

XANTHOMATOUS HYPOPHYSITIS AS A CAUSE OF CLUSTER HEADACHE

A CASE REPORT

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ABSTRACT

Introduction: Hypophysitis is an inflammatory disease of the pituitary gland that may mimic pituitary tumors clinically and radiologically. Primary hypophysitis has traditionally been classified as lymphocytic (LH), granulomatous (GH), and xanthomatous (XH).

Case description: We report on a case of a xanthomatous hypophysitis initially diagnosed as pituitary adenoma. A 23-year-old man suffered from typical cluster type headache. Two years after the first symptoms, we confirmed diabetes insipidus. All the anterior pituitary hormone levels were normal. Sella MRI scan depicted a 14x10x17 mm inhomogenous mass.

Transphenoidal surgery was performed; the removed tissue showed accumulation of foamy cells and *xanthomatous epithelioid cells*. Following an uneventful postoperative recovery, severe cluster type headache returned after stopping the hydrocortisone therapy. The endocrine work-up revealed hypoadrenia (morning cortisol: 96 nm/l, ACTH:3.38 pm/l), hypothyroidism (ft4:10.5 pm/l), hypogonadism (testosterone: 3.44 nm/l) with normal FSH and LH (FSH:3.3 mIU/l,LH:2.8 mIU/l). We restarted hormonal therapy: hydrocortisone, levothyroxine and testosterone were stepwise reintroduced. During the follow-up period we could stop the hydrocortisone and levothyroxine supplementations, whereas the patient has permanently required desmopressin and testosterone substitution. Control sella MRI scans revealed no progression of the initially seen pituitary mass.

Conclusion: We describe an unusual case of xanthomatous hypophysitis causing cluster type headache and permanently requiring ddAVP (desmopressine) and testosterone supplementation without requiring maintenance medication with hydrocortisone and levothyroxin.

Our case:

We report a **23-year-old** man with XH who presented with cluster type headache, diabetes insipidus and MRI-proven pituitary intrasellar mass.

Since 2009 our patient suffered from recurrent **headache**. CT scan, ophthalmological, neurological investigations revealed no obvious cause of the symptoms.

In April 2011, polyuria-polydipsia occurred and endocrine investigations revealed **diabetes insipidus**. Anterior pituitary hormone levels were normal:

TSH: 1.3 mIU/l, FSH: 2.4 IU/l, LH: 3.7 IU/l, PR L: 197 mIU/l, ACTH: 7.78 pm/l, cortisol 08 h: 444 nm/l. After initialization of ddAVP treatment, diuresis returned to normal.

The pituitary MRI scan revealed a 14x10x17 mm inhomogenous lesion with the disappearance of the hyperintense signal of the neurohypophysis.

In July 2011, transsphenoidal surgery was performed and histology proved **xanthomatous hypophysitis**.

We could stop the glucocorticoid (GC) treatment without having any perioperative complication. The headache resolved but the diabetes insipidus persisted.

The anterior pituitary function after the surgery was normal: serum cortisol 08 h: 404-445 nm/l, ACTH:6.49 pm/l, FSH:3.1 mIU/l, LH:4.2 mIU/l, TSH:1.61 mIU/l.

2 months later severe cluster type headache occurred. Endocrine investigations revealed **hypoadrenia, hypothyroidism** and peripheral **hypogonadism**:

serum cortisol 08 h: 96 nm/l, TSH: 1.32 mIU/l, ft4: 10.5 pm/l, testosterone: 3.44 nm/l, FSH: 3.3 mIU/l, LH: 2.8 mIU/l, ACTH: 3.38pm/l.

LHRH test results: FSH: 0 min: 2.8, 30 min: 4.7, 60 min: 5.1 mIU/l, LH: 0 min: 2.9, 30 min:13.5, 60 min:13.8 mIU/l.

The postoperative pituitary MRI scan proved the persistent presence of the inhomogenous mass.

After initialization of glucocorticoid replacement the headache disappeared. With levothyroxin, testosterone supplementation and gradually lowered dosage of GC and all symptoms disappeared with the exception of diabetes insipidus.

Despite of low IGF 1 (92 ng/ml,age matched reference rate:117-329 ng/ml) and hGH (0.08 ng/ml) levels GH therapy was not introduced.

Autoimmune screen: ANA, antiCL, anti2GP, antitransglutaminase, antiTPO and antiparietal cell antibody was negative.

Regularly performed sella MRI scans showed no change in tumor size and appearance after the surgery and after the introduction of hormone replacement therapy.

The patient requires GC supplementation only in case of recurrent cluster type headache, but no persistent replacement is needed.

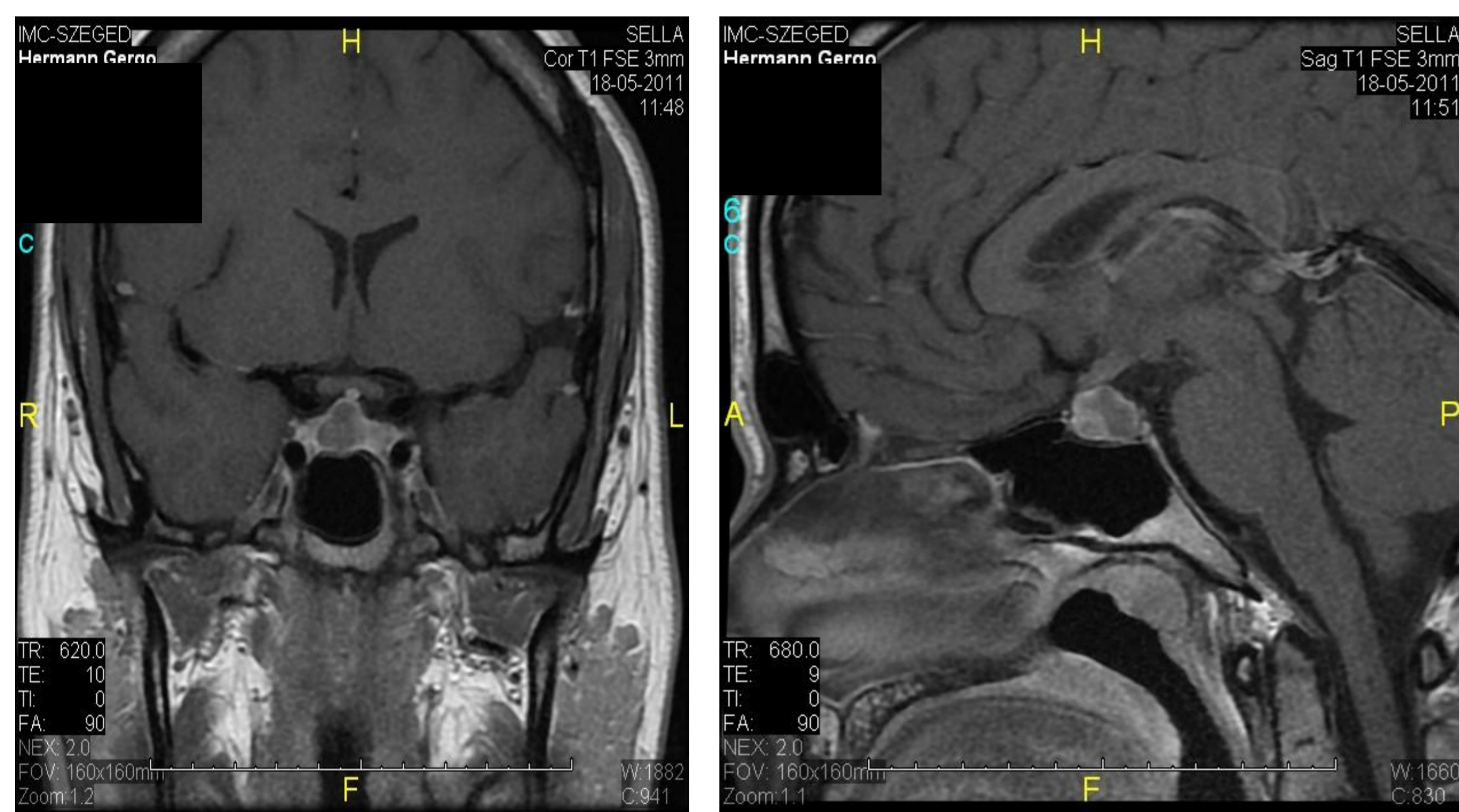
Conclusion:

Typical cluster type headache and diabetes insipidus were the two main syndromes of the XH In our case.

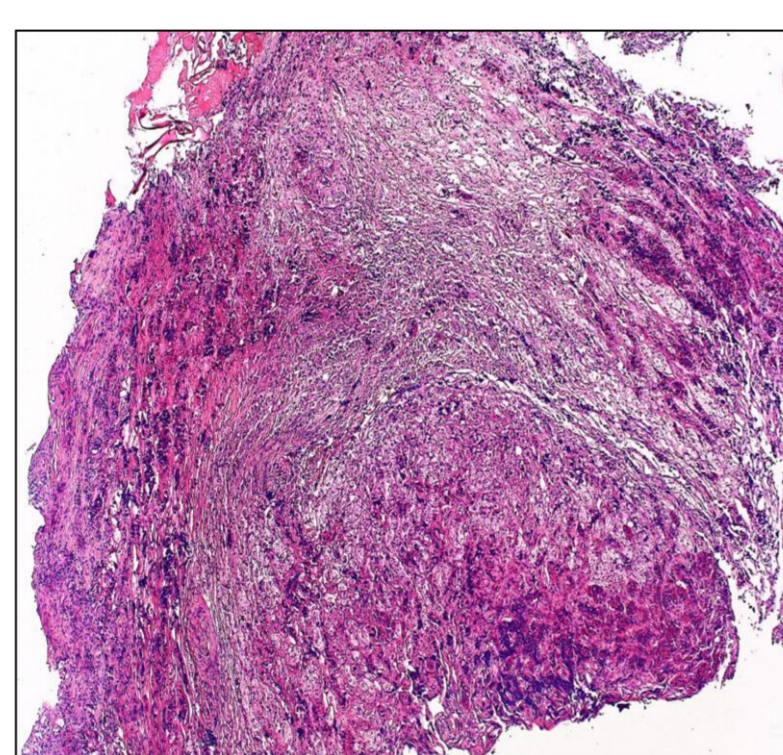
The patient requires GC supplementation only in case of recurrent cluster type headache, but no persistent replacement is needed.

The cause of the XH is still unknown, but the regular endocrine check-up can reveal disturbances in the pituitary function and, as in our case, glucocorticoid replacement seems to be effective in the treatment of the disease.

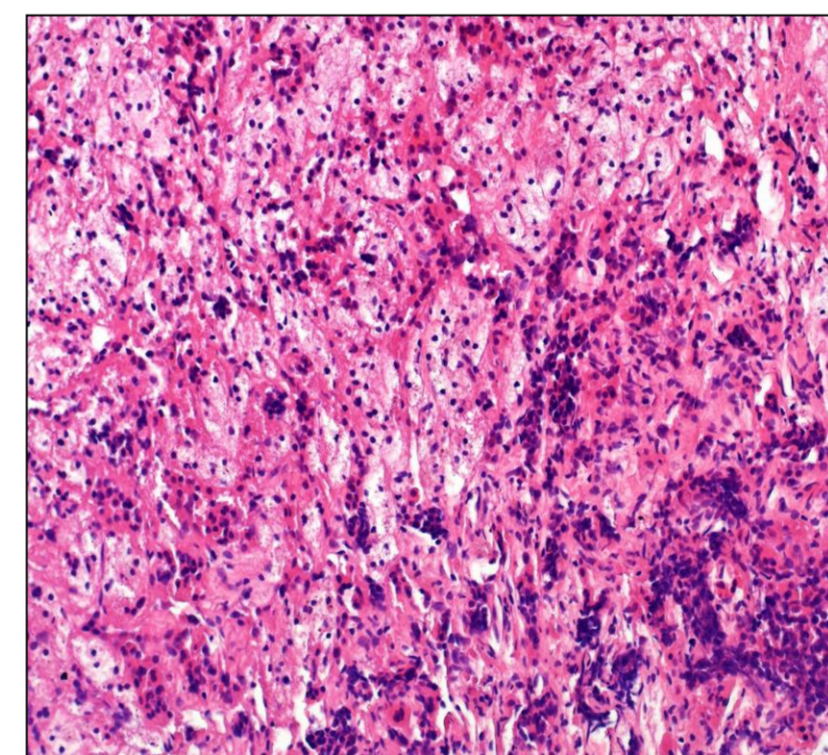
MRI



	Preoperative	Postoperative 1.	Postoperative 2. (headache)	Postoperative 3. (1year)	Reference range
TSH (mIU/L)	1.3	1.61	1.32	1.4	0.27-4.2
ft4 (pM/L)	14.7	14.7	10.5	14.9	12-22
ACTH (pg/mL)	7.78	6.49	3.38	6.36	1.6-13.9
Cortisol (nM/L)	444	445	96	445	171-530
FSH (IU/L)	2.4	3.1	3.3	1.4	1.5-12.4
LH (IU/L)	3.7	4.2	2.8	1.2	1.7-8.6
PRL (mIU/L)	197	88	202	151	87-327
Testosterone (nM/L)	7.36	3.87	3.44	2.05	9.9-28
SHBG (um/L)	19.4	16.5	15.7	13.1	14.5-48.4
hGH (ng/mL)	0.13	0.07	0.05	0.15	0.0-8.0
IGF1 (ng/mL)	<25	<25	163	137	117-329



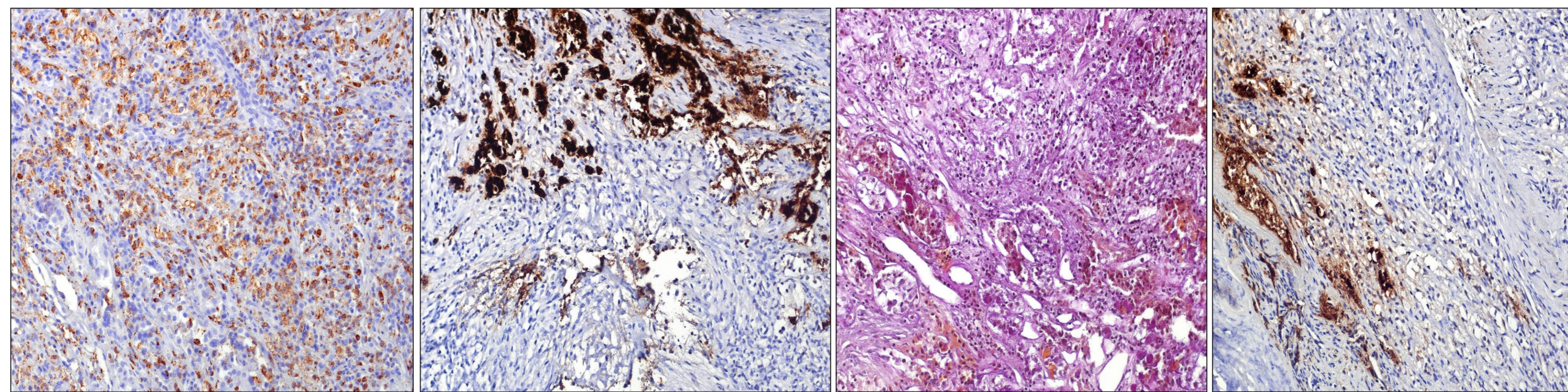
HE,5x



HE,20x

Histology

Immunohistochemistry



CD68, 20x

GH, 20x

PAS, 20x

PRL, 20x

The main symptoms of the **cluster type headache** are: high intensity,onesided, periodical headache. The incidence of this disease is between 0,07-0,7%. Men are 2,5 times more frequently affected than women. The **episodic form**, ~5% of the cases, cause 6 weeks long headache periods every year with long symptom-free intervals. The **chronic form**, ~15% of the cases, leads to long periods of headache with shorter asymptomatic ones. The headache is more painful than by migraine.

Primary hypophysitis is characterized by the focal or diffuse inflammatory infiltration and **destruction of the pituitary gland, causing varying degrees of endocrine dysfunction**.

Primary hypophysitis is divided into three categories: **lymphocytic (LH), granulomatous (GH) and xanthomatous**.

Xanthomatous hypophysitis (XH) is characterized by an infiltration of mixed inflammatory cells - foamy cells, plasma cells and small mature lymphocytes, in the anterior pituitary gland. The histological **differential diagnosis** includes other causes of hypophysitis, ECD, Langerhans cell histiocytosis, Rosai-Dorfman disease and plasma cell granuloma. Hypophysitis is a rare inflammatory disease of the pituitary gland that may be **misdiagnosed** by the radiologists as a pituitary adenoma or other sellar mass, such as a Rathke's cleft cyst. XH is the rarest form of primary hypophysitis.

The **pathogenesis, etiology, epidemiology, natural history, and prognosis** of the disease are unknown.

Transsphenoidal surgery is both diagnostic and therapeutic, and therefore should be performed in patients with progressive compression or those in whom radiological and/or clinical progression occurs during conservative medical management.

XH was first described by Folkert et al. in three patients in 1998. To our knowledge, approximately **15 patients with XH have been described**.

The overall **prognosis** for XH is good, but improvement of pituitary function after transsphenoidal surgery has been reported in less than 50% of patients.

Glucocorticoid therapy has been advocated to reduce inflammation and has been temporarily effective in some patients with primary hypophysitis. However, Gutenberg et al. (2006) demonstrated that methylprednisolone therapy, administered to one of four patients with XH, did not yield an efficient outcome. Steroid therapy seems to be less effective in XH compared to other kinds of primary hypophysitis

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