Xanthomatous Hypophysitis Secondary to a Ruptured Rathke's Cleft Cyst: A Case Report

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Case report

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Abstract

Purpose

Hypophysitis (HP) is a rare disease which develops secondary to chronic or acute inflammation of the pituitary gland and may cause symptoms related to pituitary dysfunction and mass compression. Lymphocytic HP is the most common subtype of primary HP, while xanthomatous HP (XHP) is considered the rarest form, with 35 reported cases, to date.

Case Report

A 35-year-old woman was initially admitted to a Gynecology clinic with a 2-year history of amenorrhea and headache. She was started on cabergoline 0.5 mg twice a week for macroprolactinoma. Due to persistent amenorrhea with low gonadotropins, she was referred to our Endocrinology clinic. Her pituitary function profile revealed panhypopituitarism and a 13 x 11 x 12 mm sized sellar mass with diffuse enhancement which sustained toward the infundibulum and dura was observed on the gadolinium-enhanced pituitary MRI. The patient underwent an endoscopic endonasal transsphenoidal approach for tumor resection and thick yellowish fluid draining from the lesion was observed. The histopathological diagnosis was reported as a rupture of an Rathke's cleft cyst and a xanthomatous hypophysitis. The surgery did not improve the symptoms/pituitary functions, however, headache recovered immediately after the first dose of high dose methylprednisolone treatment.

Conclusion

The inflammatory process in a xanthomatous lesion may actually be a secondary response to mucous fluid content release from a ruptured cyst, thus recommended to classify XHP as secondary hypophysitis. Since the differentiation of XHP from other pituitary tumors may be challenging preoperatively, surgery is the major diagnostic tool and also, the most recommended therapeutic option.

Introduction

Hypophysitis (HP) is a rare disease which develops secondary to chronic or acute inflammation of the pituitary gland and may cause symptoms related to pituitary dysfunction and mass compression. HP can be classified based on the anatomical location of pituitary involvement (adenohypophysitis, infundibulo-neurohypophysitis, or panhypophysitis), the etiology (primary or secondary), and the histopathology (lymphocytic, granulomatous, xanthomatous, IgG4, necrotizing, or mixed forms) [2, 5, 8, 10]. Lymphocytic HP is the most common subtype of primary HP, while xanthomatous HP (XHP) is considered the rarest form, with 35 reported cases, to date [17].

The exact mechanism by which XHP occurs still remains unclear. The development of the characteristic histopathological lesion which consists of lipid-laden "foamy" histiocytes and CD68 positive macrophages has been previously attributed to the extension of an autoimmune/lymphocytic spectrum

[3, 12, 13, 20]. On the other hand, various recent case presentations have reported to consider the inflammatory process of XHP related to the rupture of a Rathke's cleft cyst (RCC) [7, 10, 14, 22]. In our report, we describe a case with panhypopituitarism due to XHP secondary to the rupture of an RCC.

Case Report

A 35-year-old woman was admitted to our Endocrinology clinic with a 2-year history of headache and amenorrhea. She was initially admitted to a Gynecology clinic with amenorrhea 6 months prior to the admission to our institution. Initial laboratory testing revealed hyperprolactinemia with a prolactin level of 125 ng/ml (normal range: 4.7–23.3 ng/ml). Pituitary magnetic resonance imaging (MRI) showed a macroadenoma in the sella measuring 13 x 10 x 12 mm. Thus, she was started on cabergoline 0.5 mg twice a week; however, she was referred to an Endocrinology clinic 6 months after starting the cabergoline treatment, due to persistent amenorrhea with low gonadotropins.

Her personal medical and family histories were unremarkable with no autoimmune disease. On physical examination, no abnormality observed in her temperature, blood pressure, body mass index, pulse and respiratory rates with a completely normal visual field. Her pituitary function profile revealed panhypopituitarism (Table 1) and a 13 x 11 x 12 mm sized sellar mass with diffuse enhancement which sustained toward the infundibulum and dura was observed on the gadolinium-enhanced pituitary MRI (Fig. 1). On both T1- and T2-weighted imaging, the lesion demonstrated heterogenous intensity. All these findings were reported as suggestive of a complicated cyst or cystic adenoma, hemorrhage, and/or hypophysitis. She was placed on hydrocortisone 10 mg twice daily, followed by a levothyroxine dose of 50 µg daily. As a diagnostic and therapeutic tool, the patient underwent an endoscopic endonasal transsphenoidal approach for tumor resection with a steroid coverage. Intraoperatively, thick yellowish fluid draining from the lesion was observed (Fig. 2). Histological examination revealed that the resected lesion was infiltrated with lymphoplasma cells, foamy histiocytes, cholesterol clefts, multinucleated giant cells, and fibrosis (Fig. 3). Immunohistochemically, these inflammatory cells were CD68, CD3, CD20 and CD138 positive. The final histopathological diagnosis was reported as a rupture of an RCC and a xanthomatous hypophysitis.

Table 1
– Pituitary function tests and the symptoms of our case

	Before Surgery		After Surgery[γ]		Normal Range
	Before Cabergoline[*]	Under Cabergoline[**]	1 month	8 months[α]	
Prolactin (ng/ml)	125	0.65	0.25	5.18	4.8–23.3
FSH (mIU/ml)		2.14	3.95	7.9	
LH (mIU/ml)		1.17	2.82	9.94	
Estradiol (pg/ml)		< 10	< 10	< 10	
fT4 (ng/dl)		0.45	0.80	1.12	0.6–1.2
TSH (mIU/ml)		2.35			0.4–5.3
Cortisol (µg/dl)		2.5			6.7–22.6
ACTH (pg/ml)		36			0–45
GH (ng/ml)		1.02	0.96	1.95	> 8
IGF-1 (µg/ml)		61	69	128	72–233
Headache	+	+	+	-	
Amenorrhea	+	+	+	+	
[*]Initial admission to the Gynecology clinic					
[**]At the time of admission to the Endocrinology clinic six months after starting cabergoline therapy					
[γ]Under maintaining glucocorticoid and levothyroxine treatments					
[α]Four months after high dose glucocorticoid therapy initiation					

At 1-month follow-up postoperatively there was no improvement in the symptoms of our patient, i.e., amenorrhea, headache, and the lab results were still consistent with panhypopituitarism (Table 1). Gonadal hormone replacement therapy was not initiated in order to precisely observe the progression in the pituitary functions, and it was decided to follow the patient for 2 more months under the glucocorticoid and levothyroxine maintenance therapies. At the 3-month visit the patient was still complaining of headache and the absence of menstruation. In addition to that, a repeat pituitary MRI showed postoperative surgical changes with no remarkable residual lesion. Consequently, the patient started high dose glucocorticoid therapy. A 64 mg daily dose of methylprednisolone was prescribed for 2

weeks and it was tapered by 4 mg weekly to the maintenance dose of 4 mg/day methylprednisolone. At 8-month follow-up postoperatively (4 months after methylprednisolone initiation), her headache completely resolved and a slight improvement was observed in the pituitary function tests (Table 1); however, there was no recovery in her menstrual cycle. Repeat pituitary MRI demonstrated no residual lesion. The patient still requires ongoing levothyroxine and glucocorticoid replacement and has not started gonadal hormone replacement therapy, yet, for the future evaluation of her gonadal axis. Gonadal hormone replacement therapy is planned to initiate 3 months later, if her menstrual cycle would not be recovered.

Discussion

XHP is the rarest form of primary hypophysitis with a female preponderance (27/35 [77.1%]) and a mean age of 39.3 years [17]. The first three cases of XHP have been reported in 1998 [9], and since then, our 35-year-old female patient is the 36th reported XHP case worldwide and the 2nd case in Turkey [19]. Headache, impaired menstrual cycles, hyperprolactinemia, diabetes insipidus, and panhypopituitarism have been reported as the most common presenting symptoms in a recent review [17] and our patient presented all these symptoms, except diabetes insipidus. In line with the literature which reported a low prevalence of visual disturbances in patients with XHP, no visual field abnormality was demonstrated in our patient [11, 12].

Since the pathophysiological mechanism of XHP has not been elucidated, yet, XHP has been classified as primary hypophysitis [2]. A possible autoimmune mechanism which might be involved in the development of XHP has been suggested by three case reports, in which the cases with ulcerative colitis, Hashimoto's thyroiditis, rheumatoid arthritis and Sjogren's syndrome have been presented [3, 13, 20]. Dissimilar to these reports, recent evidences suggest that the inflammatory process in a xanthomatous lesion may actually be a secondary response to mucous fluid content release from a ruptured cyst, most commonly from an RCC [1, 4, 6, 14, 15, 17, 18, 21, 23]. Moreover, Duan *et al*. have presented a cohort of 7 XHP cases, in which 6 cases harbored concurrent findings of a ruptured RCC and the last case had a history of a surgery for an RCC [7]. In the same cohort, thick yellowish drainage within a cystic lesion was observed in 4 cases intraoperatively, which was similar to that described in our case.

Gadolinium-enhanced pituitary MRI is the preferred modality for hypophysitis, and XHP usually presents as a cystic sellar mass, which generally shows a peripheral enhancement [5]. In addition to that, Mathkour *et al*. reported a case, in which the sellar lesion had a suprasellar expansion with the infiltration of the cavernous sinus which has been considered as adenoma over RCC on MRI [17]. As a result, it may be difficult to differentiate XHP on MRI from a cystic adenoma, RCC, hemorrhage, or a pituitary abscess. Heterogenous intensity on both T1- and T2-weighted imaging and diffuse pituitary enhancement which was displayed by MRI in our case were primarily suggestive of a complicated cyst/cystic adenoma or hemorrhage, while the infundibular and dural enhancement indicated a diagnosis of hypophysitis, as well.

The management of XHP may be challenging due to the ambiguous pathogenesis of the disease. Unlike the treatment for lymphocytic hypophysitis, glucocorticoid therapy is less effective in XHP and a surgical intervention is often required to alleviate the compressive symptoms and pituitary dysfunction [10, 12]. The only XHP case which was radiologically responsive to high dose steroid has been described by Joung *et al*. and the authors have reported a significant mass reduction at the sella and suprasellar area following a 500 mg intravenous methylprednisolone treatment for 3 days. In addition to playing an essential role in making the histological diagnosis of XHP, surgery has been generally considered in cases with progressive visual field deficits or impaired pituitary function [12]. In the literature, the first case with XHP which had a full recovery of pituitary dysfunction following a transsphenoidal surgery has been reported by Burt *et al*. and that patient had only a 3-month history of hypogonadism at the initial admission. In another case report, diabetes insipidus completely cured after surgery in a XHP patient with a 4-month history of polyuria and polydipsia [16]. Similarly, a case of XHP with a 2-month history of amenorrhea, galactorrhea, and mild weight gain achieved remission following a complete resection of the lesion [17]. The rate of pituitary function improvement following surgery in XHP cases has been reported less than 50%, which attributed to the duration of the impairment [3]. Chronic inflammation has been considered responsible for irreversible pituitary dysfunction via fibrosis and tissue destruction. In addition to that, headache has been reported to improve in most of patients with XHP who had surgery [11]. Headache and panhypopituitarism of our patient did not recover within 6 months after surgery, possibly due to a 2-year history of the presented symptoms. Interestingly, headache disappeared completely within a few days after the first dose of high dose steroid therapy. Moreover, the pituitary function tests showed a slight improvement, i.e., normalization of IGF-1 level and a mild increase in the other anterior pituitary function tests; however, at 10-month follow-up, our patient has still been requiring hormone replacement therapies.

In conclusion, XHP is an uncommon inflammatory process of the pituitary gland which should be included in the differential diagnoses, if a patient presents with headache, panhypopituitarism and if yellowish fluid is drained from a cystic lesion intraoperatively. In agreement with the recent reports, our case presentation may also indicate a recommendation to classify XHP as secondary hypophysitis which could be caused by a ruptured cystic lesion. Since the differentiation of XHP from other pituitary tumors may be challenging preoperatively, surgery is the major diagnostic tool and also, the most recommended therapeutic option, despite low remission rates (< 50%) reported following surgery. Here, we present a patient with XHP which developed as an inflammatory response to a ruptured RCC and the transsphenoidal surgery did not improve the symptoms/pituitary functions, while headache recovered immediately after the first dose of high dose methylprednisolone treatment.

Declarations

Funding:

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Conflicts of interest:

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Consent for publication:

Informed consent for publication was obtained from the patient.

Ethics approval and consent to participate:

Not applicable

Author's contribution:

EG, BÇ, ZC, AS, MS and DK participated in the management of the patient both pre- and post-operatively. SC and BÇ operated the patient, and BYB performed the histopathological evaluation of the pituitary lesion.

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Code availability:

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Figures

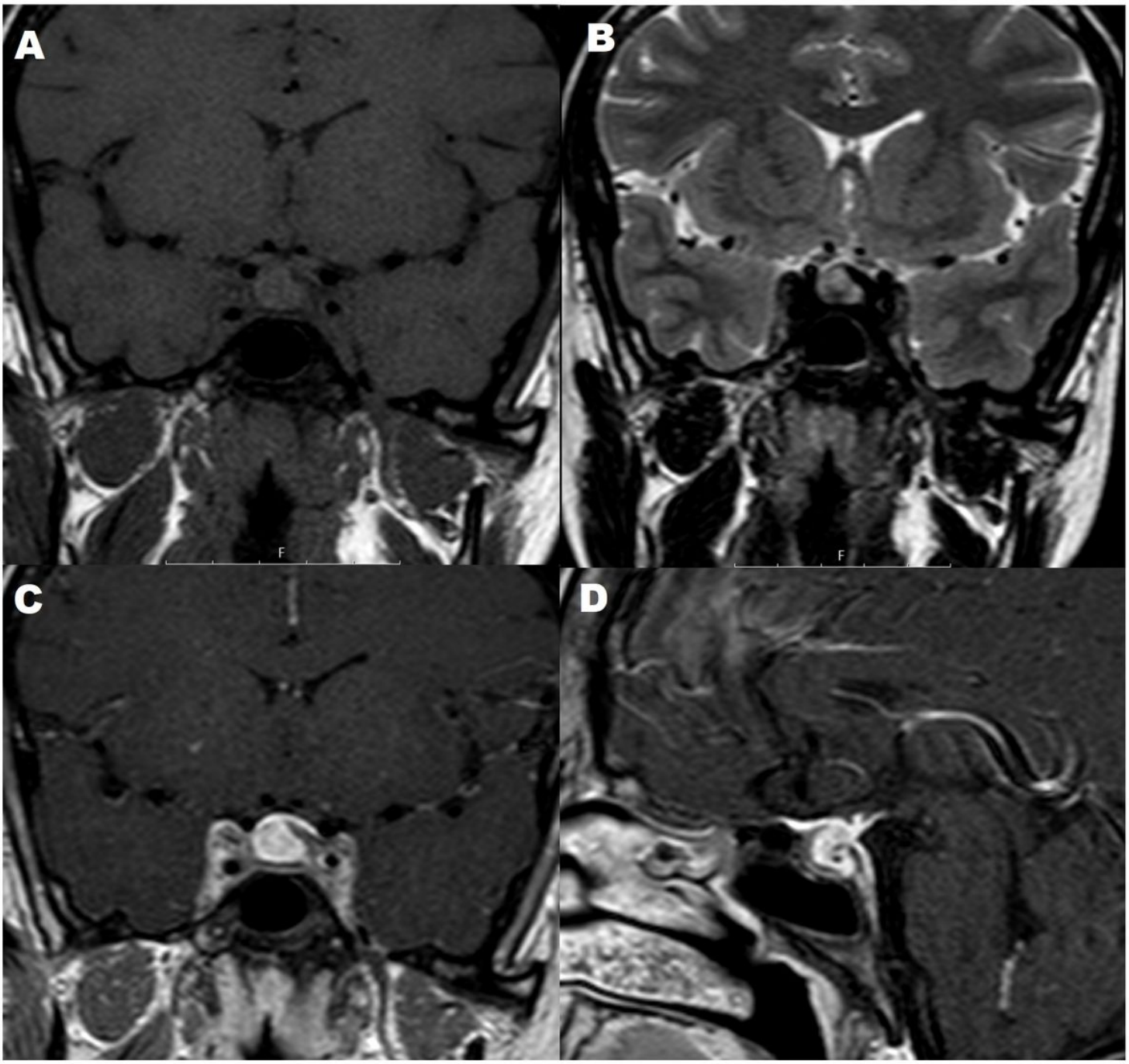

Figure 1

Preoperative gadolinium-enhanced magnetic resonance imaging (MRI) scan of xanthomatous hypophysitis secondary to Rathke's cleft cyst. (A) Pre-contrast coronal T1-weighted MR image, (B) coronal T2-weighted MR image, (C) post-contrast coronal and (D) sagittal T1-weighted MR images of the pituitary lesion.

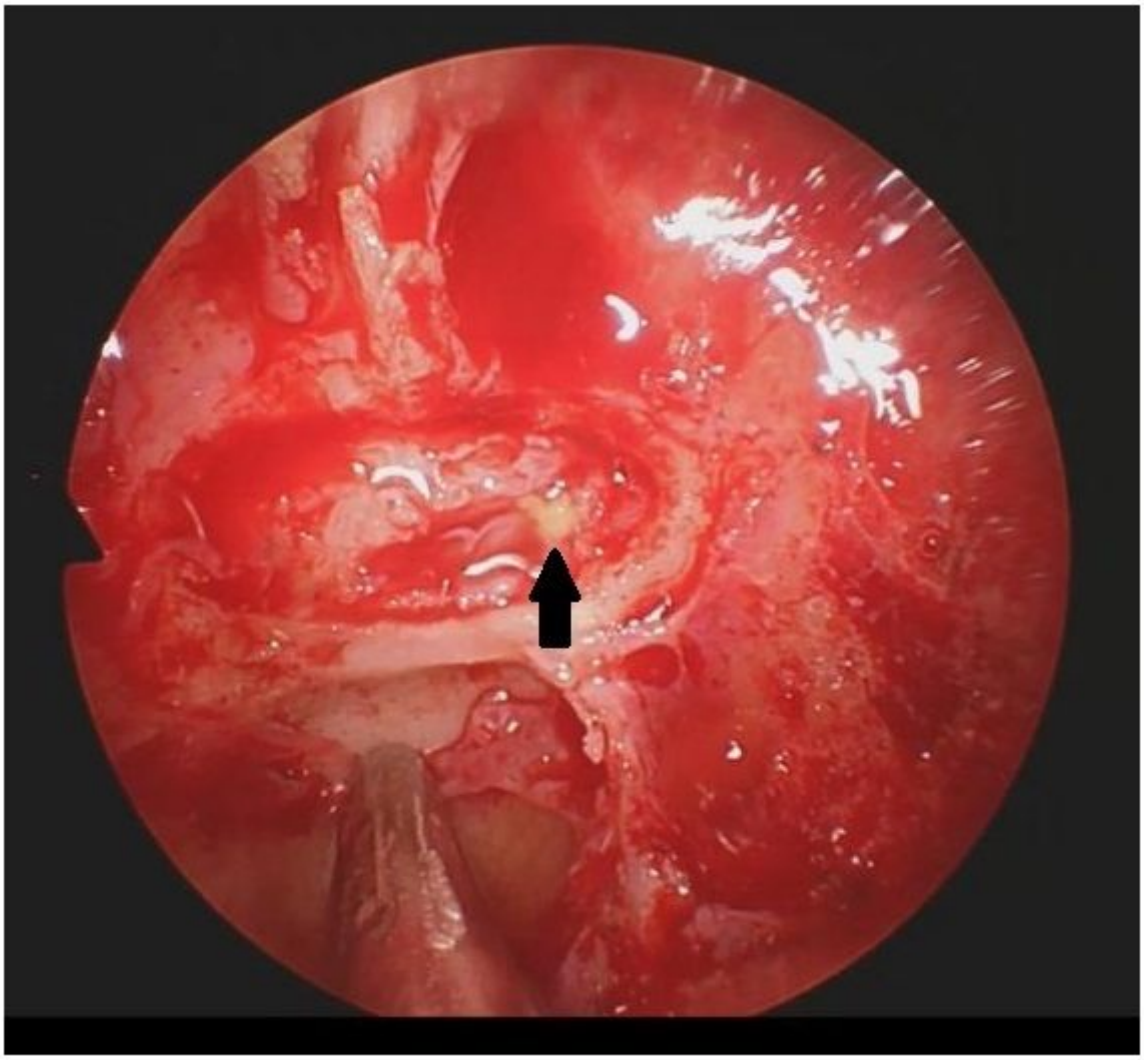

Figure 2

Intraoperative image demonstrating thick yellowish fluid draining from the pituitary lesion.

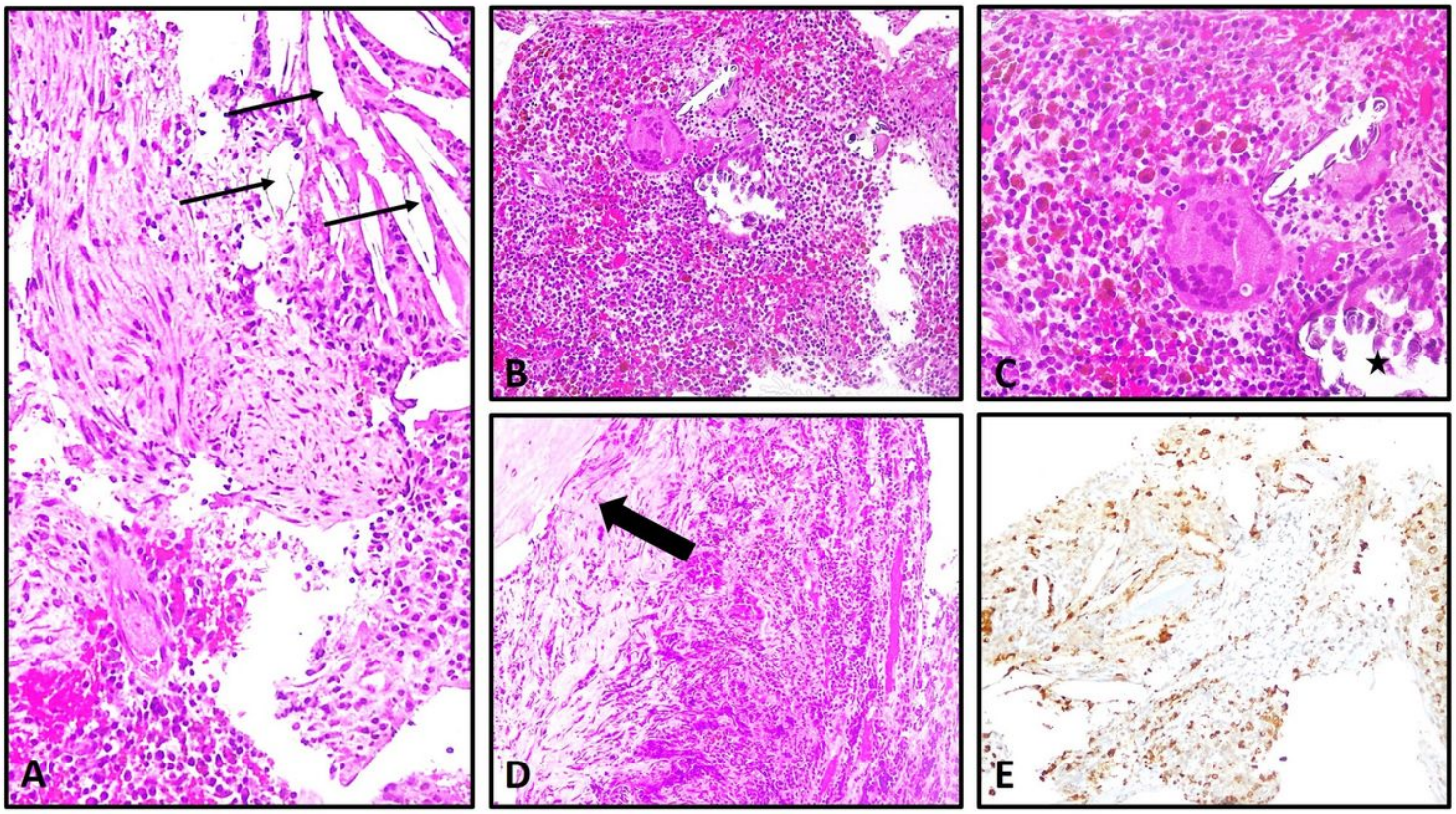

Figure 3

Histological images of the resected pituitary lesion. (A) Numerous cholesterol clefts in sections obtained from the pituitary mass (H&E, x200), (B) An area of lymphoplasmacytic cells with multinucleate giant cells and microcalcification (H&E, x100), (C) Numerous foamy and hemosiderin-containing macrophages with admixed lymphocytes and histiocytes and higher magnification of the B (H&E, x200), (D) Dense fibrous tissues containing chronic inflammatory cells (H&E, x100), (E) Histiocytes stained positively with CD68 (CD68, x100).