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BRIEF REPORT

Uncommon presentations in ANCA vasculitis: clinical characteristics and outcomes

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Abstract

ANCA-associated vasculitis (AAV) can present in an atypical manner and obscure the clinical picture. We sought to characterize clinical characteristics and outcomes in these uncommon presentations. We conducted a retrospective study of 171 AAV patients in our vasculitis database to identify patients with atypical presentation of AAV. Patient demographics, serologies, renal indices, and treatment regimens were assessed. Of the 171 patients, eight were identified to have uncommon presentations. These patients were usually extremes of age with three being less than 30 years and four being more than 70 years. Six patients were positive for PR3 antibodies. The mean delay in diagnosis from time of symptom development was 12 months. All patients developed acute kidney injury during their clinical course. Pancreatitis was the most frequent atypical presentation ($n = 3$), with pulmonary pathologies (cystic lung disease and usual interstitial pneumonia) and splenic infarcts being present in two patients each. The diagnosis of AAV was established by positive ANCA serology and renal or lung biopsy evidence of vasculitis. Six patients received induction therapy with steroids and rituximab, while two received steroids and cyclophosphamide. One patient died of respiratory failure in the first month following diagnosis while the remaining patients achieved disease remission. One patient developed end-stage renal disease. Uncommon presentations of AAV afflict extremes of age with a PR3 ANCA predominance and are associated with subsequent development of AKI. This case series demonstrates that a significant delay in diagnosis can be associated with these presentations.

Key Points

• *Uncommon manifestations of AAV are seen more often with PR3 ANCA disease and respond to standard induction therapy of AAV.*
• *High index of suspicion is required to avoid delays in diagnosis.*

Keywords ANCA vasculitis · Outcomes · Uncommon presentation

Introduction

ANCA-associated vasculitis (AAV) are systemic autoimmune diseases that affect small- to medium-sized blood vessels, and are generally grouped into granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). ANCAs, myeloperoxidase (MPO-ANCA), or proteinase 3 (PR3-ANCA) stimulate neutrophil-induced cytotoxicity toward endothelial cells, leading to vessel wall inflammation, obliteration, and damage [1]. The overall annual incidence of AAV in Europe and Northern America is about 20 per million [2]. The clinical spectrum of ANCA-associated vasculitis (AAV) is broad, and presentation can vary from a skin rash to multisystem disease, often leading to significant delay in diagnosis. AAV most commonly involves the renal and pulmonary systems, but often extend beyond these organ systems as well. Although advances in therapy have improved the overall

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mortality of AAV, prompt diagnosis and timely institution of therapy is critical to prevent vasculitic organ damage and associated morbidity. We sought to characterize clinical characteristics and treatment outcomes in uncommon presentations of AAV in this single center study.

Materials and methods

This retrospective study was performed with data from our IRB-approved vasculitis center database to identify patients with ANCA vasculitis with atypical presentations. AAV patients were categorized as GPA, MPA, or EGPA based on the revised Chapel Hill Consensus nomenclature [3].

Patient demographics, serologies, renal indices, and treatment regimens were assessed. Atypical presentation was defined as an uncommon vasculitic organ manifestation at disease onset which is not captured in the Birmingham Vasculitis Activity Score (BVAS) version 3 scoring system [4]. On discerning atypical presentations, time to onset of AAV from initial symptom presentation, ANCA serotype, serum creatinine/GFR at the time of diagnosis of AAV, and renal biopsy results were ascertained. Estimated GFR was calculated using the modification of diet in renal disease (MDRD) formula [5]. Remission of vasculitis was defined as stabilization or improvement in serum creatinine with resolution of hematuria and absence of extra-renal signs of vasculitis with a BVAS score of zero.

Results

Among 253 patients in the vasculitis database, 171 AAV patients were identified. Of the 171 patients, eight were observed to have atypical presentations. These patients were usually extremes of age with three being less than 30 years and four being more than 70 years. The median delay in diagnosis from time of symptom onset was 4 months with a range from 1 to 35 months.

Clinical phenotype was GPA in six patients and MPA in one patient. One patient had a prior use of methotrexate while others were not on any immunosuppressive medications at the time of diagnosis. Six patients were positive for PR3 antibodies, and four of these patients had other notable serologies (ANA, anti-cardiolipin, anti-glomerular basement membrane antibody, rheumatoid factor). Pancreatitis was the most frequent atypical presentation ($n = 3$), with pulmonary pathologies (cystic lung disease and usual interstitial pneumonia) and splenic infarcts being present in 2 patients each (Tables 1 and 2). All patients subsequently developed acute kidney injury.

The diagnosis of AAV was established in these patients by positive ANCA serology in all patients, by renal biopsy evidence of pauci-immune crescentic and necrotizing GN in seven patients, and by evidence of necrotizing fibrinoid necrosis in lung in one patient (Table 3). Six patients had an induction regimen of steroids and rituximab, while the remainder received steroids and cyclophosphamide. One patient died of respiratory failure in the first month following diagnosis while the remaining patients achieved disease remission. One patient reached end-stage renal disease (ESRD) (Table 4).

Discussion

We report a series of AAV patients characterized by uncommon vasculitic presentation at disease onset and describe their clinical course and outcome. All patients had evidence of AKI during their clinical course, the etiology of which was

Table 1 Demographic, clinical, and serologic features

PID	Age	Disease phenotype	ANCA type	Other serologies	Symptoms at presentation	Atypical features
1	19	GPA	PR3	N/A	Sinusitis, myalgia, generalized malaise	Raynaud's, renal and splenic infarcts
2	85	GPA	PR3	NA	RUQ pain, generalized malaise	Obstructive jaundice, CBD thickening, para-aortic enhancing soft tissue, hypo enhancing renal lesions, pancreatitis
3	26	GPA	PR3	ANA, RF anti-cardiolipin	Rash, joint pain	Scleritis, cystic lung disease, /granulomas/reticulonodular ILD
4	70	GPA	PR3	Anti- GBM	DVT, PE, Melena, abdominal pain	Pancreatitis
5	71	GPA	MPO	N/A	Headache, retro-orbital pain	Pachymeningitis
6	59	GPA	PR3	RF	Shortness of breath	Pericardial tamponade, fibrinoid pericarditis, splenic infarct, renal infarct
7	71	MPA	MPO	N/A	Shortness of breath	Sub-pleural peripheral fibrosis, honeycombing, UIP
8	21	GPA	PR3	N/A	Abdominal pain, arthralgia	Pancreatitis

ANA anti-nuclear antibody, *anti-GBM* anti-glomerular basement membrane antibody, *RF* rheumatoid factor, *RUQ* right upper quadrant, *CBD* common bile duct, *ILD* interstitial lung disease, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *UIP* usual interstitial pneumonia

Table 2 Frequency of atypical presentations in our AAV patients

Pancreatitis (%)	3/171 (1.7%)
Splenic infarcts (%)	2/171 (1.2%)
Pulmonary pathology (UIP, cystic lung disease) (%)	2/171 (1.2%)
Pericarditis/tamponade (%)	1/171 (0.6%)
Pachymeningitis (%)	1/171 (0.6%)

subsequently confirmed via renal biopsy. Treatment with systemic glucocorticoids combined with either rituximab or cyclophosphamide was effective in inducing remission in these patients.

The most common atypical presentation of AAV was pancreatitis in our cohort. Two different pancreatic manifestations of AAV have been reported in the literature: pancreatic mass mimicking a tumor or acute pancreatitis, both of which are rare. Patients who present with pancreatic mass often undergo extensive surgical management prior to establishment of diagnosis, while those presenting with acute pancreatitis tend to have an aggressive course with fatal outcome [6]. A case series of 62 vasculitis patients with gastrointestinal involvement demonstrated a diagnosis of acute pancreatitis in only 3 patients and that first presentation of GPA, bowel perforation, or infarction was associated with poor prognosis [7]. Initial pancreatitis, followed by diffuse alveolar hemorrhage, AKI, and small bowel necrosis, has been noted in MPO antibody vasculitis [8]. After diagnosis, this patient was started on steroids, rituximab, and underwent seven sessions of plasma exchange, with rapid improvement. Another case report reported a 64-year-old Japanese woman who presented with acute renal failure, diagnosed with AAV based on MPO-ANCA positivity and biopsy-proven pauci-immune glomerulonephritis, and prior to initiation of therapy was incidentally discovered to have concomitant pancreatitis with enlarged pancreas on imaging as well as elevated enzymes [9].

Splenic infarction was another common atypical presentation in our cohort. Spleen involvement has only been reported in a few cases of granulomatosis with polyangiitis, with a range of abnormalities that include splenomegaly, capsular adhesions, dysfunction, and infarction [10]. Spleen infarction is often clinically silent and detected incidentally on imaging, as was the case in the two presentations in our cohort. This is congruent with findings from a case series of 18 patients with AAV splenic involvement, in which only eight patients were symptomatic, generally complaining of diffuse or left upper quadrant abdominal pain [10].

In a review of pulmonary involvement in 140 newly diagnosed AAV patients, the most common abnormality was nodular disease (24%), followed by bronchiectasis and pleural effusion (19%, each), pulmonary hemorrhage and lymph node enlargement (14%, each), emphysema (13%), and cavitary

Table 3 Laboratory, imaging, and pathology data at time of diagnosis

PID	ESR	Hb (g/dl)	Serum creatinine (mg/dl)/e-GFR (ml/min)	Urinalysis	Imaging/pathology
1	86	9.4	4.07/13	1.2 g proteinuria, hematuria	CT abdomen: wedge-shaped infarcts in spleen and both kidneys. Renal biopsy: mixed class pauci-immune GN
2	105	9.8	1.5/42	2.3 g proteinuria, hematuria	CT abdomen with hypodense lesion in pancreas and kidney. Renal biopsy: focal class GN
3	37	10.4	0.4/70	1.5 g proteinuria, hematuria	CT chest: cystic lung disease, cavitation/granulomas/ reticulonodular ILD. Renal biopsy: focal class GN
4	38	6.0	18.8/5	1+ proteinuria, hematuria	CT abdomen with hypodense lesion in pancreas. Renal biopsy: crescentic class pauci-immune GN
5	116	8.1	2.1/31	840 mg proteinuria, hematuria	MRI brain with pachymeningeal enhancement with dural pathology moderately dense infiltrate of lymphocytes, macrophages, and a multinucleated giant cell few plasma cells. Renal biopsy: mixed class pauci-immune GN
6	49	9.6	8.0/7	2.2 g proteinuria, hematuria	CT with splenic and renal infarcts, lung biopsy with necrotizing fibrinoid necrosis. Renal biopsy with infarcted glomeruli with fibrinoid necrosis in blood vessel
7	70	10.5	1.7/40	560 mg proteinuria, hematuria	CT chest with sub-pleural peripheral fibrosis, honeycombing, UIP. Renal biopsy with focal class GN
8	55	7.1	2.86/23	2.6 g proteinuria, hematuria	Renal biopsy: crescentic class pauci-immune GN

ESR erythrocyte sedimentation rate, *Hb* hemoglobin, *e-GFR* estimated glomerular filtration rate, *GN* glomerulonephritis

Table 4 Treatment and renal outcomes of patients

PID	Delay in Dx (months)	HD on admission	Induction	Remission achieved	Creatinine LFU mg/dl	Maintenance
1	1	N	S + RTX	Yes	2	RTX
2	5	N	S + RTX	Yes	1.1	RTX
3	35	N	S + RTX	Yes	0.6	RTX
4	3	Y	S + CYC + PLEX	NA	NA due to patient death	NA
5	35	N	S + RTX	Yes	1.8	RTX
6	2	Y	S + CYC	Yes	ESRD	N/A
7	12	N	S + RTX	Yes	1.1	RTX
8	2	N	S + RTX + PLEX	Yes	1.1	RTX

Dx diagnosis, *RTX* rituximab, *CYC* cyclophosphamide, *PLEX* plasma exchange, *ESRD* end-stage renal disease, *LFU* last follow-up

lesions (11%) [11]. Usual interstitial pneumonitis (UIP) and bronchiectasis were more prevalent in MPO-ANCA-positive patients, similar to the one UIP case noted in our cohort. Cavitary lung disease was seen in our cohort, and has been cited in the literature as presenting symptoms in GPA. One case report demonstrated a 52-year-old male presenting with fever, dyspnea, and rash and was subsequently found to have multiple cavitary lesions and PR3+ ANCA vasculitis [12]. This is consistent with the case in our cohort demonstrating rash and joint pain preceding cavitary lung disease in PR3+ ANCA vasculitis.

Pleural and pericardial involvements are well recognized in EGPA but considered rare manifestations of GPA and MPA. Using an institutional database of 1882 AAV patients, one study demonstrated pleuritis and/or pericarditis as a presenting feature in 6.3% of GPA, 7.3% of MPA, and 15.5% of EGPA patients [13].

Pachymeningitis is characterized by headache and cranial nerve dysfunction, and has been noted as a presenting symptom in AAV [14]. One case report demonstrated a 67-year-old male who presented with progressive hearing loss, followed by 2 months of headache, and was eventually diagnosed with ANCA vasculitis [15]. In a review of 32 cases of pachymeningitis associated with AAV, patient age ranged from 20s–80s, and all patients had severe headache at onset as one of the main complaints. MPO-ANCA was slightly more prevalent than PR3-ANCA in these presentations, consistent with our cohort. The patient with pachymeningitis in our cohort, however, was treated with glucocorticoids and rituximab, rather than cyclophosphamide as used in the case series. In another study, MPO-ANCA was suggested as a predictable factor for relapse of pachymeningitis in AAV [16].

The mean delay in diagnosis in our cohort was 12 months, consistent with a recent large survey of patients with ANCA-associated vasculitis demonstrating a lag time of 3 to 12 months between disease onset and diagnosis [2]. In our cohort, those with the longest delay in diagnosis (12–35 months) also had lower creatinine on admission, suggesting that these milder renal presentations may have delayed consideration of vasculitis on the differential diagnosis. Conversely, the patient with the highest creatinine on presentation requiring HD on admission had the shortest delay in diagnosis, suggesting that index for suspicion for vasculitis was higher in a more severe presentation. Although pulmonary and renal involvements are considered the classic organ systems to be involved in vasculitis, two out of three patients with atypical pulmonary involvement in our cohort had a delay in diagnosis above the mean. Furthermore, while ANCA-associated vasculitides is thought to have an average age of diagnosis in the fifth decade, our patients were at the extremes of age [17].

These cases highlight that uncommon presentations of AAV afflict extremes of age with a PR3 ANCA predominance and are associated with subsequent development of AKI. This case series demonstrates that a significant delay in diagnosis can be associated with these presentations.

Expedient renal biopsy should be done to evaluate AKI in such atypical cases with concomitant ANCA positivity in order to promptly begin therapy and help prevent the devastating consequences of unmitigated disease.

Compliance with ethical standards

Conflict of interest Duvuru Geetha: Consultant to ChemoCentryx and consultant to Kyowa Hakko Kirin.

The other authors have disclosed no conflicts of interest.

References

1. Tseng S-T, Tseng M-H, Huang J-L (2015) Concurrent pulmonary hemorrhage and deep vein thrombosis in a child with ANCA-associated vasculitis: case report and review of literature. Pediatr Rheumatol 13(1):20. https://doi.org/10.1186/s12969-015-0015-y
2. Abdou NI, Kullman GJ, Hoffman GS, Sharp GC, Specks U, McDonald T (2002) Wegener's granulomatosis: survey of 701 patients in North America. Changes in outcome in the 1990s. J Rheumatol 29:309–316
3. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CGM, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DGI, Specks U, Stone

JH, Takahashi K, Watts RA (2013) 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65(1):1–11. https://doi.org/10.1002/art.37715
4. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, Flossman O, Hall C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Lugmani RA (2009 Dec) Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 68(12):1827–1832. https://doi.org/10.1136/ard.2008.101279
5. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann Intern Med 130(6):461–470
6. Chawla S, Atten MJ, Attar BM (2011 Mar 9) Acute pancreatitis as a rare initial manifestation of Wegeners granulomatosis. A case based review of literature. J Pancreas 12(2):167–169
7. Pagnoux C, Mahr A, Cohen P, Guillevin L (2005) Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. Medicine 84:115–128
8. Segraves JM, Iyer VN (2017) Microscopic polyangiitis: atypical presentation with extensive small bowel necrosis, diffuse alveolar hemorrhage, and renal failure. Respir Med Case Rep 21:12–15. https://doi.org/10.1016/j.rmcr.2017.03.001
9. Iida T, Amari Y, Yurugi T, Nakajima F (2015) MPO-associated glomerulonephritis with acute pancreatitis: a case report. Nihon Jinzo Gakkai Shi 57(4):783–788 https://www.ncbi.nlm.nih.gov/pubmed/26126336
10. Ghinoi A, Pipitone N, Cavazza A, Boiardi L, Salvarani C (2008) Wegener granulomatosis with spleen infarction: case report and review of the literature. Semin Arthritis Rheum 37(5):328–333. https://doi.org/10.1016/j.semarthrit.2007.07.009
11. Mohammad AJ, Mortenson KH, Babar J, Smith R, Jones RB, Nakagomi D, Sivasothy P, Jayne D (2017) Pulmonary involvement in ANCA-associated vasculitis: the influence of ANCA subtype. J Rheumatol 44(10):1458–1467. https://doi.org/10.3899/jrheum.161224.
12. Oliveira RVD, Zanetti G, Marchiori E (2012) Multiple pulmonary nodules. Wegeners granulomatosis simulating pulmonary metastases. QJM 106(12):1143–1144. https://doi.org/10.1093/qjmed/hcs202
13. Thompson G, Bourne M, Moura MC et al (2018) Prevalence of pleuritis and pericarditis in anca-associated vasculitis. Chest 154(4):1019A–1020A. https://doi.org/10.1016/j.chest.2018.08.921
14. Choi HA, Lee MJ, Chung C-S (2017) Characteristics of hypertrophic pachymeningitis in patients with granulomatosis with polyangiitis. J Neurol 264(4):724–732. https://doi.org/10.1007/s00415-017-8416-0
15. Li S, Tang H, Rong X, Huang X, Li Q (2015) Pachymeningitis as a manifestation of ANCA-associated vasculitis: a care report and literature review. Int J Clin Exp Med 8(4):6352–6359 www.ijcem.com /ISSN:1940-5901/IJCEM0006344
16. Horino T, Takao T, Taniguchi Y (2010) Hypertrophic pachymeningitis with MPO-ANCA-positive vasculitis. Clin Rheumatol 29:111–113. https://doi.org/10.1007/s10067-009-1269-x
17. Kaur P, Palya A, Hussain H, Dabral S (2010) Microscopic polyangiitis presenting as early cardiac tamponade. JCR: J Clin Rheumatol 16(2):86–87. https://doi.org/10.1097/rhu.0b013e3181d06b55