and 1 had chronic kidney disease. The HV group was younger than every other group ($p < 0.001$). No significant difference was seen among the groups in patient age at the onset of RA. The RA w/o MAC group used prednisolone (PSL) more frequently than the RA only group ($p < 0.05$). According to the radiological findings of the 14 patients in the RA + MAC-PD group, 2 were determined to have FC disease, 11 were determined to have NBE disease, and 1 was unclassifiable. The radiological findings of the 20 patients in the RA w/o MAC group were similar: 1 was determined to have FC disease, 19 manifested a predominant finding of NBE disease in the baseline CT, and 1 was determined to have FC disease. Figure 1 shows representative CT images of the RA + MAC and RA w/o MAC.

Levels of Anti-GPL Antibodies

The levels of serum anti-GPL antibody in the RA + MAC, RA w/o MAC, RA only, and HV groups were 2.87 ± 2.83, 0.50 ± 0.45, 0.31 ± 0.24, and 0.38 ± 0.10 U/ml, respectively (fig. 2). Serum anti-GPL antibody was significantly higher in the RA + MAC group than in the other three groups ($p < 0.001$).

Sensitivity and Specificity

A receiver-operating characteristic (ROC) curve constructed for RA + MAC and RA w/o MAC had an area under the curve of 0.95 (fig. 3). Fourteen RA + MAC patients and 20 RA w/o MAC patients were included in the ROC analysis. The best cutoff value obtained by measuring the shortest distance between the coordinate point (0, 100) and the respective points on the ROC curve was 0.7 U/ml. A cutoff value of 0.7 U/ml resulted in 90.0% (18/20) specificity and 100% sensitivity (14/14).

Treatments and Levels of Anti-GPL Antibodies

The levels of serum anti-GPL antibodies were compared according to the treatment regimen in the 14 RA + MAC patients. No significant differences in the levels of anti-GPL antibodies were found among these regimens (fig. 4).

Correlations between the Extent of Disease and Levels of Anti-GPL Antibodies

Correlations between the extent of disease and levels of anti-GPL antibodies were investigated in 14 RA + MAC patients who underwent chest CT and serologic tests at the same time. No correlations were found between the extent of disease and the levels of anti-GPL antibodies (fig. 5).

Table 1. Characteristics of the study subjects

Characteristics	RA + MAC	RA w/o MAC	RA only
Patients	14	20	20
Age	66.0±9.5[a]	66.0±10.2[a]	60.9±9.9[a]
Range	50–87	38–80	35–75
Sex			
Male/female	2/12	2/18	1/19
Duration			
MAC disease	2.3±1.7	N/A	N/A
Age at RA onset	52.0±11.0	56.5±14.7	55.5±12.8
CT classification			
FC	2	1	
NBE	11	19	N/A
Unclassifiable	1	0	
Therapy for RA			
DMARDs total	14	19	19
PSL	2	10*	2
MTX	8	12	14
TAC	2	4	1
Anti-TNFα	0	6	5
Therapy for MAC-PD			
3 drugs	3		
1 drug	8	N/A	N/A
No treatment	3		

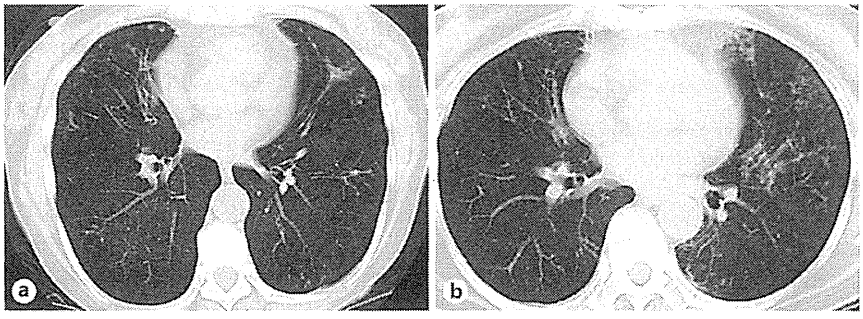
Data are shown as mean ± SD years or numbers. N available; DMARDs = disease-modifying anti-rheuma MTX = methotrexate; TAC = tacrolimus. * $p < 0.05$ vs. [a] $p < 0.001$ vs. HV.

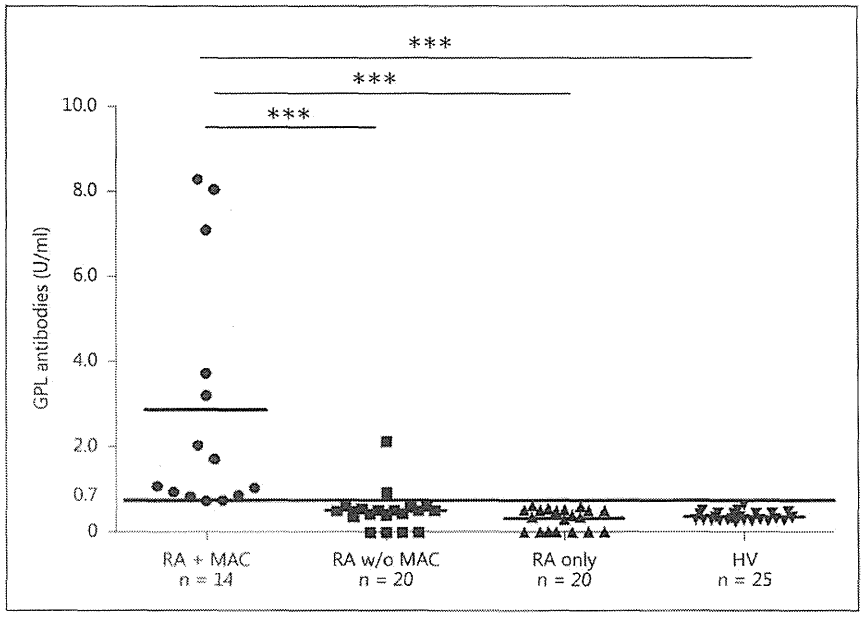
Discussion

The present study showed that EIA for anti-G body can be a useful tool for detecting MAC-P tients with RA. With the cutoff value set at 0.7 U ROC analysis had a sensitivity of 100% and spec 90%.

In 2007, a new set of diagnostic guidelines f disease was published by the ATS and Infectious Society of America (IDSA). Not long after, counterparts published new NTM guidelines wit fications almost identical to those of the ATS an The bacteriological criteria are now somewhat than those described under the ATS diagnostic from 1997 [16]. It remains difficult, however, to MAC-PD diagnosis bacteriologically in RA patie manifest abnormal shadows characteristic of M particularly when bronchoscopy is unfeasible or ture for bronchial lavage fluid is negative.

A + MAC: axial CT shows cylin-
onchiectasis and independent
ı the right middle lobe and a larg-
in the left upper lobe. **b** RA w/o
al CT shows cylindrical bronchi-
the right middle lobe and centri-
›acities in the left upper lobe.





vels of serum anti-GPL antibody
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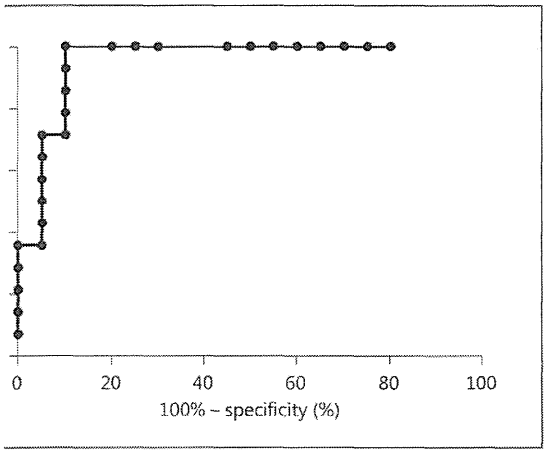

C constructed for RA + MAC and RA w/o MAC patients.

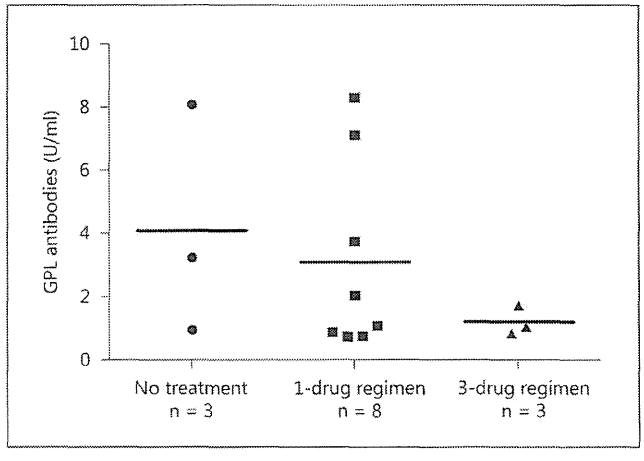

Fig. 4. Comparison of antibody levels between 3-drug, 1-drug, and no-treatment regimens. Horizontal bars indicate the means.

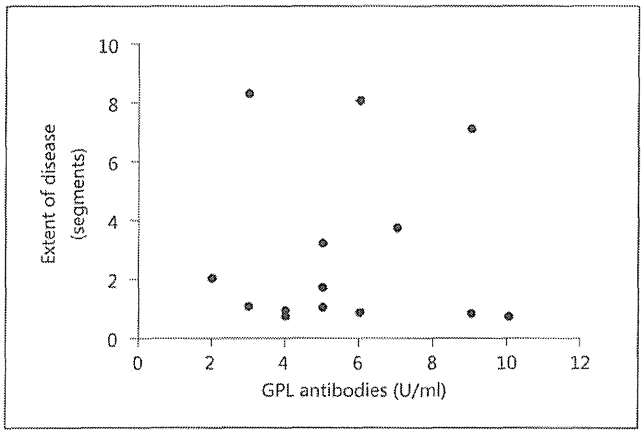

Fig. 5. Correlation between antibody levels and radiographic severity by chest CT in 14 RA patients with MAC-PD.

RA patients have pulmonary lesions such as follicular bronchitis and bronchiectasis [7, 8]. Lesions of the respiratory tract on chest CT are reportedly found in 40% of RA patients [17]. While the frequency of NTM infection has yet to be identified in RA, Wickremasinghe et al. [18] reported a 2% rate of NTM infection in bronchiectasis patients in their study. This radiological similarity between MAC-PD and RA lung has often made a differentiation between both diseases difficult. In the present study, we were able to distinguish the levels of serum IgA antibody to GPL core between RA + MAC and bronchitis or bronchiectasis associated with RA.

The most critical tool for MAC-PD diagnosis is generally thought to be smear results and culture of bronchial washing. Among 57 MAC-PD patients tested by Yamazaki et al. [19], sputum acid-fast smears were positive in 11 patients (19.2%) and sputum MAC cultures were positive in 21 (36.8%). In the deteriorated patient group of their study, cultures obtained by fiberoptic bronchoscopy proved to be positive for MAC in 49 patients (85.9%) and negative for MAC in 17% [19]. In serodiagnosis studies by Kitada et al. [20, 21], the EIA for anti-GPL antibody had a sensitivity and specificity of 84.3 and 100%, respectively, in a Japanese population and 87.9 and 94.2%, respectively, in an American population. The sensitivity and specificity in the present study were similar to those reported previously [21, 22].

Two patients manifesting anti-GPL antibodies above our cutoff value of 0.7 were mixed into the RA w/o MAC group in the present study. Though still unable to identify the cause of this discrepancy, RF stands out as a possible culprit. RF interferes with immunoassa ways, namely, in how it reacts with polyethylene the reagent and in how it recognizes animal anti the reagent as antigens and produces immunop in response. RF nonspecifically binds to the Fc IgG and IgM-RF immunocomplex in the RF fa can form a bridge structure when it reacts with agent [23]. False-positive results can also result f eases of other mycobacteria such as *Mycobacte tuitum*, *chelonae*, *abscessus*, or *scrofulaceum*, o that similarly possess GPLs on their cell wall surf 26].

False negatives occurred in 15.7% of the patie MAC-PD in the study by Kitada et al. [21]. HI may govern the immune responses to GPL core, ation in these responses among individuals ma cause of false negatives [27]. Another possible ca immunosuppressive agents the RA patients may ceived. In our study, 14 patients received PSL (2 MAC, 10 in RA w/o MAC, and 2 in RA only), a in RA + MAC, 12 in RA w/o MAC, and 14 in I table 1) received methotrexate. While most of tients used >1 drug for RA treatment, a significa ber of patients in the RA w/o MAC group recei alone. The levels of anti-GPL antibodies did no cantly differ between the patients receiving PSL tients not receiving PSL (2.40 ± 1.87 vs. 2.95 ± 3.(+ MAC, $p = 0.584$, and 0.633 ± 0.552 vs. 0.386 ± RA w/o MAC, $p = 0.224$, Mann-Whitney U test)

The recommended treatment for NTM-PD s release of the ATS guideline in 1997 has been a regimen of clarithromycin (CAM), ethambutol (rifabutin (RBT) or rifampicin (RFP) for 12 mo negative smear results. For more severe cases, the mendation has been a 4-drug regimen (CAM, E tomycin, and RBT or RFP) for 2 months, follov switch to a 3-drug regimen for 12 months after th results are negative [28]. Sixty to 80% of MAC-I were reported to be smear negative after the fir ment using this standard regimen [29, 30]. In ou 14 patients with RA w/o MAC were classified in categories according to the treatment received were no significant differences in the levels of G bodies among the three regimens, though the an did tend to be lower in the patients on the 3-dr men. Eight of the RA + MAC patients received a treatment for MAC infection for the reasons indi the Materials and Methods. We have not measur GPL antibodies in our subjects since the end of th When Kitada et al. [12] compared serum IgA an

)efore and after chemotherapy in both cured (14 tients) and uncured patients (13 MAC patients), ıd significantly decreased GPL core antibodies in d MAC patients who had responded to the che- py.

y, Kitada et al. [14] reported that the levels of re-specific IgA antibodies correlated with the of involved chest CT segments in patients with ng disease. In our study, we found no such cor- ; between the extent of the disease and GPL an- evels (fig. 4). We may have overestimated the .ons with MAC in our study because of the RA

tudy has several limitations. First, the sample size ;es is small. Our sample for RA + MAC, only 14 . is especially small, as few cases of RA + MAC :d at our institution between April 2009 and Sep- 2011. Second, the timing for the blood collection ince our data were retrospective. Among our 14 RA + MAC patients, blood was collected before the MAC diagnosis in 9 patients and after the diagnosis in 5. Finally, this study was a derivation cohort but not a validation cohort.

In conclusion, a serologic test for anti-GPL antibody is useful for the diagnosis of MAC-PD in RA.

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Financial Disclosure and Conflicts of Interest

None of the authors has financial relationships with commercial entities that have interests in the subject of this paper.

·ences

1 DE, Aksamit T, Brown-Elliott BA, aro A, Daley C, Gordin F, Holland SM, ırgh R, Huitt G, Iademarco MF, Ise- 1, Olivier K, Ruoss S, Fordham von ', Richard J, Wallace RJ Jr, Winthrop K, lycobacterial Diseases Subcommittee: ıcial ATS/IDSA statement: diagnosis, ent, and prevention of nontuberculous acterial diseases. Am J Respir Crit Care)07;175:367–416.

nmittee of the Joint Tuberculosis ittee of the British Thoracic Society: ement of opportunist mycobacterial ons: Joint Tuberculosis Committee nes 1999. Thorax 2000;55:210–218.

K, Fisher D, Cowie RL: *Mycobacterium* complex pulmonary disease in patients ıt HIV infection. Chest 2004;126:566–

K, Cowie RL: Lung disease due to the common nontuberculous mycobacte- est 2006;129:1653–1672.

K, Wang J, Marras TK: Nontubercu- ycobacterial sensitization in the Unit- es: national trends over three decades. Respir Crit Care Med 2007;176:306–

ni M: Nontuberculous mycobacterio- present status of epidemiology and l studies. Kekkaku 1999;74:377–384.

awa H, Sato A, Imokawa S, et al: Bron- disease in rheumatoid arthritis. Am J Crit Care Med 1996;154:1531–1536.

AF: Bronchiectasis. N Engl J Med 46:1383–1393.

9 Ehlers S: Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? Clin Infect Dis 2005;41:199S–203S.

10 Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO: Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004;38:1261–1265.

11 Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, Mudano A, Pisu M, Elkins-Melton M, Outman R, Allison JJ, Suarez Almazor M, Bridges SL, Chatham WW, Hochberg M, MacLean C, Mikuls T, Moreland LW, O'Dell J, Turkiewicz AM, Furst DE: American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762–784.

12 Kitada S, Maekura R, Toyoshima N, Naka T, Fujiwara N, Kobayashi M, Yano I, Ito M, Kobayashi K: Use of glycopeptidolipid core antigen for serodiagnosis of *Mycobacterium avium* complex pulmonary disease in immunocompetent patients. Clin Diagn Lab Immunol 2005;12:44–51.

13 Moore EH: Atypical mycobacterial infection in the lung: CT appearance. Radiology 1993; 187:777–782.

14 Kitada S, Nishiuchi Y, Hiraga T, Naka N, Hashimoto H, Yoshimura K, Miki K, Miki M, Motone M, Fujikawa T, Kobayashi K, Yano I, Maekura R: Serological test and chest computed tomography findings in patients with *Mycobacterium avium* complex lung disease. Eur Respir J 2007;29:1217–1223.

15 Obayashi Y, Fujita J, Suemitsu I, Kamei T, Nii M, Takahara J: Successive follow-up of chest computed tomography in patients with *Mycobacterium avium-intracellulare* complex. Respir Med 1999;93:11–15.

16 Chae DR, Kim YI, Kee SJ, Kim YH, Chi SY, Ban HJ, Kwon YS, Oh IJ, Kim KS, Kim SO, Kim YC, Lim SC: The impact of the 2007 ATS/IDSA diagnostic criteria for nontuberculous mycobacterial disease on the diagnosis of nontuberculous mycobacterial lung disease. Respiration 2011;82:124–129.

17 Miyazaki Y: Sinusitis and bronchiectasis in rheumatoid arthritis. Riumatika 2008;40: 386–392.

18 Wickremasinghe M, Ozerovitch LJ, Davies G, Wodehouse T, Chadwick MV, Abdallah S, Shah P, Wilson R: Non-tuberculous mycobacteria in patients with bronchiectasis. Thorax 2005;60:1045–1051.

19 Yamazaki Y, Kubo K, Takamizawa A, Yamamoto H, Honda T, Sone S: Markers indicating deterioration of pulmonary *Mycobacterium avium-intracellulare* infection. Am J Respir Crit Care Med 1999;160:1851–1855.

20 Kitada S, Levin A, Hiserote M, Clark BJ, Harbeck RJ, Lichtenstein KA, Czaja CA, Huitt GA, Kasperbaur SH, Perez-Velez CM, Daley CL: Serodiagnosis of *Mycobacterium avium* complex pulmonary disease in the United States. Am J Respir Crit Care Med 2010; 181:A2614.

21 Kitada S, Kobayashi K, Ichiyama S, Takakura S, Sakatani M, Suzuki K, Takashima T, Nagai T, Sakurabayashi I, Ito M, Maekura R, MAC Serodiagnosis Study Group: Serodiagnosis of *Mycobacterium avium*-complex pulmonary disease using an enzyme immunoassay kit. Am J Respir Crit Care Med 2008;177:793–797.

22 Watanabe M, Banno S, Sasaki K, Naniwa T, Hayami Y, Ueda R: Serodiagnosis of *Mycobacterium avium*-complex pulmonary disease with an enzyme immunoassay kit that detects anti-glycopeptidolipid core antigen IgA antibodies in patients with rheumatoid arthritis. Mod Rheumatol 2011;21: 144–149.

23 Ohtake T, Kano S, Watanabe K: Interference in turbidimetric immunoassay for serum C-reactive protein due to serum protein abnormalities an immune complex and rheumatoid factor (in Japanese). Rinsho Byori 2000;48: 752–759.

24 Aspinall GO, Chatterjee D, Brennan PJ: The variable surface glycolipids of mycobacteria: structures, synthesis of epitopes, and biological properties. Adv Carbohydr Chem Biochem 1995;51:169–242.

25 Brennan PJ, Nikaido H: The envelope of mycobacteria. Annu Rev Biochem 1995;64:29–63.

26 Chatterjee D, Khoo KH: The surface glycopeptidolipids of mycobacteria:structures and biological properties. Cell Mol Life Sci 2001; 58:2018–2042.

27 Arend SM, Geluk A, van Meijgaar Dissel JT, Theisen M, Andersen I TH: Antigenic equivalence of cell responses to *Mycobacterium t* specific RD1-encoded protei ESAT-6 and culture filtrate protei mixtures of synthetic peptides. In 2000;68:3314–3321.

28 American Thoracic Society: Dia treatment of disease caused by n lous mycobacteria. Am J Respi Med 1997;156:S1–S25.

29 Wallace RJ Jr, Brown BA, Griffith WM, Murphy DT: Clarithromyci for pulmonary *Mycobacterium a* plex. The first 50 patients. Am J Care Med 1996;153:1766–1772.

30 Tanaka E, Kimoto T, Tsuyuguch nabe I, Matsumoto H, Niimi A, Su rayama T, Amitani R, Kuze F: E rithromycin regimen for *Mycobac um* complex pulmonary disease. A Crit Care Med 1999;160:866–872.

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CASE REPORT

Successful treatment of eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg–Strauss syndrome) with rituximab in a case refractory to glucocorticoids, cyclophosphamide, and IVIG

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Abstract

A 44-year old woman with eosinophilic granulomatosis with polyangiitis (EGPA) developed sequential paralysis of different cranial nerves despite treatments including methylprednisolone pulse therapy, intravenous immunoglobulins (IVIG), and cyclophosphamide. Infusions of rituximab ameliorated her neurological symptoms and serological inflammatory findings. Rituximab, a specific B cell-targeting therapy, might offer an alternative for refractory EGPA with possible advantages of cost and ease of use compared to IVIG, which also targets (at least in part) B lymphocytes and immunoglobulin production.

Keywords

Eosinophilic granulomatosis with polyangiitis, IVIG, Rituximab

History

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg–Strauss syndrome) is a systemic granulomatous vasculitis with eosinophilia in a patient with a history of allergic disease. The involvement of small to medium vessels is characteristic of EGPA, as is the presence of antineutrophil cytoplasmic antibody (ANCA) in the serum. Both of these features qualify EGPA for inclusion as an ANCA-associated vasculitis (AAV).

Although high-dose glucocorticoids (GC) with cyclophosphamide (CPA) has been the main treatment applied in severe cases of EGPA, about 10 % of these cases have been found to be treatment resistant [1]. Further therapeutic options have been sought for such cases, and successful induction of remission has been reported with the use of both intravenous immunoglobulins (IVIG) and rituximab (RTX) [2]. However, repeated administration and/or combination therapies are sometimes required to achieve maximum benefit [3].

Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody that has been approved for use in cases of lymphoid malignancy, rheumatoid arthritis, and, more recently, microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA). Although it has proven to be efficacious for AAV in two randomized controlled studies [4, 5], its efficacy in EGPA cases has remained unclear.

We hereby present a case of EGPA resistant to both CPA and IVIG, which was successfully treated with RTX.

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Case report

A 44-year-old woman with a history of bronchial asthma was admitted to a local hospital in June 2011 for fever with numbness and weakness of her extremities. Laboratory data showed peripheral eosinophilia (6579/μl) and elevated CRP (34.5 mg/l), as well as the presence of MPO–ANCA (180 EU/l). Nerve conduction test revealed low amplitude in the right median, the left ulnar, and the right sural nerves, suggestive of mononeuritis multiplex. She was diagnosed with EGPA, and treatment was initiated with intravenous pulses of methylprednisolone.

Peripheral blood eosinophil count and MPO–ANCA normalized within six weeks during the oral prednisolone (PSL) taper. However, she remained febrile, her neurological symptoms persisted, and her CRP remained elevated (Fig. 1). A trial of IVIG (400 mg/kg/day over five days) was ineffective, with a new left facial nerve paralysis developing during the second course. One intravenous dose of CPA (500 mg) was administered along with the initiation of trimethoprim-sulfamethoxazole for preventing pneumocystis pneumonia, during which time the facial nerve paralysis worsened. There was no evidence of meningitis or hypertrophic pachymeningitis by cerebrospinal fluid analysis and brain MRI.

At this point (in August), the patient was transferred to our hospital, and she still presented febrile. The physical examination revealed that the cranial nerves other than the left facial nerve were intact and that paresthesia and weakness of her extremities had persisted. Peripheral blood count showed an absence of eosinophils, with total white blood cells 17,200/μl, hemoglobin level 8.2 g/dl, and platelets 469,000/μl. Serum CRP (159 mg/l) and eosinophil cationic protein (ECP; 36 μg/dl) were elevated, while MPO–ANCA remained negative. Serum IgG concentration was 1517 mg/ml (normal range: 868–1780 mg/ml). Methylprednisolone pulses improved the facial nerve palsy and the patient became

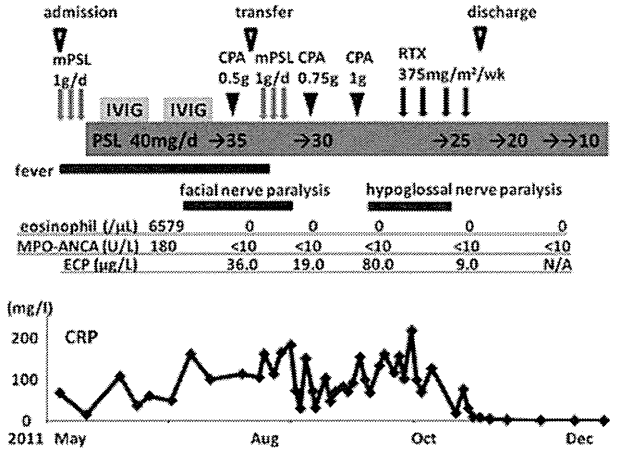

Fig. 1 Clinical course. This EGPA patient was resistant to corticosteroid, IVIG, and CPA. Treatment with RTX ameliorated cranial nerve involvement and reduced serum ECP and CRP levels. She remains in remission with B-cell depletion six months after RTX therapy. *mPSL* methylprednisolone, *PSL* prednisolone, *IVIG* intravenous immunoglobulin, *CPA* cyclophosphamide, *RTX* rituximab, *ECP* eosinophil cationic protein

afebrile, although her CRP remained high. Two additional intravenous doses of CPA (750 mg, followed by 1000 mg) also failed to decrease the CRP. Moreover, the patient started to complain of difficulty swallowing, and paralysis of the right hypoglossal nerve was demonstrated clinically. Serum ECP rose to 80 μg/dl while serum IgG decreased to 801 mg/ml.

Subsequently, RTX was administered at a dose of 480 mg (375 mg/m^2) once a week for four weeks under written informed consent. Three weeks after the first dose, the hypoglossal nerve paralysis had disappeared completely, with decreased peripheral B-cell counts of 2 cells/μl as compared to 164 cells/μl before the RTX administration. Serum CRP and ECP diminished to within normal ranges by the time of the fourth dose, although the peripheral neuropathy at the extremities did not improve. There was no occurrence of adverse events despite the depletion of peripheral B cells and the low serum IgG concentration (760 mg/ml). At six months after completing treatment with RTX, the patient remained in remission on PSL 10 mg/day without peripheral B-cell recovery.

Discussion

Rituximab showed dramatic efficacy in our patient who had EGPA that was resistant to both conventional treatment and IVIG. The success obtained with RTX in the present case is consistent not only with the demonstrated efficacy of RTX in cases of MPA and GPA [4, 5], but also with the results achieved when it was used in eleven previously reported cases (Table 1) [6–11]. Among these 12 cases (including the case herein), three were resistant to previous IVIG, and at least five achieved remission without concomitant immunosuppressants or high-dose corticosteroids, suggesting a possible advantage of RTX in remission induction. As IVIG is presumed to exert its efficacy partly by providing a negative feedback signal on B cells mediated through FcγRIIB [12], the depletion of B cells using RTX may be a more potent and direct mechanism.

The efficacy of IVIG in EGPA has been previously demonstrated in two nonrandomized interventional studies. Tsurikisawa et al. [13] reported that IVIG showed significantly greater improvement of muscle weakness, dysesthesia, and cardiac output in 22 EGPA patients refractory to conventional treatment compared to 24 patients who did not receive IVIG. In a separate report, Danieli et al. [14] found that repeated IVIG combined with plasmapheresis in addition to conventional treatment achieved a significantly higher remission rate (100 %) than conventional treatment alone (44 %) in newly diagnosed EGPA. Based on these findings, IVIG can be recommended in particular for cases with persistent neurological deficits and/or cardiac dysfunction, as well as for difficult-to-treat cases. The efficacy of IVIG monotherapy for inducing remission remains unproven.

Although the potential clinical superiority of RTX needs to be demonstrated in larger studies, its economic and logistical advantages are clear. The administration of IVIG requires hospitalization, which sometimes needs to be repeated. Furthermore, the clinical status of the patient may dictate the need for concomitant plasma exchange, significantly increasing the cost of treatment. Logistically, the availability of IVIG has been problematic globally, and the use of alternative treatments, when possible, has

Table 1. Cases of EGPA successfully treated with RTX

Patient no. [reference]	Age, sex	Involved organs	ANCA	Previous treatments (other than GC)	Concomitant treatments with RTX	Observation period after RTX administration/relapse	Additional RTX use/its indication
1 [6]	49, M	Kidney, skin	PR3	IVCY, AZA	PSL 30 mg/day	3 months/not relapsed	None
2 [7]	37, F	Myocarditis	(–)	IVCY, IVIG, MMF, alemtuzumab	PSL 15 mg/day	9 months/not relapsed	At 6 months/ prophylaxis
3 [7]	37, F	PNS, skin	(–)	CPA, AZA, MMF, alemtuzumab	PSL 10 mg/day	12 months/relapsed at 6 months	At 6 months/ relapse
4 [8]	40, M	Lung	PR3	IVCY, PE	PSL[a] + CPA	9 months/not relapsed	None
5 [8]	66, M	PNS	MPO	IVIG, IVCY, PE	Low-dose PSL[a]	3 months/not relapsed	None
6 [9]	46, F	CNS	MPO	IVCY, MMF	PSL 5 mg/day + MMF	4 months/not relapsed	None
7 [10]	50, M	PNS, skin	(–)	MTX, CyA, AZA IFX, anakinra	PSL[a]	12 months/not relapsed	At 6 and 12 months/ prophylaxis
8 [10]	35, F	Lung	(–)	AZA	PSL[a]	6 months/not relapsed	At 6 months/ prophylaxis
9 [11]	54, F	Kidney	MPO	IVCY, MTX	PSL 1 mg/kg/day	12 months/relapsed at 6 months	At 6 months/ relapse
10 [11]	54, F	Kidney, PNS	MPO	(–)	PSL 1 mg/kg/day	12 months/not relapsed	None
11 [11]	65, M	Kidney, PNS	MPO	(–)	PSL 1 mg/kg/day	12 months/not relapsed	None
12 (present case)	44, F	CNS, PNS	MPO	IVIG, IVCY	PSL 25 mg/day	6 months/not relapsed	None

PNS peripheral nervous system, *CNS* central nervous system, *IVCY* intravenous CPA pulse therapy, *IVIG* intravenous immunoglobulin, *AZA* azathioprine, *MMF* mycophenolate mofetil, *CPA* oral cyclophosphamide, *PE* plasma exchange, *MTX* methotrexate, *CyA* cyclosporine A, *IFX* infliximab
[a]The dosage of PSL was not available

been recommended. Compared with IVIG, one course of RTX may provide sustained efficacy for approximately six months or longer, with at least some of the infusions possible in an outpatient setting.

As pharmacotherapeutic decisions need to be made by weighing up the balance of efficacy and safety, the risk of progressive multifocal leukoencephalopathy (PML) needs to be considered specifically for RTX. Fortunately, these cases are rare; most of them are associated with either previous or concomitant exposure to other immunosuppressive agents. Still, when compared to the safety of IVIG, the risk of developing serious infections should be an important consideration with RTX.

RTX could be an alternative for remission induction in EGPA cases. However, it remains unclear whether the scheduled RTX treatment or treatments with other oral immunosuppressants should be followed as maintenance therapy. In the present case, azathioprine was used successfully, in accordance with the EULAR recommendation for maintenance therapy after the conventional remission induction treatments [2]. An ongoing randomized controlled trial of RTX versus azathioprine as maintenance therapy (MAINRITSAN) will provide us with important information.

In general, peripheral eosinophil counts as well as serum ECP levels serve as biomarkers of the disease activity of EGPA [15, 16]. In the present case, the ECP level reflected the disease activity better than the eosinophil count. Together with another report that described a discrepancy between the levels of these two biomarkers [17], our observation suggests that serum ECP might be the more sensitive biomarker.

In conclusion, RTX is a potent alternative therapy for refractory EGPA. Further clinical investigations, especially with larger numbers of patients, are needed to confirm its efficacy and safety, as well as its most appropriate position in the therapeutic armamentarium.

Conflict of interest

PYS is currently employed by UCB Japan, Co., Ltd. All other authors have declared no conflict of interest.

References

1. Cohen P, Pagnoux C, Mahr A, Arene JP, Mouthon L, Le Guern V, et al. Churg–Strauss syndrome with poor-prognosis factors: a prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum. 2007;57:686–93.
2. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68:310–17.
3. Taniguchi M, Tsurikisawa N, Higashi N, Saito H, Mita H, Mori A, et al. Treatment for Churg–Strauss syndrome: induction of remission and efficacy of intravenous immunoglobulin therapy. Allergol Int. 2007;56:97–103.
4. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. J N Eng Med. 2010;363:211–20.
5. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Eng J Med. 2010;363:221–32.
6. Kaushik VV, Reddy HV, Bucknall RC. Successful use of rituximab in a patient with recalcitrant Churg–Strauss syndrome. Ann Rheum Dis. 2006;65:1116–7.
7. Koukoulaki M, Smith KG, Jayne DR. Rituximab in Churg–Strauss syndrome. Ann Rheum Dis. 2006;65:557–9.
8. Pepper RJ, Fabre MA, Pavesio C, Gaskin G, Jones RB, Jayne D, et al. Rituximab is effective in the treatment of refractory Churg–Strauss syndrome and is associated with diminished T-cell interleukin-5 production. Rheumatology (Oxford). 2008;47:1104–5.
9. Saech J, Owczarczyk K, Rosgen S, Petereit H, Hallek M, Rubbert-Roth A. Successful use of rituximab in a patient with Churg–Strauss syndrome and refractory central nervous system involvement. Ann Rheum Dis. 2010;69:1254–5.
10. Donvik KK, Omdal R. Churg–Strauss syndrome successfully treated with rituximab. Rheumatol Int. 2011;31:89–91.
11. Cartin-Ceba R, Keogh KA, Specks U, Sethi S, Fervenza FC. Rituximab for the treatment of Churg–Strauss syndrome with renal involvement. Nephrol Dial Transplant. 2011;26:2865–71.
12. Sewell WA, Jolles S. Immunomodulatory action of intravenous immunoglobulin. Immunology. 2002;107:387–93.
13. Tsurikisawa N, Saito H, Oshikata C, Tsuburai T, Akiyama K. High-dose intravenous immunoglobulin treatment increases regulatory T cells in patients with eosinophilic granulomatosis with polyangiitis. J Rheumatol. 2012;39:1019–25.
14. Danieli MG, Cappelli M, Malcangi G, Logullo F, Salvi A, Danieli G. Long term effectiveness of intravenous immunoglobulin in Churg–Strauss syndrome. Ann Rheum Dis. 2004;63:1649–54.
15. Herrmann K, Gross WL, Moosig F. Extended follow-up after stopping mepolizumab in relapsing/refractory Churg–Strauss syndrome. Clin Exp Rheumatol. 2012;30:S62–5.
16. Guilpain P, Auclair JF, Tamby MC, Servettaz A, Mahr A, Weill B, et al. Serum eosinophil cationic protein: a marker of disease activity in Churg–Strauss syndrome. Ann N Y Acad Sci. 2007;1107:392–9.
17. Hurst S, Chizzolini C, Dayer JM, Olivieri J, Roux-Lombard P. Usefulness of serum eosinophil cationic protein (ECP) in predicting relapse of Churg and Strauss vasculitis. Clin Exp Rheumatol. 2000;18:784–5.

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CASE REPORT

Recurrent mitral valve regurgitation with neutrophil infiltration in a patient with multiple aseptic abscesses

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Abstract

Aseptic abscess (AA) is characterized by accumulation of neutrophils without evidence of infection, no response to antibiotics, and rapid response to corticosteroids. We report a case of multiple abscesses in the subcutaneous tissues and joints, and severe mitral valve regurgitation. Although AA did not respond to antibiotic therapy, it improved dramatically with corticosteroid treatment. However, repeated valvuloplasty was required for the mitral valve regurgitation. The mitral valve tissue showed neutrophil infiltration without any bacterial invasion. This is the first case of AA to show involvement of cardiac valves, indicating the importance of systematic examination for patients with AA and cardiac valve involvement.

Keywords

Aseptic abscesses, Mitral valve regurgitation, Neutrophil

History

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Introduction

Aseptic abscess (AA) was first described in 1995 [1] and is characterized by accumulation of neutrophils without evidence of infection, no response to antibiotics, and rapid response to corticosteroids. It was reported that 31 of 49 patients with AA had inflammatory bowel diseases, whereas only three patients had no underlying disease [2]. We describe a case of AA with multiple abscesses in the subcutaneous tissues and joints in a patient with severe mitral valve regurgitation with neutrophil infiltration in the valve.

Case report

A 57-year-old woman without any previous medical history presented with a 3-month history of fever, and pain in the ankle and hip joints. Physical examination identified systolic murmur at the apex and tenderness and swelling of the right shoulder and pubic region. Laboratory tests showed increased leukocyte count [13,100/μl (neutrophil 81.8 %)] and C-reactive protein (CRP 22.72 mg/dl). Autoantibodies, such as antinuclear antibodies, rheumatoid factor and antineutrophil cytoplasmic antibodies, were negative. Human leukocyte antigen (HLA) typing was A24, A26, B54, and B62. Echocardiography showed mild mitral valve regurgitation without vegetation. Although bacterial endocarditis was initially suspected, repeated blood cultures were negative. Magnetic resonance imaging revealed multiple cystic lesions in the pubic joint and subcutaneous tissue of the coccygeal region (Fig. 1a, b). Contrast-enhanced computed tomography showed similar lesions around the right shoulder (Fig. 1c). Increased fluorine-18-deoxyglucose (FDG) uptake was found in both shoulders and pubic joint by positron emission tomography (FDG-PET) (Fig. 1d). Arthrocentesis from the pubic joint showed increased inflammatory cells with a cell count of 33,333/μl (polymorphonuclear cells 90 %), but cultures for bacteria and acid-fast bacilli were negative.

The patient was initially treated with several kinds of antibacterial, antituberculosis, and antifungal agents for more than 2 months, but showed no clinical response. Mitral valve regurgitation had been worsening and resulted in heart failure, which was treated with furosemide. As antibiotic therapy was not at all effective for the abscesses and the mitral valve regurgitation, in addition to negative cultures from the abscesses and blood, we finally diagnosed her as AA. Accordingly, she was treated with 30 mg/day prednisolone (PSL), which resulted immediately in resolution of the fever, marked improvement of joint pain, and reduction in CRP to an undetectable level (Fig. 2). Repeated imaging showed cystic lesions became smaller in all areas. Subsequently, PSL was gradually tapered to 15 mg/day, however; this resulted in a rise in CRP to around 1 mg/dl, necessitating the addition of methotrexate (MTX) at 8 mg/week. As severe mitral valve regurgitation persisted even with corticosteroid therapy, following the tapering of PSL to 5 mg/day, mitral valvuloplasty was performed. During surgery, perforations at the posterior leaflet and posterolateral commissure were revealed, which were sutured. She was discharged 1 month after the surgery.

While our patient was maintained by 5 mg/day PSL and 8 mg/week MTX in the outpatient clinic, any symptom such as high-grade fever or arthralgia did not develop. However, serum CRP level was around 3 mg/dl, suggesting that the disease activity was not fully controlled. Two months after discharge, she was hospitalized again because of syncope and severe anemia. Physical examination identified systolic murmur at the apex, and laboratory tests showed decreased hemoglobin (8.8 g/dl) and increased lactase dehydrogenase (2940 IU/l) and CRP (6.3 mg/dl). Severe mitral valve regurgitation was revealed again by echocardiogram. Therefore, we diagnosed her condition as mechanical hemolytic anemia due to relapsed valve regurgitation.

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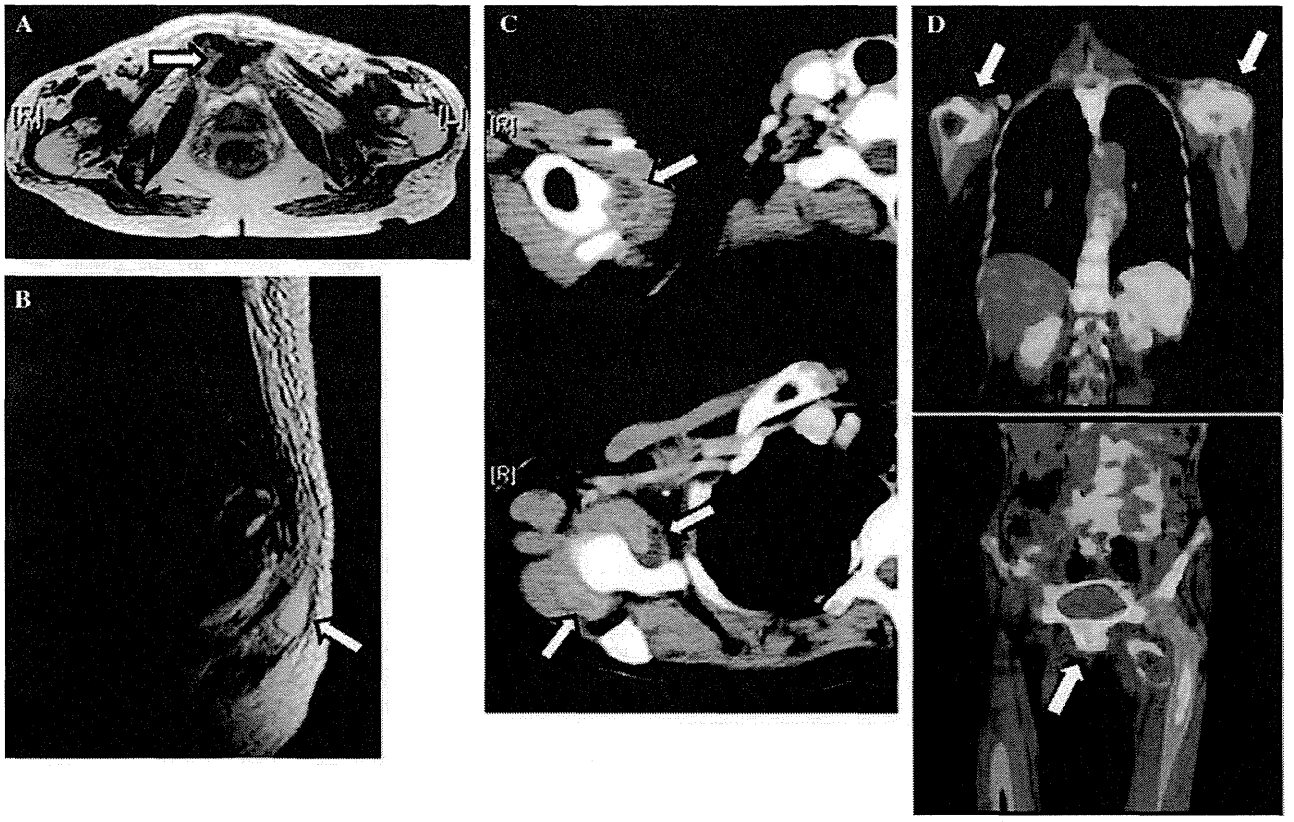

Fig. 1 Findings of magnetic resonance (MR) and computed tomography (CT) imagings. **a** Gadolinium-enhanced T1-weighted MR imaging showed low-intensity areas with enhanced margin in the pubic joint. **b** T2-weighted imaging showed high-intensity mass in the subcutaneous tissues of the coccygeal region. **c** Contrast-enhanced CT showed multiple cystic lesions with enhanced margins around the right shoulder. **d** Fluorine-18-deoxyglucose positron emission tomography (FDG-PET) showed increased FDG uptake in both shoulders and pubic joint. *Arrows* indicate affected lesions

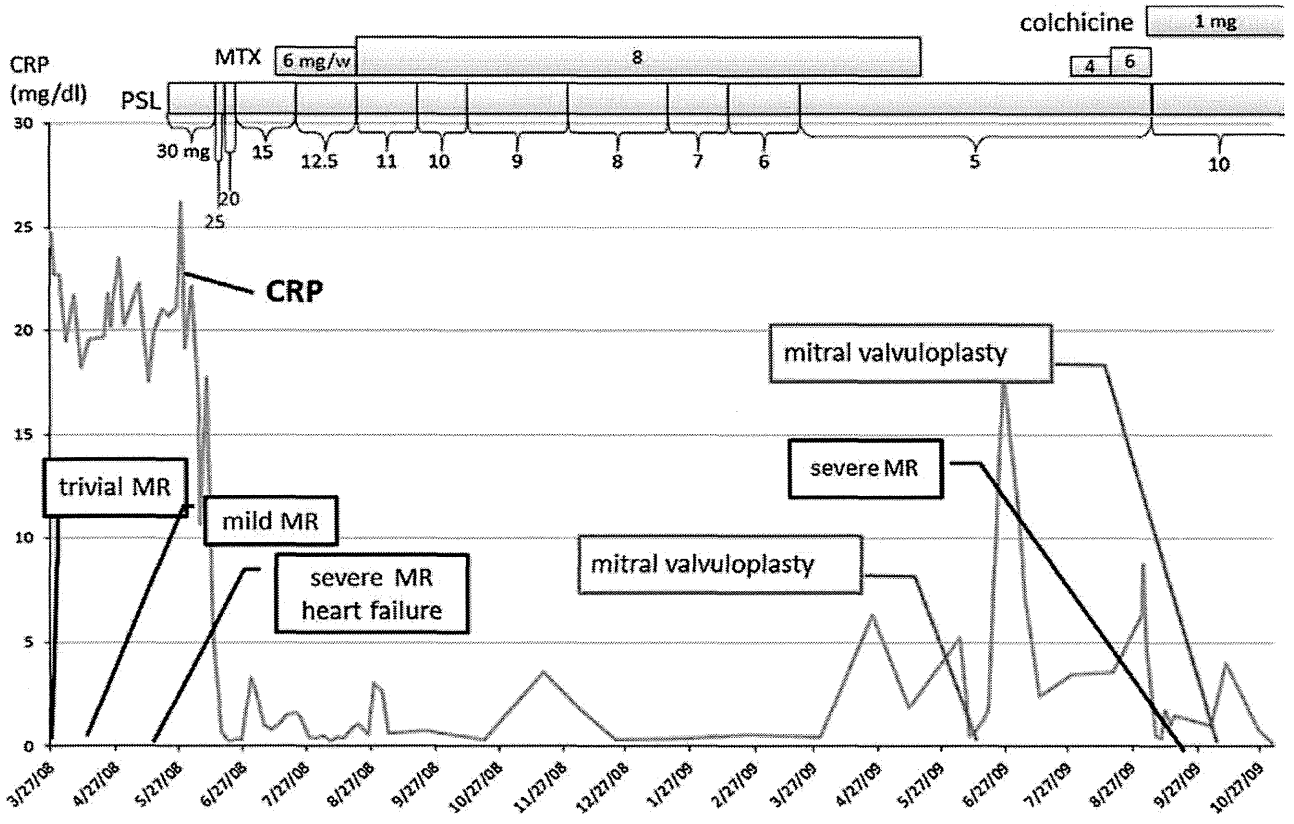

Fig. 2 Clinical course

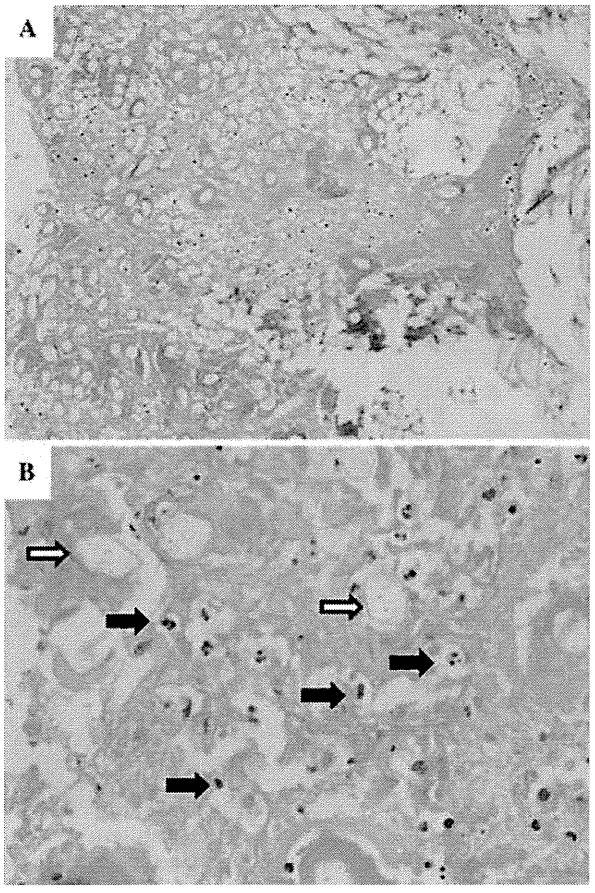

Fig. 3 Histological examination of the mitral valve. Note infiltrated polymorphonuclear neutrophils in the mitral valve (*black arrows*). *White arrows* indicate filaments of suture. Hematoxylin and eosin staining: **a** ×100, **b** ×400

The valvuloplasty was thus repeated. In the open heart surgery, another perforation was found next to the sutured one at the posterior leaflet. Histological findings of mitral valve tissue showed neutrophil infiltration (Fig. 3). No bacterial invasion was detected by Gram staining. Disease activity was subsequently well controlled with maintenance therapy of 10 mg/day PSL and 1 mg/day colchicine.

Discussion

Aseptic abscess is diagnosed based on criteria by André et al. [2]: (1) deep abscess detected by radiologic examination associated with neutrophilia; (2) negative cultures of blood and pus from abscess; (3) lack of response to antibiotic therapy; (4) rapid clinical improvement following initiation of corticosteroids. Previous case series reported AA appeared mostly in viscera, such as spleen (70 %), abdominal lymph nodes (53 %), liver (40 %), lung (17 %), pancreas (10 %), and brain (10 %). In addition, involvement of soft tissue in AA patients was also reported [2–4]. All patients were treated with corticosteroids; however, some patients required additional drugs, such as azathioprine (30 %), colchicine (27 %), cyclophosphamide (17 %), antitumor necrosis factor agent (10 %), and MTX (3 %) [2]. We treated our patient with 30 mg/day (0.6 mg/kg/day) of PSL with MTX. Furthermore, colchicine was added with the expectation of suppressing augmented neutrophil activity.

In this case, mitral valve regurgitation without vegetation occurred with multiple abscesses. Antibiotics were not effective, and cultures from the abscesses and blood were negative. The mitral valve regurgitation relapsed during maintenance therapy, with CRP elevation, suggesting disease activity was not well controlled. Moreover, histological findings of the mitral valve revealed neutrophil infiltration without bacterial invasion. Taken together, we considered that this mitral valve regurgitation was derived from AA. To our knowledge, this is the first case in the literature to show involvement of the cardiac valves in AA.

Although autoinflammatory diseases such as familial Mediterranean fever, hyperimmunoglobulinemia D with periodic fever syndrome, pyogenic arthritis, pyoderma gangrenosa and acne syndrome, tumor-necrosis-factor-receptor-associated periodic syndrome, and cryopyrin-associated periodic syndromes were suspected in our patient, she did not have any disease-related nucleotide polymorphisms [5]. Genetic abnormalities of AA have not been reported.

It is reported that 7–46 % of patients with Behçet's disease develop cardiovascular complications—including valve diseases, which frequently relapse [6, 7]—and some require valvuloplasty [8]. However, this patient showed no typical manifestations of Behçet's disease, such as oral ulcerations, urogenital lesions, cutaneous lesions, or ocular disease.

In conclusion, ours is the first case of AA affecting the mitral valve reported in the literature. Patients with AA should be systemically and carefully examined, including cardiac valve involvement. Furthermore, once AA is diagnosed, disease activity should be tightly controlled.

Conflict of interest

None.

References

1. André M, Aumaitre O, Marcheix JC, Piette JC. Unexplained sterile systemic abscesses in Crohn's disease: aseptic abscesses as a new entity. Am J Gastroenterol. 1995;90:1183–4.
2. André MF, Piette JC, Kémény JL, Ninet J, Jego P, Delèvaux I, et al. Aseptic abscesses: a study of 30 patients with or without inflammatory bowel disease and review of the literature. Medicine (Baltimore). 2007;86:145–61.
3. Lamport RD, Cheskin LJ, Moscatello SA, Nikoomanesh P. Sterile epidural and bilateral psoas abscesses in a patient with Crohn's disease. Am J Gastroenterol. 1994;89:1086–9.
4. Leibovitch I, Galanopoulos A, Selva D. Suppurative granulomatous myositis of an extra-ocular muscle in Crohn's disease. Am J Gastroenterol. 2005;100:2136–7.
5. Aksentijevich I, Kastner DL. Genetics of monogenic autoinflammatory diseases: past successes, future challenges. Nat Rev Rheumatol. 2011;7:469–78.
6. Bletry O, Mohattane A, Wechsler B, Beaufils P, Valère P, Petit J, et al. Cardiac involvement in Behçet's disease. 12 cases. Presse Med. 1988;17:2388–91.
7. O'Duffy JD. Vasculitis in Behçet's disease. Rheumatol Dis Clin North Am. 1990;16:423–43.
8. Erentug V, Polat A, Bozbuga NU, et al. Valvular surgery in Behcet's disease. J Card Surg. 2006;21:289–91.

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ORIGINAL ARTICLE

Clinical characteristics and risk factors for *Pneumocystis jirovecii* pneumonia in patients with rheumatoid arthritis receiving adalimumab: a retrospective review and case–control study of 17 patients

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Abstract
Objectives To investigate the clinical characteristics and risk factors of *Pneumocystis jirovecii* pneumonia (PCP) in rheumatoid arthritis (RA) patients treated with adalimumab.

Methods We conducted a multicenter, retrospective, case–control study to compare RA patients treated with adalimumab with and without PCP. Data from 17 RA patients who were diagnosed with PCP and from 89 RA

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patients who did not develop PCP during adalimumab treatment were collected.
Results For the PCP patients, the median age was 68 years old, with a median RA disease duration of eight years. The median length of time from the first adalimumab injection to the development of PCP was 12 weeks. At the onset of PCP, the median dosages of prednisolone and methotrexate were 5.0 mg/day and 8.0 mg/week, respectively. The patients with PCP were significantly older ($p < 0.05$) and had more structural changes ($p < 0.05$) than the patients without PCP. Computed tomography of the chest revealed ground-glass opacity without interlobular septal boundaries in the majority of the patients with PCP. Three PCP patients died.
Conclusions PCP may occur early in the course of adalimumab therapy in patients with RA. Careful monitoring, early diagnosis, and proper management are mandatory to secure a good prognosis for these patients.

Keywords Adalimumab · *Pneumocystis jirovecii* pneumonia · Rheumatoid arthritis · TNF antagonist

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by persistent synovitis and structural damage to multiple joints. Tumor necrosis factor (TNF) is abundantly produced in the inflamed synovium and contributes to the imuunopathogenesis of the disease. Adalimumab is the first fully human monoclonal antibody against TNF; treatment with this biologic agent has been well established in patients with RA in multiple clinical trials [1–3]. On the other hand, treatment with adalimumab, as well as infliximab and etanercept, has been associated with increased risk for opportunistic and serious infections in cohort studies using RA patient registries [4–7]. In Japan, strict post-marketing surveillance (PMS) programs have been conducted for patients with RA given TNF antagonists. The numbers of RA patients with *Pneumocystis jirovecii* (*P. jirovecii*) pneumonia (PCP) who were treated with infliximab, etanercept, or adalimumab were 22 (0.4 %) out of 5,000 patients, 25 (0.18 %) out of 13,894 patients, and 25 (0.33 %) out of 7,469 patients, respectively, in these PMS programs [6–8]. Note that these incidence rates of PCP in Japan are apparently higher than the corresponding figure (0.01 %) reported from the United States [9].

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We have previously described the clinical characteristics and risk factors for PCP in RA patients treated with infliximab [10, 11] and etanercept [12]. These risk factors included older age and presence of coexisting lung diseases for both TNF antagonists, a higher daily dose of prednisolone (PSL) for infliximab, and a higher weekly dose of methotrexate (MTX) for etanercept. Considering the similar incidence of PCP in the PMS programs among the three TNF antagonists, it is clinically important and intriguing to characterize PCP in RA patients given adalimumab and to compare the results with those obtained for RA patients treated with other TNF antagonists.

In this paper, we report detailed clinical, laboratory, and radiographic features of PCP that developed in RA patients during treatment with adalimumab. Furthermore, we compared 17 RA patients receiving adalimumab who developed PCP with 89 RA patients who did not develop PCP during treatment, and identified risk factors for PCP in patients with RA treated with adalimumab.

Materials and methods

Patients

Patients included in the present study fulfilled the 1987 American College of Rheumatology (formerly the American Rheumatism Association) criteria for RA [13] and received adalimumab (40 mg every two weeks) with or without concomitant MTX. Between April 2008 and April 2010, 17 patients with PCP (PCP group) were collected from 16 hospitals through either the PMS program for adalimumab ($n = 16$) or through a voluntary case report by attending physicians at a scientific meeting ($n = 1$). We convened a face-to-face meeting in March 2011 to discuss diagnosis and treatment for the collected cases among the investigators of this study. RA patients who did not develop PCP during adalimumab therapy for at least one year from the first dose of adalimumab (non-PCP group, $n = 89$) were randomly collected from the participating hospitals of this study. Other eligibility criteria for the non-PCP group were registration in the PMS program of adalimumab and the use of adalimumab five times or more. The median (range) observation period for the non-PCP group treated with adalimumab was 365 (63–365) days. To increase the statistical power of this case–control study, the number of patients in the non-PCP group was designed to be about five times as many as that in the PCP group [14].

Diagnostic criteria for PCP

Previously established diagnostic criteria for PCP [15, 16] were used in the present study [10]. A diagnosis of PCP was considered definitive if a patient fulfilled the following four conditions: clinical manifestations (fever, dry cough, or dyspnea), hypoxemia, interstitial infiltrates on chest radiographs, and microscopic detection of *P. jirovecii* in induced sputum or bronchoalveolar lavage fluid. The diagnosis of PCP was considered presumptive if a patient fulfilled all of these conditions except for the microscopic detection of *P. jirovecii* in the absence of other infectious diseases and the presence of either a positive polymerase chain reaction (PCR) test for *P. jirovecii* DNA or increased serum 1,3-β-D-glucan (BDG) levels (Fungitec G test MK; Seikagaku, Tokyo, Japan or Wako β-D-glucan test; Wako Pure Chemical Industries, Tokyo, Japan) [17, 18] along with a response to standard treatments for PCP. Both the PCR test for *P. jirovecii* DNA and that for serum BDG are commercially available, validated, and officially approved as clinical laboratory tests by the Ministry of Health, Labour, and Welfare in Japan.

Collection and analysis of clinical data

Clinical information was collected using a standardized format to evaluate demographic information, Steinbrocker's radiographic stage and functional class [19], comorbidities, concomitant drugs, laboratory data, radiographic data, treatment, and outcome. Chest radiographs and computed tomography (CT) scans were evaluated by a pulmonologist (H.S.) and a diagnostic radiologist (F.S.). CT findings were categorized into three patterns, as we did in previous studies [12, 20]: (a) diffuse ground-glass opacity (GGO) distributed in a panlobular manner; that is, GGO was sharply demarcated from the adjacent normal lung by interlobular septa (type A GGO); (b) diffuse GGO that is homogeneous or somewhat inhomogeneous in distribution but without the sharp demarcation caused by interlobular septa (type B GGO); (c) other patterns, such as mixed consolidation and GGO (type C).

Statistical analyses

Demographic data and baseline data were compared between the PCP and non-PCP groups using the χ^2 test for categorical variables and the Mann–Whitney test for continuous variables. To identify risk factors for PCP, the Cox proportional-hazards regression model was used. All analyses were performed using SPSS software, version 16.0 (SPSS Japan, Tokyo, Japan).

Ethics

The guidelines of the Declaration of Helsinki (revised in 2008) and the ethics guidelines for epidemiologic research in Japan were followed. The study protocol was approved

by the Institutional Ethics Committee of the Tokyo Medical and Dental University Hospital (#863 in 2010).

Results

Diagnosis and clinical characteristics of RA patients with PCP

We applied the above diagnostic criteria to the 17 RA patients in the PCP group. Of the 17 cases, three (patients 8, 14, and 17) met the criteria for definitive PCP, and 14 met the criteria for presumptive PCP. The clinical characteristics of each patient are summarized in Table 1. The median age of the 17 patients was 68 years (range 48–78 years), and 12 (71 %) were female. The median duration of RA was eight years. Fourteen patients were at Steinbrocker's stage III or IV. All patients received MTX and 13 (77 %) received corticosteroids from baseline to the onset of PCP. At the onset of PCP, the median dosages of prednisolone and MTX were 5.0 mg/day (range 2.5–9 mg/day) and 8.0 mg/week (range 4–15 mg/week), respectively. One patient was receiving another immunosuppressive drug, tacrolimus, at 3 mg/day. Eight patients had pulmonary comorbidities, including interstitial pneumonia ($n = 4$), chronic obstructive pulmonary disease ($n = 4$), and old pulmonary tuberculosis ($n = 2$). Four patients had diabetes mellitus. None of the patients received chemoprophylaxis for PCP at the time of PCP diagnosis. The median interval between the first injection of adalimumab and the onset of PCP was 12 weeks (range 4–38 weeks). Thirteen patients (76 %) developed PCP within 26 weeks after the first injection. Fever was the most common clinical symptom (it was observed in 15 patients; 88 %), followed by dyspnea on effort (82 %) and dry cough (41 %).

Laboratory and radiographic features of the PCP patients

Laboratory data at the onset of PCP are summarized in Table 2. Fourteen patients either had severe hypoxia (with $PaO_2 < 60$ mm Hg on room air) or required immediate oxygen therapy at the onset of PCP. Peripheral blood lymphocyte (PBL) counts at the onset of PCP were <500 cells/μl in three patients, 500–1,000 cells/μl in five patients, and $>1{,}000$ cells/μl in nine patients. *P. jirovecii* was microscopically identified in three patients. The polymerase chain reaction test for *P. jirovecii* DNA was positive in 13 patients, using either induced sputum (11 patients) or bronchoalveolar lavage fluid (four patients), but three patients were not examined. Serum levels of BDG, one of

Table 1 Characteristics of rheumatoid arthritis patients treated with adalimumab at the onset of PCP

Pt	Age/sex	Stage/class	Number of injections[a]	Treatment duration (days)[b]	MTX (mg/w)	PSL (mg/d)	Lung disease	DM	Clinical manifestations
1	48/F	III/I	7	105	8	2.5	–	–	Fever/DOE
2	69/M	IV/III	4	62	10	0	E	–	Cough/DOE
3	74/F	IV/II	9	131	8	5	IP E	–	DOE
4	52/M	III/II	5	59	4	8	IP	–	Fever/cough/DOE
5	61/F	IV/II	3	45	8	9	–	–	Fever
6	67/F	III/III	3	28	8	8	IP	–	Fever/cough/DOE
7	61/F	IV/II	4	59	6	0	Old TB	–	Fever/DOE
8	77/F	IV/II	6	129	6	5	–	+	Fever/DOE
9	52/F	III/I	3	55	8	5	–	–	Fever/DOE
10	78/M	III/III	6	86	8	0	IP	+	Fever/DOE
11	66/F	I/III	6	106	8	3	–	–	Fever/cough
12	70/F	II/II	2	23	8	5	Old TB	–	Fever/cough/DOE
13	68/M	I/II	3	28	8	0	E	+	Fever/DOE
14	71/F	III/II	15	214	8	7.5	–	–	Fever/DOE
15	73/M	III/II	18	268	15	3	–	+	Fever/cough/DOE
16	65/F	III/II	16	227	8	2	–	–	Fever/DOE
17	78/F	IV/II	16	252	4	4	–	–	Fever/cough

PCP Pneumocystis jirovecii pneumonia, *Pt* patient, *w* week, *d* day, *M* male, *F* female, *MTX* methotrexate, *PSL* prednisolone, *E* emphysema, *IP* interstitial pneumonia, *old TB* old tuberculosis, *DM* diabetes mellitus, *DOE* dyspnea on effort, *cough* dry cough

[a] Number of injections of ADA prior to the diagnosis of PCP

[b] Treatment duration with ADA before the onset of PCP

Table 2 Laboratory data of rheumatoid arthritis patients treated with adalimumab at the onset of PCP

Pt	WBC (/μl)	Lymphocytes (/μl)	SpO_2 or PaO_2 (Torr) [O_2, l/min][a]	Serum β-D-glucan (μg/ml) [normal range at the institute]	*Pneumocystis jirovecii* PCR
1	7,870	912	SpO_2 96 % [0]	289 [<11]	+
2	5,100	1,989	SpO_2 92 % [0]	30.5 [<11]	+
3	6,300	252	55.1 [0]	1041 [<11]	NA
4	6,200	874	68.0 [0]	25.76 [<11]	+
5	8,050	1,110	60.4 [0]	50.3 [<20]	NA
6	6,400	716	58.9 [0]	37.8 [<6]	+
7	5,660	1,041	71.8 [0]	22.1 [<11]	+
8	6,800	279	31.3 [0]	29 [<11]	+[b]
9	15,900	832	85.7 [3]	79.5 [<20]	+
10	7,500	1,350	65.4 [0]	22.3 [<20]	+
11	8,400	3,696	69.5 [0]	16.4 [<11]	+
12	11,700	1,029	26.1 [0]	21.06 [3.5]	+
13	7,950	1,761	SpO_2 85 % [2]	160 [<5]	+
14	9,580	34	56.7 [0]	13.0 [<11]	NA[b]
15	5,700	1,140	55.1 [0]	13.0 [<11]	–
16	7,000	1,330	56.1 [10]	21.38 [<11]	+
17	3,200	704	52.5 [0]	419 [<11]	+[b]
Median (IQR)	7,000 (5950–8225)	1,029 (710–1340)	Not applicable	Not applicable	Not applicable

PCP Pneumocystis jirovecii pneumonia, *Pt* patient, *WBC* white blood cell, *PCR* polymerase chain reaction, *NA* not assessed, *SpO2* oxygen saturation measured using a pulse oximeter, *IQR* interquartile range

[a] Oxygen therapy during the measurement of PaO_2

[b] *Pneumocystis jirovecii* microscopically detected in bronchoalveolar-lavage fluid

the major components of the cell walls of fungi and a serum maker for PCP [17, 18], were elevated in all patients. Results of sputum culture performed in 14 patients revealed no causative bacteria or fungi.

Chest radiographs and thoracic CT scans were analyzed for all 17 patients. The most common CT finding was ground-glass opacity (GGO) (in 17 patients), either with sharp demarcation by interlobular septa in one patient (type A GGO) (Fig. 1a) or without interlobular septal boundaries in 14 patients (type B GGO) (Fig. 1b). Two patients demonstrated mixed patterns (type C).

Treatment and clinical course of PCP in patients with RA receiving adalimumab

All patients were hospitalized on the same day that PCP was suspected. Fourteen patients (all except for patients 2, 5, and 11) received oxygen therapy on admission. MTX and adalimumab were immediately discontinued in all patients. All patients received therapeutic doses of trimethoprim/sulfamethoxazole (TMP/SMX). Because of adverse drug reactions that included skin eruptions, liver dysfunction, thrombocytopenia, and hyperpotassemia, TMP/SMX was reduced or stopped in eight patients. One patient was changed to pentamidine isethionate. Sixteen patients were concomitantly treated with high-dose corticosteroids within a few days after admission. Eleven patients were empirically treated with antibiotics and four with antifungal agents. Three patients (patients 1, 3, and 8) were intubated on the day of admission because of progressive respiratory failure; two of these patients responded to treatment and were successfully weaned from artificial ventilation. One patient (patient 17) died because of PCP with progressive respiratory failure. Two patients died because of multiple organ failure (patient 12) and gastrointestinal bleeding, cytomegalovirus infection, and multiple organ failure (patient 3) after improvement of PCP.

Case–control study

In order to characterize the PCP group more precisely, we compared demographic information, comorbidities, treatments, and laboratory data at baseline (i.e., at the initiation of treatment with adalimumab) between the PCP and non-PCP groups using a univariate analysis (Table 3). The PCP group was significantly older ($p = 0.003$) and had a more advanced radiographic stage (Steinbrocker's stage III or IV) ($p = 0.010$) than the non-PCP group. Although the rates of patients with preexisting pulmonary diseases and diabetes mellitus in the PCP group were numerically higher, these differences were not statistically significant. There were no differences in disease duration and the dosages of prednisolone and methotrexate between the two groups. None of the patients in the PCP group and fourteen patients in the non-PCP group received prophylaxis for

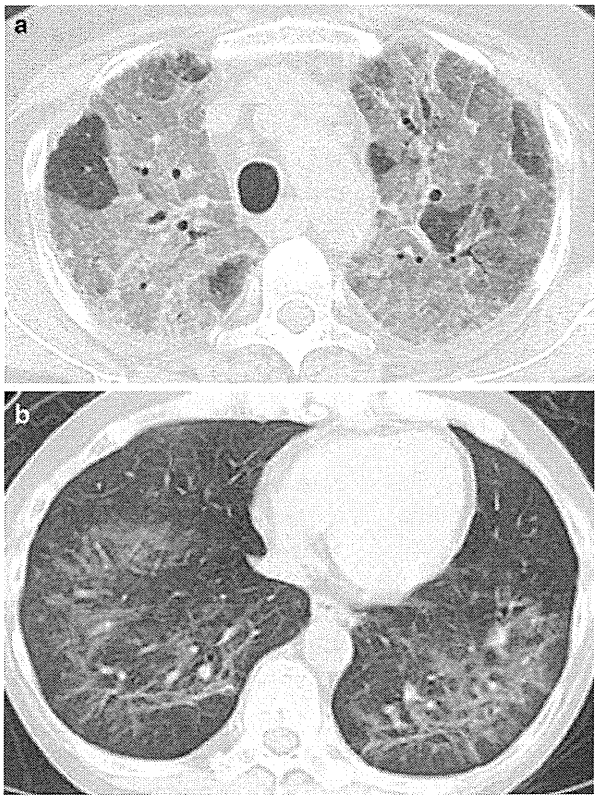

Fig. 1 Representative thoracic computed tomography findings of rheumatoid arthritis patients who developed *Pneumocystis jirovecii* pneumonia while receiving adalimumab. **a** Ground-glass opacity (GGO) with sharp demarcation by interlobular septa (type A) (patient 12). **b** Inhomogeneous GGO without obvious demarcation by interlobular septa (type B) (patient 1)

PCP for at least three months during the observation period. Twelve patients used TMP/SMX and two used aerosolized pentamidine.

Based on the results of the univariate analysis, age, sex, pulmonary comorbidities and Steinbrocker's stage of RA were analyzed as candidate predictors for the development of PCP. The Cox proportional-hazards regression analysis revealed a significant association between advanced radiographic stage (stage III or IV) and development of PCP (hazard ratio (HR) 3.76, 95 % confidence interval (CI) 1.03–7.30, $p = 0.045$). While the hazard ratios of older age and preexisting pulmonary diseases tended to be higher, they did not reach statistical significance (Table 4).

Because 14 patients in the non-PCP group received prophylaxis for PCP, we performed the multivariate analysis after excluding these 14 patients, and found a significant association between older age and development of PCP (HR 3.31, 95 % CI 1.09–10.0, $p = 0.034$). The HR of the radiographic stage did not reach statistical significance (HR 2.82, 95 % CI 0.74–10.7) in this model.

Discussion

We accumulated the largest possible number of patients with RA who developed PCP during treatment with adalimumab, and described the clinical and radiologic characteristics of the 17 patients that we found.

Adalimumab is the third TNF antagonist to be approved in Japan. We have already reported the clinical characteristics and risk factors for PCP in RA patients treated with infliximab or etanercept [10–12]. The median interval (range) between the first dose of TNF antagonists and the onset of PCP was 12 weeks (range 4–38) for adalimumab, nine weeks (range 2–90) for infliximab [11], and 14 weeks (range 3–43) for etanercept [12]. PCP developed within six months in the majority of RA patients after the initiation of each TNF antagonist: 90 % for infliximab, 80 % for etanercept, and 76 % for adalimumab.

Previous studies have revealed that patients without HIV infection develop PCP abruptly and progress to fulminating pneumonia with acute respiratory failure [21, 22]. We also reported that RA patients treated with infliximab or etanercept developed PCP rapidly and progressed to severe respiratory failure [10–12]: 18 out of 21 PCP patients using infliximab, all 15 PCP patients using etanercept, and 14 of 17 PCP patients in this study showed severe hypoxemia and required oxygen therapy. The mortalities of the patients with PCP given infliximab (0 %) or etanercept (6.7 %) are numerically lower than the mortality of this study, in which three patients (17.6 %) died. Walzer etal. [23] identified older age, second or third episode of PCP, low hemoglobin level, low PaO_2 breathing room air at admission, pulmonary Kaposi sarcoma, and presence of medical comorbidity as early predictors of mortality of PCP in HIV-infected patients. Although such prognostic factors in non-HIV PCP patients are unknown, all three patients in our study who died were females over 70 years old, and their PaO_2 on admission was less than 60 Torr. Two of these patients had pulmonary comorbidities. One patient had a quite high serum level of BDG, and one was positive for both microscopic detection and the PCR test for the organism. These data would suggest severe pulmonary injury at presentation and a high burden from *P. jirovecii*.

In our study, all patients received therapeutic doses of TMP/SMX. However, eight patients (47.1 %) were obliged to reduce the dosage or stop using the drug due to adverse drug reactions, such as gastrointestinal symptoms and hematological abnormalities. Kameda et al. [24] also reported that more than one-third of the patients could not complete the standard protocol of the TMP/SMX treatment. These data indicate that the optimal dosage and treatment period of TMP/SMX for PCP should be investigated. The clinical benefit of adjunctive corticosteroid

Table 3 Baseline characteristics of patients with rheumatoid arthritis treated with adalimumab

Characteristic	PCP group ($n = 17$)	Non-PCP group ($n = 89$)	p value
Age (years)[a]	68 (48–78)	60 (24–79)	0.003
Female (%)	70.6	80.9	0.255
Disease duration (years)[a]	8.0 (0.7–36)	9.5 (3–40)	0.491
Chronic pulmonary disease (%)	47.1	22.5	0.107
Diabetes mellitus (%)	23.5	7.9	0.074
Steinbrocker's radiographic stage (III or IV) (%)	82.4	48.3	0.010
Steinbrocker's functional class (III or IV) (%)	17.6	19.1	0.596
MTX (%)	100	86.5	0.108
MTX (mg/week)[a]	8.0 (4–10)	8.0 (4–15)	0.119
MTX ≥ 8 mg/week (%)	11.8	28.1	0.228
PSL (%)	76.5	56.2	0.118
PSL (mg/day)[a]	5.0 (3–12)	5.0 (1–17)	0.529
PSL ≥ 5 mg/day (%)	52.9	33.7	0.131
WBC <4,000/μl (%)	0	2.2	0.731
Serum IgG (mg/dl)[a]	1421 (846–1954)	1316 (827–3165)	0.817

PCP Pneumocystis jirovecii pneumonia, *MTX* methotrexate, *PSL* prednisolone, *Chronic pulmonary disease* = interstitial pneumonia, bronchiectasis, chronic obstructive pulmonary diseases, bronchial asthma, middle lobe syndrome, old pulmonary tuberculosis

p values were calculated using the Mann–Whitney test for continuous variables or χ^2 test for categorical variables

[a] Median (range)

Table 4 Cox regression analysis of risk factors for the development of PCP in rheumatoid arthritis patients treated with adalimumab

	Hazard ratio (95 % CI)	p value
Age (≥ vs. <65 years old)	2.38 (0.80–7.05)	0.119
Gender (female vs. male)	0.53 (0.18–1.58)	0.258
Chronic pulmonary disease (yes vs. no)	2.14 (0.79–5.76)	0.133
Steinbrocker's radiographic stage (III/IV vs. I/II)	3.76 (1.03–7.30)	0.045

PCP Pneumocystis jirovecii pneumonia, *CI* confidence interval

Chronic pulmonary disease = interstitial pneumonia, bronchiectasis, chronic obstructive pulmonary diseases, bronchial asthma, middle lobe syndrome, old pulmonary tuberculosis

therapy for PCP patients without HIV infection has not been established [25]. All patients except for one in this study received adjunctive corticosteroid therapy with various treatment durations and dosages, including intravenous methylprednisolone pulse therapy. Nineteen out of 21 PCP patients who used infliximab and nine out of 15 PCP patients who used etanercept used adjunctive corticosteroid therapy as well [11, 12]. Pareja etal. [26] retrospectively analyzed the clinical courses of 30 cases of severe PCP without HIV infection, among which 16 cases who received high doses of adjunctive corticosteroid therapy presented a good clinical outcome. Considering the intense inflammatory response to the organism in non-HIV PCP patients [25] and the favorable effectiveness of adjunctive corticosteroid therapy in previous studies, it is necessary to consider treatment with corticosteroids for PCP patients with RA who show hypoxemia at presentation or during their clinical courses.

In the present study, using the Cox proportional-hazards analysis, Steinbrocker's radiographic stage III or IV was identified as a statistically significant risk factor for the development of PCP in patients receiving adalimumab. Although there was no significant difference in Steinbrocker's functional class, it is plausible that advanced radiographic stages associated with decreased physical function contributed to the development of PCP. Steinbrocker's functional class may be less sensitive to the detection of such differences in physical function. On the other hand, older age was a significant risk factor in another Cox proportional-hazards regression analysis after excluding those who received TMP/SMX or aerosolized pentamidine for prophylaxis at least three months from the non-PCP group. The different results from the Cox proportional-hazards regression analyses can be explained by the fact that nine out of 14 patients given prophylaxis were aged 65 or older. Pulmonary diseases were not significant risk factors for PCP in either Cox proportional-hazards analysis, perhaps because of the small number of PCP cases enrolled.

None of the 17 patients had received prophylaxis for PCP. Vananuvat etal. [27] conducted a retrospective cohort study for patients with connective tissue diseases (CTD) who were at risk for PCP in order to examine the effectiveness of primary prophylaxis with TMP/SMX and the incidence of adverse drug reactions (ADR) of TMP/SMX. Six patients without and none with prophylaxis developed PCP; the overall incidence rate was 4.3 % and the relative risk reduction was 100 %. Five patients (8.5 %) developed ADR: four had drug eruptions and one had mild hepatitis. These data indicate that TMP/SMX can be used effectively for primary prophylaxis against PCP.

There are definite limitations to our study. First, we included definite and presumptive cases of PCP in our analysis. It has been well documented that the microscopic detection of *P. jirovecii* is difficult in non-HIV PCP [28, 29], as confirmed in this and our previous studies. To increase the specificity of the diagnosis of PCP without detecting the organism microscopically, we utilized composite diagnostic criteria, including clinical symptoms, laboratory tests, radiological findings, and the clinical

course. Kameda etal. found no difference in clinical characteristics of PCP in RA patients between definite PCP (i.e., acute-onset diffuse interstitial lung disease and microscopic positivity for *P. jirovecii* or positivity in both PCR test and BDG) and probable PCP (acute-onset diffuse interstitial lung disease and positivity in either PCR test or BDG) [24]. Their data support the use of composite diagnostic criteria for PCP in patients with RA. Second, we had only 17 RA patients with PCP, which decreased the sensitivity of the Cox proportional-hazards analysis for detecting statistically significant risk factors. Third, a higher incidence of PCP in Japanese RA patients receiving TNF antagonists and their risk factors have gained widespead recognition in the past few years by Japanese rheumatologists who use TNF antagonists; this may have affected the characteristics of the patients who were treated with adalimumab. For example, we found a significant difference in the daily dose of PSL between the PCP and non-PCP groups in our previous two studies, but not in this study.

In summary, the results of this study show that PCP is a serious complication in patients with RA who receive treatment with adalimumab. The majority of the patients developed PCP early in the course of adalimumab treatment and progressed to respiratory failure. Treating physicians should therefore take prophylaxis with TMP/SMX or other agents into consideration in RA patients with a high risk for PCP. Careful monitoring of clinical manifestations and laboratory tests for early diagnosis and treatment of PCP are strongly recommended.

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References

1. Miyasaka N, Investigators CS. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol. 2008;18(3):252–62.
2. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, etal. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48(1):35–45.
3. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, etal. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54(1):26–37.
4. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, etal. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3,000 patients. Mod Rheumatol. 2011 Oct.
5. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, etal. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2011;50(1):124–31.
6. Koike T, Harigai M, Inokuma S, Inoue K, Ishiguro N, Ryu J, etal. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. J Rheumatol. 2009;36(5):898–906.
7. Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, etal. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008;67(2):189–94.
8. Abbott Laboratories. HUMIRA (prescribing information online). 2011. http://db.e-humira.jp/dra/report/download.php/225/適正使用情報%20Vol.6.pdf. Accessed Nov 2011 (in Japanese).
9. Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. Drug Saf. 2004;27(5):307–24.
10. Harigai M, Koike R, Miyasaka N, Group PPuA-TNFTPS. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med. 2007;357(18):1874–6.
11. Komano Y, Harigai M, Koike R, Sugiyama H, Ogawa J, Saito K, etal. *Pneumocystis jiroveci* pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and

case-control study of 21 patients. Arthr Rheum. 2009;61(3): 305–12.
12. Tanaka M, Sakai R, Koike R, Komano Y, Nanki T, Sakai F, etal. *Pneumocystis jirovecii* pneumonia associated with etanercept treatment in patients with rheumatoid arthritis: a retrospective review of 15 cases and analysis of risk factors. Mod Rheumatol. 2012 Feb.
13. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, etal. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315–24.
14. Strom B. Sample size considerations for pharmacoepidemiology studies. In: Strom B, editor. Pharmacoepidemiology. Chichester: Wiley; 2000. p. 31–9.
15. Furrer H, Egger M, Opravil M, Bernasconi E, Hirschel B, Battegay M, etal. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. N Engl J Med. 1999;340(17):1301–6.
16. Ledergerber B, Mocroft A, Reiss P, Furrer H, Kirk O, Bickel M, etal. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. N Engl J Med. 2001;344(3):168–74.
17. Marty FM, Koo S, Bryar J, Baden LR. (1→3)Beta-D-glucan assay positivity in patients with *Pneumocystis* (*carinii*) *jiroveci* pneumonia. Ann Intern Med. 2007;147(1):70–2.
18. Yasuoka A, Tachikawa N, Shimada K, Kimura S, Oka S. (1→3) Beta-D-glucan as a quantitative serological marker for *Pneumocystis carinii* pneumonia. Clin Diagn Lab Immunol. 1996;3 (2):197–9.
19. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc. 1949;140(8):659–62.
20. Tokuda H, Sakai F, Yamada H, Johkoh T, Imamura A, Dohi M, etal. Clinical and radiological features of *Pneumocystis* pneumonia in patients with rheumatoid arthritis, in comparison with methotrexate pneumonitis and *Pneumocystis* pneumonia in acquired immunodeficiency syndrome: a multicenter study. Intern Med. 2008;47(10):915–23.
21. Sepkowitz KA, Brown AE, Telzak EE, Gottlieb S, Armstrong D. *Pneumocystis carinii* pneumonia among patients without AIDS at a cancer hospital. JAMA. 1992;267(6):832–7.
22. Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. Mayo Clin Proc. 1996;71(1):5–13.
23. Walzer PD, Evans HE, Copas AJ, Edwards SG, Grant AD, Miller RF. Early predictors of mortality from *Pneumocystis jirovecii* pneumonia in HIV-infected patients: 1985–2006. Clin Infect Dis. 2008;46(4):625–33.
24. Kameda H, Tokuda H, Sakai F, Johkoh T, Mori S, Yoshida Y, etal. Clinical and radiological features of acute-onset diffuse interstitial lung diseases in patients with rheumatoid arthritis receiving treatment with biological agents: importance of *Pneumocystis* pneumonia in Japan revealed by a multicenter study. Intern Med. 2011;50(4):305–13.
25. Limper AH, Offord KP, Smith TF, Martin WJ. *Pneumocystis carinii* pneumonia. Differences in lung parasite number and inflammation in patients with and without AIDS. Am Rev Respir Dis. 1989;140(5):1204–9.
26. Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV *Pneumocystis carinii* pneumonia. Chest. 1998;113(5):1215–24.
27. Vananuvat P, Suwannalai P, Sungkanuparph S, Limsuwan T, Ngamjanyaporn P, Janwityanujit S. Primary prophylaxis for *Pneumocystis jirovecii* pneumonia in patients with connective tissue diseases. Semin Arthritis Rheum. 2011;41(3):497–502.
28. Thomas CF, Limper AH. Pneumocystis pneumonia: clinical presentation and diagnosis in patients with and without acquired immune deficiency syndrome. Semin Respir Infect. 1998;13(4):289–95.
29. Thomas CF, Limper AH. *Pneumocystis* pneumonia. N Engl J Med. 2004;350(24):2487–98.