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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,[1,5] Christopher Karakasis, MD,[1,6] Anzar Haider, MD,[1,7] and Neha Patel, MD[1,3,4]

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

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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).[3] 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).

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

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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 somatotropin 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

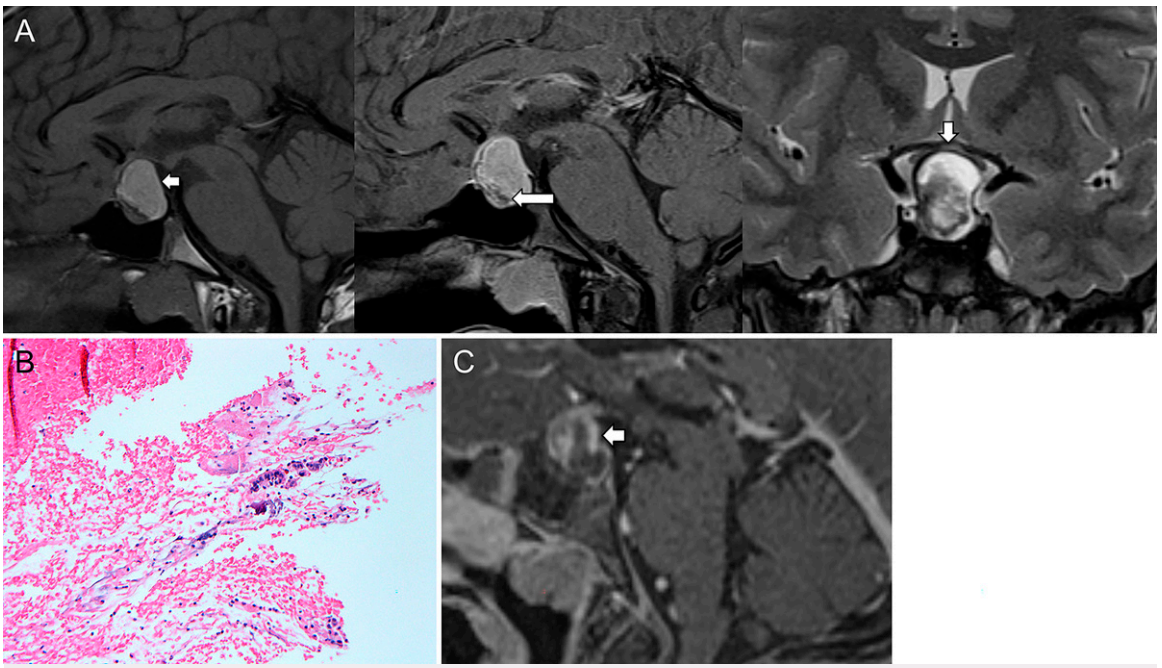

FIG. 1. Imaging and Histopathology at diagnosis. **A:** Sagittal precontrast T1-weighted (*left*), sagittal postcontrast T1-weighted (*center*), and coronal T2-weighted (*right*) MRI at diagnosis showed a sellar and suprasellar mass with predominantly hyperintense intrinsic T1 signal internally (*white arrow, left*) with heterogeneously enhancing tissue anteriorly (*white arrow, center*), mixed hyperintense and hypointense T2 signal, and a thin enhancing capsule. The optic chiasm is superiorly displaced and splayed over the mass (*white arrow, right*). The infundibulum and native pituitary gland are not clearly visualized. **B:** Histopathology at the first resection: 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 (hematoxylin and eosin [H&E], original magnification $\times$200). **C:** 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 (*white arrow*) and improved mass effect.

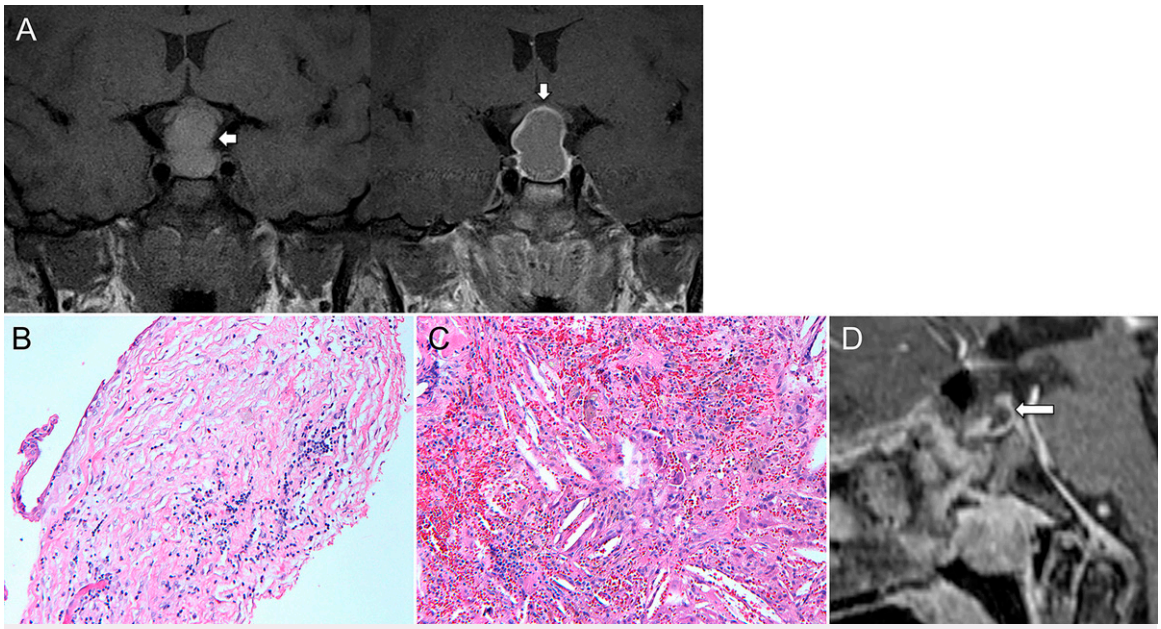

FIG. 2. Imaging and histopathology at the first recurrence. **A:** Coronal precontrast T1-weighted (*left*) and postcontrast T1-weighted (*right*) MRI at symptomatic progression showed a recurrent sellar and suprasellar mass with predominantly hyperintense intrinsic T1 signal (*white arrow, left*) and 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*).

graft from a dural substitute and a nasoseptal flap and supplemented with a lumbar drain. Five days postoperatively, the patient presented to the emergency department with positional headaches that subsequently resolved after an epidural blood patch; he otherwise did well. Surgical pathology demonstrated organizing hemorrhage with hemosiderin deposition. Focally, an attenuated epithelial lining with associated fibrosis and chronic inflammation were observed (Fig. 2B). Additionally, cholesterol clefts with giant cells, fibrosis, and chronic inflammation were seen, consistent with an XG of the sella or xanthogranulomatous reaction due to repeated hemorrhages (Fig. 2C).

Immediate postoperative MRI revealed lesion debulking with some residual tissue and decompression of the mass effect on the optic chiasm (Fig. 2D). Despite this second extensive surgery that included sacrifice of the infundibulum, reaccumulation of the proteinaceous and presumed inflammatory fluid in the suprasellar region was visualized on subsequent surveillance imaging, which continued to increase in size on later scans. He remained clinically asymptomatic until 8 months following his second surgery, when he once again presented with severe bifrontal headaches. Ophthalmological examination at that time revealed possible slight visual field worsening without optic disc 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.[3–18] Traditionally, these lesions have been divided into two distinct categories: XH and XG; however, there is growing evidence of clinicopathologic

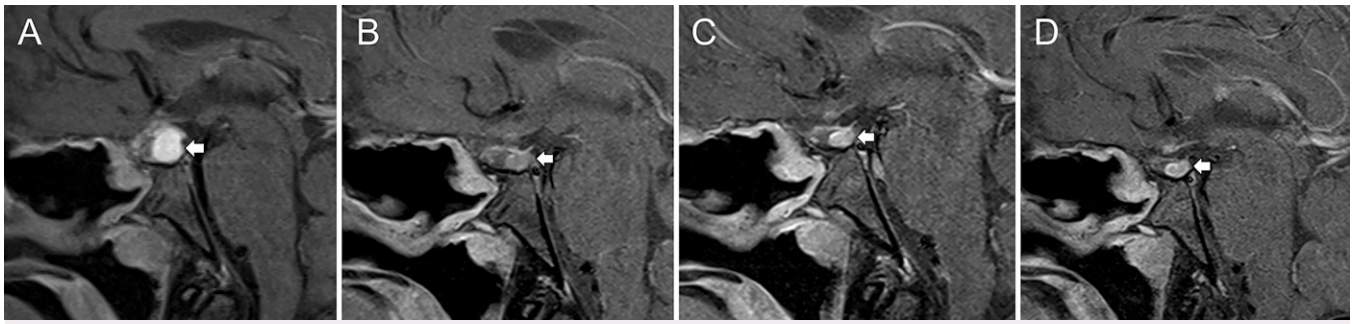

FIG. 3. MRI at the second recurrence through treatment. **A:** Sagittal postcontrast T1-weighted MRI at the second recurrence showed a recurrent heterogeneous mass with hyperintense intrinsic T1 signal (*white arrow*) with heterogeneously enhancing tissue anteriorly and superiorly. No significant mass 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*).

overlap between them.[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.[3] In contrast, XG typically contains marked hemosiderin deposits in addition to cholesterol clefts, lymphoplasmacytic infiltrates, fibrosis, multinucleated giant cells, eosinophilic necrotic debris and macrophage accumulation.[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.[3] In fact, the majority of xanthomatous sellar lesions are felt to be linked to rupture, hemorrhage, or leakage of RCCs.[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.[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.[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.[3] Overlapping epithelial features between RCC, craniopharyngioma, and epidermoid cysts have been described, and some feel that they too may exist on a continuum.[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.[19,20] In one series by Kleinschmidt-DeMasters et al.,[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

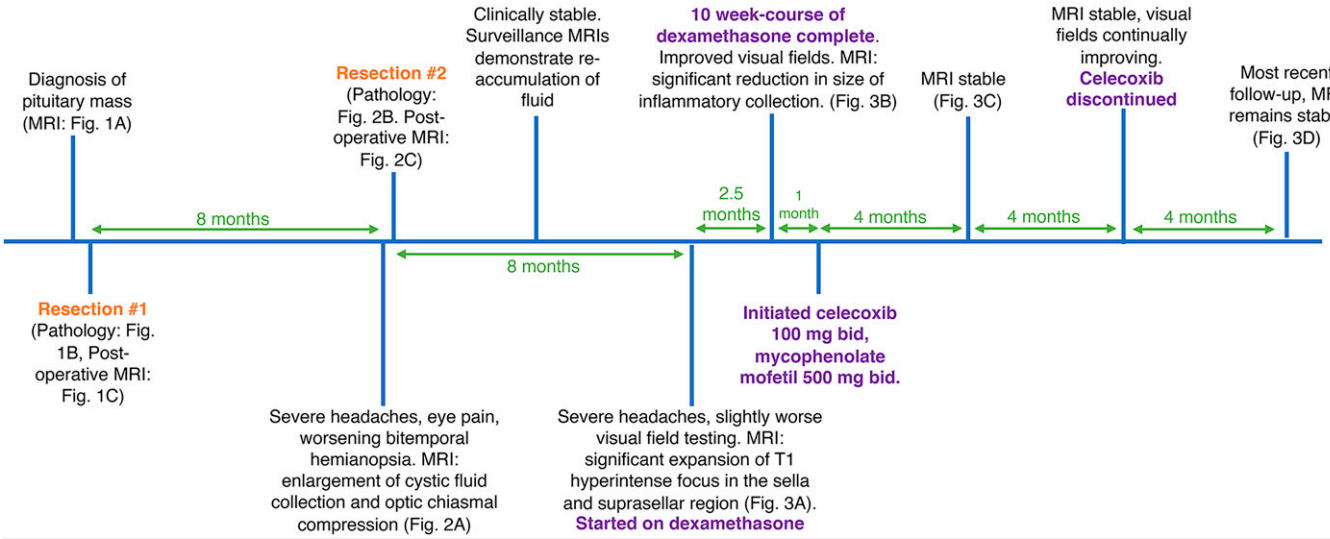

FIG. 4. Timeline of patient course. bid = twice per day.

had subtotal resections.[6] Similarly, there were no cases of recurrence in another retrospective series of 6 patients with XG following gross total resection.[7] 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.[12,14] In one case described by Joung et al.,[13] 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.,[4] 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.[4,17,21] In one case observed by Deodhare et al.,[18] corticosteroid therapy temporarily shrunk an XH lesion; however, the lesion significantly expanded following discontinuation of the therapy. In another report by Wong et al.,[15] a 14-year-old female with XH experienced gradually increasing size of her sellar mass for 2 years following partial resection, at which point she was treated with high-dose prednisolone. A significant reduction in the mass size was demonstrated 6 months later as a response to the steroid therapy. However, this effect was not sustained, and azathioprine was started as a steroid-sparing agent, which led to stabilization of mass size.

Outside of recurrent XH and XG, glucocorticoids are considered the cornerstone of medical management for the more common autoimmune hypophysitis.[22] 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.[22,23] 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.[22] Methotrexate, cyclosporine, MMF, infliximab, rituximab, gamma knife surgery, and stereotactic radiotherapy have all been reportedly used as well in individual cases.[22]

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. MMF has been previously used in pediatric populations, is usually well tolerated in low doses, and can be taken orally and weaned easily. To provide a durable response and prevent recurrence of this patient's XGH, celecoxib and MMF were continued and slowly weaned over 1 year with meticulous evaluation of the side effects from these drugs and monitoring of the suprasellar process on imaging. In this patient, we were able to use this regimen to successfully prevent recurrence of his XGH. This combination proved to be safe and well-tolerated in our patient. It is prudent to note that one limitation of this report is the relatively short-term follow-up period of 1 year. However, one strength of this report is that, to our knowledge, this is the second case to utilize a noncorticosteroid-immunosuppressive medication in the treatment of recurrent XH, XGH, or XG, and the first to use this unique maintenance regimen of celecoxib and MMF. Application of this proposed regimen can potentially be considered in other cases of refractory XGH. It could also be possibly considered in other types of primary and secondary hypophysitis; however, further investigation to demonstrate efficacy and safety in larger patient volumes is warranted.

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.

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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.