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DIFFICULT CASE

Lymphocytic Hypophysitis

Late Recurrence Following Successful Transsphenoidal Surgery

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Lymphocytic hypophysitis (LH) is an inflammatory disease of the anterior pituitary. The varying clinical presentation and the short-term outcome of LH have been extensively described in several case reports or small cohort studies. However, little is known about the long-term outcome of this disease. It is currently believed that if left untreated it may run a self-limited course followed by full resolution of the mass with or without persisting pituitary failure. We describe a 29-yr-old female who presented with secondary amenorrhea, headaches, visual defects, and a pituitary mass, which was removed by transsphenoidal surgery. Histology was consistent with the diagnosis of LH. Following surgery the patient demonstrated a gradual recovery of gonadotroph function with restoration of menses and a successful pregnancy. However, 3 yr after delivery and 6 yr following her initial presentation she developed amenorrhea, headaches, and a pituitary mass. Institution of steroid therapy resulted in resolution of the pituitary mass. In summary, this case illustrates that similarly to many other disorders of autoimmune origin LH may run a fluctuating course and late recurrence is possible even after the successful removal of the inflammatory mass, thus necessitating long-term follow-up of these patients.

Key Words: Recurrent hypophysitis.

Introduction

Lymphocytic hypophysitis (LH) is an inflammatory disease of the anterior pituitary gland first described by Goudie and Pinkerton in 1962 *(1)*; since then, more than 120 cases have been reported. Pathologically, LH is characterized by infiltration of inflammatory cells into the pituitary gland *(2)*. Although the etiology of LH remains unknown, considerable evidence exists for an autoimmune pathogenesis *(3–5)*. The disease affects mainly women, most commonly during the peripartum period, with a female to male ratio of approximately 8.5:1. Half of the cases that develop in association with pregnancy occur during late pregnancy or within 18 mo postpartum. One possible mechanism is that induction of the autoimmune process is initiated by an increased amount of antigen being produced by the hyperplastic pituitary of pregnant women. Alternatively, as the autoantigen associated with LH has been identified recently to be α-enolase *(6,7)*, its expression in placenta may provide a link between LH and pregnancy.

The varying clinical presentation of LH has been reported in many case reports and cohort studies *(8–12)*. Clinically, the disorder often mimics pituitary adenoma. Manifestations that are more commonly encountered in LH than in adenomas include headaches and diabetes insipidus *(9)*. Hormonal abnormalities associated with LH include mild to moderate hyperprolactinemia and varying degrees of pituitary failure. Corticotroph and thyrotroph cells are most commonly affected *(13–15)*. The underlying mechanism that determines the pattern of pituitary hormone deficiency in LH is not well understood *(16–18)*. Whereas radiologic examination shows a pituitary and/or suprasellar mass reminiscent of a pituitary macroadenoma, certain features such us pituitary stalk enlargement and tongue-shaped extension of the lesion along the basal hypothalamus are suggestive of LH *(8,19)*.

The aim of diagnosing LH on clinical and radiological grounds is that many of these patients could avoid unnecessary surgery. It is currently believed that LH even, if left untreated, may run a self-limited course followed by full resolution of the mass with or without persisting pituitary failure *(2,20)*. This fact provides grounds for a watchful waiting strategy with appropriate hormone replacement therapy in the absence of significant pressure effects. When pressure effects prevail, most authors advocate transsphenoidal surgery, which is considered both diagnostic and therapeu-

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tic *(12,21,22)*. Alternatively, a course of steroids may be administered *(8,22–24)*; however, a beneficial response is unpredictable.

Although the short-term outcome of surgically or non-surgically treated LH has been extensively described, little is known about the long-term outcome of this disease. So far no recurrences have been reported following surgery for LH. It should be noted, however, that long-term follow-up of surgically treated LH has rarely been reported. Herein, we report a case of LH that recurred 6 yr after successful transsphenoidal surgery.

Case Presentation

A 29-yr-old female presented with a 2-yr history of secondary amenorrhea, headache for the last 3 mo, and a 2 cm pituitary mass on CT scan. She was first seen by a gynecologist who noted mild hyperprolactinemia and prescribed bromocriptine, which resulted in normalization of prolactin levels without restoration of menses. A CT scan showed a pituitary mass and the patient was referred to our clinic for further evaluation. Medical history showed that she had her last delivery 8 yr ago and a miscarriage 5 yr ago. No symptoms suggestive of diabetes insipidus were present. Physical examination was unremarkable. Visual field test showed superior bitemporal quadrantic defects. Routine chemistries were normal. Baseline hormonal investigations showed mild hyperprolactinemia (PRL 28.2 ng/mL) and secondary hypogonadism (FSH: 2.1 mU/mL, LH: <1 mU/mL); thyroid function tests were within the normal range (T3: 161 ng/dL; T4: 7.8 μg/dL; TSH: 0.06 μU/mL), basal GH was 2.4 ng/mL, morning cortisol 14.7 μg/dL and ACTH 26 pg/mL. MRI of the sella showed a pituitary mass (2 × 1.5 × 1.2 cm in diameter) impinging on the optic chiasm (Fig. 1). Although the presence of a thickened pituitary stalk raised the possibility of an infiltrative lesion, because of the impairment of the visual fields she underwent transsphenoidal surgery.

For histology and immunohistochemistry, 4-mm-thick sections cut from formalin fixed-paraffin embedded tissue samples were used. For immunohistochemistry, the standard ABC technique was applied. Primary antisera were directed toward GH, PRL, ACTH, β-TSH, β-FSH, β-LH, and α-LH (α-SU). Microscopic examination revealed a diffuse inflammatory infiltrate composed mainly of lymphocytes forming occasional lymphoid follicles, some plasma cells, and a few neutrophils, establishing the diagnosis of lymphocytic hypophysitis (Fig. 2). The parenchyma showed severe destruction of the acinar architecture with focally massive fibrosis and hyalinization. Immunohistochemistry for LCA confirmed the presence of lymphocytes, whereas a few amounts of histiocytes were demonstrated by CD-68. Giant cells were not present. Remnants of acini exhibited immunoreactivity toward GH, PRL, ACTH, β-TSH, β-FSH, β-LH and α-SU.

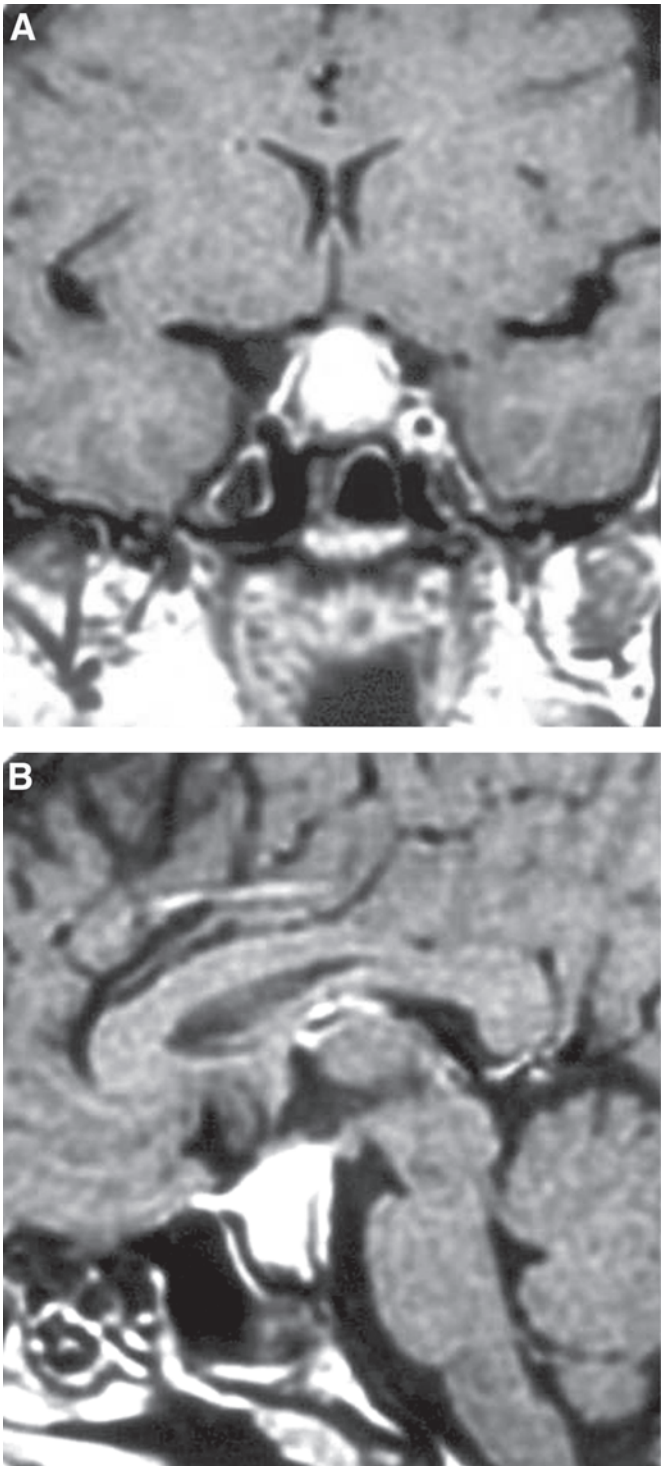

Fig. 1. Coronal gadolinium-enhanced T1 MRI. Demonstration of a heterogeneous lesion 2 × 1.5 × 1.2 cm in diameter impinging on the optic chiasm.

Postoperatively she developed symptoms suggestive of diabetes insipidus (DI) requiring desmopressin supplementation. She had normal prolactin levels (12 ng/mL) and thyroid function tests (T3: 121 ng/dL; T4: 10.8 μg/dL; TSH: 0.9 μU/mL), but the secondary amenorrhea persisted. A glu-

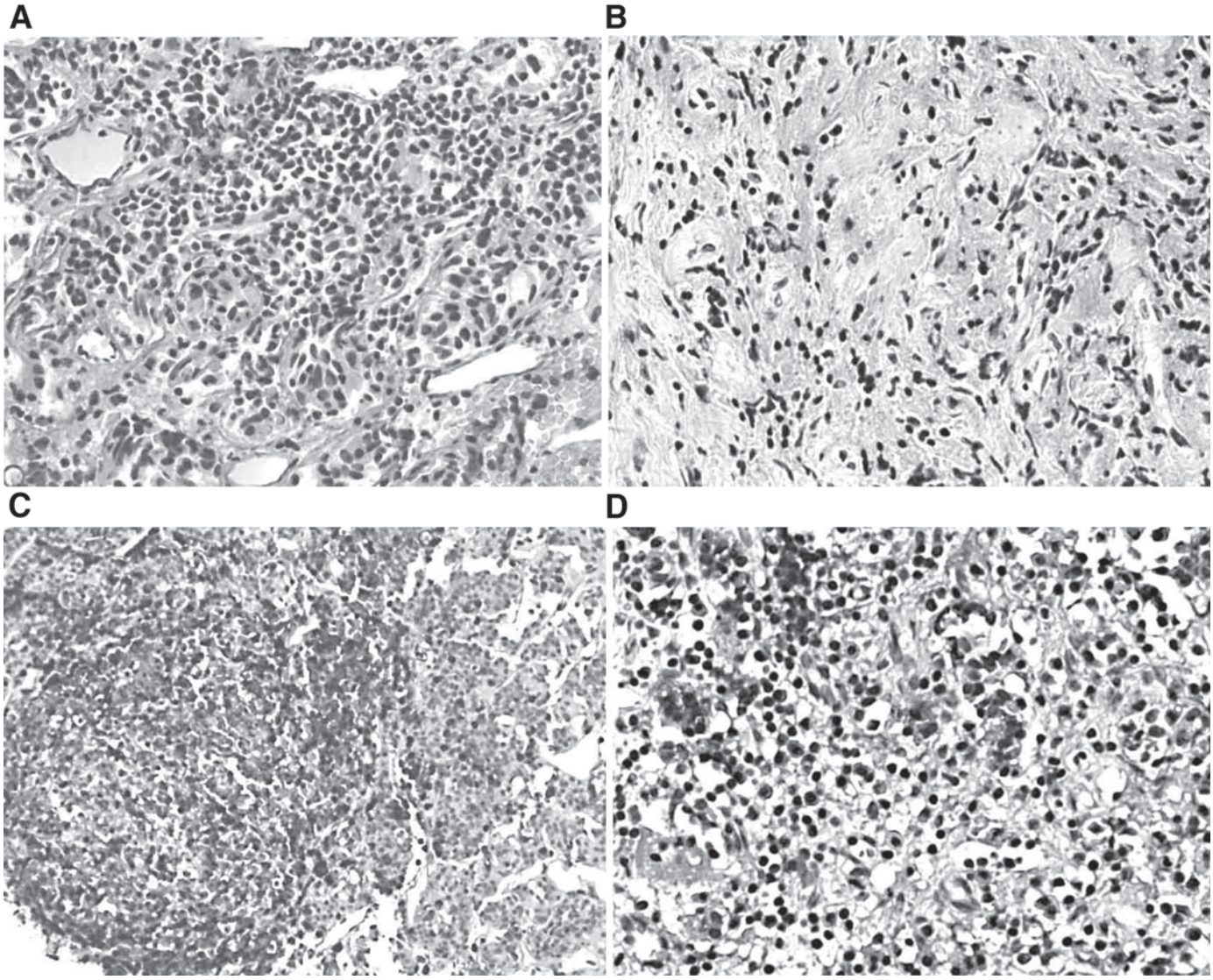

Fig. 2. (**A**) Diffuse inflammatory infiltration of the adenohypophysial parenchyma mostly composed of lymphocytes. A few acini contain pituitary cells with dark nuclei and eosinophilic cytoplasm. (**B**) Scattered inflammatory and isolated adenohypophysial cells embedded in a fibrosing stroma (H&E 80×). (**C**) Infiltration of the anterior pituitary by lymphocytes immunoreactive for LCA, with lymphoid follicle formation at the left side of the picture (ABC–LCA 80×). (**D**) Remnants of adenohypophysial cells immunoreactive for α-SU (ABC 80×).

Table 1
Results of Glucagon Test in the Immediate Post-Operative Period

	0	30 min	60 min	90 min	120 min	150 min	180 min
Glucose (mg/dL)	77	145	163	117	88	75	71
Cortisol (μg/dL)	15.7	12.6	9.9	10.4	15.9	20.1	20.2
GH (ng/mL)	1	0.7	1.1	0.9	0.7	0.8	0.9

cagon test was performed that showed an appropriate rise in cortisol but a subnormal GH response (Table 1). A MRI performed 2 mo postoperatively showed no residual pathologic tissue (Fig. 3). Visual fields were normal. Pituitary function gradually resumed. One year following transsphenoidal surgery regular menses were restored. Two years postoperatively desmopressin was discontinued on the basis of a normal water deprivation test and shortly after, she became

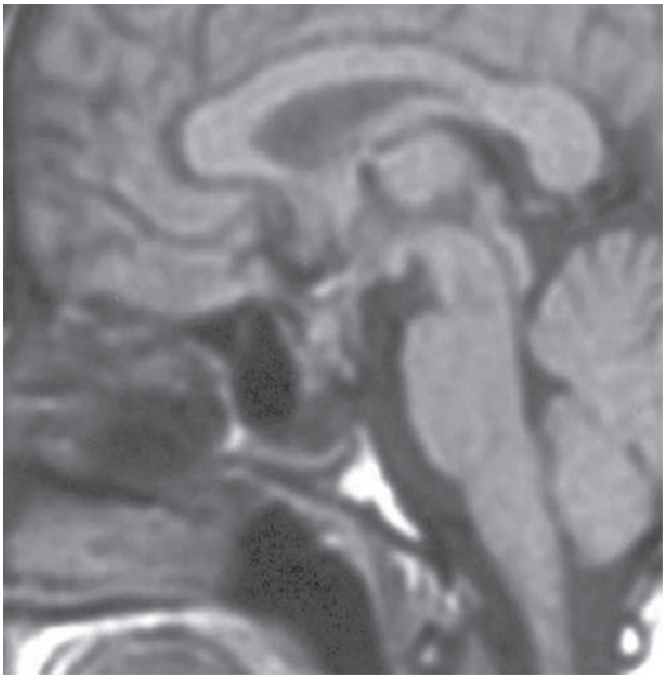

Fig. 3. Sagittal gadolinium-enhanced MRI performed 2-mo postoperatively showing no residual pathologic tissue.

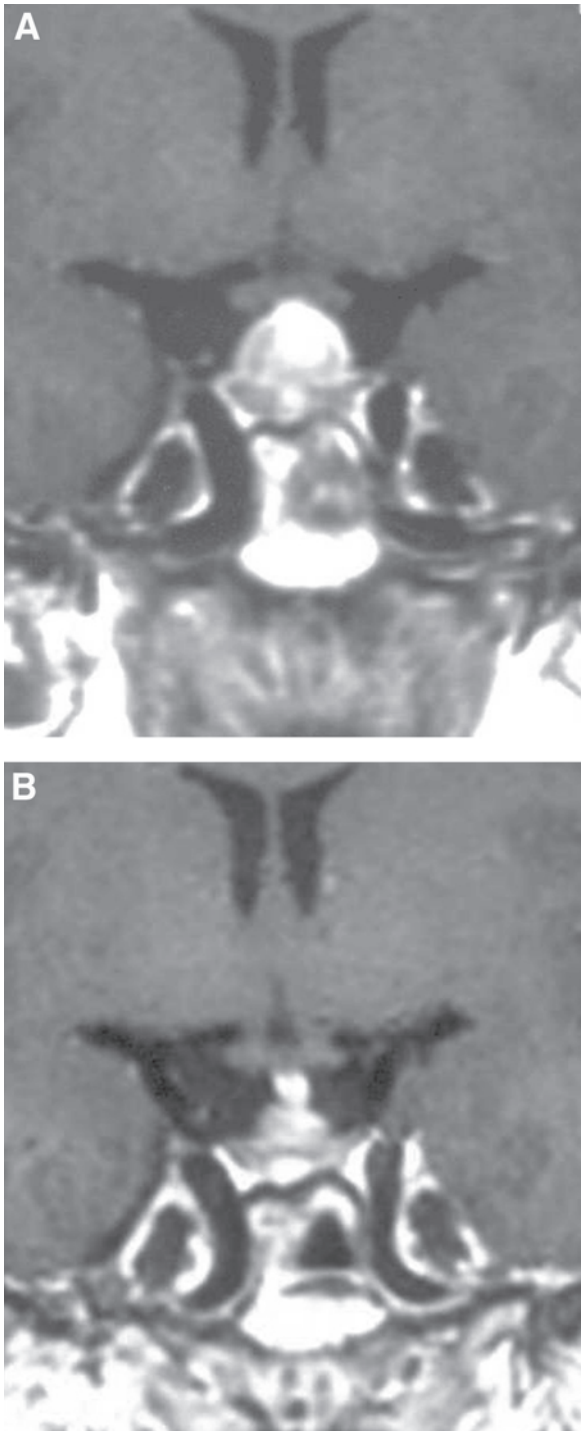

Fig. 4. (**A**) Coronal gadolinium-enhanced MRI showing reappearance of a pituitary mass bulging upward toward the optic chiasm. (**B**) Coronal gadolinium-enhanced MRI two-months after initiation of glucocorticoid therapy. Resolution of the lesion is noted.

pregnant and delivered a healthy boy. She was followed on an annual basis without any clinical or radiological evidence of residual disease. However, 6 yr after the transsphenoidal operation and 3 yr following delivery, amenorrhea, polydipsia, polyuria, and headaches recurred. Her visual fields were normal, but a new MRI showed reappearance of a pituitary mass bulging upward toward the optic chiasm (Fig. 4A). Endocrine evaluation revealed secondary hypogonadism (LH: 0.9 mU/mL; FSH: 3.4 mU/mL), FT4 was in the low normal range (0.8 ng/dL), morning cortisol level was 16.8 μg/dL, ACTH was 29.8 pg/mL, GH was 1.9 ng/mL, and PRL was 11.6 ng/mL. Desmopressin in a low dose was recommended. Because of persistent severe headache she was also started on high doses of glucocorticoids (methylprednisolone 16 mg × 3 for 3 wk, 16 mg × 2 for the next 2 wk followed by 16 mg × 1 for 1 mo and then at gradually decreasing doses). She responded remarkably well with remission of the headaches and 1 mo later she restored regular menses. A new MRI 2 mo after initiation of glucocorticoid therapy revealed resolution of the mass (Fig. 4B). Endocrine reevaluation showed normal thyrotroph and gonadotroph function and normal PRL levels. Corticotrophs were not assessed because she was on steroid therapy. The patient continues to do well, albeit symptoms of mild diabetes insipidus persist.

Discussion

Being a rare disorder, the long-term outcome of LH remains uncertain. Based on current experience it is generally thought that LH is a one-time event. Herein we report a patient with LH that recurred 6 yr after surgical removal of the inflammatory mass. To our knowledge this is the first

histologically confirmed case of LH that relapsed after a long interval following successful transsphenoidal surgery.

A search of the literature revealed only one previous report of LH recurrence after a long interval. Nishioka et al. *(25)* described a recurrence of LH in a postmenopausal woman who presented with central diabetes insipidus and a small intrasellar lesion. Two years after biopsy of the lesion and following a transient recovery of DI, the patient manifested visual field defects due to a pituitary mass with suprasellar extension, which responded to steroid therapy. Our case differed from that described above in respect to the size of the inflammatory lesion at presentation and the much longer time interval elapsed between the initial insult and the appearance of recurrence. Furthermore, in our case the inflammatory mass was surgically removed.

Late recurrences of surgically treated LH have not yet been described. It should be noted, however, that long-term follow-up after surgery has rarely been reported *(10,11,26, 27)*. Moreover, panhypopituitarism is usually present following surgery *(19,27,28)*. In our patient not only pituitary function was preserved but a spontaneous recovery occurred, at least of gonadotroph function. It could therefore be suggested that preservation of normal pituitary might provide the substrate for continuing or recurring LH. This is of particular relevance in view that in those patients suspected to present with LH a more conservative surgical removal is currently advocated *(12,22–24)*. Thus, more long-term follow-up observations are required in order to assess whether there is an increased risk of late recurrence following conservative transsphenoidal surgery for LH.

This patient's initial presentation and subsequent course was also remarkable in several other aspects. Over half of the female cases of LH reported in the literature presented in late pregnancy or within 18 mo postpartum *(9,12,24,29)*. In our patient when first presented there was no history of recent pregnancy. Furthermore, recurrence of LH occurred 3 yr following her second pregnancy. The possibility of an insidious onset of LH following this latter pregnancy cannot be supported based on the careful follow-up after delivery demonstrating a normal sized pituitary and no evidence of pituitary dysfunction. Thus, it is most likely that this case represents a non-pregnancy related form of LH. It is currently unclear whether this latter form of LH is more prone to relapse than the classical pregnancy-related LH.

It has been suggested that in LH, corticotroph and thyrotroph cells are most commonly affected leading to secondary adrenal and thyroid failure *(13–15)*. Gonadotropin deficiency was the predominant pituitary defect in our case associated with a diminished GH secretory reserve and mild DI but with no evidence of corticotroph or thyrotroph failure. Gonadotrophin deficiency in our case did not resolve immediately after transsphenoidal surgery. Instead it resolved spontaneously 1 yr later despite the histological findings of extensive stromal fibrosis with severe destruction of adenohypophysial cells. It seems that during remission of LH, with the progressive disappearance of the inflammatory components, stromal edema, and shrinkage of the fibrotic tissue, even few remaining adenohypophysial cells are adequate to restore pituitary function and progressively reverse hypopituitarism. Interestingly, our patient had a more rapid recovery of gonadotrophin function following the institution of anti-inflammatory doses of steroid therapy on recurrence than following transsphenoidal removal of the inflammatory mass at presentation.

In summary, this case illustrates that the outcome of LH is more complicated than previously thought; similarly to many other disorders of autoimmune origin, LH may run a fluctuating course and, late recurrence is possible even after the successful removal of the inflammatory mass, necessitating thus long follow-up of these patients.

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References

1. Goudie, R. and Pinkerton, P. (1962). *J. Pathol. Bacteriol.* **83,** 584–585.
2. Thodou, E., Asa, S., Kontogeorgos, G., Kovacs, K., Horvath, E., and Ezzat, S. (1995). *J. Clin. Endocrinol. Metab.* **80,** 2302–2311.
3. Bayram, F., Kelestimur, F., Ozturk, F., et al. (1998). *J. Endocrinol. Invest.* **21,** 193–197.
4. Pestell, R., Best, J., and Alford, F. (1990). *Clin. Endocrinol. (Oxf.)* **33,** 457–466.
5. Bottazzo, G. and Doniach, D. (1978). *J. Roy. Soc. Med.* **71,** 433–436.
6. O'Dwyer, D., Smith, A., Matthew, M., et al. (2002). *J. Clin. Endocrinol. Metab.* **87,** 752–757.
7. Crock, P. (1998). *J. Clin. Endocrinol. Metab.* **83,** 609–618.
8. Bellastella, A., Bizzarro, A., Coronella, C., Bellastella, G., Sinisi, A., and De Bellis, A. (2003). *Eur. J. Endocrinol.* **149,** 363–376.
9. Cheung, C., Ezzat, S., Smyth, H., and Asa, S. (2001). *J. Clin. Endocrinol. Metab.* **86,** 1048–1053.
10. Freda, P., Sharon, L., Wardlaw, S., Kalmon, D., and Post, K. (1996). *J. Clin. Endocrinol. Metab.* **81,** 3455–3459.
11. Cosman, F., Post, K., Holub, D., and Wardlaw, S. (1989). *Medicine (Baltimore)* **68,** 240–256.
12. McGrail, K., Beyerl, B., Black, P., Klibanski, A., and Zervas, N. (1987). *Neurosurgery* **20,** 791–793.
13. Richtsmeier, A., Henry, R., Bloodworth, J., and Ehrlich, E. (1980). *Arch. Intern. Med.* **140,** 1243–1245.
14. Gal, R., Schwartz, A., Gukovsky-Oren, S., Peleg, D., Goldman, J., and Kessler, E. (1986). *Obstet. Gynecol. Surv.* **41,** 619–621.
15. Jensen, M., Handwerger, B., Scheithauer, B., Carpenter, P., Mirakian, R., and Banks, P. (1986). *Ann. Intern. Med.* **105,** 200–203.
16. DeBellis, A., Bizzarro, A., Conte, M., et al. (2003). *J. Clin. Endocrinol. Metab.* **88,** 650–654.
17. Paja, M., Estrada, J., Ojeda, A., et al. (1994). *J. Postgrad. Med.* **70,** 220–224.

18. Goswami, R., Kochupillai, N., Crock, P., Jaleel, A., and Gupta, N. (2002). *J. Clin. Endocrinol. Metab.* **87,** 4137–4141.
19. Levine, S., Benzel, E., Fowler, M., Shroyer, J., and Mirfakhraee, M. (1988). *Neurosurgery* **22,** 937–941.
20. Gagneja, H., Arafah, B., and Taylor, H. (1999). *Mayo Clin. Proc.* **74,** 150–154.
21. Nishioka, H., Ito, H., Miki, T., and Akada, K. (1994). *Surg. Neurol.* **42,** 74–78.
22. Prasad, A., Madan, V., Sethi, P., Prasad, M., Buxi, T., and Kanwar, C. (1991). *Br. J. Neurosurg.* **5,** 639–642.
23. Yamagami, K., Yoshioka, K., Sakai, H., et al. (2003). *Intern. Med.* **42,** 168–173.
24. Feigenbaum, S., Martin, M., Wilson, C., and Jaffe, R. (1991). *Am. J. Obstet. Gynecol.* **164,** 1549–1555.
25. Nishioka, H., Ito, H., and Fukushima, C. (1997). *Neurosurgery* **41,** 684–686.
26. Naik, R. G., Ammini, A., Shah, P., Sarkar, C., Mehta, V., and Berry, M. (1994). *J. Neurosurg.* **80,** 925–927.
27. Honegger, J., Falbusch, R., Bornemann, A., et al. (1997). *Neurosurgery* **40,** 713–721.
28. Parent, A., Cruse, J., Smith, E., and Smith, R. (1988). *Adv. Biosci.* **69,** 465–469.
29. Hashimoto, K., Takao, T., and Makino, S. (1997). *J. Endocrinol.* **44,** 1–10.