Original Article

Elevated serum levels of immunoglobulin A correlate with the possibility of readmission in patients with microscopic polyangiitis

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Background: The evidence for the short-term prognosis of patients with microscopic polyangiitis (MPA) is weak, and the objective of this study was to analyze the clinical features of the disease and evaluate the risk factors for readmission in patients with MPA.

Methods: Fifty-seven patients with MPA were recruited into this study. The clinical data of these MPA patients were collected. Clinical manifestations, laboratory results, and imaging results were analyzed. Patients who were readmitted to our hospital within 6 months after their first diagnosis and treatment of MPA were defined as the readmission group; the remaining patients were defined as the control group.

Results: Respiratory symptoms, including cough, dyspnea (87.72%), and hemoptysis (3.51%), seemed to be the initial symptoms in many patients with MPA. Systemic symptoms included fever (71.93%), hearing loss (12.28%), vision loss (3.51%), and joint involvement (5.27%). The D-dimer levels of 43 patients (75.44%) were >500 ng/dL, and only three of these patients had venous thrombosis. Age and immunoglobulin A (IgA) were the risk factors for readmission in patients with MPA, with odds ratios (ORs) of 1.162 [95% confidence interval (CI): 1.025–1.317, P=0.019] and 1.010 (95% CI: 1.001–1.018, P=0.028). The days of hospitalization and the a2-globulin level were protective factors with ORs of 0.849 (95% CI: 0.725–0.993 P=0.041) and 0.789 (95% CI: 0.64–0.971, P=0.025), respectively. IgA levels were positively correlated with the number of hospitalizations, with a correlation coefficient of 0.428 (P=0.002). Receiver operating characteristic curve analysis showed that the possibility of readmission increases when the serum levels of IgA were >217.5 mg/dL.

Conclusion: The level of serum IgA is a risk factor for the readmission of patients with MPA, and correlated with the number of hospitalizations in these patients.

Keywords: Microscopic polyangiitis; readmission; immunoglobulin A; venous thrombosis

Submitted Oct 21, 2016. Accepted for publication Feb 16, 2017.
doi: 10.21037/jtd.2017.03.166
View this article at: http://dx.doi.org/10.21037/jtd.2017.03.166

Introduction

Microscopic polyangiitis (MPA) is a kind of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV). ANCA directed against myeloperoxidase (MPO) is found predominantly in patients with MPA and eosinophilic granulomatosis with polyangiitis (1). Most patients first complain about dry cough and dyspnea, and also experience renal insufficiency. In some patients, fever develops and the disease is difficult to diagnose for a long time. Because of the respiratory symptoms of patients with MPA, many cases were initially diagnosed as idiopathic pulmonary fibrosis or interstitial pneumonia on the basis of computed

tomography (CT) scan findings (2).

The current treatment regimens for patients with MPA are glucocorticoids and/or immunosuppressants. These regimens are largely successful in controlling AAV; however, in approximately one-fourth of patients, active disease persists or recurs in the first 6 months despite treatment (3). Recently, the monoclonal antibody rituximab was approved for the treatment of MPA, providing the first major alternative to cyclophosphamide for the induction therapy of AAV (4-6). Additionally, a study on 92 patients with AAV showed the clinical benefit of intravenous immunoglobulin (IVIg) as an adjunctive therapy with an acceptable tolerance profile, supporting its use in patients with AAV with relapsing disease (7). Treatment of nonsevere relapses of AAV with an increase in glucocorticoids is effective in restoring temporary remission in most patients; however, recurrent relapses within a relatively short interval remain common. Alternative treatment approaches are needed for this important subset of patients (8,9).

Many recent studies focused on the risk factors of outcomes in patients with MPA. These risk factors included renal insufficiency, lung involvement, diffuse pulmonary hemorrhage (10), any kind of infection, and venous thrombosis (11). The main causes of death within the first year were infection (48%) and active vasculitis (19%). Patients with AAV treated with conventional regimens are at an increased risk of death compared with an age- and sex-matched population (12). In another study, patients with MPA were divided into two pairs of groups: (I) a relapse group and a nonrelapse group according to whether there was recurrence or new onset of disease activity (13); and (II) an infection group and a non-infection group. The results showed that the albumin levels were significantly different between the relapse group and the nonrelapse group. Immunoglobulin G (IgG) levels were identified as factors associated with infectious complications; however, there were no differences in renal prognosis or life prognosis between the two groups (14). Another study also showed that the overall survival rates at 6 and 12 months after a diagnosis of MPA with renal involvement were 79.5% and 71.1%, respectively. Moreover, the severity of renal insufficiency was not related to the survival rate of patients with MPA with renal involvement (15).

In this study, we recruited 57 patients with MPA from our hospital and analyzed the clinical characteristics of these patients. We also evaluated the risk factors for the possibility of readmission in these patients.

Methods

Patients

This is a retrospective study. We recruited 57 patients who met the diagnosis criteria for MPA, as defined by the International Chapel Hill Consensus in 2012, from August 2009 to August 2015 at Beijing Chao-yang Hospital (1). Informed consent was obtained from all patients or their family members. Cases that were not initially diagnosed at our hospital were excluded from this study. The ethics committee of our hospital approved the study protocol.

Data collection

We reviewed the medical records, radiological images, laboratory results, and biopsy findings of the patients. The patients' age; sex; days of initial hospitalization; number of hospitalizations; symptoms; physical examination, laboratory, and radiological findings; biopsy results; and treatment were all recorded. Readmission was defined as admission at our hospital within 6 months after the first diagnosis and treatment of MPA.

Statistical analysis

Nonnormally distributed variables are summarized as medians, and the two groups were compared by using the Mann-Whitney U-test. Categorical variables are presented as percentages, and the groups were compared by using the chi-square test. Logistic regression analysis was used to screen for risk factors or protective factors. To obtain the cutoff point of variables, receiver operating characteristic (ROC) curves were generated and the area under the curve (AUC) was calculated. Pearson correlation analysis was used to calculate the correlation confidence of two variables. $P<0.05$ was considered to indicate statistical significance. SPSS 21.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Clinical manifestations

A total of 57 patients with MPA were recruited into this study. The clinical manifestations are summarized in *Table 1*. This study group comprised 34 male and 23 female patients. The median age of these patients was 66 years (range, 32–85 years). The median number of days of

Table 1 Clinical manifestations and laboratory results of 57 patients with Microscopic polyangiitis

Variables	MPA patients (n=57)	MPA patients (N=1, n=22)	MPA patients (N>1, n=28)	P values
Age (years)	66 [32, 85]	62 [32, 83]	68 [36, 85]	0.010
Gender (F/M)	34/23	12/10	18/10	0.567
Days (days)	14 [1, 56]	16 [8, 53]	12 [1, 24]	0.004
Dyspnea (%)	50 (87.72%)	17 (77.28%)	26 (92.86%)	0.423
Hemoptysis (%)	2 (3.51%)	2 (11.77%)	0	-
Fever (%)	41(71.93%)	14 (63.64%)	20(71.43%)	0.379
Hearing loss (%)	7 (12.28%)	3 (13.64%)	4 (14.29%)	0.706
Vision loss (%)	2 (3.51%)	0	2 (7.15%)	-
Joint involved (%)	3 (5.27%)	0	3 (10.72%)	-
Interstitial pneumonia (%)	46 (80.71%)	14 (63.64%)	25 (89.29%)	0.179
Pleural effusion (%)	11 (19.30%)	5 (22.73%)	6 (21.43%)	0.747
Renal insufficiency (%)	19 (33.34%)	9 (40.91%)	10 (35.72%)	0.783
Emphysema (%)	26 (45.62%)	9 (40.91%)	17 (60.72%)	0.034
Pleural thickening (%)	26 (45.62%)	10 (45.46%)	16 (57.15%)	0.113
Urinary proteins (%)	28 (49.13%)	13 (59.09%)	15 (53.57%)	0.600
RBCs in the urine (%)	50 (87.72%)	19 (86.37%)	25 (89.29%)	1.000
Urine AEM (%)	28 (49.13%)	10 (45.46%)	15 (53.58%)	0.600
Fungal infection (%)	6 (10.53%)	2 (9.09%)	4 (14.29%)	0.423

MPA, microscopic polyangiitis; N, number of hospitalizations; Days, number of hospitalization days for the first time; RBC, red blood cells; AEM, abnormal erythrocyte morphology.

initial hospitalization was 14 days (range, 1–56 days). Respiratory symptoms seemed to be the initial symptoms in many patients, including cough, dyspnea (87.72%), and hemoptysis (3.51%). Systemic symptoms included fever (71.93%), hearing loss (12.28%), vision loss (3.51%), and joint involvement (5.27%). As shown in these patients, respiratory symptoms seemed to be the initial symptoms in most of them.

Laboratory results

Regular tests

After admission to our hospital, all patients underwent urinalysis; biochemical tests (including tests for liver function, renal function, and electrolyte levels) and D-dimer and coagulation tests (*Table 2*). The median count of white blood cells was 7.59 10^9/L (range, 0.69×10^9/L to 19.24×10^9/L), and the median proportion of neutrophil and eosinophil was 76% and 1.9%, respectively. The peripheral blood platelet counts ranged from 16 10^9/L to 148 10^9/L. Among the 57 patients, 50 (87.72%) had red blood cells in urine showing abnormal erythrocyte morphology. The amount of urine proteins also increased in 28 of these 57 patients (49.13%), and 19 (33.34%) of them developed renal insufficiency. The D-dimer levels of 43 patients with MPA (75.44%) were >500 ng/dL, and only three patients had venous thrombosis according to the ultrasound results. The coagulation tests were normal in most of the patients.

Immunity related tests

In addition, analyses of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), anti-double stranded DNA antibody (anti-ds-DNA), ANCA, immunoglobulin, and complement levels were also tested. The ESR and CRP levels were elevated in most of the recruited patients, with median values of 39.5 mm/h and 12.9 mg/dL, respectively. The median value of MPO-ANCA of all patients with MPA was

Table 2 Laboratory results of 57 patients with Microscopic polyangiitis

Variables	MPA patients (n=57)	MPA patients (N=1, n=22)	MPA patients (N>1, n=28)	P values
WBC ($\times10^9$/L)	7.59 (0.69, 19.24)	9.16 (3.73, 18.04)	8.86 (0.69, 19.24)	0.561
Neutrophil (%)	76 (41.6, 97.1)	76.15 (42.6, 97.1)	76 (46.1, 93.9)	0.600
Eosinophil (%)	1.9 (0, 18.5)	2.1 (0, 17.5)	2 (0, 7.5)	0.453
Hemoglobin (g/L)	105 [61, 148]	103.5 [61, 147]	108 [74, 146]	0.684
PLT ($\times10^9$/L)	264 [16, 591]	265 [18, 460]	261 [16, 591]	0.913
ESR (mm/h)	39.5 [0, 93]	33.5 [0, 89]	49 [5, 93]	0.719
CRP (mg/dL)	12.9 (0.1, 114.3)	4.8 (0.12, 112.3)	7.42 (0.14, 18.6)	0.943
IgG (mg/dL)	1390 (134, 3070)	1380 (686, 3060)	1660 [134, 2,310]	0.151
IgA (mg/dL)	248.5(38.5, 616)	189 (38.5, 522)	302 (57.5, 616)	0.003
IgM (mg/dL)	94.6 (18.3, 330)	103.3 (24.1, 316)	88.7 (18.3, 330)	0.670
C3 (mg/dL)	101 (10.5, 159)	102.5 (11.5, 159)	99.8 (42.8, 156)	0.488
C4 (mg/dL)	22.8 (9.37, 74)	22.8 (15.1, 40.7)	24.4 (9.37, 74)	0.932
Albumin (g/L)	45 (3.7, 55.6)	45 (3.9, 55.6)	45 (36.4, 55.1)	0.239
a1 globulin (g/L)	7.4 (3.3, 12.6)	7.4 (4.1, 11.2)	7.8 (3.3, 12.6)	0.190
a2 globulin (g/L)	13.3 (6.8, 19.8)	13.4 (6.8, 18.8)	13.1 (8.8, 17.8)	0.036
r globulin (g/L)	22.1 (6.5, 36.2)	21.3 (6.9, 36.2)	24.5 (6.6, 29.7)	0.150
MPO-ANCA (RU/mL)	118.7 (28.7, 285.7)	114.88 (28.7, 271.2)	123.09 (36.2, 285.7)	0.383
D-Dimer (ng/dL)	1,669.7 (256.67, 7,712.39)	1,719.38 (276.67, 7,085.92)	1,619.72 (315.44, 7,712.39)	0.610
PT (s)	11.8 (10, 17.1)	11.5 (12, 17.1)	12.4 (10.1, 16.1)	0.690
PA (%)	86.7 (52.5, 108)	89.6 (53.5, 102.7)	85.2 (55.9, 108)	0.482
PR	1.07 (0.88, 1.54)	1.04 (0.91, 1.54)	1.09 (0.88, 1.47)	0.572
INR	1.06 (0.88, 1.96)	1.02 (0.91, 1.57)	1.09 (0.88, 1.96)	0.357
APTT (s)	29.7 (20.4, 48.8)	29.9 (20.4, 39.2)	29.6 (22.5, 48.8)	0.801
Fibrinogen (mg/dL)	437.5 (246.8, 778.2)	440 (278.8, 778.2)	432.8 (246.8, 720.4)	0.801
TT (s)	19 (16.2, 25.4)	19.1 (16.6, 23.4)	18.9 (16.2, 22.8)	0.972

WBC, white blood cells; PLT, blood platelet; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IgA, immunoglobulin A; MPO-ANCA, anti-neutrophil cytoplasmic autoantibody directed against myeloperoxidase; PT, prothrombin time; PA, prothrombin activity; PR, prothrombin time ratio; INR, international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time.

118.7 RU/mL (range, 28.7–275.7 RU/mL), and PR3-ANCA and MPO-ANCA were both positive in only one patient. ANA was positive in 19 patients (33.34%), and ds-DNA was positive in only 2 patients (3.51%). Many patients had increasing immunoglobulin levels and decreasing C3 levels. MPO-ANCA was positive in all of the MPA patients.

Imaging results and pulmonary function tests

All 57 patients with MPA underwent high-resolution CT scan of the chest. According to their chest CT scan results, 46 (80.71%) patients had interstitial pneumonia and 29 (50.88%) of these patients had pulmonary fibrosis. Twenty-six (45.62%) patients also had complications including

emphysema (45.62%), pleural thickening (45.62%), and pleural effusion (19.30%) (*Table 1*). Twenty-four patients (42.11%) underwent pulmonary function tests; 14 of these 24 patients were found to have restrictive ventilatory dysfunction, 6 patients had obstructive ventilatory dysfunction and small airway dysfunction, and 4 patients had normal results. Echocardiography was also performed on all of our patients; six patients showed pulmonary artery hypertension and two patients had pericardial effusion. Finally, electromyography was performed on only two patients, which revealed peripheral neuropathy in one patient and normal results in the other patient. Most MPA patients had interstitial pneumonia.

Renal biopsy and treatment

Many patients with MPA develop renal injury. Therefore, we also performed renal biopsy in nine patients, and the results showed focal proliferative and necrotizing glomerulonephritis, which was compatible with kidney injury in AAV. After the diagnosis, all patients with MPA were treated with prednisone or methylprednisolone, and cyclophosphamide.

Correlation between IgA and the readmission possibility of MPA patients

Among the 57 patients, 5 patients were excluded from the readmission analysis because of the short time since their discharge from our hospital. In addition, two patients with MPA who died during their first admission were also excluded. Therefore, we divided the remaining 50 patients with MPA into two groups according to their number of hospitalizations: 22 of these patients had only one hospitalization and were considered as group 1, and the other 28 patients had more than one hospitalization and were considered as group 2. All of the above-mentioned parameters were compared between these two groups. As a result, age (P=0.01), number of days of initial hospitalization (P=0.004), emphysema (P=0.034), IgG level (P=0.003), and a2-globulin level (P=0.036) were all significantly different between the two groups. Then, univariate logistic regression analysis was performed on all the variables shown in *Tables 1* and *2*. After the analysis, variables with P<0.1 including age (P=0.024), number of days of initial hospitalization (P=0.021), pleural thickening (P=0.079), emphysema (P=0.026), IgA (P=0.011), a2-globulin (P=0.037), r-globulin (P=0.062), and O-type blood (P=0.092) were entered into multivariate logistic regression analysis (forward conditional). The results revealed that age, number of days of initial hospitalization, IgA, and a2-globulin could be entered into the regression analysis. Age had the highest odds ratio (OR) of 1.162 [95% confidence interval (CI): 1.025–1.317, P=0.019], followed by IgA with an OR of 1.010 (95% CI: 1.001–1.018, P=0.028). Hence, age and levels of serum IgA were risk factors for readmission in patients with MPA. The number of days of initial hospitalization and the a2-globulin level were protective factors with ORs of 0.849 (95% CI: 0.725–0.993, P=0.041) and 0.789 (95% CI: 0.64–0.971, P=0.025), respectively (*Table 3*). Pearson correlation analysis showed that only IgA levels were positively correlated with the number of hospitalizations with a correlation coefficient of 0.428 (P=0.002) (*Figure 1A*). The ROC curve analysis showed that the AUC was 0.726 (0.578–0.873, P=0.007). Moreover, when the serum levels of IgA were >217.5 mg/dL, the possibility of readmission increased (*Figure 1B*). These data showed that the level of serum IgA was a risk factor for the readmission of patients with MPA, and correlated with the number of hospitalizations in these patients.

Discussion

This study had two important findings. First, most of the patients had elevated levels of D-dimers; however, only three patients had venous thrombosis. The coagulation function was normal in most of the patients with MPA in our study group. Second, age and levels of IgA were risk factors for the possibility of readmission in patients with MPA. Furthermore, the number of days of initial hospitalization and the a2-globulin levels were protective factors in these patients. The levels of IgA were positively correlated with the number of hospitalizations.

Venous thrombosis is a new risk factor in patients with MPA (11,16). Allenbach performed a retrospective, systematic analysis of 1,130 patients with systemic vasculitis. Their results showed that venous thromboembolic events (VTEs) occurred in 18 of 236 (7.6%) patients with MPA, and multivariate analysis retained age, male sex, or previous VTE or stroke with motor deficit as factors associated with a higher VTE risk (17). We found that 3 of the 57 patients (5.2%) in this study developed deep vein thrombosis during their first-time admissions; however, we did not perform follow-up for this condition. The D-dimer levels were elevated in most of these patients with MPA, because the endothelial cells were damaged and the coagulation system

Table 3 Logistic regression analysis of variables

Variables	P value	OR (95% CI)	P value	OR (95% CI)
Age	0.024	1.074 (1.009, 1.143)	0.019	1.162 (1.025, 1.317)
Days	0.021	0.902 (0.827, 0.985)	0.041	0.849 (0.725, 0.993)
Pleural thickening	0.079	2.603 (0.896, 7.563)	-	-
Emphysema	0.026	3.556 (1.166, 10.84)	-	-
IgA	0.011	1.007 (1.002, 1.012)	0.028	1.010 (1.001, 1.018)
a2-globulin	0.037	0.916 (0.844, 0.995)	0.025	0.789 (0.64, 0.971)
r-globulin	0.062	0.955 (0.911, 1.002)	-	-
O-type blood	0.092	0.316 (0.082, 1.209)	-	-

OR, odd rate; CI, confidence interval.

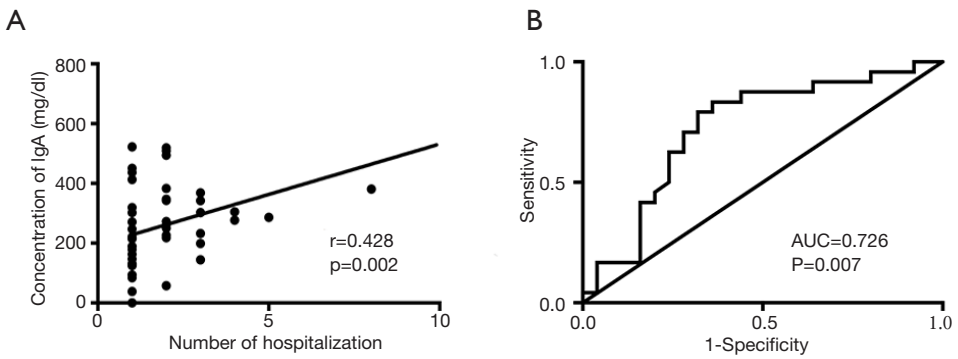

Figure 1 Comparison of serum levels of immunoglobulin A (IgA) between group 1 (N: number of hospitalization, N=1) and group 2 (N>1). (A) Pearson correlation analysis between serum IgA levels and number of hospitalizations; (B) receiver operating characteristic curve and area under the curve of serum IgA levels in group 1 and group 2.

was activated during disease induction (18,19).

As we have described before, in approximately one-fourth of patients with MPA, active disease persisted or recurred in the first 6 months despite treatment (3). Consequently, many studies were performed to evaluate the risk factors of relapse or readmission. A previous study revealed that an increase in ANCA level during remission was associated with a risk of disease relapse. An increase in the ANCA level may be useful for guiding treatment decisions in appropriate subsets of patients with AAV (20). In addition, many novel risk factors were also reported, including exposure to farms and farm animals (21). Within 5 years of diagnosis of Wegener's granulomatosis or MPA, 14% of patients will have a 5-year cardiovascular risk event (22). As for the prognosis of patients with MPA, evidence showing the short-term prognosis of MPA is weak. The mortality of MPA is mainly concentrated in the first months after diagnosis. The long-term prognosis of MPA is less severe; however, relapses are frequent. Early diagnosis, early treatment according to risk factors, and a longer follow-up of patients are needed (23). Additionally, age ≥65 years and development of pulmonary infections after immunosuppressive treatments were identified as risk factors for death during hospitalization (24), especially infection. A previous study analyzed the infection conditions of 61 patients with MPA. A total of 61 patients developed 147 infections, showing that infectious events are frequent. The results also showed that relapse and infection shared similarities during the course of vasculitis (25). Hence, in our study, we did not analyze the reasons for readmission of patients with MPA. The IgG levels were identified as factors associated with infectious complications (14), and no research has been reported about the correlation between IgA and patients with MPA. Previous study reported a

pedipediatric case of microscopic polyangiitis with skin manifestations resembling vesiculobullous type erythema elevatum diutinum with immunoglobulin A antineutrophil cytoplasmic antibody. So far, no direct evidence proved the relation between Ig A levels and MPA patient. More investigations still need to be performed.

This study has several limitations. The study population was relatively small, and more patients should be recruited. Many test results were missing, and only nine patients underwent renal biopsy. However, we still had a novel finding. This is the first report to demonstrate that the IgA levels of patients with MPA on their first-time admissions were correlated with the possibility of readmission in these patients.

Conclusions

In conclusion, most patients with MPA have high levels of D-dimers. Age and serum IgA are risk factors for the readmission of patients with MPA.

Acknowledgements

Funding: This work was supported by the National Science Foundation of China (81500003) and Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ID: ZYLX201312).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The ethics committee of our hospital approved the study protocol.

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Cite this article as: Wang H, Zhang C, Tong Z, Bu X. Elevated serum levels of immunoglobulin A correlate with the possibility of readmission in patients with microscopic polyangiitis. J Thorac Dis 2017;9(5):1201-1208. doi: 10.21037/jtd.2017.03.166

