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Case Report Open Access

Pituitary involvement in a case of granulomatosis with polyangiitis: case report and literature review

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Granulomatosis with polyangiitis (GPA, also known as Wegener's) is an anti-neutrophil cytoplasmic antibody-associated multisystem disease characterized by necrotizing small vessel vasculitis which mainly affects the upper and lower respiratory tracts as well as the kidneys. Involvement of the central nervous system is uncommon in GPA and might be difficult to treat. Pituitary involvement is a rare presentation in GPA. Presented herein is the case of a 28-year-old woman with GPA involving the pituitary gland and other systemic manifestations of the disease.

Keywords: Granulomatosis with polyangiitides, Wegener granulomatosis, Wegener's granulomatosis

Introduction

Granulomatosis with polyangiitis (GPA) is a vasculitis with an unknown etiology that involves small to medium vessels in the respiratory tract and kidney. It is associated with positive proteinase-3 (PR3) and anti-neutrophil cytoplasmic antibody (ANCA) blood tests [1, 2]. GPA is not a prevalent disorder; according to a study published in 2019, the prevalence of GPA among adults is 12.8 cases/million persons per year. The prevalence of GPA among children is 1.8 cases/million persons per year. In both pediatric and adult GPA cohorts, a significant female prevalence has been reported, confirming the slight female predominance [3]. Nervous system manifestations are common with the peripheral nervous system most commonly affected. Central nervous system (CNS) involvement is not common in GPA; the prevalence has been reported to be 7% to 11% of patients and higher when cranial neuropathies are included. It has mostly been reported in later stages of the disease, although its development as the first manifestation may occur. CNS vasculitis in GPA can affect pituitary gland, meninges, and cerebral vasculature [4-6]. Pituitary involvement in GPA is uncommon, however, it can result in partial or complete pituitary dysfunction [7-13]. We present a rare case of GPA with pituitary granuloma in a patient involving pulmonary and neurological manifestations.

Case presentation

A 28-year-old woman was referred to our hospital with a periorbital headache and otalgia for the past 11 months. At the time of admission, she had malaise, bi-temporal headache, otalgia, arthralgia, polyuria, polydipsia (approximately 5 liters of water per day), and non-bloody cough with progressive dyspnea. During a physical examination, post nasal discharge, tachypnea, and bilateral lower lung field rales were noted. The results of neurology and ophthalmology examinations, including the visual field, were normal. The patient was admitted to the internal ward, where she underwent a laboratory and imaging evaluation (laboratory data are presented in Table 1).

The patient had a history of severe otitis media and minimal response to antibiotics. She visited an ears, nose, and throat (ENT) specialist and underwent bilateral myringotomy and T-Tube implantation; however, her symptoms worsened three months later, and she was admitted to our hospital. Lung computed tomography (CT) scan identified a mass lesion in the apex of the left lung with cavitary change and air bronchogram, multinodular pattern in both lungs, diffused ground-glass opacities (GGO) in both lungs, as well as lymphadenopathies in both hila (Figure 1). Lung mass biopsy was in favor of extensive necrosis with acute and chronic inflammation. No sign of malignancy and a negative PAS stain were found. The electrocardiography (ECG) and echocardiography were both normal.

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Table 1. laboratory data

		Hematology	
		First	**Second**
WBC *10^3, /mm3		13,7	15,1
Hb, gr/dl		6.2	10.5
Plt (103) /m		494 1000	244
MCV, fl		75.15	75
RDW		17.9	18.4
RBC		2,9	3
		Biochemistry	
BUN (mg/dl)	5		7
Cr (mg/dl)	0.5		0.67
Na (mEq/L)	143	117 143	
K (mEq/L)	4.4		4.3
FBS (mg/dl)	**91**		
		Blood Gas Analysis	
pH		7.52	7.44
PCO2		38.4	36.5
PO2		65.2	52.3
HCO3 mmol/L		31.2	24.8
BE		8.4	1.8
PT, sec		13.6	
INR		1.01	
PTT,sec		30.6	
		LFT	
AST, U/L		25	
ALT, U/L		14	
Alk. Ph., U/L		273	
T. Bili., mg/dl		2.4	
D. Bili., mg/dl		0.9	
Protein, gr/dl		4.9	
Albumin, gr/dl		2.8	
Calcium (mg/dl)		8.4	
Mg (mg/dl)		2.3	

Hematology		
	First	**Second**
Ph (mg/dl)	4.7	
Uric Acid (mg/dl)	1.7	
CPK(U/L)	21	
LDH (U/L)	1020	800
CRP(mg/L)	64	78
ESR(mm/hr)	130	19
UA	nl	
U/C and B/C	neg	
Serum Iron(mcg/dl)	52	
TIBC (mcg/dl)	315	
Ferritin(ng/ml)	2517	1482
CEA (ng/ml)	1.2	
CA 19-9 (U/ml)	14.04	
CA125 (U/ml)	98.6	
C-ANCA (U/ml)	107.9	98
P-ANCA (U/ml)	2.3	
ANA (U/ml)	0.1	
Anti dsDNA (IU/ml)	11.6	
Anti CCP (U/ml)	5.5	
Wright	Neg	
2ME (mosm/l)	Neg	
Coombs (mosm/l)	Neg	
Retic count(%)	1.9	
Urine K random	17.64	
Urine Na random	44.4	
TSH (mIU/ml)	2.32	
ACTH (pg/ml)	10.3	
LH (mIU/ml)	0.21	
Prolactin (ng/ml)	20.97	
FSH (mIU/ml)	5.97	
Pleural pr.	2.8 (serum:5.4)	
Pleural LDH	417(serum:589)	
U24hr,pr (mg/24h)	261.8	
U24hr,V (ml/24h)	850	
U24h,rcr (mg/24h)	510	
HBS Ag, HCV Ab, HIV Ag-Ab: All non-reactive		
ACE: negative		

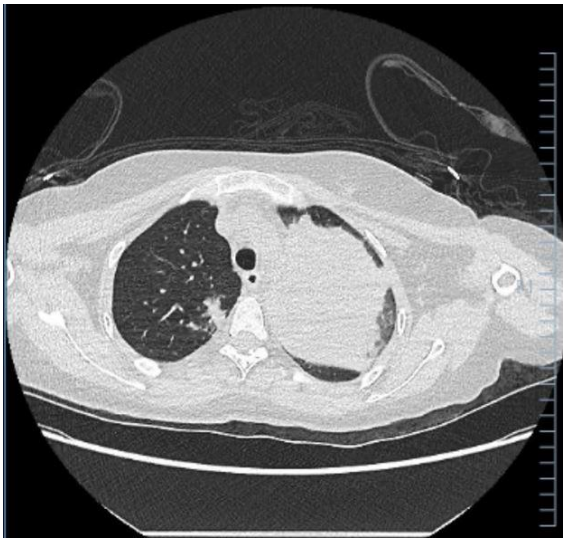

Figure 1. Lung CT scan

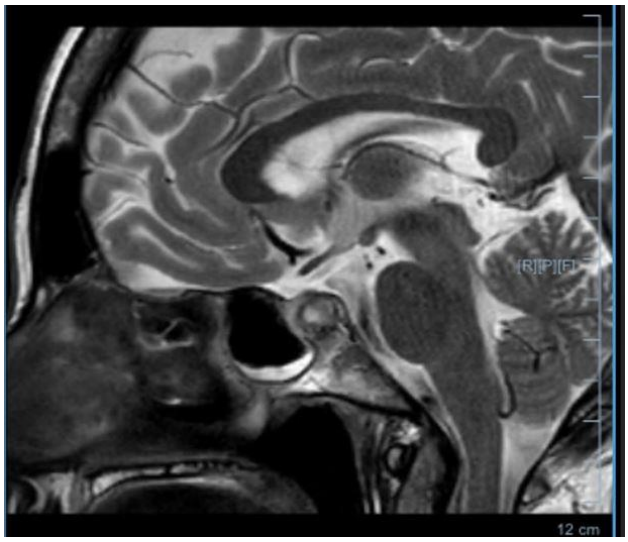

Figure 2. Pituitary MRI indicates no pressure on chiasma

SPIRAL CT SCAN OF PARA NASAL SINUSES WITHOUT CONTRAST (axial and coronal):
Multiple axial and coronal images through the paranasal sinuses are obtained which reveals:

Evidence of mucosal thickening in left maxillary sinus is noted.
The other para nasal sinuses are normally aerated with no evidence of sinusitis.
The ostiomeatal complexes bilaterally are patent.
Nasal septum is in mid line.
Nasal turbinates have normal shape.
Pterygopalatine fossa have normal symmetrical shape.
Maxillofacial structures show normal symmetrical anatomic configuration.
Bony orbits demonstrate normal symmetrical shape.

*AF Sincerely: Davani,MD.

Figure 3. Paranasal CT-scan report

At the time of admission, the patient was polyuric and polydipsic having about 20-liter urination per 24 hours. The water deprivation test was in favor of central diabetes insipidus (DI). After the patient refused a pituitary biopsy, desmopressin was started. A brain magnetic resonance imaging (MRI) was normal. Polyuria and polydipsia were resolved, and the patient's serum sodium level returned to a normal value, but the malaise, fatigue, and respiratory manifestations persisted. In addition, the patient developed hyponatremia, which led to the discontinuation of desmopressin (DDAVP). Due to severe dyspnea and a low oxygen saturation of 85%, the patient was transferred to the ICU.

In the ICU, rheumatological laboratory tests were requested for the patient, including antinuclear antibody (ANA), cytoplasmic-ANCA (C-ANCA), perinuclear-ANCA (P-ANCA), anti-double stranded DNA (anti-dsDNA), anti-cyclic citrullinated peptides (Anti-CCP), C3, C4, and rheumatoid factor (RF). Except for C-ANCA, all results were negative. C-ANCA was found to be positive at a high titer (C-ANCA = 98 (positive > 18 AU/ml)). The result of a skin purified protein derivative (PPD) test was negative. A pituitary MRI was also ordered for the patient, and the results indicated that she had a pituitary adenoma (Figure 2). Thereby, GPA was diagnosed for the patient. The patient refused a pituitary biopsy; thus, the diagnosis was made based on typical pituitary involvement of GPA manifestations, such as the absence of the posterior hyperintense signal and thickness of the pituitary stalk.

Treatment included methyl prednisolone pulse (1 g for three days) and prednisolone (50 mg per day) with a tapering schedule. Rituximab (2 g in two weeks) and cotrimoxazole were also prescribed for the patient. Medication had a profound effect on her. Coughing and sputum production ceased, and oxygen saturation rose to 98% in room air.

The patients had no complaints and denied any signs of polyuria and polydipsia 45 days later in outpatient follow-ups. Serum C-ANCA levels dropped to less than 10 AU/ml

(negative) and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels declined dramatically, although serum sodium, renal, and liver function tests remained normal. The osmolarity of the serum and urine were both normal, and urine analysis was likewise negative. The patient, however, refused to have a follow-up chest CT scan and a brain MRI.

Discussion

One of the most common clinical signs of ANCA-associated vasculitis (AAV), which can be life-threatening and cause considerable impairment, is involvement of the nervous system [9, 14, 15]. Some people may develop neurological symptoms at the onset of the condition [16]. In up to 67% of GPA patients, vasculitis of the vasa nervorum induces peripheral nervous system (PNS) involvement [sensory-motor polyneuropathy, 55%; mononeuritis multiplex, 45%] [17]. PNS involvement is more common in elderly males, who are more susceptible to kidney diseases at the time of GPA onset [12]. Three theories can explain the particular patterns of CNS involvement in the GPA pathocascase: 1) Inflammation spreading from sinonasal structures to neighboring tissues; 2) Intracerebral development of granulomatous lesions; 3) Primary vasculitis of small and medium CNS arteries [18-21].

Pituitary involvement accounts for roughly 1% of GPA and was first documented in 1953. As far as we know, less than 100 GPA cases with hypophysial involvement have been reported to date [22]. In diverse reports, the age of affected individuals has ranged from 28 to 67 years old, with no gender differences, and the median time to diagnosis of pituitary dysfunction (PD) after GPA was 10.4 months (range: 1–36 months) [23-25]. In 46% of cases, PD was the first manifestation of GPA, especially in younger ages, with ⁄. 2.5% having PD as the only sign of GPA.

When patients presented with PD and other systemic signs at the same time, the period between disease presentation and diagnosis of GPA was 1.5 months. Considering the fact that GPA is not usually suspected when PD exists in the absence of typical GPA features, vasculitis was diagnosed after a longer period of time (3-36 months) [26-28]. The most common clinical presentations of patients with PD were diabetes insipidus (DI) and hypogonadism (87.5% and 75%, respectively). Because of the effects of medications like cyclophosphamide and glucocorti-costeroids, hypogonadism may have been overstated in some trials. Hyperprolactinemia (about 50% of cases) and even panhypopituitarism (around 25% of cases) have also been documented as a result of compression of the pituitary stalk by an enlarged pituitary gland [28-30].

Polyuria, polydipsia, hypernatremia, and a urine osmotic pressure lower than plasma were used to diagnose DI in the majority of cases. In several cases, a water deprivation test confirmed the diagnosis [31]. Other PD-related clinical manifestations in different studies were headaches, vomiting, visual field defects, asthenia, amenorrhea, galactorrhea, decreased libido, muscular atrophy, and hair loss [24, 26, 27]. Accordingly, hormone studies are recommended in patients with suspected GPA and PD to diagnose hypogonadism, hypothyroidism, adrenal deficit, GH/IGF-1 deficiency, and hyperprolactinemia [26, 28, 29, 31]. Additionally, other systemic manifestations of GPA-related PD in addition to CNS implication included ENT involvement in 90% of cases, lung involvement in 43.5% of cases, eye involvement in 32.5% of cases, and kidney involvement in 21% of cases [28].

Pituitary MRI is the gold standard imaging for diagnosing pituitary involvement in GPA, with 94.1% of cases showing some abnormalities. The most prevalent finding was a pituitary enlargement or adenoma (in 80% of cases). A thickening of the pituitary stalk and the absence of the posterior hyperintense signal on T1-weighted imaging are also common findings. Pituitary adenoma can mimic the above MRI pattern, although patients with pituitary adenoma seldom present with DI, and other differentials such as GPA, sarcoidosis, and metastasis should be explored in such situations [32-35]. Interestingly, according to some research, younger women with GPA had a graver prognosis, with more common suprasellar expansion of the pituitary tumor and a higher risk of headache, hypopituitarism, and visual abnormalities [4, 20, 29, 31]. Serology tests in people with GPA and PD have yielded contradictory evidence. C-ANCA or anti-PR3 was shown to be positive in 91% of individuals in a recent study [28]. According to available reports, pituitary biopsy was performed in roughly 28% of suspected cases, and the results were in favor of well-formed non-caseous granulomas, lymphocyte and plasmocytic infiltration, and intercellular amorphous material deposition [28]. Pituitary biopsy is an invasive procedure and should be reserved for patients who have no classic GPA symptoms or surrogate indicators, such as upper and lower respiratory tract or kidney involvement, or who have failed to respond to standard treatments, particularly in the absence of positive ANCA [31]. Furthermore, a pituitary biopsy is not always diagnostic and can be confused with another conditions [32]. Other associated tissues' pathologic results may also help in making the correct diagnosis [34].

No randomized clinical trials have addressed the appropriate management for GPA and hypophysitis patients. The most commonly used drugs were glucocorticoids in high doses, cyclophosphamide or azathioprine, and rituximab, with remission attained in two thirds of patients [24, 27, 36]. Some studies reserved rituximab for individuals with refractory disease because of the granulomatous character of pituitary involvement and the lower efficiency of rituximab in patients with granuloma-related clinical symptoms. In many scenarios, drugs are chosen based on the presence of other organ involvement. Transsphenoidal surgery may be considered in patients who show symptoms of hypophysis compression. Recurrence of postoperative pituitary enlargement has been also reported. In 62.5% to 86% of patients, necrotizing granulomatous inflammation may cause lifelong pituitary dysfunction with minimal response to treatment [5, 33, 37-39]. We treated our patient as a case of GPA with pituitary involvement because of the presence of surrogate signs (otitis media and lung mass) and a positive C-ANCA. Although no specific pathology was

found in her lung tissue and she refused a pituitary biopsy, her satisfactory clinical response to glucocorticosteroids and rituximab after four months, the elimination of the need for desmopressin, and the normal serum sodium, urine, and serum osmolality all pointed to a diagnosis of vasculitis in the form of GPA.

Conclusion

Presented herein was a case of GPA with pituitary involvement as the first disease manifestation. Pituitary involvement is rare in GPA patients, and while there is no standard treatment, the goal of management is to reduce systemic inflammation. Patients usually have signs of active disease in other sites, such as ENT, eye, and CNS. In patients with pituitary dysfunction and associated clinical symptoms and signs, GPA should be investigated and therapy begun as soon as feasible to promote remission and prevent permanent damage. It may also be time to reconsider the scoring system for vasculitis activity to include pituitary involvement as an important and even early sign of the disease.

Acknowledgments

None.

Conflict of interest statement

None.

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