A Case of Granulomatosis with Polyangiitis Diagnosed at Autopsy

J. Keith Pinckard

ABSTRACT

Herein is reported a case of granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, diagnosed at forensic autopsy in an 83-year-old woman with a history of Alzheimer disease. Significant findings at autopsy were cardiac hypertrophy, nephroarteriosclerosis, hemorrhagic lungs, and necrotizing granulomatous inflammation with vasculitis involving the lungs and kidneys. Semiquantitative immunofluorescence testing was positive for cytoplasmic antineutrophil cytoplasm antibodies at a titer of 1:40. An enzyme-linked immunosorbent assay for proteinase 3 was strongly positive at 134 units (reference range: positive greater than 30 units). The cause of death was therefore determined to be granulomatosis with polyangiitis. Presentation of GPA at such an advanced age is rare, especially with the presentation at death. *Acad Forensic Pathol.* 2017 7(2): 288-298

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STATEMENT OF HUMAN AND ANIMAL RIGHTS

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STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

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INTRODUCTION

Granulomatosis with polyangiitis (GPA) was formerly known by the name Wegener's granulomatosis, named after Friedrich Wegener, who described the disease in 1936. In recent years, Woywodt and Matteson have promoted the abandonment of eponyms in the classification of diseases not only for Wegener's granulomatosis but also for other diseases (1, 2), resulting in the modern name, granulomatosis with polyangiitis, being adopted (3).

Granulomatosis with polyangiitis is one of the anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides as defined by the 2012 Chapel Hill consensus conference, together with microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg-Strauss syndrome) (4).

Most cases of ANCA-associated vasculitides present between the ages of 40 and 50 years (5). Herein is described a case of GPA in an elderly woman who died of GPA, in which the diagnosis was made at autopsy.

CASE REPORT

The case involves an 83-year-old woman with a history of Alzheimer disease, hypertension, and seasonal allergies. Her prescription medications included aripiprazole and donepezil for her dementia, hydrochlorothiazide for hypertension, and loratadine for her allergies. She had been complaining of sinus pain and had seen her primary care physician, who had prescribed amoxicillin for a presumed sinus infection, which she had taken the night before she died. She was last known to be alive the prior evening when she and her husband went to bed. Her husband awoke the next morning and found her unresponsive; emergency medical services were called and she was pronounced dead at the scene. The case was referred to the medical examiner's office for autopsy.

The body measured 163 cm (64 in) long and weighed 55.3 kg (122 pounds). The external examination was unremarkable; her body appeared well developed and well nourished. Internal examination revealed an enlarged heart (550 g). The coronary arteries all exhibited less than 25% luminal stenosis by atherosclerotic plaque. The cortical surfaces of the kidneys were markedly granular, with pitted scars. The right and left lungs weighed 1425 and 800 g, respectively. Cut surfaces of the pulmonary parenchyma exuded blood-tinged fluid and although markedly heavy, did not appear to be otherwise abnormal.

Microscopically, the lungs exhibited prominent and widespread alveolar hemorrhage (**Image 1**) with focal hyaline membranes (**Image 2**). The pulmonary parenchyma was largely overtaken by epithelioid granulomas with multinucleated giant cells; several were necrotizing (**Images 3 through 5**). Small arterioles exhibited acute vasculitis with fibrinoid necrosis (**Image 3**). Acid fast (Ziehl-Nielsen) and Gomori methenamine silver stains did not reveal the presence of acid fast bacilli or fungal organisms, respectively. Microscopic sections of kidney demonstrated loosely formed necrotizing granulomas with multinucleated giant cells (**Image 6**) as well as multifocal vasculitis with infiltration of vessel walls, predominantly by neutrophils, and fibrinoid necrosis (**Images 7 and 8**). No other organs exhibited similar microscopic findings.

Indirect semiquantitative immunofluorescence staining of neutrophils mixed with the decedent's serum demonstrated positivity in a cytoplasmic distribution (c-ANCA) at a titer of 1:40. Reflex enzyme-linked immunosorbent assay (ELISA) testing for proteinase 3 (PR3)-ANCA was positive, with a result of 134 Units (reference range: negative < 20 Units; weak positive 21-30 Units; and positive > 30 Units). Myeloperoxidase (MPO)-ANCA testing by ELISA was negative.

The microscopic findings and ANCA testing results are diagnostic of GPA, which was determined to be the cause of death.

DISCUSSION

Epidemiology

The differential diagnosis of the ANCA-positive vasculitides includes GPA, MPA, and EGPA. The ANCA-associated vasculitides affect males and females approximately equally, with most patients in between 40 and 50 years of age (5, 6). The vast majority of patients are Caucasian or of Hispanic descent (5). The incidence of GPA has been reported to be between two and 12 per million per year (7).

Clinical Features

Patients with GPA generally exhibit pneumonitis, chronic sinusitis, nasopharyngeal mucosal ulceration, and renal disease (6).

Diagnosis

Staining of neutrophils with ANCA antibodies in a cytoplasmic distribution in GPA patients was reported over 30 years ago (8) and was later demonstrated to exhibit high sensitivity and specificity (93% and 97%, respectively) in clinical studies (8, 9). In contrast, the

Image 1: Diffuse alveolar hemorrhage (H&E, x40).

other ANCA-positive vasculitides, MPA and EGPA, generally exhibit immunofluorescence in a perinuclear pattern. Combining the results of indirect immunofluorescence for ANCA with ELISAs detecting specific antibodies to PR3 and myeloperoxidase (MPO) increased the diagnostic specificities to 99%; the combination of c-ANCA staining and positivity for PR3 was demonstrated to be highly specific for GPA (10).

Pathology

Granulomatosis with polyangiitis is characterized by a pathologic triad: 1) a necrotizing granulomatous inflammation that can involve any portion of the respiratory tract; 2) a small- to medium-sized vessel granulo-

matous vasculitis that may or may not be necrotizing, which is commonly seen in the respiratory system but can also affect other sites, including the kidney; and 3) necrotizing glomerulonephritis (in some but not all cases), that may progress to crescentic glomerulonephritis (6), which was not seen in the presented case.

The histopathologic features and associations with ANCA are summarized in **Table 1**.

Pathogenesis

The disease is thought to represent an autoimmune disease involving an abnormal T-cell response to inhaled antigens. Indeed, the disease responds to immunosup-

Image 2: Alveoli with hyaline membranes (H&E, x100).

Table 1: Pathologic Diagnosis of the Antineutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitides

	Granulomatosis with Polyangiitis (GPA)	Microscopic Polyangiitis (MPA)	Eosinophilic Granulomatosis with Polyangiitis (EGPA)
Typical histopathology	Granulomatous, necrotizing vasculitis	Nongranulomatous, necrotizing vasculitis	Granulomatous, necrotizing vasculitis with eosinophils
Typical ANCA immunofluorescence pattern	Cytoplasmic	Perinuclear	Perinuclear
Typical ANCA specificity	PR3	MPO	MPO

PR3 - Proteinase 3

MPO - Myeloperoxidase

Image 3: Pulmonary parenchyma with multiple granulomas containing multinucleated giant cells, some of which exhibit necrosis. Vasculitis involving small vessel (arrow) (H&E, x200).

pressive therapy (see below). The autoantibodies to MPO and PR3, in addition to being disease markers, have also been hypothesized to play a pathogenic role in the ANCA-associated vasculitides; however, the precise mechanisms are not entirely clear, especially in the case of PR3-ANCA and GPA, and are reviewed elsewhere (11, 12).

Treatment and Prognosis

Granulomatosis with polyangiitis is rapidly fatal without treatment (6); however, advances in medical treatment include steroids, chemotherapy, and anticytokine therapies that have greatly prolonged survival (5, 11).

CONCLUSION

The presented case is an atypical presentation of a relatively rare disease. The decedent in this case presented at 83 years of age, which is several decades later than is typical for GPA, although small series of cases have been reported in the elderly, indicating higher mortality rates in this population as well as higher rates of renal and central nervous system involvement (13, 14). The presented case was especially unique given the fact the individual did not carry a diagnosis of GPA; rather, her first clinical presentation was at death.

Image 4: Pulmonary granulomas with multinucleated giant cells and prominent necrosis (H&E, x200).

Image 5: Pulmonary granuloma with several multinucleated giant cells (H&E, x400).

Image 6: Kidney with necrotic granuloma containing multinucleated giant cells (H&E, x200).

Image 7: Renal arteriole with acute vasculitis (H&E, x200).

Image 8: Renal arteriole with acute vasculitis (H&E, x400).

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