Relapses in Patients with Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis: Likely to Begin with the Same Organ as Initial Onset

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ABSTRACT. ***Objective.*** In antineutrophil cytoplasmic antibody-associated vasculitis (AAV), relapses constitute a challenge despite initial good control. Our objective was to investigate whether patients with relapses shared the same initial organ involvement.

Methods. One hundred sixty patients with AAV in our center were investigated. Of these 160, 38 experienced relapse during followup. Clinical and laboratory data were analyzed.

Results. Among the 38 patients, there was a total of 55 relapse events, 39 (70.9%) of which had the same initial organ as in the initial onset.

Conclusion. Relapses in AAV were likely to begin with the same organ as in the initial onset; this facilitates early recognition of relapses. (First Release Dec 15 2007; J Rheumatol 2008;35:448–50)

Key Indexing Terms:
VASCULITIS ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES RELAPSE

The prognosis of untreated antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is poor. Although corticosteroid and cyclophosphamide improved the outcome dramatically[1], many patients experienced relapses despite longterm immunosuppressive therapy. Therefore, early recognition of relapses might be crucial for improving the prognosis of AAV.

Although many organs could be involved in relapses, we had an impression from clinical practice that those with relapses tended to have the same first organ involved as in the initial onset. We retrospectively analyzed patients with AAV who experienced relapses, and a comparison was made in each patient between initial onset and relapse.

MATERIALS AND METHODS

Patients. One hundred sixty consecutive patients with AAV, diagnosed from 1998 to 2006 in our hospital, were recruited. All patients met the Chapel Hill Consensus Conference definition for AAV[2]. Clinical and laboratory data were analyzed with informed consent. ANCA were tested by indirect immunofluorescence and antigen-specific ELISA (expressed as a percentage of known positive controls). During followup, patients were seen once a month. Organ involvement was defined as renal or extra-renal signs and symptoms of vasculitis, or abnormalities related to vasculitis detected by various examinations.

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Treatment and disease activity states. Treatment protocols were as described[3]. Disease activity states were defined according to the European League Against Rheumatism guidelines on conducting clinical trials[4]. Remission was defined as "absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy." Response was defined as "50% reduction of disease activity score and absence of new manifestations." Major relapse was defined as "recurrence or new onset of potentially organ- or life-threatening disease attributable to active vasculitis." Minor relapse was defined as "recurrence or new onset of disease attributable to active vasculitis that is neither potentially organ- nor life-threatening."

Statistics. Differences of quantitative and qualitative measures were assessed using t-tests and chi-square tests, respectively. Kaplan-Meier curves were used to analyze patients' outcomes. Analysis was performed with SPSS software (SPSS, Chicago, IL, USA).

RESULTS

Demographic features and ANCA specificity. Thirty-eight of 160 (23.8%) patients with AAV experienced relapse during a median followup duration of 24.0 (range 8–192) months. At diagnosis, 33/38 sera were perinuclear ANCA (pANCA) positive, 32/33 recognized myeloperoxidase (MPO) only, and one recognized both MPO and PR3; 5/38 sera were cytoplasmic ANCA (cANCA) positive and all recognized PR3. Fourteen of 38 and 24/38 patients were diagnosed with Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA)[2], respectively.

Manifestations of initial onset. Manifestations of initial onset are listed in Table 1. Compared with patients who did not experience relapse, those who experienced relapse tended to have higher prevalence of upper respiratory tract involvement (26.3% vs 17.2%), but the difference did not reach statistical significance (Table 1).

After induction therapy of a mean duration of 5.53 months,

Table 1. Clinical manifestations of the patients.

	Patients with Relapse (n = 38) First Onset	Relapse	Patients without Relapse (n = 122)
Age, yrs	55.2 ± 15.7		56.1 ± 15.1
Male/female	14/24		58/64
cANCA/pANCA	5/33		12/110
Kidney, n (%)	29 (76.3)	24 (63.1)	116 (95.1)
Lung, n (%)	26 (68.4)	18 (47.4)	69 (56.6)
Upper respiratory tract, n (%)	10 (26.3)	4 (10.5)	21 (17.2)
Nerve, n (%)	4 (10.5)	5 (13.2)	25 (20.4)
Eye, n (%)	9 (23.7)	4 (10.5)	34 (27.9)
Ear, n (%)	14 (36.8)	5 (13.2)	43 (35.2)
Skin, n (%)	8 (21.1)	1 (2.6)#	17 (13.9)
Joint and muscle, n (%)	14 (36.8)	8 (21.1)	58 (47.5)
Fever, n (%)	22 (57.9)	16 (42.1)	77 (63.1)
Fatigue, n (%)	13 (34.2)	7 (18.4)	74 (60.1)
Weight loss, n (%)	11 (28.9)	9 (23.7)	54 (44.2)
BVAS	17.8 ± 7.1	11.9 ± 7.1*	20.6 ± 6.0

# $p < 0.05$, * $p < 0.01$, compared to "first onset." cANCA: cytoplasmic antineutrophil cytoplasmic antibodies; pANCA: perinuclear ANCA; BVAS: Birmingham Vasculitis Activity Score.

20 patients achieved remission and 18 had response; ANCA levels declined in 28/38 patients, including 14 turning negative. The levels of PR3-ANCA and MPO-ANCA dropped from 67.8% ± 6.7% to 30.6% ± 17.7% ($p < 0.01$) and from 89.3% ± 25.0% to 35.2% ± 42.2% ($p < 0.01$), respectively. The level of the Birmingham Vasculitis Activity Score[5] dropped from 17.8 ± 7.1 to 2.73 ± 3.73 ($p < 0.001$).

Characteristics of relapses. During followup, there was a total of 55 relapse events; 35 were "major relapse" and 20 "minor relapse." Twenty-nine of 38, 5/38, 2/38, 1/38, and 1/38 patients experienced 1, 2, 3, 4, and 6 relapse events, respectively. Forty-eight of 55 relapse events occurred between visits and the other 7/55 were recognized during clinic visits. Kidney and lung were the 2 most common organs involved (63.1% and 47.4%, respectively) at relapse. Among the 29 patients with kidney involvement at first onset, 21 (72.4%) also had kidney involvement at relapses. Details of relapse are given in Table 1.

The mean duration from the initiation of immunosuppressive therapy to the first relapse was 23.5 (range 2~126) months. Among those relapsing more than once, the mean duration to the next relapse was 16.2 (range 3~49) months.

At relapse, all patients had elevated erythrocyte sedimentation rate and/or C-reactive protein. ANCA levels were elevated in 23/51 (45.1%) relapse events. The levels of PR3-ANCA and MPO-ANCA increased from 17.0% ± 20.4% to 21.1% ± 29.1% ($p > 0.05$) and from 37.8% ± 45.0% to 54.4% ± 48.3% ($p < 0.01$), respectively.

Most patients who experienced relapse achieved remission/response again by immunosuppressive therapy, except for 4 who died because of late referral.

Among the 122 patients without relapse during followup, 90 were well, 27 died, and 5 had grumbling disease in ear, nose, and throat (ENT) (Figure 1).

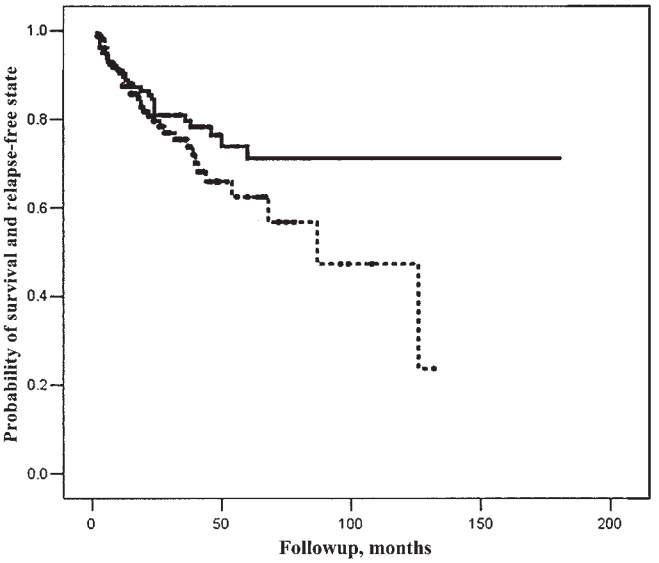

Figure 1. Relapse and survival of the patients. Solid line: survival; broken line: relapses.

Consistency of initial organ involved between relapses and first onset. Among the 55 relapse events, 39 (70.9%) had the same initial organ involved as in the first onset. The prevalence of relapse events with the same initial organ involved as first onset was significantly higher than that without (70.9% vs 29.1%; chi-square = 19.2, $p < 0.001$). For each initial organ involved at first onset, the proportions of relapse events with same initial organ involved as the first onset were: lung (19/25, 76.0%), kidney (3/5, 60.0%), ENT (5/9, 55.6%), joint and muscle (9/11, 81.8%), skin (1/1, 100%), eye (1/1, 100%), testicle (0/1, 0%), and fever (1/2, 50.0%). There were no significant differences in the consistency rates between patients with WG and those with MPA, between patients with PR3-

ANCA and MPO-ANCA, or between first and multiple relapse.

DISCUSSION

Relapses of AAV, associated with subsequent progression to endstage renal disease[6], are still a challenge to physicians despite successful initial treatment[7-13]. However, early identification of relapse is not easy.

Our study suggested that most relapse events began with the same organ as in the initial onset. Although the mechanisms were not clear, it was speculated that the pathogenesis of relapses and initial onset of AAV might be the same. The current therapy might just provide immunosuppression rather than a clearance of etiology despite the impressive initial response. Localized subclinical disease might persist during an apparent remission and progress to fulminant active disease after remission. Especially in WG, it seemed that relapse was generally related to the existence of granuloma, since the current immunosuppressive therapy had less effect on granulomatous inflammations than on vasculitis. It might resolve and then develop again or persist in a subclinical and inactive condition. Thus, the persistent granuloma might be the root of relapses of WG[14].

Relapses in AAV are likely to begin with the same organ as in the initial onset, which facilitates early recognition of relapses, for both physicians and patients.

REFERENCES

1. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983;98:76-85.
2. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: the proposal of an international consensus conference. Arthritis Rheum 1994;37:187-92.
3. Chen M, Yu F, Zhang Y, Zhao MH. Clinical and pathological characteristics of Chinese patients with antineutrophil cytoplasmic autoantibody associated systemic vasculitides: a study of 426 patients from a single center. Postgrad Med J 2005;81:723-7.
4. Hellmich B, Flossmann O, Gross WL, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: Focus on ANCA-associated vasculitis. Ann Rheum Dis 2007;66:605-17.
5. Luqmani RA, Bacon PA, Moots RJ, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994;87:671–8.
6. Hogan SL, Falk RJ, Chin H, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Ann Intern Med 2005; 143:621-31.
7. Reinhold-Keller E, Beuge N, Latza U, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum 2000; 43:1021-32.
8. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488-98.
9. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003,349:36-44.
10. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-9.
11. Booth AD, Almond MK, Burns A, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis 2003;41:776-84.
12. Gordon M, Luqmani RA, Adu D, et al. Relapses in patients with a systemic vasculitis. Q J Med 1993;86:779-89.
13. Slot MC, Tervaert JW, Boomsma MM, Stegeman CA. Positive classic antineutrophil cytoplasmic antibody (C-ANCA) titer at switch to azathioprine therapy associated with relapse in proteinase 3-related vasculitis. Arthritis Rheum 2004;51:269-73.
14. Bacon PA. The spectrum of Wegener's granulomatosis and disease relapse. N Engl J Med 2005;352:330-2.