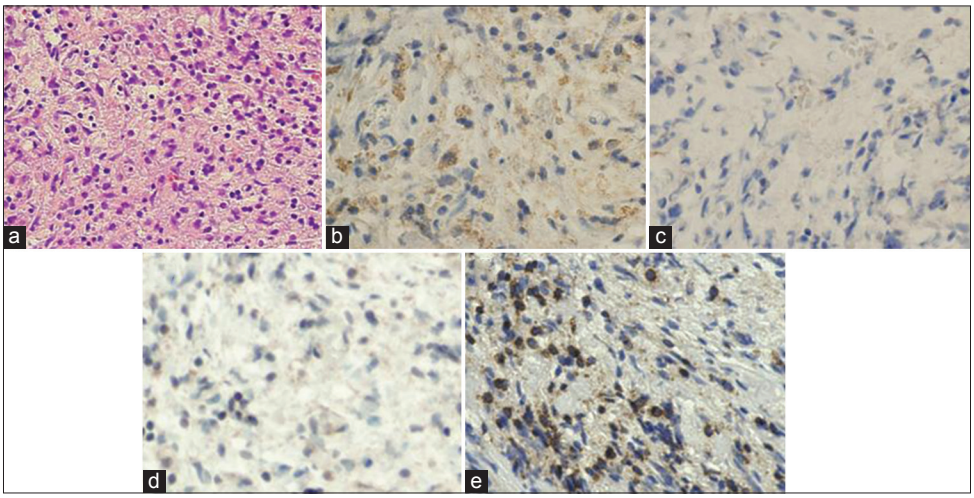

Figure 3: Pathological findings of the lesion. The cystic lesion was histologically characterized by infiltration of the anterior pituitary by foamy histiocytes, plasma cells, and lymphocytes (a, ×200). The foamy cells were immunopositive for the macrophage marker CD68 (b, ×200) and immunonegative for CD1a (c, ×200) and S-100 protein (d, ×200). The majority of lymphocytes are immunopositive for CD3 (e, ×200). There was no evidence of pituitary adenoma or granuloma or necrosis

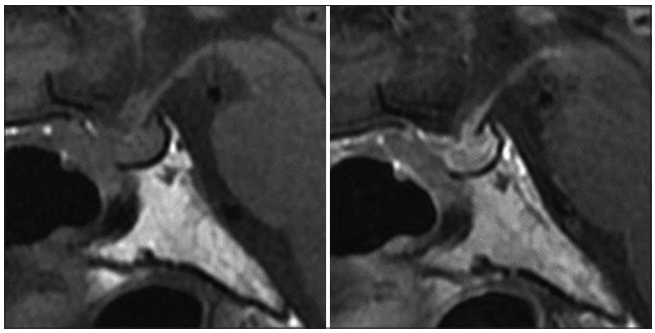

Figure 4: Magnetic resonance imaging after surgery. The postoperative series of magnetic resonance imaging 1 year after the surgery showed no progression of the lesion

Steroid therapy has been reported to temporarily relieve inflammation in some patients with primary hypophysitis, particularly lymphocytic hypophysitis, which is believed to arise from an autoimmune mechanism. Gutenberg *et al.* reported that one patient with XH who was treated with methylprednisolone did not show any improvement.[7] Conversely, Joung *et al.* reported that MRI performed after methylprednisolone pulse therapy showed marked reduction of a recurrent lesion that had been identified as XH based on histological findings after initial surgical resection.[10] Their results suggested that high-dose glucocorticoid administration may be an effective treatment option. Deodhare *et al.* observed that corticosteroid replacement resulted in temporary shrinkage of an XH lesion; however, the lesion returned after discontinuation of the therapy.[4] Overall, we believe that the effectiveness of steroid therapy remains controversial.

Aste *et al.* reported a case of XH with ulcerative colitis[1] and Joung *et al.* also reported a case of XH with Hashimoto's thyroiditis.[10] In addition to these associations of autoimmune disease with XH, positive responses to glucocorticoid therapy in several XH cases suggest that XH may involve an autoimmune mechanism.[4,10] Microscopic examination showed infiltration by inflammatory cells including large numbers of foamy histiocytes mixed with small, round lymphocytes and plasma cells. The majority of T-lymphocytes were CD8 immunopositive.[4] These results suggest that a delayed type of hypersensitivity reaction may contribute to the development of XH.

Our patient had a history of rheumatoid arthritis and Sjögren's syndrome and had received steroid therapy for 6 months. When she presented with initial endocrinological symptoms indicative of XH, steroid therapy was suspended and arthralgia attributed to rheumatoid arthritis returned. However, after initiating hormone replacement therapy, the patient's symptoms rapidly improved, and MRI revealed gradual shrinkage of the suprasellar lesion during the 2 months after onset. Although there are limited data to support an autoimmune etiology, we speculate that autoimmune disease may not only be associated with the development of XH, but may also reflect its activity.

XH has been shown to be highly prevalent in young women. The mean age of clinical onset among previously reported cases is 37.4 ± 14.8 years. Our patient, a 72-year-old female, is the oldest of all previously reported cases. If an autoimmune mechanism contributes to the development of XH, as described above, the age of XH onset may correspond to that of the associated autoimmune disease. In support of this hypothesis, the XH patients described above with ulcerative colitis and Hashimoto's thyroiditis were 31- and 36-year-old, respectively, near the peak ages of onset for ulcerative colitis (20–30 years) and Hashimoto's thyroiditis (35–55 years).[1,10] Our patient developed rheumatoid arthritis at 66-year-old, which is within the peak age range of rheumatoid arthritis onset (50–75 years). Sjögren's syndrome is often associated with rheumatoid arthritis. Thus, XH may arise in elderly patients if there is an associated autoimmune disease that contributes to its development. If MRI in elderly patients with hypopituitarism shows cystic lesions along the pituitary stalk, XH should be taken into consideration as a potential diagnosis.

CONCLUSION

XH occurs less frequently than the other two types of primary hypophysitis. Similar to lymphocytic hypophysitis, XH may be associated with autoimmune diseases. If cystic lesions along the pituitary stalk are detected in elderly patients with hypopituitarism and autoimmune disease such as rheumatoid arthritis, XH should be considered as a possible diagnosis.

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Conflicts of interest
There are no conflicts of interest.

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