Introduction

Rheumatoid arthritis (RA) is an inflammatory disease of unknown etiology. RA mainly affects the joint synovial membranes, but is a systemic disease in itself as well. Rheumatoid vasculitis (RV) is among such systemic presentations of the disease. RV most commonly occurs in patients with longstanding and destructive RA and is sometimes even life-threatening. Here, we describe a case of a new-onset RV, the diagnosis of which was made difficult by the co-existence of *Pneumocystis jirovecii* pneumonia (PCP).

Case report

A 71-year-old man was admitted to Saitama Medical University Hospital. Approximately 15 years prior he had been diagnosed with RA. Since then, he had been prescribed a variety of disease-modifying anti-rheumatic drugs (DMARDs), including bucillamine (BUC), leflunomide and actarit over a period of 13 years. However, the efficacy of the treatment proved insufficient and the level of serum C-reactive protein (CRP) continued to be more than 2.0 mg/dL during this time period. Two years before this admission, methotrexate (MTX: 6 mg/week) and etanercept (ETN: 25 mg/week) were started. Those drugs proved effective and the CRP level decreased to less than 0.5 mg/dL. He had been doing well until five months previously, when he had begun to feel fatigued, without any joint pain. Three months before the admission, the CRP level increased to 2.0 mg/dL and the dose of ETN was increased from 25 to 50 mg/week, without much improvement. The CRP level reached 9.0 mg/dL and abatacept (ABT) was started in place of ETN. Ten days later, 21 days before the admission, MTX was switched to BUC and oral prednisolone (PSL: 5 mg/day). Two days before this admission, fever, severe dyspnea and cough developed. The next day, he visited his physician. A chest X-ray revealed diffuse consolidation in the middle parts of the bilateral lungs. The patient was referred and admitted to this hospital.

On examination, the body temperature was 37.2°C, blood pressure 109/83 mmHg, pulse 105 beats per minute and oxygen saturation 92% while breathing ambient air. Fine crackling sounds were heard at the bases of the bilateral lungs. He had pain and swelling in the wrists and ankles. Rheumatoid nodules were observed on the right metatarsophalangeal joints and bilateral knee joints. The remainder of the physical examination was normal. Blood gas analysis revealed a partial pressure of arterial oxygen at 68.4 mmHg and carbon dioxide at 29.2 mmHg. The leukocyte count was 7630/µL (82.6% neutrophils, 10.5% lymphocytes), the hemoglobin level was 10.5 g/dL and the platelet count was 36.1×10^4/µL. The CRP level was 18.6 mg/dL and that of β-D-glucan was 37.3 pg/mL (reference range, 0 to 11). The patient’s liver function, kidney function, blood electrolyte levels and
Urinalysis were normal. The anti-cyclic citrullinated peptide antibody was 68.8 IU/mL (reference range, 0 to 4.4), the IgM-rheumatoid factor was 569 IU/mL (reference range, 0 to 15) and metalloproteinase-3 was 186.1 ng/mL (reference range, 36.9 to 121.0). The test for cryoglobulin was positive. The 50% hemolytic unit of complement (CH50) was 38.2 IU/mL (reference range, 31.6 to 65.6), the C3 level was 98 mg/dL (reference range, 86 to 160), the C4 level was 20 mg/dL (reference range, 17 to 45) and the C1q based solid phase enzyme immunoassay for circulating immune complex (IC-C1q) was 6.1 µg/mL (reference range, 0 to 3). The anti-nuclear antibodies were of the discrete speckled type (1:80). Anti-double-stranded deoxyribonucleic acid antibody, anti-Sm antibody, anti-ribonucleoprotein antibody and anti-neutrophil cytoplasmic antibody (ANCA: myeloperoxidase antibody and proteinase 3 antibody) were negative. The RA stage was IV according to Steinbrocker’s criteria\(^1\) (Fig. 1). The disease activity of RA was moderate with disease activity score 28 based on ESR (DAS28-ESR) was 4.0\(^2\).

Thoracic computed tomography revealed bilateral diffuse ground-glass opacity (Fig. 2A) and fibrotic cysts (honeycomb changes) in the bilateral lower lobes (Fig. 2B).

He was diagnosed with PCP. On the first hospital day, he began to be treated with oral trimethoprim-sulfamethoxazole (TMP-SMX: 960/4800 mg/day) and high dose PSL (80 mg/day), based on the regimen of human immunodeficiency virus (HIV) infected patients with moderate or severe PCP (80 mg/day until the fifth day, 40 mg/day from the sixth day to the 10th day and 20 mg/day from the 11th day to the 20th day)\(^3\). *Pneumocystis jirovecii* DNA was later detected in the patient’s sputum by real-time PCR, which confirmed the initial diagnosis.

Although TMP-SMX was terminated due to side effects (rash, hyperkalemia and hyponatremia) on the 14th day, the treatment seemed effective. On the fifth day, Chest X-ray revealed improvement of the consolidation. On the seventh day, the CRP level decreased to 1.01 mg/dL. On the 11th day, the level of β-D-glucan came within the normal range (< 6.0 pg/mL). PSL was tapered slowly after the 21st day. Although the level of β-D-glucan remained below the detection limit, the CRP level rebounded and exceeded 8 mg/dL (Fig. 3) and, accordingly, the disease activity became high (DAS28-ESR: 6.3) on the 23rd day. We suspected the exacerbation of RA, so we added salazosulfapyridine (SASP: 500 mg/day) on the 29th day, which was increased to 1000 mg/day on the 44th day. Nevertheless, the CRP level did not decrease. On the 41st day, he developed ulcers on

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*Fig. 1  X-Ray of the hands and wrists*

The X-Ray shows rheumatoid erosions and bony ankylosis, indicating stage IV of the disease.

*Fig. 2  Computed tomography scans of the lung show bilateral diffuse ground-glass opacity (A), and fibrotic cysts (honeycomb changes) in the lower lobes (B)
his heels. On the 48th day, the level of CH50 decreased to 16.1 IU/mL and that of IC-C1q was 4.0 µg/mL. Skin biopsy of the ulcer lesion was performed and the specimen revealed small vessel vasculitis with fibrinoid necrosis (Fig. 4A–B). Thus, we diagnosed him as having RV. Cardiac ultrasonography and nerve conduction velocity test were normal. He had neither episcleritis nor iritis. We increased PSL from 14 to 30 mg/day on the 56th day, followed by administration of tacrolimus (TAC: 3 mg/day) on the 67th day. The CRP level gradually decreased. On the 73rd day, the levels of CRP, CH50 and IC-C1q were 0.84 mg/dL, 28.4 IU/mL and 4.0 µg/mL, respectively. The ulcers were getting smaller. On the 85th day, the dose of PSL was tapered to 25 mg/day. The CRP level remained between 0.5 and 2.0 mg/dL and never came within normal range. We administrated ABT (500 mg) in place of TAC on the 88th day. PSL was tapered to 20 mg/day on the 99th day, followed by a second administration of ABT (500 mg) on the 101st day. Although the CRP level remained positive, his general condition had improved. On the 103rd day, he was discharged and continued to be treated at the clinic of this hospital. We tried to taper the dose of PSL, but the CRP level gradually increased and reached 11.1 mg/dL while that of CH50 remained as low as ~30 IU/mL. Thus, we gave up using ABT and SASP, increased the dose of PSL from 12 to 20
mg/day, and added azathioprine (AZA). This combination proved effective and in the latest visit, he was doing well with the CRP level of 0.30 mg/dL and that of CH50 58.7 IU/mL, all the while treated with 17 mg/day of PSL and 50 mg/day of AZA.

Discussion

We would like to take into consideration three points here. (1) The prevention of opportunistic infection in RA, (2) the cause of vasculitis in this case, and (3) the best treatment strategy for RV. First, this patient was admitted because of acute interstitial pneumonia with respiratory failure. As *Pneumocystis jirovecii* DNA was detected by PCR, PCP was diagnosed. If the patient was not suffered from PCP, RV might be diagnosed earlier. Thus the prevention of PCP was important point for the patient. He had not been treated with high dose glucocorticoid, however, as two immunosuppressant drugs (MTX and either ETN or ABT) along with a low dose glucocorticoid (PSL 5 mg/day) had been administered just prior to admission. Tanaka et al. reported the risk factors for PCP in RA patients treated with ETN to be (i) an age of at least 65 years, (ii) concomitant MTX treatment (iii) the presence of coexisting pulmonary disease, emphasizing that patients with two or three risk factors displayed a significantly higher probability of developing PCP than those with no or only one risk factor\(^4\). Our patient exhibited fibrotic cysts (honeycomb changes) in the bilateral lower lobes, indicating the presence of old interstitial pneumonia. Because he had all of the three risk factors, prophylactic use of TMP-SMX appeared to be warranted.

Second, several differential diagnoses were considered in regard to the vasculitis observed in this patient, including vasculitis associated with tumor necrosis factor (TNF) inhibitors and cryoglobulinemic vasculitis. Ramos-Casals et al. reported 113 cases of vasculitis associated with TNF inhibitors\(^5\). Most of the patients used either ETN (52%) or infliximab (42%). Vasculitis presented mainly as cutaneous lesions (87%) and peripheral nerve involvements (16%). The duration of TNF inhibitor administration was 9.5 ± 2.3 months. The conditions of almost all of the patients improved upon withdrawal of the biologics. In our patient, ETN was administered for two years and terminated just before this admission. Our patient’s vasculitis became evident during the course of hospitalization. Thus, ETN was unlikely to have been the cause of the vasculitis. It does not explain the hypocomplementemia, either. Another possibility is cryoglobulinemia, which is defined as the presence of serum immunoglobulins that precipitate with cold temperature and dissolve with rewarming *in vitro*. Cryoglobulinemia is associated with hepatitis C virus (HCV) infection, B-cell disorders and autoimmune diseases, including RA. Cryoglobulinemia causes systemic vasculitis with skin, joint, peripheral nervous system and kidney involvement, while skin lesions are most likely induced by exposure to low temperatures\(^6\). In our patient, the presence of cryoglobulin and the low levels of complement were compatible with cryoglobulinemic vasculitis. However, the skin ulcers had developed during the summer and, moreover, the skin biopsy specimen did not display any pseudothrombi, making cryoglobulinemic vasculitis less likely. Thus, we believe RV is the most likely diagnosis, although no signs of neurologic or ocular disease were observed. A relatively long history of RA (~15 years in this case), high titer of rheumatoid factor and the presence of rheumatoid nodules are all associated with the presence of RV. A low complement and positive immune complex C1q in the serum were also compatible with RV. All of the drugs for RA were terminated due to the development of PCP except for glucocorticoids. Indeed, administration of high dose glucocorticoid and its rapid tapering may have elicited ulceration of the skin, one of the symptoms of RV.

The final subject concerns the treatment of this patient. Intensive immunosuppression is generally required for the treatment of RV, but the patient had just undergone PCP and was considered to be immunocompromised. The ground-glass opacity almost disappeared, however, the fibrotic change remained. In addition, we had to cease using TMP-SMX due to side effects. Thus, the presence of remaining bacteria was our concern. As the level of β-D-glucan came within the normal range, we judged that we could intensify immunosuppressive therapy, although with great caution. Thus, we began treatment by moderately increasing the glucocorticoid dose (PSL, from 14 mg to 30 mg) and administering TAC. The skin ulcer became smaller but the CRP level did not normalize, so we replaced TAC with ABT. ABT was reported to be effective in a patient with refractory RV\(^7\) and has
been reported to be relatively safe for RA patients with a risk of infection\(^8\). Unfortunately, ABT did not diminish the inflammatory response, and we replaced ABT with AZA, which is often used for maintenance therapy after the induction of remission\(^9\). Since then, the inflammation of the patient has been under control and the dose of PSL has been tapered gradually.

To the best of our knowledge, this is the first report of new-onset RV during treatment of PCP. The infectious comorbidity complicated the diagnosis as well as the treatment of RV. Accumulation of similar cases would be of great help in establishing more effective and safer treatments for this dangerous condition.

Reference