Anti-neutrophil cytoplasmic antibody associated vasculitis in patients with rheumatoid arthritis

Haiting Wu¹, Yiyun Lu², Rongrong Hu¹, Wei Ye¹, Yubing Wen¹, Jianfang Cai¹,³*, Hang Li¹ and Xuemei Li¹

Abstract

Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) may coexist with rheumatoid arthritis (RA). However, it is unclear whether the manifestations of AAV with and without coexisting RA are similar. This observational study aimed to investigate the clinicopathological manifestations of AAV with coexisting RA and to explore potential predictors for identifying AAV superimposed on RA.

Methods: Patients with both AAV and RA were identified by searching our hospital database and the literature. Data including age, sex, clinical manifestation, laboratory tests, renal pathology, and therapeutic regimens were retrieved. To assess the difference in clinical features and renal pathology between AAV patients with and without RA, we conducted 1:4 matched case-control studies.

Results: A total of 47 patients were identified, 15 from our hospital and 32 from the literature, and 33 (70.2%) were women. AAV was diagnosed later than RA in 83.0% of the patients and manifested as microscopic polyangiitis (MPA) in 78.7% of the patients. The kidney was the most frequently involved extra-articular organ (74.5%), followed by the lung (51.1%), and skin (8.5%). Patients with both AAV and RA were more likely to be asymptomatic (26.7% vs 3.3%, \( p = 0.013 \)) than those with isolated AAV. However, they did not differ in other clinicopathological features. In RA patients, those with ANCA associated glomerulonephritis, were more likely to have decreased renal function at renal biopsy as opposed to those with primary glomerulonephritis.

Conclusions: AAV can coexist with RA. In this coexistence, AAV usually develops after RA, is more likely to be asymptomatic, and manifests predominately as MPA with renal involvement. Thus, we should remain vigilant to superimposed AAV on RA.

Keywords: Anti-neutrophil cytoplasmic antibody associated vasculitis, Rheumatoid arthritis, Glomerulonephritis

Key points

- RA patients may have a greater tendency to develop AAV
- AAV superimposed on RA may be asymptomatic with elevated serum creatinine.

*Correspondence: caijfbj@126.com
³ Division of Nephrology, Fuwai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100037, China

Full list of author information is available at the end of the article

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patients with RA appear to have smoldering clinical features and may result in late referral from rheumatologists to nephrologists and therefore have a poor prognosis [3]. However, research on patients with the coexistence of AAV and RA is limited, and most studies are case reports. It is unclear whether there are any differences between AAV with and without coexisting RA. We therefore reviewed cases with these coexisting diseases in our hospital and in the literature, and summarized the clinical manifestations in these patients. We also attempted to identify the clinicopathological characteristics of AAV patients superimposed on RA by comparing them to those with AAV without RA. In consideration of the poor prognosis of AAV-associated glomerulonephritis, we analyzed the risk factors for AAV renal involvement in RA patients by renal biopsy in our center to timely identify these patients.

Methods

Study subjects

Patients with both AAV and RA in the Peking Union Medical College Hospital from January 2000 to December 2018 were included in this study. AAV was diagnosed based on the criteria proposed by the Chapel Hill Conference [4]. The diagnosis of RA complied with the 2010 ACR/EULAR RA classification criteria [5]. Cases before 2010 were reassessed and re-diagnosed. We also searched for cases of both AAV and RA published in English or Chinese between January 2000 and December 2018 in MEDLINE, EMBASE, and Chinese databases including China National Knowledge Infrastructure, Wanfang Database, and VIP Database. The keyword for RA was “rheumatoid arthritis”. The keywords for AAV were “anti-neutrophil cytoplasmic antibody associated vasculitis”, “anti-neutrophil cytoplasmic antibody associated nephritis”, “anti-neutrophil cytoplasmic antibody”, “small vessel vasculitis”, “rapidly progressive glomerulonephritis”, “microscopic polyangiitis”, “granulomatosis with polyangiitis”, “Wegener’s granulomatosis”, “Churg-Strauss syndrome”, “eosinophilic granulomatosis with polyangiitis” and “allergic granulomatous angitis” (Supplementary Fig. 1). We excluded patients exposed to potential AAV-inducing drugs such as tumor necrosis factor-α inhibitors, penicillamine, and propylthiouracil [6].

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) and compared using the Student t-test or Mann-Whitney U test as appropriate. Categorical variables are presented as n (%) and compared using the chi-square test or Fisher’s exact test. Logistic regression was employed to assess the association between RA and ANCA associated glomerulonephritis in renal-biopsied patients by adjusting for sex and age. All statistical tests were 2-sided, with significance defined as p < 0.05. All statistical analyses were performed using the SPSS 23.0 (IBM).

Results

Clinical features of AAV coexisting with RA

Patients with both AAV and RA in our center

In total, 15 patients with both AAV and RA were identified in our center (Table 1). Of these patients, all were categorized as MPA, 9 (60.0%) were women, and 9 (60.0%) had renal pathology and were diagnosed with ANCA associated glomerulonephritis. MPA was diagnosed 5.0 (2.0–20.0) years later than RA. At diagnosis of MPA, the patients were on average 54 ± 17 years old and the kidney (86.7%) was most frequently involved, followed by the lung (53.3%). Kidney involvement manifested as elevated serum creatinine (80.0%), proteinuria (86.7%), and hematuria (86.7%). All patients received glucocorticoids and 14 (93.3%) cases received immunosuppressants, cyclophosphamide in 13 and mycophenolate mofetil in one, to treat AAV. During a median follow-up of 12 (1–60) months, 4 of 14 patients progressed to end-stage renal disease (ESRD) and 2 died due to rupture of an abdominal aortic aneurysm and pulmonary infection, respectively.
Table 1  Clinical characteristics of patients with AAV and coexisting RA

| Characteristics                        | Our center (n = 15) | Literature (n = 32) | Total (n = 47) |
|----------------------------------------|--------------------|---------------------|----------------|
| **Female**                             | 9 (60.0%)          | 24 (75.0%)          | 33 (70.2%)     |
| **Age at diagnosis of AAV (ys)**       | 54 ± 17            | 50 ± 15             | 51 ± 15        |
| **ANCA serology**                      |                    |                     |                |
| P-ANCA or myeloperoxidase -ANCA        | 14 (93.3%)         | 24 (75%)            | 38 (80.9%)     |
| C-ANCA or proteinase 3-ANCA            | 2 (13.3%)          | 6 (18.8%)           | 8 (17.0%)      |
| negative                               | 0 (0.0%)           | 2 (6.3%)            | 2 (4.3%)       |
| **Vasculitis diagnosis**               |                    |                     |                |
| Microscopic Polyangiitis               | 15 (100.0%)        | 22 (68.8%)          | 37 (78.7%)     |
| Granulomatosis with polyangiitis       | 0 (0.0%)           | 10 (31.3%)          | 10 (21.3%)     |
| **Chronological order of diseases**    |                    |                     |                |
| Rheumatoid arthritis first             | 13 (86.7%)         | 26 (81.3%)          | 39 (83.0%)     |
| ANCA associated vasculitis first       | 0 (0.0%)           | 4 (12.5%)           | 4 (8.5%)       |
| Contemporaneous                        | 2 (13.3%)          | 2 (6.3%)            | 4 (8.5%)       |
| **Interval between diagnosis of RA and AAV (ys)** | 5.0 (2.0–20.0)     | 6.5 (1.6–12.0)      | 5.0 (2.0–12.0) |
| **Organs involved**                    |                    |                     |                |
| Kidney                                 | 13 (86.7%)         | 22 (68.8%)          | 35(74.5%)      |
| Lung                                   | 8 (53.3%)          | 16 (50.0%)          | 24(51.1%)      |
| Skin                                   | 1 (6.7%)           | 3 (9.4%)            | 4(8.5%)        |
| Nose                                   | 0 (0.0%)           | 2 (6.3%)            | 2(4.3%)        |
| Nervous system                         | 1 (6.7%)           | 0 (0.0%)            | 1 (2.1%)       |
| **Renal manifestations**               |                    |                     |                |
| Serum creatinine (umol/L)              | 164 (106–471)      | 292 (148–352)       | 282(132–379)   |
| 24-h urine protein(g/d)                | 1.56(0.38–4.79)    | 0.94 (0.50–3.10)    | 1.25(0.50–3.40) |
| Rapidly progressive glomerulonephritis | 2(13.3%)           | 4(12.5%)            | 6(12.8%)       |
| **Therapy for RA**                     |                    |                     |                |
| Gold compounds                         | 1 (8.3%)           | 5 (17.2%)           | 6(15.6%)       |
| Methotrexate                           | 1 (8.3%)           | 10(34.5%)           | 11(26.8%)      |
| Leflunomide                            | 4 (33.3%)          | 2(6.9%)             | 6(14.6%)       |
| **Therapy for AAV**                    |                    |                     |                |
| Glucocorticoid                         | 1 (6.7%)           | 4 (12.9%)           | 5(10.9%)       |
| Glucocorticoid plus cyclophosphamide   | 13 (86.7%)         | 16 (51.6%)          | 29(63.0%)      |
| Glucocorticoid plus other immunosuppressants | 1 (6.7%)   | 9 (29.0%)           | 10(21.7%)      |
| None                                   | 0 (0.0%)           | 2 (6.5%)            | 2(4.3%)        |
| **Prognosis**                          |                    |                     |                |
| Improved                               | 8 (57.1%)          | 22 (71.0%)          | 30(66.7%)      |
| End Stage Renal Failure                | 4 (28.6%)          | 7 (22.6%)           | 11(24.4%)      |
| Death                                  | 2 (14.3%)          | 2 (6.5%)            | 4(8.9%)        |

Abbreviations: ANCA anti-neutrophil cytoplasmic antibody, AAV ANCA-associated vasculitis, RA rheumatoid arthritis

* One patient in our center was both myeloperoxidase -ANCA and proteinase 3-ANCA positive

Cases from the literature had missing data related to some parameters. For a parameter with missing data, we gave a specific number of participants with data on this parameter.
Patients with both AAV and RA from our center and the literature

We further identified 32 cases with both AAV and RA from the literature (Table 1). Patients with suspected drug-induced AAV were excluded. We pooled these cases with those from our center [3, 8–24]. The pooled 47 patients were aged 51 ± 15 years at diagnosis of AAV and 33 (70.2%) were women. AAV was diagnosed before, at the same time, and after the diagnosis of RA in 4 (8.5%), 4 (8.5%), and 39 (83.0%) cases, respectively. Of these patients, 37 (78.7%) were categorized as MPA and 10 (21.3%) as GPA. The kidney was the most frequently involved extra-articular organ, followed by the lung and skin. Renal involvement manifested as hematuria, moderate proteinuria and renal insufficiency. At diagnosis of AAV, the patients with renal involvement had a median creatinine level of 282 (132–379) μmol/L. Glucocorticoids with or without immunosuppressants were prescribed to treat AAV in 95.7% of patients. Glucocorticoid plus cyclophosphamide was the first-choice regimen (63.0%), followed by glucocorticoid plus other immunosuppressants (21.7%), and glucocorticoid alone (10.9%). In our center, cyclophosphamide was given intravenously at a dose of 0.4–0.6 g per week during hospitalization and then orally after discharge. However, in the literature, cyclophosphamide was given orally, intravenously, or both. During a median follow-up of 12 months, 30 (66.7%) of 45 patients showed improved renal function, 11 (24.4%) developed ESRD, and the remaining 4 patients (8.9%) died.

Differences in clinical features and renal pathology between AAV patients with and without RA in our center

As all of the patients with AAV and coexisting RA in our center had MPA, we restricted the comparison of clinico-pathological features between MPA with and without RA. Between January 2000 and December 2018, 411 MPA patients without RA were identified in our center. Patients with both MPA and RA were marginally younger than those with isolated MPA (54 ± 17 vs 61 ± 14 years, p = 0.052), but they did not differ in sex distribution (60% female vs 52.2% male, p = 0.55).

We then matched 15 patients with both MPA and RA to 60 patients with isolated MPA by age, sex, and presence of renal involvement and renal biopsy (Table 2). Patients with both MPA and RA were more likely to be asymptomatic (p = 0.013) and less likely to have fever (p = 0.010) at diagnosis of MPA as opposed to those with isolated MPA. However, the two groups did not differ in other clinical features and renal pathology, including weight loss, lung involvement, presence of rapidly progressive glomerulonephritis, severity of proteinuria, baseline estimated glomerular filtration rate (eGFR),

Table 2. Clinical characteristics of MPA patients with or without RA

| Clinical symptoms | With RA (n = 15) | Without RA (n = 60) | P  |
|------------------|----------------|-------------------|----|
| None             | 4(26.7%)       | 2(3.3%)           | .013|
| Fever            | 4(26.7%)       | 39(65.0%)         | .010|
| Weight loss      | 5(33.3%)       | 27(45.0%)         | .56 |

| Organ involvement | With RA (n = 15) | Without RA (n = 60) | P  |
|-------------------|----------------|-------------------|----|
| Lung              | 8(53.3%)       | 34(56.7%)         | 1.00|
| rapidly progressive glomerulonephritis | 3(20.0%) | 25(41.7%) | .15 |
| Other organs      | 9(60.0%)       | 40(66.7%)         | .76 |

| Laboratory tests  | With RA (n = 15) | Without RA (n = 60) | P  |
|-------------------|----------------|-------------------|----|
| Hemoglobin (g/L)  | 92 ± 26        | 97 ± 22           | .43 |
| ESR (mm/h)        | 72 ± 45        | 70 ± 41           | .86 |
| C-creative protein (mg/L) | 3.08 (1.05,7.92) | 3.35 (1.25, 13.94) | .60 |
| Albumin (g/L)     | 32 ± 7         | 31 ± 6            | .51 |
| 24-h urine protein (g) | 1.56(0.38–4.79) | 1.10(0.53–2.45) | .81 |
| eGFR [ml.min⁻¹. (1.73 m²)⁻¹] | 34.8 ± 28.4 | 41.5 ± 30.6 | .45 |
| BVAS              | 14 ± 5         | 17 ± 8            | .27 |

| Normalization of SCr or decrease of SCr by 50% at 6th month | With RA (n = 15) | Without RA (n = 60) | P  |
|-----------------------------------------------------------|----------------|-------------------|----|
| Normalization of SCr or decrease of SCr by 50% at 6th month | 4(28.6%, n = 14) | 22(40.0%, n = 55) | .43 |

Abbreviations: ESR erythrocyte sedimentation rate, eGFR estimated glomerular filtration rate, BVAS Birmingham Vasculitis Activity Score, SCr serum creatinine

* Patients with both AAV and RA in our center were 1:4 matched with patients with isolated AAV adjusted by sex, age, AAV type, and presence of renal involvement and renal biopsy

Laboratory tests were recorded at diagnosis of AAV
Birmingham Vasculitis Activity Score (BVAS), and improvement in renal function after 6 months.

In order to assess the difference in renal pathology between patients with both MPA and RA and those with isolated MPA, we further matched the 9 patients with both pathology-proved ANCA associated glomerulonephritis and RA to 36 patients with isolated pathology-proved ANCA associated glomerulonephritis by age and sex (Table 3). The two groups had renal histopathology consistent with pauci-immune crescentic glomerulonephritis and did not differ in the percentage of global glomerulosclerosis, cellular crescents, and histopathological classes recommended by Berden et al. [7].

ANCA-associated glomerulonephritis in RA patients undergoing renal biopsy in our center

Between January 2000 and December 2018, 55 RA patients underwent renal biopsy in our center, 9 had ANCA associated glomerulonephritis, 23 had renal impairment caused by other systemic conditions such as lupus nephritis, diabetic glomerulopathy, hepatitis B virus associated glomerulonephritis, and drug-induced renal injury, and the remaining 23 patients had primary glomerulonephritis (glomerulonephritis without apparent secondary causes other than RA). Of these 23 patients, membranous nephropathy and IgA nephropathy were the top two pathological types (11 and 5 patients, respectively). RA patients with ANCA associated glomerulonephritis, as opposed to those with primary glomerulonephritis, tended to have lower eGFR and hemoglobin and higher levels of serum albumin at biopsy (Table 4). Multivariable logistic regression analysis revealed that an eGFR < 30 ml. min\(^{-1}\) (1.73 m\(^2\)) at renal biopsy was associated with ANCA associated glomerulonephritis in renal-biopsied RA patients (OR 25.13 [1.07–592.06], \(p = 0.046\)) adjusted for age, sex, serum albumin and hemoglobin.

### Table 3 Renal histopathology in MPA patients with or without RA

|                      | With RA\((n = 9)\) | Without RA\(^b\)(\(n = 36\)) | \(P\)   |
|----------------------|---------------------|--------------------------------|--------|
| Percentage of normal glomeruli | 24.3 ± 10.8%        | 27.9 ± 22.7%                  | .64    |
| Percentage of cellular crescent glomeruli | 23.1 ± 18.7%        | 34.0 ± 18.4%                  | .10    |
| Percentage of global sclerotic glomeruli | 37.0 ± 23.5%        | 26.9 ± 24.0%                  | .26    |
| Tubulointerstitial chronic index | 1.9 ± 0.9           | 1.6 ± 0.9                     | .46    |
| Histopathological classification\(^b\) |                      |                                |        |
| Focal class           | 1 (11.1%)           | 7 (19.4%)                     | .51    |
| Crescent class        | 1 (11.1%)           | 9 (25.0%)                     |        |
| Mixed class           | 3 (33.3%)           | 13 (36.1%)                    |        |
| Sclerotic class       | 4 (44.4%)           | 7 (19.4%)                     |        |

\(^a\) Renal-biopsied patients with both MPA and RA in our center were 1:4 matched with patients with isolated MPA adjusted by sex and age

\(^b\) ANCA-associated glomerulonephritis was classified according to the histopathological classification proposed in 2010 [7]

### Table 4 Clinical characteristics of RA patients with pathology-proved ANCA-associated glomerulonephritis and primary glomerulonephritis

|                      | ANCA-associated glomerulonephritis \((n = 9)\) | Primary glomerulonephritis \((n = 23)^a\) | \(P\) |
|----------------------|---------------------------------------------|------------------------------------------|-------|
| Age (ys)             | 49 ± 21                                     | 51 ± 11                                   | .75   |
| Female               | 7 (77.8%)                                   | 18 (78.3%)                                | 1.00  |
| Duration of rheumatoid arthritis (ys) | 5 (4–20)                                   | 9(1–14)                                  | .49   |
| Hemoglobin (g/L)     | 97 ± 19                                     | 120 ± 21                                  | .009  |
| ESR (mm/h)           | 66 ± 42                                     | 71 ± 31                                   | .70   |
| eGFR [ml.min\(^{-1}\)(1.73 m\(^2\))\(^{-1}\)] | 24.4 ± 15.1                                | 84.8 ± 21.2                               | <.001 |
| Serum albumin (g/L)  | 35 ± 7                                      | 27 ± 9                                    | .018  |
| 24-h urine protein (g) | 1.73 (0.37,4.47)                           | 4.20 (2.31,9.07)                          | .07   |
| Hematuria            | 9 (100.0%)                                  | 19 (82.6%)                                | .30   |
| Treated with immunosuppressants | 5 (55.6%)                                | 12 (52.2%)                                | 1.00  |

Abbreviations: ANCA anti-neutrophil cytoplasmic antibody, ESR erythrocyte sedimentation rate, eGFR estimated glomerular filtration rate

\(^a\) RA patients with renal biopsy results were included. Among them, renal injuries secondary to other systemic diseases such as lupus nephritis and diabetic nephropathy were excluded

Laboratory tests were recorded at renal biopsy.
Discussion

RA is largely an inflammatory disease limited to joints, whereas AAV is a systemic autoimmune disease usually with multi-organ destructive processes and devastating outcomes. It has been reported that AAV can coexist with RA [3, 8–24]. This coexistence may not be entirely coincidental, as evidenced by facts such as ANCA positivity in 20% of RA patients [25], a positive association between ANCA titer and rapid joint destruction in early RA [26], the presence of myeloperoxidase-ANCA in synovial fluid of RA patients [27], and AAV sharing susceptibility loci with RA [28, 29]. Our finding, that renal-biopsied patients with RA were more likely to have AAV than those without RA, adds new evidence to the inherent association between RA and AAV.

In our center, as well as in the literature, AAV usually occurred after RA in patients with both RA and AAV [10–24]. This may partially be ascribed to the successful inhibition of RA occurrence by intense immunosuppression in the treatment of AAV. Alternatively, disease modifying antirheumatic drugs used for RA may also change the typical manifestations of AAV to a less extra-renal and extra-articular presentation, with a lower frequency of rapidly progressive glomerulonephritis, and more chronicity in renal pathology, as demonstrated in our and Kurita’s study [3]. This deviation may hamper or delay our recognition of AAV in RA patients and finally result in a poor outcome.

Renal involvement is a major feature of AAV and is not rare in RA patients. In RA patients with biopsy-proved primary glomerulonephritis, membranous nephropathy and IgA nephropathy were the top two histopathological patterns as revealed by our and previous studies [30]. RA patients with ANCA-associated glomerulonephritis were more likely to have renal dysfunction than those with primary glomerulonephritis. Therefore, ANCA should be assessed in RA patients with renal dysfunction.

Our study revealed an overwhelming predominance of MPA in AAV patients when AAV coexists with RA. This is consistent with findings in the literature. However, the underlying mechanism of this phenomenon is unclear. There are some limitations in this study. First, because this was a retrospective study and the patients enrolled were highly selected, there was inevitable bias, which may have undermined the robustness of the study findings. Second, most of the patients from our center underwent renal biopsy. As such, the findings of the present study may be biased by the variable indications of renal biopsy for different underlying renal disease. Third, given the small sample in the study, care should be taken regarding generalization of the results of the study.

In conclusion, AAV may not be as rare as we thought in patients with RA. In patients with both AAV and RA, AAV usually developed after RA, was more likely to be asymptomatic, and manifested as MPA with renal involvement. We recommend routine assessment to determine the presence of AAV in RA patients with renal involvement, especially in those with renal dysfunction.

Abbreviations
AAV: ANCA associated vasculitis; ANCA: Anti-neutrophil cytoplasmic antibody; BVAS: Birmingham Vasculitis Activity Score; eGFR: Estimated glomerular filtration rate; ESR: Erythrocyte sedimentation rate; ESRD: End stage renal disease; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; RA: Rheumatoid arthritis; SCr: Serum creatinine.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-022-02788-6.

Additional file 1.
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