Hypophysitis in granulomatosis with polyangiitis: rare presentation of a multisystem disease

Manjunath P Ramakrishna[1], Chankramath S Arun[2], Praveen V Pavithran[3], Mithun C Bhagavaldas[4], Harish Kumar[5]

Abstract

Granulomatosis with polyangiitis (GPA) is a type of granulomatous vasculitis that can involve any organ in the body. The pituitary gland is one of the uncommon sites to be involved in this condition, with only a few cases reported in the literature. Our patient initially presented with central diabetes insipidus, epistaxis and haematuria. Diagnosis was established by antineutrophil cytoplasmic antibodies (cANCA) positivity against a background of typical clinical features and a bulky pituitary on magnetic resonance imaging (MRI) scan. Patient was started on steroids and methotrexate which were later changed to mycophenolate mofetil due to intolerance. Due to the refractory nature of the disease the patient was treated with one course of rituximab. Since then she has not had epistaxis, joint pains or haematuria. She continues to have diabetes insipidus although the requirement of desmopressin has come down. We thus report a case of GPA with hypophysitis which is one of the rare manifestations of the disease.

Correspondence to:
Arun Chankramath Somasekharan
Department of Endocrinology,
23 Vineyard Meadows,
Eroor South, Ernakulam,
Kerala, India 682306

Email:
csarun2003@yahoo.co.uk

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Introduction

Granulomatosis with polyangiitis (GPA) is small-to-medium vessel vasculitis with antibodies against anti-proteinase-3. GPA involving the pituitary can have both anterior and posterior pituitary manifestations with gonadotrophin deficiency and central diabetes insipidus being most common. Diagnosis is usually made on the basis of typical serological and radiological features with histological diagnosis required only in refractory disease or when pituitary manifestation is the sole presenting feature. Patients respond to immunosuppressive therapy and rarely require surgical intervention. Some patients can have permanent pituitary damage in spite of resolving systemic vasculitis. Hence early diagnosis and treatment is crucial in this condition to avoid lifelong complications such as hypopituitarism.

Case presentation

A 46-year-old perimenopausal female presented with headache, pedal oedema, polyuria, polydipsia, low backache and intermittent epistaxis of two years' duration. She gave a short history of excessive fluid intake, more than ten litres daily, with a similar amount of urine output. She had no past history of postpartum haemorrhage or snake bite. She denied any visual defects, galactorrhoea, weight loss, cough, fever, dyspnoea, skin rash or abdominal symptoms.

Initial investigations revealed a persistently raised erythrocyte sedimentation rate (ESR) (90 mm/hr) and hypernatraemia (160 mEq/l) (Table 1). She was not dehydrated. She had a mild goitre, enlarged tonsils bilaterally, but no lymphadenopathy. The nasal mucosa was noted to be friable and unhealthy. Her initial Birmingham Vasculitis Activity Score (BVAS) was nine.

Clinical and biochemical evidence of central diabetes insipidus, epistaxis, haematuria, raised ESR and a bulky pituitary gland pointed to a multisystem disease. The differential diagnosis included GPA, lymphoma, tuberculosis, sarcoidosis and Langerhans histiocytosis. Serum electrophoresis was negative, with no increase in light chains; serum angiotensin converting enzyme (ACE) levels were within normal range; c3, c4 complements were normal. antineutrophilcytoplasmic autoantibody (cANCA) was positive by immunofluorescence method with negative perinuclear anti-

[1]Senior Resident, Department of Endocrinology, Amrita Institute of Medical Sciences, Kochi, India; [2,3,5]Professor, Department of Endocrinology, Amrita Institute of Medical Sciences, Kochi, India; [4]Associate Professor, Department of Rheumatology, Amrita Institute of Medical Sciences, Kochi, India

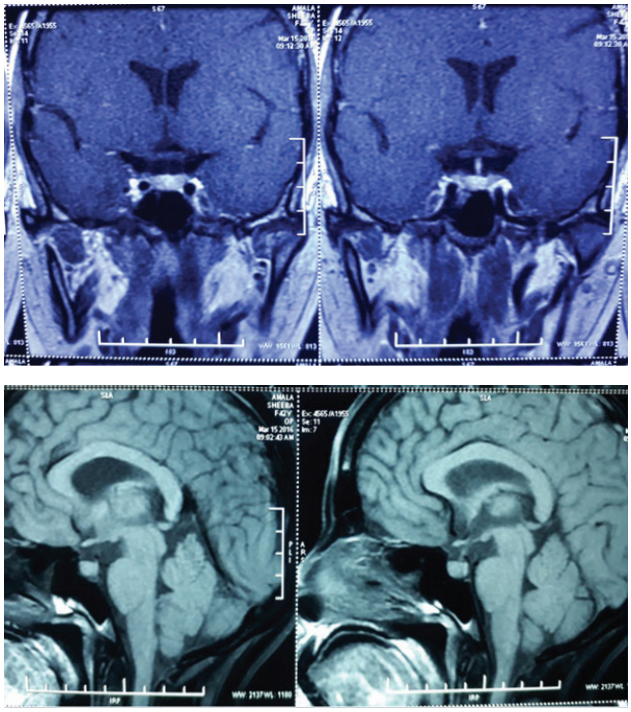
Table 1 Results of routine biochemical investigations and vasculitis workup done at presentation

	Value	Normal range
Haemoglobin (gm/dl)	11.4	12.0–15.0
AST IU/l	15	0.0–32
ALT IU/l	12	0.0–33
Serum albumin (gm/dl)	3.4	3.5–5.2
Serum globulin (gm/dl)	3.4	2.5–4.0
ESR (mm/hr)	90	8.0–20.0
LDH U/l	160	140 –280
Serum sodium (mmol/l)	160	136.0–145.0
Serum potassium (mmol/l)	3.7	3.5–5.1
Serum calcium (mg/dl)	9.2	8.6–10.0
HbA1c (%)	5.8	0.0–5.9
Urine routine	Numerous red blood cells present, no casts, no protein	
Urine osmolality (mosm/kg)	123	
Urine sodium (mEq/l)	50	<20
Serum cortisol (mcg/dl)	7.2	
Serum prolactin (ng/ml)	13.6	<20
TSH (miu/l)	1.94	0.4 to 4.0
Total T4 (mcg/dl)	11.2	4.5–12
Total T3 (ng/dl)	140	60–200
Complement C3 (mg/dl)	185	90–180
Complement C4 (mg/dl)	59.1	5.7–26.3
Serum electrophoresis	No M band	
cANCA	Positive	<8 units/ml
pANCA	Negative	<8 units/ml
ANA(IFA)	Negative	
ACE	19.3	16 – 85 U/l
Anti-PR3 antibodies (RU/ml)	4.9	<20
Anti-MPO antibodies (RU/ml)	7.6	<20
Mantoux test	Negative	
X-ray Lumbo-sacral spine	L5 spondylolysis	
Chest X-ray	Normal	

ASP: aspartate aminotransferase; ALT: alanine aminotransferase; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; HbA1c: glycated haemoglobin; TSH: thyrotrophin stimulating hormone; cANCA: cytoplasmic antineutrophil cytoplasmic antibodies; pANCA: perinuclear antineutrophil cytoplasmic antibodies; ANA: antinuclear antibody; ACE: angiotensin converting enzyme

neutrophil cytoplasmic antibodies (pANCA) and antinuclear antibody (ANA). Anti-myeloperoxidase antibodies and anti-proteinase-3 antibodies were negative by enzyme-linked immunosorbent assay (ELISA). A Mantoux test was also negative. MRI brain revealed pituitary gland measuring 10x 7.8 x 12 mm and stalk measuring 2.7 mm at the base (Figure 1). Fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan showed uptake in both tonsils, cervical lymph

Figure 1 MRI brain of the patient at presentation



nodes and right lung upper lobe. Paranasal sinuses did not show any increased uptake. The pituitary stalk was normal with no uptake (Figure 2). Nasal biopsy was reported as showing non-specific inflammatory tissue.

A final diagnosis of GPA was made and the patient was started on prednisolone and methotrexate with good clinical response. She had significant reduction in urine red blood cells as well as reduction in polyuria. She later developed intolerance to methotrexate and was started on mycophenolate mofetil with prednisolone. However, because of persistent disease activity suggested by a raised ESR, she was treated with two doses of rituximab 1000 mg, 15 days apart. She responded well to it and has remained in remission after two years of follow-up. Her Birmingham Vasculitis Activity Score came down from nine to zero and has since remained at that level (Table 2). She is currently on mycophenolate mofetil 500 mg twice daily, prednisolone 5 mg daily and vasopressin 100 mcg daily.

Discussion

Hypophysitis refers to acute or chronic inflammation of the pituitary gland and can be classified as adenohypophysitis, infundibulohypophysitis, or panhypophysitis based on the site of involvement.[1] They can also be termed primary or secondary based on the pathology.[1] Primary hypophysitis is further classified into lymphocytic, granulomatous, xanthomatous, necrotising and IgG4 varieties. Secondary hypophysitis can be inflammatory, infectious, infiltrative or iatrogenic type. GPA is a vasculitic disorder that rarely manifests with hypophysitis.[2]

GPA involves small to medium vessels and is associated with antineutrophil cytoplasmic antibodies (ANCA) directed

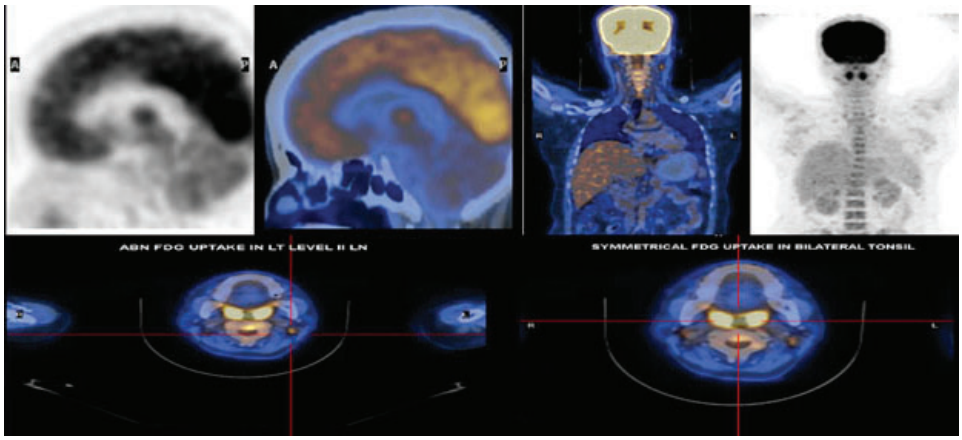


Figure 2 FDG PET CT

Pituitary gland and stalk normal with no uptake. Uptake in both tonsils (Suv Max 9.1), left level II cervical lymph node (Suv Max 3.2) and right lung upper lobe (7 x 6 mm non-avid).

against enzyme proteinase 3.[3] GPA can involve almost any organ in the body but has a predilection for the upper respiratory system, lungs, and kidneys. Central nervous system involvement is rare in this disorder (7–11%), pituitary gland involvement is rarer and occurs later in the disease process.[4,5] Common central nervous system presentations are cranial neuropathies, cerebral vasculitis and meningitis due to granulomatous process from the sinuses, orbits, vasculitis of the cerebral vessels.[6] A previous case series showed that 13% of cases had only anterior pituitary abnormalities, 52% only central diabetes insipidus and 35% had both anterior and posterior pituitary involvement. Central diabetes insipidus, when it occurs, can present earlier than manifestations of anterior pituitary disease.[7]

Clinical features provide clues to the diagnosis, but serological investigations help in the diagnosis. cANCA is positive in up to 90% of the cases and anti-proteinase-3 antibodies in 70–80%.[8] Radiological findings are present in the majority of cases, the most common being pituitary enlargement. Loss of posterior pituitary bright spot, pituitary nodules or infundibular thickening are other MRI findings. Occasionally the pituitary imaging can be normal.[9] Histological confirmation is required only in cases where pituitary disease is the sole presentation and in patients who are poorly responding to treatment.[10]

BVAS/ GPA has been one of the most successful disease activity scores that has been used in clinical trials as well as in assessment of patients with GPA. The absence of BVAS items is considered to be a valid indicator of remission.[11,12]

The importance of making an accurate diagnosis in such cases can be crucial as inflammatory or autoimmune hypophysitis is responsive to immunosuppression and thus readily amenable to treatment. Initial treatment is either high-dose corticosteroids or cyclophosphamide.[13,14] If the response is not satisfactory, azathioprine, methotrexate or mycophenolate mofetil are alternatives.[15,16] Humanised monoclonal antibodies such as rituximab and alemtuzumab have also been tried with variable success in refractory cases.[17] Recovery of the pituitary functions in patients with GPA hypophysitis is rare and may persist in spite of remission of the systemic vasculitis.[15,16] Hence early diagnosis of this condition helps us to manage serious consequences such as cortisol deficiency and diabetes insipidus more effectively.

Conclusion

In this case of GPA with multisystem involvement affecting nasal, renal, pulmonary and pituitary gland, cANCA positivity lead to the diagnosis, but anti-myeloperoxidase antibodies and anti-proteinase-3 antibodies were negative. Although many cases respond well to first-line immunosuppressive agents, occasionally rituximab might be required.

Table 2 Results of follow-up investigations performed over the next 22 months

Date	Baseline	1 month later	6 months later	9 months later	18 months later	22 months later
ESR (mm/hour)	76	86	74	21	12	7
CRP (mg/l)	33		47	18.2	20.6	2.82
Urine RBCs	7	40	2	0	0	0
Sodium (mmol/l)	140	141	139	144	139	
Potassium (mmol/l)	3.1	3.9	3.5	3.2	4.1	3.2
Input (litres)	12		1.5	1.5		1.5
Output (litres)	15		2	2.5		2
BVAS	9	6	6	0	0	0

BVAS: Birmingham Vasculitis Activity Score

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