Pituitary (2007) 10:107–111
DOI 10.1007/s11102-007-0016-z

CASE REPORT

Fatal inflammatory hypophysitis

Elizabeth A. McIntyre · Petros Perros

Published online: 22 February 2007

Abstract A young female patient presented as an acute medical emergency with hypoglycaemia. Investigations revealed panhypopituitarism and an inflammatory pituitary mass. An antibody screen was negative for anti-neutrophil cytoplasmic antibodies with cytoplasmic distribution (cANCA). Pituitary histology showed lymphocytic infiltration and a few Langerhan's cells. The pituitary mass rapidly expanded to involve the optic nerves and led to bilateral blindness. Later, the patient developed diarrhoea, a vasculitis rash, scleritis, and proteinuria. In subsequent investigations cANCA became positive. The patient responded to steroids and cyclophosphamide treatment and remained in partial remission for six months before dying of severe sepsis. This is the first description of Wegener's granulomatosis presenting with acute anterior pituitary failure in the absence of other organ involvement and negative serology.

Keywords Pituitary mass · Wegener's granulomatosis · Hypophysitis

Introduction

A heterogeneous group of diseases can present as an inflammatory mass in the pituitary fossa [1]. These diseases are either primary (intrinsic to the pituitary, aetiology unknown) or secondary (an etiologic agent or systemic disease is implicated). The clinical presentation of such lesions is often similar to pituitary adenomas, although headache, nausea and vomiting and posterior pituitary involvement are more common presentations of hypophysitis than pituitary adenomas [1]. Infection is a rare cause of hypophysitis but should be considered in the differential diagnosis of hypophysitis [2]. If suspected pre-operatively, full clinical and laboratory assessment of patients may provide the definitive diagnosis allowing the institution of appropriate medical therapy. However in the absence of a definitive clinical diagnosis at the time of presentation, surgery and histological diagnosis is essential to reach the ultimate diagnosis.

E. A. McIntyre · P. Perros (✉)
Endocrine Unit, Newcastle Hospitals NHS Trust, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK
e-mail: petros.perros@ncl.ac.uk

Case report

A 22-year-old female was admitted to hospital as an emergency following a collapse five weeks before referral to our centre. She was hypothermic, hypoglycaemic and hypotensive with no axillary and scanty pubic hair. Investigations confirmed the clinical suspicion of an acute pituitary insufficiency (Table 1). She was resuscitated and subsequently stabilised on hydrocortisone, thyroxine, and oestrogen replacement therapy. An MRI revealed a heterogeneous enhancing pituitary mass and thickened mucosa of the sphenoid sinus (Fig. 1). On review of her past medical history her menarche was at 11 years. She developed secondary amenorrhoea at the age of 14. At 17 years of age her serum gonadotrophins, oestradiol and prolactin concentrations were measured and found to be low as part of a gynaecological assessment for her amenorrhoea. No further investigations were undertaken at that time. Throughout her teenage years, she had

Table 1 Laboratory parameters of the patient

A. At the time of first presentation with acute hypopituitarism	
Serum sodium	135 mmol/l (135–145)
Serum potassium	4.9 mmol/l (3.4–5)
Serum creatinine	74 mcmol/l (75–120)
Plasma glucose	1.8 mmol/l
Haemoglobin	12.9 g/dl (13–18)
White cell count	8.5×10^9/l (4–11)
Platelets	367×10^9/l (150–450)
Serum Free Thyroxine	7 pmol/l (11–23)
Serum TSH	<0.1 mU/l (0.3–4.7)
Serum prolactin	<14 mIU/l (0–450)
Serum LH	<0.5 U/l (follicular phase 2–12)
Serum FSH	<0.4 IU/l (follicular phase 2–9)
Serum estradiol	<60 pmol/l (follicular phase 60–355)
Serum cortisol	
baseline	<18 nmol/l (9 am 190–650)
30′ after 250 mcg intravenous tetracosactrin	37 nmol/l
ESR	15 mm/h (1–19)
CRP	<5 mg/l (0–5)
B. Five weeks after the first presentation with acute hypopituitarism	
ANCA	negative
ACE	22 u/l (8–52)
Serology for parvovirus, mycoplasma, herpes simplex, varicella, rubella, leptospira, brucella, cryptococcus	negative
Culture and PCR of pituitary tissue for mycobacteria	negative
C. Six months after the first presentation with acute hypopituitarism	
Creatinine	90 mcmol/l (75–120)
ESR	35 mm/h (1–19)
CRP	60 mg/l (0–5)
CANCA	positive 1:80
Proteinase three antibody	positive

recurrent headaches diagnosed as migraine. She denied symptomatic sinusitis, chronic rhinitis or epistaxis. For six months prior to her collapse she had been generally unwell with increasing frequency and severity of headaches. A month before her admission she had an episode of confusion lasting for 30 min.

Five weeks after her presentation with collapse, she continued to have headaches. She was referred to our centre for further assessment. Auto-antibody titres including anti-nuclear cytoplasmic antibodies (ANCA), serum angiotensin converting enzyme (ACE), a chest X-ray and urine microscopy were

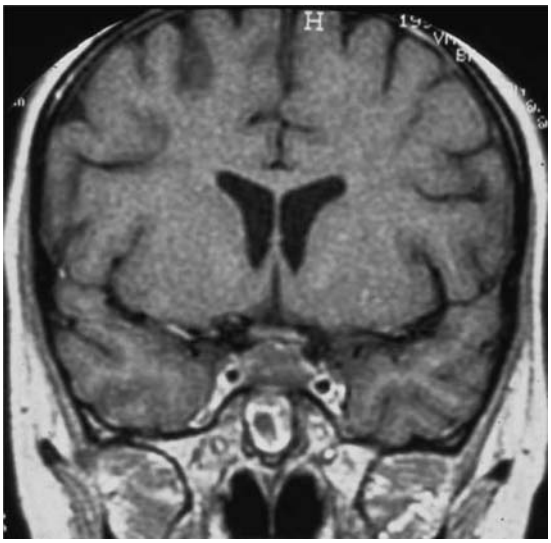

Fig. 1 T1 weighted MRI scan coronal section through the pituitary fossa demonstrating a heterogeneous mass in the pituitary fossa with suprasellar extension, but without significant compression of the optic chiasm, visual field assessment was normal. Also seen is thickening of the sphenoid sinus lining

normal. She underwent trans-sphenoidal surgery six weeks after her initial presentation with collapse. At surgery a firm mass of fibrous tissue was found occupying the pituitary fossa. Excision of the pituitary mass was impossible but biopsies were taken. Histology showed a dense fibrous infiltrate with a few nests of non-specific chronic inflammatory cells. On the second post-operative day she developed a partial right third nerve palsy. Repeat MRI scan revealed expansion of the tissue mass into the right cavernous sinus. Despite high doses of dexamethasone the partial third nerve palsy persisted, although the headache improved. She awoke on the sixth post-operative day with bilateral blindness and fixed dilated pupils. She underwent emergency transfrontal craniotomy. Both optic nerves and the optic chiasm were infiltrated by a dense waxy fibrous mass extending from the pituitary fossa. Biopsies were taken. Histology showed a chronic inflammatory process and Langerhan's cells were identified. A working diagnosis of Langerhan's cell histiocytosis was reached. External beam radiotherapy to the pituitary was commenced three months after her initial presentation with collapse. The radiotherapy was discontinued after nine fractions when further information from immuno-histochemistry of the inflammatory pituitary mass from her second operation showed a necrotizing infiltrative inflammatory reaction with no staining for S100 or CD1a. Meantime culture and PCR analysis of the pituitary tissue for acid fast bacilli and serology for parvovirus, mycoplasma, herpes simplex, measles, varicella zoster, rubella, leptospira, brucella

and cryptococcus were negative. A new histopathological diagnostic consensus of atypical lymphocytic hypophysitis was reached.

In the subsequent two months the patient remained a difficult management problem with severe headaches, helped little by a spectrum of analgesics including opioid analgesics and high dose oral steroids. Five months after the original presentation with acute pituitary insufficiency, the patient developed polyuria and polydipsia and investigations confirmed cranial diabetes insipidus. She was treated with desmopressin.

Six months after her initial presentation with collapse, repeat MRI scans showed further expansion of the pituitary mass with significant involvement and enhancement of the meninges bilaterally over the frontal lobes (Fig. 2). A week later she developed a vasculitic rash on her limbs, abdominal pain and diarrhoea. Her inflammatory markers, for the first time during her illness became raised (Table 1). Skin biopsy showed inflammation and microabscesses either secondary to septic emboli, or a primary vasculitic process. Cultures of blood, urine, faeces, and skin biopsy specimens were negative, echocardiography was normal as was CT of chest and abdomen. Lumbar puncture was normal. A formal dura biopsy was considered however over the following week she became drowsy, developed recurrent left hemiparesis, sensorineural hearing impairment and necrotizing scleritis of both eyes. Serum cANCA titre (previously negative on several occasions) was positive and proteinase three antibody was also positive (Table 1). Six and a half months after her initial presentation with collapse and acute hypopituitarism a diagnosis of Wegener's granulomatosis (WG) was made. Examination of the urine showed red cell casts on microscopy, urine culture was negative and serum creatinine remained normal (Table 1).

The patient commenced on intravenous high dose methyl-prednisolone and cyclophosphamide therapy. After three pulsed doses of immunosuppressive therapy the vasculitic rash and diarrhoea resolved, serum ANCA titres fell to 1 in 20 and the patient's higher cerebral function improved dramatically, however she remained blind with some hearing impairment. In the following six months she achieved a stable partial remission, maintained with cyclophosphamide and steroids, however the patient then presented with overwhelming sepsis and died 13 months after her initial presentation.

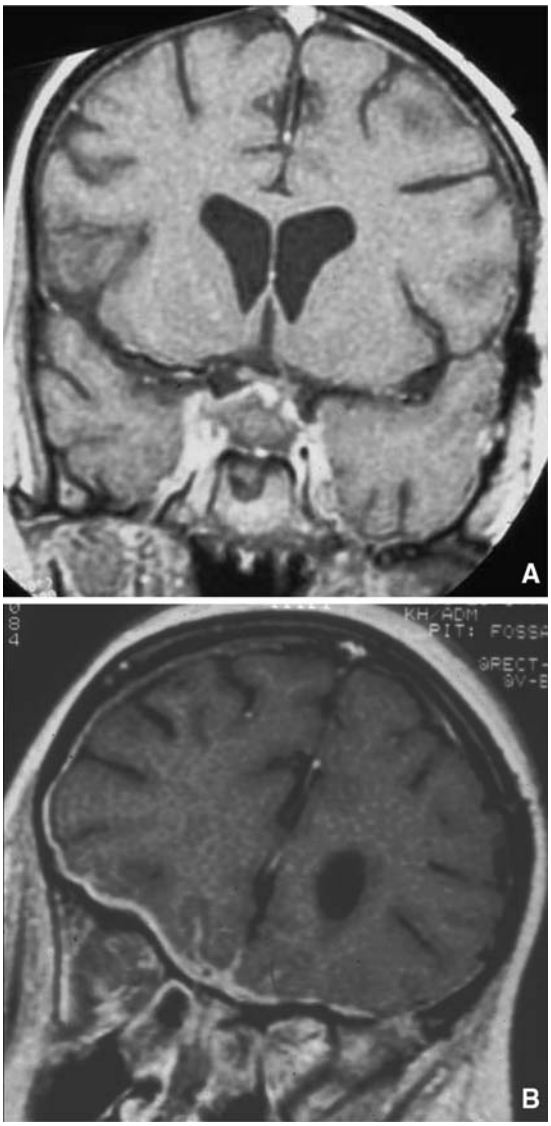

Fig. 2 T1 Weighted contrast enhanced MRI scan coronal section through pituitary fossa. (**A**) shows enlargement of the sellar and suprasellar mass, invasion of the right more than left cavernous sinus and thickening of the dura. (**B**) illustrates marked meningeal enhancement over both frontal lobes, right greater than left

Discussion

Histology in our patient showed a mixed chronic inflammatory cell infiltrate, no caseous necrosis was seen and PCR and cultures were negative for TB. Sarcoidosis was considered unlikely as there was no systemic manifestation of this disease and serum ACE levels were negative. The cell infiltrate was not monoclonal excluding conditions such as lymphoma. Initial histology showed sheets of histiocytes possibly supporting the diagnosis of Langerhan's histiocytosis. The absence of immunohistochemical staining for S100 protein led to the rejection of this diagnosis [3]. The spectrum of disorders associated with inflammatory hypophysitis is broad and includes lymphocytic hypophysitis, granulomatous hypophysitis, xanthomatous

hypophysitis [1, 2]. Lymphocytic hypophysitis usually presents in young women and may present in late pregnancy or in the early post-partum period [2]. An association with autoimmune conditions, particularly type 1 diabetes has been described and the histology typically shows lymphocytic infiltration forming follicles. The pathogenesis is probably autoimmune [4, 5]. The presentation of lymphocytic hypophysitis is commonly with hypopituitarism, the effects of an expanding pituitary mass (appearing as a solid mass on pituitary imaging), hyperprolactinaemia and less frequently posterior pituitary disturbance. Granulomatous hypophysitis, is rare and comprises less than 1% of all pituitary disorders with an incidence of 1 in 10 million per annum [2, 6]. It affects both sexes equally with a peak incidence in the second decade of life for women and fifth decade for men. Common presenting features are nausea, vomiting, meningitis, hyperprolactinaemia and diabetes insipidus. The radiological appearances are non-specific and consist of pituitary mass, which may be have both cystic and solid components and may extend beyond the sella [2, 7]. Histological characteristics include histiocytes, multinucleated giant cells and other inflammatory cells. Xanthomatous hypophysitis is very rare and characterised by the presence of foamy histiocytes [2, 8]. Occasionally hypophysitis may be associated with ruptured Rathke's cleft cyst [9], Takayasu's disease [10] or Crohn's disease [11].

Our patient had atypical histology. There was only one giant cell granuloma identified hence a diagnosis of granulomatous hypophysitis could not be reached. It was relatively late in the natural history of the disease process, when a definitive diagnosis of WG could be made based on clinical and serological criteria.

WG is a systemic small vessel vasculitis, which mainly affects sinuses, lungs and kidneys [12] but can affect several other organs including the central nervous system [13] and rarely the pituitary [14–18]. Granulomas are rare in WG involving head and neck [19]. The prevalence of ANCA in the serum of WG patients at some time in the course of their disease is 85–90% [20]. About 90% of patients with active untreated systemic WG have proteinase three-specific ANCA (PR3-ANCA) [21].

A few cases have been previously reported in which pituitary dysfunction was the first manifestation of WG, in all of these cases patients presented with diabetes insipidus [14, 15, 17, 18, 22].

Our patient was unusual in that she presented with acute anterior pituitary failure in the absence of involvement of any other organs by WG, while inflammatory markers were not raised and cANCA was undetectable. Our patient only developed weakly positive titres when her disease was multi-system and advanced. In retrospect the history of secondary amenorrhoea associated with biochemical evidence of gonadotrophin deficiency and headaches, suggest that the onset of WG may have been five years earlier.

MRI features of intracranial WG have been described in some detail and can be useful diagnostically especially when there is continuity of the lesion with orbital, nasal or paranasal sinuses [6, 23].

In our patient, the diagnosis was delayed because initial MRI and pituitary histology were not diagnostic. The serology turned positive for cANCA only late in the course of disease, at which time the patient had evidence of multi-system involvement. Previous reports illustrate that cANCA may be negative in 25% of localised WG [24]. Titres of cANCA tend to reflect disease activity [24, 25] and hence the seroconversion of our patient was indicative of increased disease activity and development of multi-organ involvement.

This rare presentation of WG posed significant diagnostic and management dilemmas to the physicians and surgeons involved and highlights several key learning points: (a) WG can rarely present with pituitary failure; (b) localised WG may not be associated with positive ANCA titres to aid diagnosis; (c) pituitary histopathology may not be diagnostic of the disease process, and therefore clinical suspicion is important; (d) in patients presenting with atypical pituitary lesions, especially when headache is a dominant symptom [26, 27] or if cranial nerve involvement is also present, WG should be considered in the differential diagnosis. cANCA should be measured repeatedly when the nature of a pituitary inflammatory mass remains unclear.

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