Azathioprine as an alternative treatment in primary hypophysitis

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Abstract Primary hypophysitis (PH) is an unusual disorder characterized by inflammatory infiltration of the pituitary gland with various degree of pituitary dysfunction. Glucocorticoids are the treatment of choice in the majority of patients. Still, in patients with poor response in glucocorticoids or when their administration is accompanied with serious side effects, the use of alternative agents should be considered; up to now, data on other therapeutic approaches remains scant mainly due to the rarity of the disease. Among them, the immunosuppressant azathioprine could represent an effective and safe alternative. In this article, we present our clinical experience of two cases with PH successfully treated with azathioprine following serious side effects after initial treatment with glucocorticoids and provide a brief review of the existing literature.

Keywords Pituitary gland · Primary hypophysitis · Azathioprine · Glucocorticoids

Introduction

Primary hypophysitis (PH) is an uncommon disorder characterized by focal or diffuse inflammatory infiltration of the pituitary gland. It is commonly presented as a sellar mass difficult to differentiate from other space-occupying lesions. In clinical practice, the diagnosis of PH is actually made after excluding all other causes of hypophysitis. Secondary hypophysitis can either occur in patients with systemic disease or infections (sarcoidosis, Wegener granulomatosis, histiocytosis, tuberculosis, syphilis) or it can originate from neighboring lesions (germinomas, Rathke’s cleft cysts, craniofaryngiomas and pituitary adenomas) [1].

Under the term PH three histopathologic subtypes can be recognized: lymphocytic (LH), granulomatous (GH) and xanthomatous hypophysitis (XH), whereas according to some investigators xanthogranulomatous and necrotizing hypophysitis should also be added in the PH classification [2–5]. In histological examination, the adenohypophysis shows a lymphocytic infiltration variably associated with destruction and fibrosis of the parenchyma. As a rule, there is an overlap among different types of hypophysitis [5].

A variety of clinical manifestations has been described including symptoms of sellar compression (headache, visual disturbances and decreased acuity and more rarely diplopia) and of anterior and posterior pituitary deficiency. Interestingly, ACTH deficiency usually occurs first -and in some cases solely- followed by impairment of the thyrotroph and gonadotroph cells, whereas mild hyperprolactinemia is also commonly observed. Common features in PH and sometimes adjuncts to the differential diagnosis (DD) are the discordance between the neuroimaging findings and the pituitary hormonal deficiencies, as well as the sudden onset of diabetes insipidus seen in 14–20% of lymphocytic hypophysitis cases [6, 7].

The natural history of PH is incompletely understood and varies from spontaneous partial or total remission of the pituitary function [8, 9] to permanent pituitary failure [10]. For this reason, conservative management with a watch n’ wait strategy is required in subclinical cases or where
diagnosis is not clear. In symptomatic patients, individualized treatment and close follow-up are of utmost importance. Glucocorticoids are considered the treatment of choice, whereas the attempt to use immunosuppressive drugs, like azathioprine, methotrexate and cyclosporine A, has been proven justified and could represent a viable alternative in PH [11–13]. A more aggressive surgical approach should be applied in the subset of patients unresponsive to medical therapy or with compressive symptoms.

Following, two female patients with PH successfully treated with azathioprine are presented along with a review of the current literature.

Patients and methods

The first patient is a 42-year-old woman referred to our Endocrinology Department for evaluation of iatrogenic Cushing’s syndrome. Six months ago, she presented with frontal headache and diplopia. She has a medical history of Hashimoto’s thyroiditis and reports regular menses. Neurological examination revealed bilateral sixth nerve palsy and on pituitary magnetic resonance imaging (MRI) a 2.5 cm pituitary mass was identified (Fig. 1a). The pituitary mass was considered to be a macroadenoma and she underwent trans-sphenoidal surgery. Unfortunately, data from the preoperative endocrinological evaluation is missing.

Histological examination of the resected tissue was consistent with parenchyma of adenohypophysis with acinar structure, without notable stromal fibrosis. Some tissue fragments showed dense infiltration by foam histiocytes, admixed with inflammatory cells including lymphocytes, plasma cells and few eosinophils. No multinuclear giant cells were present, whereas necrosis was present in a tissue fragment. Leucocytes and histiocytes were immunoreactive for LCA and CD-68 respectively. The adenohypophysial cells were variably immunopositive for all examined anterior pituitary hormones and glycoprotein hormone subunits (GH, PRL, ACTH, $\beta$-FSH, $\beta$-LH and $\alpha$-subunit). The histological findings were consistent with the diagnosis of xanthogranulomatous hypophysitis (Fig. 1b, c).

Postoperatively, she developed panhypopituitarism [fT4 10.1 pmol/l (NR 9.01–19.05), T3 0.45 ng/ml (NR 0.58–1.59), TSH 0.02 lIU/ml (NR 0.35–4.94), FSH

![Fig. 1](image_url)

**Fig. 1**  
**a** Preoperative coronary precontrast T1-weighted image showing diffuse inhomogeneous enlargement of the pituitary gland compressing the optic chiasm and extending intracavernosally in the left sinus. **b** Typical xanthogranulomatous hypophysitis including a sheath of foam cell histiocytes (center) and areas of lymphocytic infiltration, particularly in the margins, and foci of necrosis (right and left) (H&E, 25X). **c** Dense inflammatory infiltrate composed mainly of lymphocytes. Dispersed, isolated foam histiocytes are also noted (H&E, 25X). **d** Postoperative coronary T1 pituitary MRI showing sellar enlargement with diffuse inhomogeneous enhancement, thickened pituitary stalk and optic chiasm. **e** Coronary T1 pituitary MRI following 4 week azathioprine treatment with prominent shrinkage of the pituitary lesion.
0.60 mIU/ml, LH < 0.07, E2 < 10 pmol/l, morning cortisol 50 nmol/l (NR 138–690) and ACTH < 5 pg/ml (NR 9–52), PRL 12 ng/ml (NR 1.2–29), hGH 0.1 ng/ml (NR 0–6), IGF-1 78 ng/ml (NR 90–360), urinary osmolality 167 mOsm/Kg (NR 0–1250), serum osmolality 297 mOsm/Kg (NR 270–2900). Consequently, the patient was placed on substitution therapy with hydrocortisone, thyroxine and desmopressin. Three months postoperatively, the patient reported worsening headache episodes; on clinical examination visual field defects were present and pituitary MRI showed enlargement of the gland. Guided by the clinical picture of recurrent disease and the histology findings, her treatment was modified and hydrocortisone was replaced by high doses of methylprednisolone (16 mg tid).

Three months later, the patient developed Cushing’s phenotype (buffalo hump, hirsutism and abdominal obesity), as well as uncontrolled hypertension and diabetes mellitus and she was admitted to our clinic. The attempt to gradually reduce glucocorticoid dosage was unsuccessful, since the pituitary lesion size increased and patient’s visual fields and acuity further deteriorated suggesting PH relapse (Fig. 1d).

The second patient is a 45-year-old woman presented to our Department with a 3 month history of persisting headache and progressively worsening muscle weakness, as well as a 6 month history of secondary amenorrhea. She is a mother of two children, 15 and 12 years old, and has no relevant medical history. Physical examination was unremarkable (BMI 29 kg/m², blood pressure 110/65 mmHg, and pulse rate 70/min) and there was no clinical evidence of autoimmune disease. The patient underwent pituitary MRI, that showed a 12 x 13 mm lesion with a thickened pituitary stalk in close relation to the optic chiasm (Fig. 2a, b). The patient’s visual field testing was normal. Hormonal investigation showed anterior pituitary deficiency and mild hyperprolactinemia [morning cortisol 49 nmol/l and ACTH < 5 pg/ml (NR 9–52), fT4 7.2 pmol/l (NR 9.01–19.05), T3 0.74 ng/ml (NR 0.58–1.59), TSH 0.43 LRU/ml (NR 0.35–4.94), FSH 4.1 mIU/ml, LH 0.94, E2 < 10 pmol/l, PRL 43 ng/ml (NR 1.2–29)], while posterior pituitary function was normal. The clinical symptoms, imaging findings and hormonal profile led to a DD between a pituitary adenoma and an infiltrative or inflammatory lesion, like PH. In order to exclude infectious or granulomatous disease, a cerebrospinal fluid (CSF)
examination was performed. Serum and CSF angiotensin converting enzyme, VDRL testing for syphilis, PCR for tuberculosis and immunological investigation were all normal, CSF cultures, including mycobacterium, were negative and thus sarcoidosis, syphilis and tuberculosis were excluded. Consequently, we initiated glucocorticoid treatment with methylprednisolone 16 mg bid and substitution therapy with thyroxine (75 μg/day). On 1 month follow up, the patient complained for lumbar pain after minimum load and vertebral fractures in L2-L4 were diagnosed attributed to corticosteroid treatment. Bone mass density (BMD) was normal without evidence of osteopenia or osteoporosis assessed with dual X-ray absorptometry (DXA) at the femoral neck (T-score -0.0 SD) and at lumbar L1-L4 vertebral column (T-score +0.4 SD).

In the search of alternative treatment strategies, azathioprine was suggested and initiated in both patients as presented in detail followingly.

Results

Regarding the first patient, after the relapse of PH following the tapering attempt of glucocorticoids, the alternative option of immunosuppressive therapy with azathioprine was considered; after thorough explanation of the potential side effects and patient’s consent, therapy was initiated with a dose of 150 mg qd. Therapy was well tolerated except for a transient two-fold elevation of alanin and aspartate aminotransferase, five-fold gamma-glutamyl transferase and transient leucopenia 10 days after therapy initiation, that subsided with dose reduction to 100 mg qd. The improvement of the clinical symptoms was evident 4 weeks later and the reduction of the pituitary mass was documented in pituitary imaging (Fig. 1e). After a 6 month follow up, the azathioprine dose was further reduced to 50 mg qd and 12 months later the patient was stable without clinical or radiological signs of the disease and therapy was discontinued. She continues substitution therapy with hydrocortisone, thyroxine, desmopressin, as well as hormone replacement therapy and on her periodic follow-up 2 years later the patient remains disease free.

In the second patient, the presence of vertebral fractures- even in the absence of osteoporosis- led to gradual reduction of the glucocorticoid dose, switch to hydrocortisone replacement and after patient’s consent- azathioprine (100 mg qd) was started as an alternative treatment. Two months later, the patient’s clinical condition was clearly improved with remission of headache and resumption of menses. Hormonal reevaluation revealed a normalization of thyrotroph, gonadotroph and corticotroph pituitary function [morning cortisol 618 nmol/l (NR138–690), ACTH 28 pg/ml (NR 9–52), T4 14.2 pmol/l (NR 9.01–19.05), T3 1.22 ng/ml (NR 0.58–1.59), TSH 1.3 μIU/ml (NR 0.35–4.94), FSH 5.1 mIU/ml, LH 4.65, E2 527 pmol/l, PRL 19 ng/ml (NR 1.2–29), hGH 0.8 ng/ml (NR 0–6), IGF-1 204 ng/ml (NR 180–406)]. Accordingly, the post-treatment pituitary MRI showed a significant shrinkage of the mass (Fig. 2c, d). Thyroxine and hydrocortisone replacement were discontinued, whereas azathioprine was well tolerated and kept in the same dose for the following 6 months. Afterwards, azathioprine dose was reduced to 50 mg/day and withdrawn 6 months later. On the first year of follow-up she has no clinical or radiological evidence of residual disease.

Discussion

PH is a rare inflammatory pituitary disorder, that causes pituitary enlargement mimicking pituitary adenoma complicating final diagnosis and proper treatment [1, 14, 15]. More than 40% of PH cases can be misdiagnosed as pituitary adenomas in high-resolution MRI imaging preoperatively [16]. Accurate diagnosis is of great significance, since PH can be treated conservatively, without increased morbidity associated with unnecessary surgical treatment and mainly hypopituitarism. The clinical course and the classical treatment strategies have been reviewed in several case reports and small cohort studies. Herein, we report two females with PH successfully treated with the immunosuppressive drug azathioprine.

In the first subject, both components of granulomatous and xanthomatous hypophysitis were evident on histological examination thus allowing the term xanthogranulomatous hypophysitis.

GH and XH are extremely rare disorders with an annual incidence of 1 in 10 millions or less [17]. There are similarities in clinical and imaging findings with the most common LH, and hence the final diagnosis can be established only histologically. XH is classically defined by the presence of lipid rich foamy histiocytes with a variable number of lymphocytes and a cystic appearance on imaging [18]. In some cases, the inflammation is considered a response to components of a ruptured cyst; however, no confirmation of a pre-existing cyst nor an infectious process have been identified in our patient. The impairment of the anterior pituitary function in XH cases is usually mild- possibly due to the circumscribed lesion [19]. However, it remains unclear whether the different forms of PH are distinct entities or represent different manifestations of the same disease [4]. The rarity of the disease and the scarce existing data make the unravelling of the pathogenesis, clinical and radiological features and clinical course of XH even more complex.

In the second patient, the relatively rapid development of hypopituitarism made the diagnosis of a pituitary
adenoma less likely and led the DD more towards the direction of hypophysitis. In accordance, the thickened but intact pituitary stalk and symmetrically enlarged pituitary gland with intense enhancement following gadolinium also favored the diagnosis of hypophysitis. After clinical work-up to exclude secondary causes and without performing a pituitary biopsy, PH- and more specifically LH- was suspected. Regarding pathogenesis of LH, an autoimmune underlying mechanism has been suggested and LH has been associated with other autoimmune diseases, mainly Hashimoto thyroiditis, autoimmune polyglandular syndrome type 2, Graves’ disease, less commonly systemic lupus erythematosus, Sjogren’s syndrome, type 1 diabetes mellitus [6, 7]. Quite striking is the association of LH with the pregnancy or postpartum period [20, 21]. Anti-pituitary antibodies were not measured in our patient. They are not routinely available in clinical practice and are considered neither sensitive nor specific markers of autoimmune pituitary disease, since they are also present in patients with pituitary adenomas or other pituitary diseases [22, 23]. Despite lack of evidence of concomitant autoimmune disease, the increased frequency of LH compared to the extremely rare XH and GH provide rationale for the otherwise presumed diagnosis of LH in our patient.

Glucocorticoids remain a first line treatment in PH in order to attenuate inflammation, shrink the pituitary mass and restore pituitary function [7, 24, 25]. The vast majority of data arises from series of patients with LH and lesser with GH, given the higher frequency of the first form of PH, whereas data from XH patients are too few for a definite approach to be proposed. Still, the effectiveness of glucocorticoids in LH is far greater than in GH and XH [19]. High dose methylprednisolone pulse therapy has also been administrated with satisfying results [26, 27]. Patients with short standing disease (less than 6 months) seem to fare better after glucocorticoid therapy, possibly due to the less extensive degree of fibrosis of the pituitary gland; in contrast, long standing LH is more likely associated with irreversible anatomic and functional pituitary alterations. Despite the effectiveness of steroid treatment, there are cases with poor response [6, 16, 28], as well as relapse after discontinuation of glucocorticoids [29].

Other immunosuppressive drugs, like azathioprine [11], methotrexate [12] and cyclosporine A [13] have been proposed as an alternative in patients with a disappointing response to glucocorticoids or where glucocorticoid therapy cannot be tolerated or is associated with major adverse effects. Trans-sphenoidal surgical decompression of the pituitary mass should be reserved for the minority of patients with severe and progressive signs of optic nerve compression or increased intracranial pressure unresponsive to medical treatment [16]. Moreover, pituitary low-dose stereotactic radiotherapy or $\gamma$-knife irradiation has been reported to be an alternative therapy in selected PH patients unresponsive to glucocorticoid or surgical treatment [16, 30, 31].

Azathioprine is an imidazolyl derivative of 6-mercaptopurine used as an immunosuppressive agent. It antagonizes purine metabolism and may inhibit synthesis of DNA, RNA and proteins. Its indications include prevention of transplant rejection and treatment of rheumatoid arthritis. Furthermore, it could be used to treat other autoimmune diseases, like inflammatory bowel disease, autoimmune hepatitis, psoriasis and multiple sclerosis. As with other cytotoxic drugs, azathioprine can affect rapidly growing cells, including bone marrow, resulting in leucopenia, anemia and thrombocytopenia. Gastrointestinal side effects, like nausea, vomiting and hepatotoxicity, are also frequent but easily managed by dosage adjustment. In addition, azathioprine may increase the patient’s risk to develop neoplasia, even though data defining the precise risk for malignancy are incongruent [32–34].

The increased risk for malignancy shown in series of transplanted patients receiving azathioprine is possibly attributed to the a priori mutagenic potential of these subjects -due to chronic antigenic stimulation by the graft and/or other factors- boosted by the high doses of the immunosuppressants. It is thus unclear whether azathioprine per se should be exclusively accused for an increased neoplastic rate [35]. In the absence of alternative options and when the benefit of treatment with azathioprine outweighs the risk of malignancy, there is no rationale in withholding or hesitating to apply an effective therapeutic approach along with a close patient’s follow-up.

Literature data on azathioprine use in PH are scant. There is a report of an aggressive case of LH with immediate relapse after steroid tapering successfully treated with azathioprine for a time period of 5 months. After an 18 month follow-up without azathioprine, there was no evidence of recurrence [11]. On the contrary, a 3 month therapy with azathioprine in a male patient with LH was not successful in restoring pituitary function or reducing the pituitary mass after an initial transient improvement with methylprednisolone pulse therapy [36]. The extensive degree of fibrosis into the pituitary gland and the short time period of azathioprine treatment are two plausible explanations for the lack of response.

Regarding our patients, both of them experienced reduction of the pituitary mass. The first patient developed permanent post-operative panhypopituitarism, while full recovery of pituitary function was achieved in the second one. Following drug discontinuation, there is still no evidence of PH recurrence. Still, long-term follow-up is mandatory for both subjects.
Conclusion

Establishing the diagnosis of PH and treating symptoms of sellar compression, as well as hormonal deficits, can be very challenging. In this article, two PH cases successfully treated with the immunosuppressant azathioprine are described. This agent should be considered an effective and safe alternative treatment in patients with poor response to glucocorticoids or when the administration of the latter is contraindicated or associated with serious side effects.

References

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