Subarachnoid Hemorrhage and Prostatic Involvement in Granulomatosis with Polyangiitis — An Atypical Presentation

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ABSTRACT

Granulomatosis with Polyangiitis (GPA) is a form of Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. We report a case of a 56-year-old man with GPA who first presented with acute urinary retention, and then developed pulmonary cavitating lesions and subarachnoid hemorrhage (SAH). The SAH was due to a ruptured right vertebral artery aneurysm, which was subsequently embolized. The patient initially had a good response to immunosuppressive therapy but later succumbed due to fulminant sepsis. SAH is a rare complication of GPA and usually not associated with a detectable aneurysm. Our patient is the second case in the literature where an aneurysm had been detected on angiography and the first case where examination of the culprit aneurysm revealed features of vasculitis.

Keywords: Wegener's Granulomatosis (WG); Granulomatosis with Polyangiitis (GPA); Anti-neutrophil Cytoplasmic Autoantibody (ANCA); Subarachnoid Hemorrhage (SAH); Intracranial Hemorrhage (ICH); Neurological; Urological; Prostate; Retention of Urine; Pulmonary; Cavitation.

INTRODUCTION

Granulomatosis with Polyangiitis (GPA) (formerly known as Wegener's granulomatosis) is a form of Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis involving the small and medium-sized vessels. Classically, the disease is a triad of upper airway, lungs and kidney vasculitis. However, all other organ systems, including the prostate and central nervous system, can also be involved. Here, we report a patient with atypical presentation of GPA which posed significant diagnostic challenges.

CASE PRESENTATION

A 56-year-old Chinese male, with history of recurrent first metatarsophalangeal joint (MTPJ) arthritis refractory to low purine diet and gout medication, first presented with acute retention of urine requiring urinary catheterization. On palpation, his prostate was large and irregular while the serum prostate specific antigen was 3.99 ng/ml (normal < 4 ng/ml). He was discharged home

with the urinary catheter in situ. A bone scintigraphy later showed no evidence of bony metastases.

Three weeks later, he was admitted to the hospital for dry cough and constitutional symptoms including fever, night sweats, and weight loss. On admission, the white cell count was $16.7 \times 10^9/L$ with 81% neutrophils, 7% lymphocytes, and 3% eosinophils, while the C-reactive protein was 166 mg/l and erythrocyte sedimentation rate was 118 mm/hr. On chest X-ray (CXR), he had a left upper lobe mass of 5 cm in diameter with cavitation. CT of the thorax revealed a loculated fluid collection in the posterior segment of the left upper lobe, as well as other small fluid collections, on a background of emphysematous changes.

The working diagnosis was multiple infective lung abscesses so he was given amoxicillin-clavulanate and then piperacillin-tazobactam. Serial CT of the thorax showed interval enlargement of the suspected lung abscesses (Figure 1) and fever was persistent. Ultrasound-guided aspiration of the left upper lobe

Figure 1. CT thorax showing progressive enlargement of cavitary lesions on days 2, 12, and 25 (from left to right).

Figure 2. CT pelvis showing progressive enlargement of prostatic mass on days 12 and 22 (from left to right).

lung abscess was repeated four times. Microbiological investigations of the abscess aspirates, blood, sputum, bronchoalveolar lavage, and urine for bacteria, fungus, and mycobacterium were all negative. On day 15, a USG-guided needle biopsy of the left lung lesion was performed. The lung biopsy revealed suppurative granulomatous inflammation and suppurative necrotic material focally rimmed by histiocytes and multinucleated giant cells. Histochemical staining did not show any microorganisms. Antibiotics were further escalated empirically to meropenem, vancomycin and micafungin.

The patient failed to wean off the urinary catheter, and required suprapubic catheter insertion on day 10 for difficult urethral catheterization. Serial CT of the pelvis revealed a multi-loculated rim-enhancing cystic prostatic mass with progressive enlargement (Figure 2). Transrectal ultrasound guided (TRUS) aspiration of the cystic mass was attempted and the pus grew carbapenem resistant Enterobacteriaceae (*Escherichia coli*), *Candida albicans*, *Bifidobacterium* species, and *Bacteroides* species, and antibiotics were changed to tigecycline. On day 26, a transurethral incision and drainage of the suspected prostate abscess was performed. The biopsy

Figure 3. CT brain showing acute subarachnoid and intraventricular hemorrhage with hydrocephalus (left) and right vertebral angiography showing right vertebral artery aneurysm (right).

specimen demonstrated necrotizing granulomatous inflammation with necrotizing granulomas rimmed by epithelioid histiocytes.

On day 24, the patient had an acute deterioration in conscious state requiring airway protection. Urgent CT brain revealed acute subarachnoid and intraventricular hemorrhage with early hydrocephalus (Figure 3). CT angiography of the cerebral arteries located a ruptured saccular aneurysm with lobulated appearance arising from the right vertebral artery. He underwent emergent external ventricular drain (EVD) insertion followed by vertebral angiography and embolization to the right vertebral artery aneurysm (Figure 3).

By the third week, serum antibody screen was done and was positive for c-ANCA. The anti-proteinase 3 (PR3) antibody level was strongly positive, > 200 RU/ml, but anti-myeloperoxidase antibody level was within normal range, 7.4 RU/ml. The diagnosis of GPA was suspected and further investigations were done to look for other organ involvement.

Review of the CT brain showed features of frontal and ethmoidal sinusitis. Nasopharyngoscopy noted

small ulcerative patches with dilated capillaries over the left lateral nasal wall and right posterior septum. Retinoscopy revealed signs of vasculitis, Roth's spots, as well as Terson's syndrome. The patient also developed maculopapular rashes over bilateral palms and soles, and skin biopsy of the right hand dorsum exhibited leukocytoclastic vasculitis. Ultrasound of his swollen right big toe revealed significant first MTPJ synovial hypertrophy. Synovial biopsy demonstrated extensive necrosis and vague granuloma without features of gouty tophi. Serum creatinine was 90 $\mu\text{mol/L}$ while estimated glomerular filtration rate was 82.8 ml/min (by MDRD equation corrected for body surface area). There was proteinuria with urine total protein-to-creatinine ratio of 1.74 mg/mg creatinine (normal < 0.2 mg/mg Cr, nephrotic range > 3.5 mg/mg Cr) but urine microscopy showed neither dysmorphic red blood cells nor red cell casts.

On the fourth week, the diagnosis of GPA was established in this patient based on a combination of positive ANCA and PR3 serology, multisystem involvement and histological evidence of necrotizing

Figure 4. AP chest X-ray on days 29 and 39, before and after pulse steroids respectively (from left to right).

vasculitis. According to the American College of Rheumatology criteria for GPA diagnosis, our patient presented with two of the four criteria, namely abnormal CXR and histological evidence of granulomatous inflammation (Sensitivity 88%, Specificity 92%). On day 29, the patient was started on intravenous methylprednisolone one gram daily for three doses, followed by prednisolone 65 mg daily. Fever subsided after the pulse steroids and serial CXR showed resolving infiltrates (Figure 4). He awoke to obey commands after weaning sedation.

Unfortunately, one week after initiating steroid therapy, the patient deteriorated with high fever, septic shock and worsening conscious state. Septic work-up was done, the external ventricular drain was removed, and meropenem was started. Repeat CT brain revealed diffuse cerebral edema and he rapidly progressed to brain death. In view of the poor neurological prognosis, the patient's family agreed to withdraw life support and he succumbed on day 39 of hospital admission. Subsequently, cultures from the blood, cerebrospinal fluid and EVD all grew extended-spectrum β -lactamase producing *Klebsiella*, which was only intermediately sensitive to meropenem.

Post-mortem examination of vertebral artery and brain were performed. Sections of the brain exhibited features of meningitis with dense neutrophilic infiltrates in the meninges. There was vasculitis in the right vertebral artery featuring disruption of the internal

elastic lamina, fibrinoid necrosis of the vascular wall associated with nuclear dusts, neutrophilic and histiocytic infiltrates. No well formed granuloma was seen. Histochemical stain for fungus and bacteria were negative. The CD163 stain highlighted the abundant histiocytes at the internal elastic lamina. Though secondary vasculitis of the vertebral artery due to meningitis could not be differentiated from primary vasculitis based on morphology, the overall picture was compatible with GPA.

DISCUSSION

In the central nervous system, GPA most commonly affects the cranial nerves but can also cause intracranial hemorrhage and cerebral vascular thrombosis [2,6]. Such manifestations range from 1.7–26.7% of GPA cases (Table 1). In a review of 104 patients, Drachman [2] found 54% of patients had some form of neurological involvement while 9% had developed cerebrovascular events. In another review of 324 patients by Nishino et al. [10], 33.6% of patients had neurological involvement while 4% had cerebrovascular events. It has been postulated that these cerebrovascular events occur as a result of vasculitis of the nervous system [2].

Subarachnoid hemorrhage is a rare complication of GPA with uncertain etiology and we have identified nine other cases (Table 2). Most of these GPA patients are of male gender. Brain autopsy was performed in only three cases, of which two showed vasculitis [1,2,6]. As GPA

Table 1. Review on clinical manifestations of patients with GPA.

Study	Total patients	Organ involvement (%)			
		Joint	PNS [†]	CNS [‡]	Renal
Drachman (1963) [2]	104	—	54	54	—
Hoffman et al. (1992) [9]	158	67	15	8	77
Nishino et al. (1993) [10]	324	—	33.6	33.6	—
Huong et al. (1995) [11]	80	45	23	8	58
Reinhold-Keller et al. (2000) [12]	155	77	40	11	70
Stone (2003) [13]	180	66.1	7.2	1.7	68
Holle et al. (2011) [14]	445	73	23	10	59.1
Mahr et al. (2013) [15]	396	—	28.3	28.3	—
Sharma et al. (2018) [16]	105	43.8	11.4	26.7	51.4

† PNS – Peripheral nervous system, ‡ CNS – Central nervous system.

Table 2. Case reports of subarachnoid hemorrhage.

Reference	Age	Sex	Cerebral angiogram	Outcome
Tuhy et al. (1958) [1]	39	Male	Not done	Died
Drachman (1963) [2]	30	Male	Not done	Died
Rordam and Hansen (1971) [3]	53	Male	Not done	Died
Venning et al. (1991) [4]	50	Male	Negative	Survived
	36	Male	Negative	Survived
Cruz and Segal (1997) [5]	71	Male	Negative	Survived
Nardone et al. (2004) [6]	78	Female	Not done	Died
Takei et al. (2004) [7]	34	Male	Left anterior choroidal artery aneurysm	Survived
Miles et al. (2011) [8]	74	Female	Not done	Died
Present case	56	Male	Right vertebral artery aneurysm	Died

typically involves small- to medium-sized blood vessels, detection of the culprit aneurysm is often difficult. Our patient is the second case where an aneurysm had been successfully identified on angiography. He is also the first patient in the literature where examination of the culprit aneurysm revealed vasculitis, although without granulomas.

As joint involvement by GPA affects 43.8–67% of patients (Table 1), we postulate that his MTPJ arthritis was an early sign of disease. Prostatic involvement by GPA, being the most common example of urogenital involvement, is quoted to range from 2.3–7.4% [17,18].

Patients typically present with chronic obstructive symptoms, hematuria, recurrent urinary tract infections, or acute urinary retention [11,19–21]. These symptoms occur at the first presentation 26% of the time. These patients often have elevated PSA and radiological lung changes, therefore are frequently mistaken to have metastatic prostate cancer [21]. Renal involvement is common and ranges from 51.4–77% (Table 1). Our patient had proteinuria but no significant renal impairment. Unfortunately, no renal biopsy was done.

Our patient presented significant diagnostic difficulty and reminds us that systemic vasculitis can

often mimic infection with persistent negative cultures. A misdiagnosis of sepsis could lead to unnecessary use of prolonged broad-spectrum antibiotics with emergence of antibiotic resistance. Pulse steroids remain the mainstay of treatment for severe GPA, rendering these patients at high risk of infections. Our patient initially had a good response to steroids, but eventually died from fulminant EVD-related intracranial infection with ventriculitis and bacteremia, caused by multi-drug resistant *Klebsiella*. EVD is frequently necessary in neurological ICU patients. However, nosocomial EVD-related infections are a significant cause of morbidity and mortality.

In conclusion, we presented a patient with GPA who developed prostatism, multiple lung lesions and SAH. Systemic vasculitis often poses challenges in diagnosis and management. It is important to recognize ANCA-associated vasculitis in view of their poor prognosis and the need for early treatment.

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