Successful immunomodulatory treatment for recurrent xanthogranulomatous hypophysitis in an adolescent: illustrative case

Sarah DeCou, BA,1 Pablo F. Recinos, MD,1–3 Richard A. Prayson, MD,1,6 Christopher Karakasis, MD,1,6 Anzar Haider, MD,1,7 and Neha Patel, MD1,3,4

1Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio; 2Department of Neurological Surgery, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio; 3Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Neurological Institute, Cleveland Clinic, Cleveland, Ohio; 4Department of Pediatric Hematology Oncology and Bone Marrow Transplant, Cleveland Clinic Children’s, Cleveland, Ohio; 5Department of Anatomic Pathology, The Robert J. Tomsich Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio; 6Department of Radiology, Cleveland Clinic, Cleveland, Ohio; and 7Center for Pediatric Endocrinology, Cleveland Clinic Children’s, Cleveland, Ohio

BACKGROUND Xanthomatous lesions of the pituitary have been linked to ruptured or hemorrhagic Rathke’s cleft cysts. Most cases are reported to resolve following radical resection. When recurrence does occur, there is no established treatment regimen. High-dose glucocorticoids have been reported to be beneficial in several published cases; however, their effects are often not sustained once therapy is discontinued.

OBSERVATIONS The authors report the case of an adolescent male who developed recurrent xanthogranulomatous hypophysitis associated with a Rathke’s cleft cyst despite two surgical interventions. He was treated with a short course of dexamethasone followed by a maintenance course of celecoxib and mycophenolate mofetil. This regimen proved to be safe and well-tolerated, and it successfully prevented another recurrence of his xanthogranulomatous hypophysitis.

LESSONS This case demonstrates a novel nonsurgical approach to the management of recurrent xanthogranulomatous hypophysitis. It suggests a potential application of a combined corticosteroid-sparing immunosuppressive and anti-inflammatory regimen in other cases of refractory xanthogranulomatous hypophysitis.

https://thejns.org/doi/abs/10.3171/CASE22191

KEYWORDS Rathke’s cleft cyst; xanthomatous; xanthogranulomatous; hypophysitis; suprasellar; immunosuppressive therapy

Hypophysitis is a diagnosis that encompasses a heterogenous group of inflammatory disorders of the pituitary gland. It is most often autoimmune in etiology (i.e., primary or lymphocytic), although it can also be secondary to infection, neoplasm, or use of immune checkpoint inhibitors.1,2 Xanthomatous lesions of the pituitary gland and sellar region represent one of the most rare histological subtypes of secondary hypophysitis.3,4 These lesions are felt to exist along a histopathological spectrum, ranging from xanthomatous hypophysitis (XH) to xanthogranulomatous hypophysitis (XGH) to xanthogranuloma (XG).5 The majority of these cases have been ultimately linked to rupture, hemorrhage, or leakage of Rathke’s cleft cysts (RCCs), although on occasion, they are due to primary autoimmunity or are secondary to other pituitary lesions.3,5 Given the rarity of XH, XGH, and XG, there are no standard management recommendations. Most patients undergo total resection and have no recurrence following surgery.3,6,7 When recurrence does happen, many patients either undergo repeat resection or are treated with high-dose corticosteroids with varying results.8–12 We report a case of an adolescent male found to have RCC with a postoperative course complicated by recurrent XGH. He experienced complete resolution of the inflammatory reaction on a short course of dexamethasone followed by a maintenance course of celecoxib and mycophenolate mofetil (MMF).

REFERENCES CSF = cerebrospinal fluid; MMF = mycophenolate mofetil; MRI = magnetic resonance imaging; XG = xanthogranuloma; XGH = xanthogranulomatous hypophysitis; XH = xanthomatous hypophysitis; RCC = Rathke’s cleft cyst.

INCLUDE WHEN CITING Published August 29, 2022; DOI: 10.3171/CASE22191.

SUBMITTED April 25, 2022. ACCEPTED June 9, 2022.

© 2022 The authors, CC BY-NC-ND 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Illustrative Case

A 16-year-old male presented with delayed puberty and delayed bone age. Comprehensive laboratory evaluation revealed low dehydroepiandrosterone sulfate, low thyroxine, and low gonadal and gonadotropin levels, consistent with central hypothalamic hypopituitarism. He was prescribed levothyroxine and hydrocortisone. He also was found to have bitemporal hemianopia on ophthalmological examination. Magnetic resonance imaging (MRI) was performed, revealing a large cystic suprasellar mass compressing the optic chiasm (Fig. 1A). He was taken for resection via an endoscopic endonasal transsphenoidal approach. Immediately after opening the sellar dura, a bland cystic mass was encountered. A small portion was sent for frozen pathological analysis and had components of normal pituitary gland and other areas suspicious for pituitary adenoma. Upon further dissection, the cystic component of the tumor was entered, and copious amounts of green viscous fluid with off-white, more crystalline contents were spontaneously expressed from the lesion. Given that the lesion did not look like a pituitary adenoma, a second specimen from the cystic capsule and contents was sent for frozen pathological analysis, which was favored to be craniopharyngioma. At the end of the procedure, all gross tumor and obvious capsule were removed, and the anterior and posterior gland were noted to descend. However, an aggressive suprasellar exploration was not performed given that no intraoperative cerebrospinal fluid (CSF) leak was noted. Formal pathological examination of the mass revealed small segments of normal anterior pituitary gland tissue. Amorphous eosinophilic material was focally seen along with the fragments of benign anterior pituitary gland tissue. Rare epithelioid cells, suggestive of a cyst wall lining such as one sees in an RCC, were noted (Fig. 1B). His postoperative MRI revealed expected postoperative changes and improved mass effect on the optic chiasm (Fig. 1C).

Following the surgery, the patient was followed closely in the same manner as those with confirmed craniopharyngioma. He developed diabetes insipidus and was treated with desmopressin. He also began somatropin for growth hormone deficiency and continued taking levothyroxine and hydrocortisone for his central hypothyroidism and adrenal insufficiency. He experienced improvement in his bitemporal hemianopia. The patient otherwise continued to be in his normal state of health until 8 months after the surgery, when he presented with intense headaches and worsening of his vision. MRI of the pituitary at that time revealed an expansile T1 hyperintense and minimally T2 hyperintense lesion in the sellar and suprasellar space (Fig. 2A). Given the recurrence and aggressive tumor behavior, a second endoscopic endonasal surgery was recommended. Intraoperatively, the tumor appeared to originate from the infundibulum and had a very fibrous quality with minimal cystic component. The decision was made to aggressively resect the entire tumor, including the infundibulum, for multiple reasons: the tumor was exhibiting aggressive behavior, the patient already had panhypopituitarism, craniopharyngioma was felt to be most likely, and to maximize chance of long-term tumor control. A repair of the expected intraoperative CSF leak was performed with a multilayered closure, including a button.
edema. MRI demonstrated significant expansion of the T1 hyperintense focus in the sella and suprasellar region, suggestive of recurrence of his xanthogranulomatous reaction (Fig. 3A). He was started on dexamethasone 2 mg four times a day. After just two doses of dexamethasone, his severe headache completely resolved. The dexamethasone was gradually weaned off over a 10-week period with no recurrence of the headaches or visual field changes. At the end of this course, MRI demonstrated a significant reduction in the size of the inflammatory collection in the sellar region, and ophthalmological examination revealed improved visual fields (Fig. 3B). The benefits of corticosteroid treatment were unfortunately met with a number of adverse effects. While on dexamethasone, the patient developed Cushingoid features, severe acne on the face, back, and trunk, behavioral changes with increased anger and depression, and sleeping difficulties.

Following the dexamethasone taper, the patient was prescribed celecoxib 100 mg twice daily and MMF 500 mg twice daily. Over a course of 1 year, the patient was gradually weaned from celecoxib and MMF. The xanthogranulomatous reaction was monitored on 4-month interval MRI scans. The inflammatory fluid collection continued to reduce in size initially and then plateaued over the year (Fig. 3C). Despite weaning of the immunomodulatory agents, the inflammation did not reoccur. At the last follow-up after 4 months off celecoxib, the MRI demonstrated no recurrence of the suprasellar cystic collection (Fig. 3D). The patient is currently on a once-daily dose of MMF, with plans to stop if the next 4-month interval MRI scan shows no recurrence of inflammation (Fig. 4). The patient tolerated the combination of celecoxib and MMF well without any adverse effects, including no recurrent infections, bleeding, gastritis, or hypertension.

**Discussion**

**Observations**

Xanthomatous lesions of the pituitary gland are a rare category of hypophysitis that have been described in several reports. Traditionally, these lesions have been divided into two distinct categories: XH and XG; however, there is growing evidence of clinicopathologic

---

**FIG. 2. Imaging and histopathology at the first recurrence.** A: Coronal precontrast T1-weighted (left) and postcontrast T1-weighted (right) MRI at symptomatic progression showed a recurrent sellar and suprasellar mass with predominantly hyperintense intrinsic T1 signal (white arrow, left) and thin enhancing capsule. Increased mass effect with optic chiasm superiorly displaced and splayed over the mass (white arrow, right). B: Histopathology at the second resection: an attenuated cyst wall lining is noted in association with fibrosis and focal lymphocytic chronic inflammation (H&E, original magnification ×200). C: An area of xanthogranulomatous inflammation with cholesterol clefts associated with histiocytes and giant cells, extravasated blood, focal lymphocytic chronic inflammation and brown pigment consistent with hemosiderin (H&E, original magnification ×200). D: Sagittal postcontrast T1-weighted MRI after surgery showed lesion debulking with decompression of mass effect on the chiasm and some residual tissue with peripheral capsule posteriorly (white arrow).
overlap between them.\textsuperscript{3} XH is histologically characterized by the presence of foamy histiocytes and lymphoplasmacytic infiltrates within the pituitary gland or sellar region with little to no hemosiderin pigment.\textsuperscript{3} In contrast, XG typically contains marked hemosiderin deposits in addition to cholesterol clefs, lymphoplasmacytic infiltrates, fibrosis, multinucleated giant cells, eosinophilic necrotic debris and macrophage accumulation.\textsuperscript{3} Given the accumulation of hemosiderin pigment in XG but not in XH, it has been suggested that XH can transition to XG through repeated or significant episodes of RCC hemorrhage.\textsuperscript{3} In fact, the majority of xanthomatous sellar lesions are felt to be linked to rupture, hemorrhage, or leakage of RCCs.\textsuperscript{3,5}

XH and XG can also be primary with an autoimmune etiology or may also arise from other sellar masses including craniopharyngiomas and colloid cysts.\textsuperscript{3,6} In most cases, it has been postulated that leakage of cyst components arising from these pituitary masses induces a severe inflammatory reaction within the surrounding tissues, ultimately leading to secondary granulomatous degeneration and development of XH and XG.\textsuperscript{3,6}

Given the rarity of this phenomenon, the histopathological diagnosis of the sellar mass and associated inflammatory fluid collection in this case proved challenging. Even without the presence of XH or XG, a percentage of cystic sellar masses are known to be difficult if not impossible to classify, even for the most experienced neuropathologists.\textsuperscript{3} Overlapping epithelial features between RCC, craniopharyngioma, and epidermoid cysts have been described, and some feel that they too may exist on a continuum.\textsuperscript{3} In this case, RCC type epithelium was initially identified, which progressed over time into a full-blown xanthogranulomatous picture at the time of the second resection. This case highlights the overlapping spectrum of XH and XG and provides further support to the idea that repeated RCC hemorrhage is a driver of XG development.

Additionally, this case describes a rare example of multiple recurrent XG. While the rate of recurrence for RCC following surgical excision has been reported between the range of 0\% and 42\%, the recurrence rate for RCC-associated XH and XG is not precisely known.\textsuperscript{19,20} In one series by Kleinschmidt-DeMasters et al.,\textsuperscript{3} only 4 of 23 patients with XH or XG required a second resection to control the condition. In another review describing a total of 27 cases of XG, only 1 recurrence was reported despite 36\% of patients having

![FIG. 3. MRI at the second recurrence through treatment. A: Sagittal postcontrast T1-weighted MRI at the second recurrence showed a recurrent heterogeneous mass with hyperintense intrinsic T1 signal (white arrow) with heterogeneously enhancing tissue anteriorly and superiority. No significant mass effect. B: Sagittal postcontrast T1-weighted MRI postdexamethasone shows decreased size of the sellar T1 hyperintense lesion (white arrow). C: Sagittal postcontrast T1-weighted MRI obtained after 4 months on celecoxib plus MMF, showing stable sellar T1 hyperintense lesion (white arrow). D: Sagittal postcontrast T1-weighted MRI obtained after 4 months off celecoxib but still on MMF, showing stable sellar T1 hyperintense lesion (white arrow).](image)

![FIG. 4. Timeline of patient course. bid = twice per day.](image)
had subtotal resections. Similarly, there were no cases of recurrence in another retrospective series of 6 patients with XG following gross total resection. In general, recurrent XH and XG appears to be very uncommon, and most patients do not require any XH- or XG-directed treatment apart from the initial resection.

When recurrence of XH or XG does occur, most patients are treated with high-dose glucocorticoids, though some undergo reoperation or radiation. In one case described by Young et al., a 3-day course of high-dose methylprednisolone was reported to cause mass reduction and symptom improvement in a 36-year-old female with recurrent XH 10 months after initial surgery. In another case reported by Gezer et al., a 35-year-old female with persistent headaches following a successful total resection for RCC-associated XH was treated with high-dose corticosteroids. Although she did not experience recurrence, her headaches completely resolved following treatment, similar to the patient in our case.

Despite success in some cases, glucocorticoid therapy has been reported to be less effective in XH and XG as compared to its routine use in more common forms of hypophysitis. Outside of recurrent XH and XG, glucocorticoids are considered the cornerstone of medical management for the more common autoimmune hypophysitis. However, even in these cases, the overall recurrence rate of hypophysitis is reportedly high, with up to 38% of patients experiencing relapse on corticosteroid therapy in one recent large cohort. Long-term treatment with corticosteroids also increases risks of adverse effects. Corticosteroid-sparing therapies have therefore also been used in primary hypophysitis, with the most common being azathioprine. Methotrexate, cyclosporine, MMF, infliximab, rituximab, gamma knife surgery, and stereotactic radiotherapy have all been reportedly used as well in individual cases.

Given the reported short-lived efficacy of glucocorticoid therapy in XH and XG, unfavorable side-effect profile of the glucocorticoid, and high risk for recurrence, we decided to implement longer term corticosteroid-sparing therapy in this case. Celecoxib and MMF were selected to provide a combination of T-cell–directed, immunosuppressive and anti-inflammatory therapy to prevent further recurrence and repeated surgery. This novel immunomodulatory regimen of celecoxib and MMF can potentially be considered in other similar cases of recurrent XGH.

Lessons
This case report aims to increase awareness of recurrent xanthomatous and xanthogranulomatous hypophysitis. It also highlights the successful and safe use of corticosteroid-sparing, T-lymphocyte–directed, immunosuppressive and anti-inflammatory therapy to prevent further recurrence and repeated surgery. This novel immunomodulatory regimen of celecoxib and MMF can potentially be considered in other similar cases of recurrent XGH.

Acknowledgments
We wish to acknowledge the contributions of Bette Kleinschmidt-DeMasters, MD, Amy Sniderman, MD, Suha Shidiac, RN, and Jennifer Weaver, RN to make this work possible.

References
1. de Vries F, van Furth WR, Biermasz NR, Pereira AM. Hypophysitis: a comprehensive overview. Presse Med. 2021;50(4):104076.
2. Gubbi S, Hannah-Shmouni F, Verbalis JG, Koch CA. Hypophysitis: an update on the novel forms, diagnosis and management of disorders of pituitary inflammation. Best Pract Res Clin Endocrinol Metab. 2019;33(6):101371.
3. Kleinschmidt-DeMasters BK, Lillehei KO, Hankinson TC. Review of xanthomatous lesions of the sella. Brain Pathol. 2017;27(3):377–395.
4. Gezer E, Cabuk B, Bayrak BY, et al. Xanthomatous hypophysitis secondary to a ruptured Rathke’s cleft cyst: a case report. Brain Tumor Res Treat. 2022;10(1):48–64.
5. Duan K, Asa SL, Winer D, Gelareh Z, Gentili F, Mete O. Xanthomatous hypophysitis associated with ruptured Rathke’s cleft cyst. Endocr Pathol. 2017;28(1):83–90.
6. Hernández-Estrada RA, Ksheetry VR, Vogel AN, Curtis MT, Evans JJ. Cholesterol granulomas presenting asellar masses: a similar, but clinically distinct entity from craniohypophysial hyperkinesia and Rathke’s cleft cyst. Pituitary. 2017;20(3):325–332.
7. Ved R, Logier N, Leach P, Davies JS, Hayhurst C. Pituitary xanthogranulomas: clinical features, radiological appearances and post-operative outcomes. Pituitary. 2018;21(3):256–265.
8. Gopal-Kothandapani JS, Bagg V, Wharton SB, Connolly DJ, Sinha S, Dimitri PJ. Xanthogranulomatous hypophysitis: a rare and often mistaken pituitary lesion. Endocrinol Diabetes Metab Case Rep. 2015;2015(14):0089.
9. Shao X, Wang C, Min J. Xanthogranuloma of the sellar region: a case report. Medicine (Baltimore). 2020;99(40):e22619.
10. Vasquez CA, Downes A, Kleinschmidt-DeMasters BK, Youssef AS. Functioning pituitary adenoma with xanthogranulomatous features: review of literature and case report. J Neurol Surg B Skull Base. 2019;80(5):449–457.
11. Stojsanovic M, Manojlovic-Gacic E, Pekic S, et al. From diabetes insipidus to sellar xanthogranuloma—a “yellow brick road” demanding teamwork. Acta Endocrinol (Bucur). 2019;15(2):247–253.
12. Zhu J, Wang Z, Wang W, et al. Xanthomatous hypophysitis: a case report and comprehensive literature review. Front Endocrinol (Lausanne). 2021;12:735655.
13. Joung JY, Jeong H, Cho YY, et al. Steroid responsive xanthomatous hypophysitis associated with autoimmune thyroiditis: a case report. Endocrinol Metab (Seoul). 2013;28(1):65–69.
14. Mathkour M, Zeoli T, Werner C, et al. Recurring primary xanthomatous hypophysitis behaving like pituitary adenoma: additional case and literature review. World Neurosurg. 2020;138:27–34.
15. Wong JSL, Nasruddin AB, Selveindran NM, et al. Xanthomatous hypophysitis presenting in an adolescent girl: a long-term follow-up of a rare case and review of the literature. AACE Clin Case Rep. 2021;7(3):220–225.

16. Kamoshima Y, Sawamura Y, Motegi H, Kubota K, Houkin K. Xanthogranuloma of the sellar region of children: series of five cases and literature review. Neurol Med Chir (Tokyo). 2011;51(10):689–693.

17. Hanna B, Li YM, Beutler T, Goyal P, Hall WA. Xanthomatous hypophysitis. J Clin Neurosci. 2015;22(7):1091–1097.

18. Deodhare SS, Bilbao JM, Kovacs K, et al. Xanthomatous hypophysitis: a novel entity of obscure etiology. Endocr Pathol. 1999;10(3):237–241.

19. Chotai S, Liu Y, Pan J, Qi S. Characteristics of Rathke’s cleft cyst based on cyst location with a primary focus on recurrence after resection. J Neurosurg. 2015;122(6):1380–1389.

20. Han SJ, Rolston JD, Jahangiri A, Aghi MK. Rathke’s cleft cysts: review of natural history and surgical outcomes. J Neurooncol. 2014;117(2):197–203.

21. Gutenberg A, Hans V, Puchner MJA, et al. Primary hypophysitis: clinical-pathological correlations. Eur J Endocrinol. 2006;155(1):101–107.

22. Joshi MN, Whitelaw BC, Carroll PV. Mechanisms in endocrinology: Hypophysitis: diagnosis and treatment. Eur J Endocrinol. 2018;179(3):R151–R163.

23. Honegger J, Buchfelder M, Schlaffer S, et al. Treatment of primary hypophysitis in Germany. J Clin Endocrinol Metab. 2015;100(9):3460–3469.

Disclosures
Dr. Recinos reported consulting fees from Stryker outside the submitted work, and ownership interest in Acera Surgical. No other disclosures were reported.

Author Contributions
Conception and design: Recinos, DeCou, Patel. Acquisition of data: DeCou, Prayson, Karakasis, Patel. Analysis and interpretation of data: Recinos, Prayson, Haider, Patel. Drafting the article: DeCou, Karakasis, Patel. Critically revising the article: Recinos, Prayson, Karakasis, Patel. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Recinos. Study supervision: Recinos, Patel.

Correspondence
Pablo F. Recinos: Cleveland Clinic, Cleveland, OH. recinop@ccf.org.