ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS IN "REAL LIFE" – SERIES OF CLINICAL CASES IN A ROMANIAN REFERENCE CENTER

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Abstract

Introduction. Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) represent a group of conditions evolving with necrotizing inflammation in small and medium-sized blood vessels. AAV are composed of GPA (granulomatosis with polyangiitis, former Wegener's granulomatosis), MPA (microscopic polyangiitis) and EGPA (eosinophilic granulomatosis with polyangiitis, former Churg-Strauss syndrome). AAV receive immunosuppressive therapy associated with a high risk of complications.

Objective. The aim of this study was to characterize a single center cohort of AAV patients regarding clinical, biological and therapeutic features.

Method. We realized a cross-sectional study by consequently enrolling all the patients registered with AAV diagnosis between 2009 and 2017 in Department of Rheumatology of "Sfânta Maria" Hospital. Demographic, disease-related and therapeutic-related parameters were collected. The data was extracted from the clinical files.

Results. The study sample included 26 cases, 15 females and 11 males: 20 patients GPA, 4 MPA and 2 cases EGPA. Mean age at the time of diagnosis was around 48 but 12 patients presented delays between age at the onset and age at the time of diagnosis (the mean delay was 2 years). The most frequent clinical manifestation identified where pulmonary, musculoskeletal and renal. 15 patients had a diagnostic biopsy performed. ANCA detection revealed 16 cases of c-ANCA and 7 cases of p-ANCA and 11 patients presented other positive serology. A combination of glucocorticoids and cyclophosphamide was used in most of the cases for remission-induction treatment and the same scheme was used for relapse cases. For maintenance phase a combination of glucocorticoids and azathioprine was preferred. 13 patients (50%) developed treatment related complications.

Conclusion. Most of the patients were diagnosed with GPA (20) and the least were diagnosed with EGPA (2). Biopsy was performed in 15 cases and it was mostly nasal. For remission-induction prevailed the combination of glucocorticoids and cyclophosphamide. Most treatment related complications were due to glucocorticoids administration. Osteoporosis was predominant.

Keywords: antineutrophil cytoplasmic antibody (ANCA), vasculitis, glucocorticoids

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) represent a group of conditions evolving with necrotizing inflammation in small arteries. Main AAV consist of GPA (granulomatosis with polyangiitis, former Wegener's granulomatosis), MPA (microscopic polyangiitis) and EGPA (eosinophilic granulomatosis with polyangiitis, former Churg-Strauss syndrome). According to guidelines AAV are currently treated with a combination of corticosteroid and immunosuppressive therapy, usually cyclophosphamide.

OBJECTIVE

The aim of this study was to characterize a single center cohort of AAV patients regarding clinical, biological and therapeutic features.

METHOD

We realized a cross-sectional study by enrolling all the patients registered with AAV diagnosis between 2009 and 2017 in Department of Rheumatology of "Sfânta Maria" Hospital. Demographic, disease-related and therapeutic-related parameters were

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collected. The data was extracted from each patient's clinical files. The statistical analysis was performed using Microsoft Office Excel 2010.

RESULTS

The study sample included 26 cases, 15 females (58%) and 11 males (42%). The most frequent vasculitis was GPA and regarding all AAV the subtypes were as follows: 20 (77%) cases of GPA (11 F, 9 M), 4 (15%) cases of MPA (2 F, 2 M) and 2 (8%) cases of EGPA (2F).

The mean age at the onset was 47 years; in 13 cases (50%) it was under age 47.

The mean age at time of diagnosis was 48 years. 12 patients (26%) presented delays between age at the onset and age at the time of diagnosis; the mean delay was 2 years (in one case of PMA the delay achieved 7 years, and in 14 cases the diagnosis was established during the same year).

Regarding clinical manifestations, the most frequent found were due to pulmonary, musculoskeletal and renal involvement, followed by upper respiratory tract and ears, cutaneous, cardiovascular, ocular and nervous manifestations.

Fig. 3 represents the distribution of the most commonly encountered clinical features of each AAV: from the whole group of 20 cases of GPA 16 presented pulmonary manifestations, 15 presented musculoskeletal symptoms and 14 presented renal manifestations. 3 patients with MPA (75%) presented renal involvement. 1 patient with EGPA (50%) presented renal involvement.

Biopsy was performed in 15 cases. The preferred site for sampling was the nasal mucosa; lung, renal, oral and sinus biopsies were also performed.

Regarding ANCA presence, we found 16 cases of c-ANCA and 7 cases of p-ANCA positivity. Two patients presented both c-ANCA and p-ANCA and 5 patients were ANCA negative. Figure 5 shows the association between vasculitis subtype and ANCA pattern. Both EGPA patients were ANCA negative. All patients with MPA presented p-ANCA and 1 patient (25%) also presented c-ANCA. Most of GPA patients were positive for c-ANCA.

11 patients also presented other positive serology, in most cases (7) rheumatoid factor; all were GPA. There were also described: anti-thyroid peroxidase antibodies, anti-mitochondrial, anti-cardiolipin, ds-DNA, Ro/SS-A, La/SS-B, ACPA, HLA-B27.

The combination of glucocorticoids (GC) and cyclophosphamide (CFM) was used in most cases for remission-induction it (the intravenous regimen was preferred). Other regimen used was the combination of glucocorticoids and azathioprine (AZA) or rituximab.

For remission maintenance were used combinations of glucocorticoids and azathioprine, cyclo-

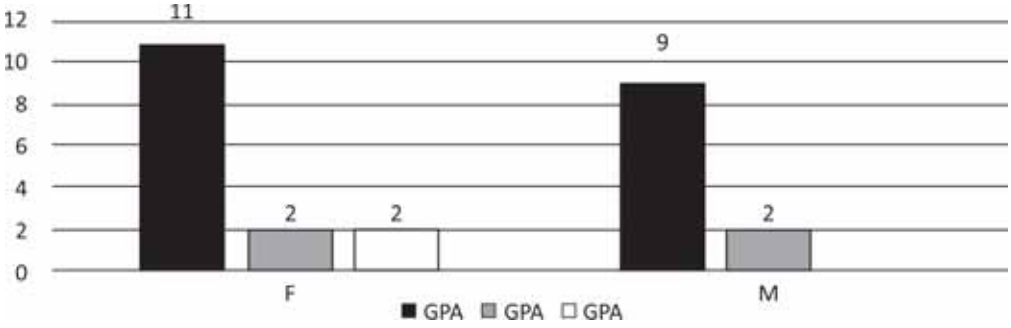

FIGURE 1. *AAV sex distribution*

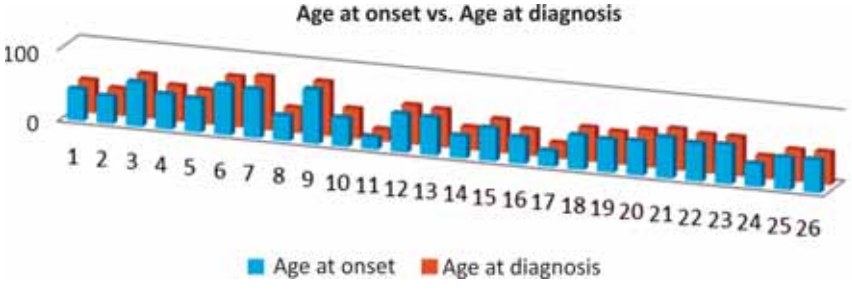

FIGURE 2. *Age at onset vs. Age at diagnosis*

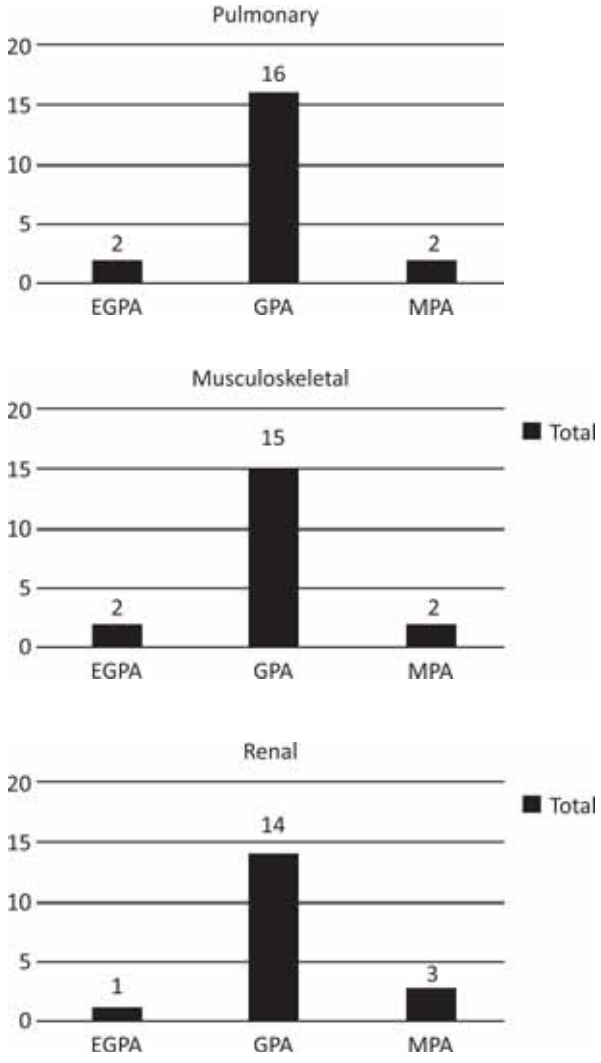

FIGURE 3. *Pulmonary, renal and musculoskeletal manifestations in GPA, MPA and EGPA*

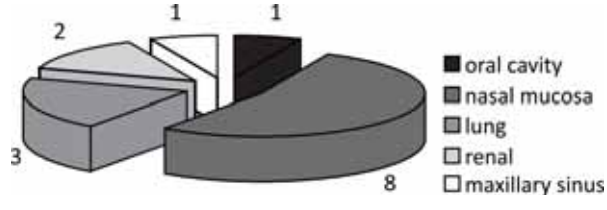

FIGURE 4. *Biopsy distribution*

phosphamide (oral, CFMo), leflunomide (LEF), mycophenolate mofetil (MMF), and in 1 case glucocorticoids alone.

Regarding relapse rate, 5 patients presented at least 1 relapse. The mean duration of remission could not be estimated because the data was incomplete: 14 patients were lost from evidence and 7 patients were in the remission-induction phase when the study ended. Using the remaining data, we noticed that treatment in this scenario consisted of combination of glucocorticoids and cyclophosphamide (intravenous pulse) in most of the cases; with the same frequency were used combinations of glucocorticoids and leflunomide, mycophenolate mofetil and rituximab.

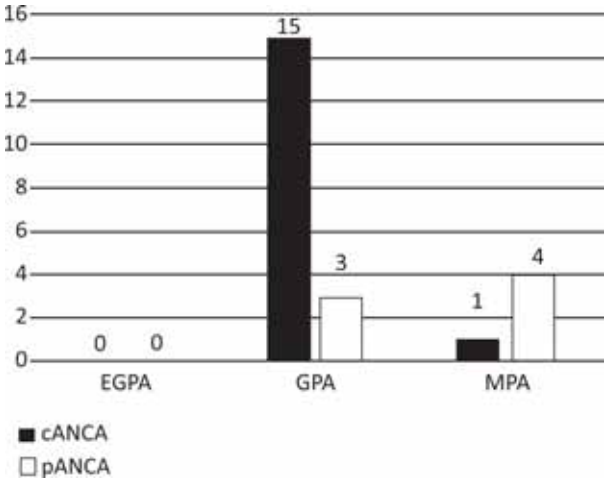

FIGURE 5. *ANCA pattern and vasculitis subtype*

For remission maintenance after relapse were used glucocorticoids alone or in combination with methotrexate (MTX), MMF and Rituximab.

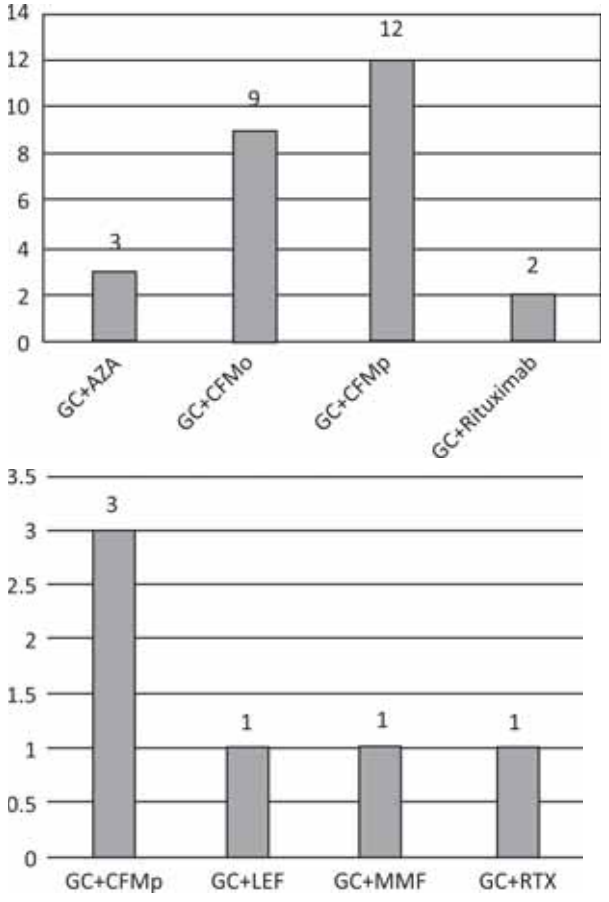

FIGURE 6. *Remission Induction vs. Relapse Remission Induction*

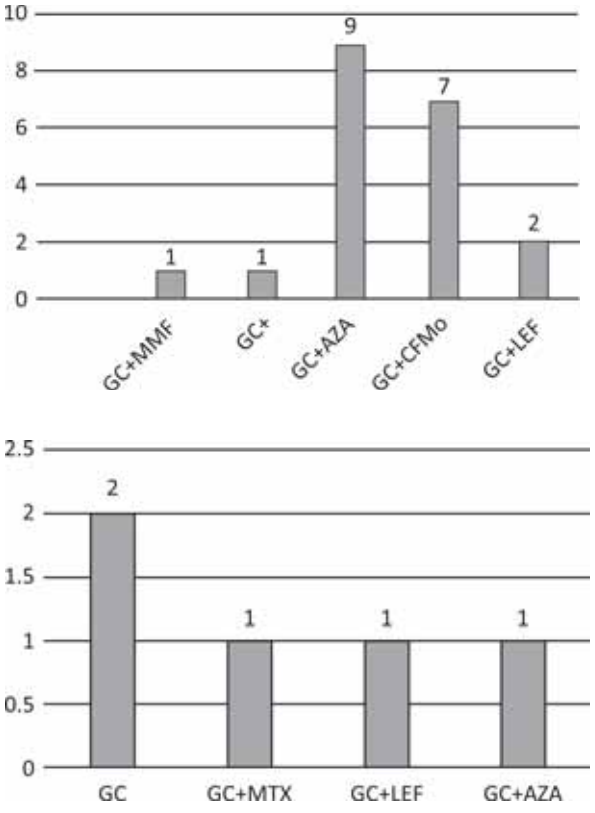

FIGURE 7. *Remission maintenance vs. Relapse remission maintenance*

As mentioned before, immunosuppressive therapy associates a high risk of complications. Most of the patients presented osteoporosis (9) and cataract (4). Other complications were noted as follows: infection (1), tuberculosis (1), glucose intolerance (1), muscle weakness (1), osteonecrosis (1), pancytopenia (1) and testicular cancer (1).

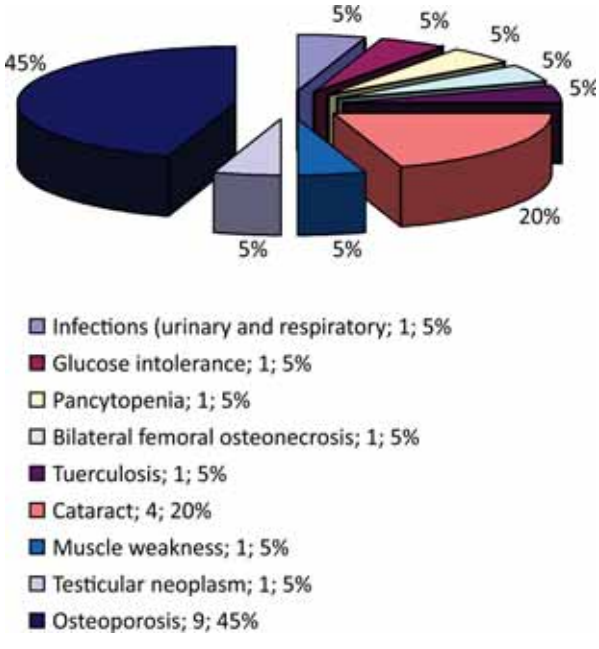

FIGURE 8. *Treatment complications*

We can easily notice that most of the complications could be associated with the chronic cotricosteroid use in AAV.

CONCLUSIONS

Most of the patients were diagnosed with GPA (20) and the least were diagnosed with EGPA (2).

Pulmonary, musculoskeletal and renal manifestations were mostly recorded, but upper respiratory tract and ears, cutaneous, cardiovascular, ocular and nervous manifestations were also noted.

There were 16 cases of cANCA and 7 cases of pANCA. 2 patients presented both c-ANCA and p-ANCA and 5 patients were ANCA negative.

Biopsy was performed in 15 cases (58%) and it was mostly nasal (8).

For remission-induction it was used in most cases the combination of glucocorticoids and cyclophosphamide.

Most treatment related complications were due to glucocorticoids administration. Osteoporosis was predominant.

DISCUSSION

GPA, MPA and EGPA have respective annual incidence rates of 2.1–14.4, 2.4–10.1 and 0.5–3.7 per million in Europe. Also in our cohort these proportions have been preserved, GPA was mostly diagnosticated and EGPA less common.

ANCAs are autoantibodies directed against MPO, PR3 or other constituents of the primary granules of neutrophils and monocyte lysosomes. The 2 types of ANCA mostly used currently are perinuclear (p-ANCA/MPO-ANCA) and cytoplasmic (c-ANCA/PR3-ANCA). ANCA testing may suggest the diagnosis when clinical features are nonspecific, but ANCA titers are poor predictors for disease activity. Also, at least 10% of patients with AAV are ANCA negative. Approximately 82-94% of patients with GPA or MPA associate ANCA. GPA primarily associate c-ANCA and MPA primarily associate p-ANCA. EGPA associates ANCA in 30-60% of cases, usually p-ANCA. So our findings are consistent to literature data.

Histopathologic analysis remains the gold standard for the diagnosis of AAV. Biopsy is recommended for diagnosis and/or prognosis whenever possible; commonly the tissue is obtained from skin or kidney, less commonly from lung (usually thoracoscopic, rarely transbronchial) and even more rare-

ly from nasal mucosa. Nasal biopsy is less invasive, but often unhelpful because it can be removed a small amount of tissue and the result is frequently nonspecific or false negative. Despite the literature data, in our study biopsy was performed mostly nasal and it revealed diagnostic lesions in all (8) cases.

In AAV patients, additional tests are performed to assess the extent of disease. Usually EGPA associate a positive rheumatoid factor at low titer. 11 patients from our analysis also presented other positive serology; 7 cases of positive rheumatoid factor were revealed (all GPA).

Most of the treatment related complications are due to glucocorticoids use, but glucocorticoids are mandatory in AAV treatment. Also, all pharmacological agents used in AAV treatment associate high risk of complications. In our study most treatment related complications were glucocorticoids related, but testicular cancer was also identified and it is probably cyclophosphamide related.

Analyzing the experience of our clinic is extremely important to improve future therapy and thus to prevent possible treatment-related complications.

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