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Mizoribine for ANCA-associated crescentic glomerulonephritis with sarcoidosis: effectiveness not only for urinalysis abnormalities but also for hilar lymph node enlargement

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Abstract

Both sarcoidosis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis are multisystem diseases, which are involved with T-helper-1-mediated immune responses. We recently experienced the case of a 57-year-old woman with sarcoidosis complicated by myeloperoxidase-ANCA-associated crescentic glomerulonephritis. We herein describe the details of her clinical course and discuss the effectiveness of mizoribine, which is relatively new anti-inflammatory immunosuppressant, not only for urinalysis abnormalities but also for bilateral hilar lymphadenopathy enlargement.

Keywords: sarcoidosis, myeloperoxidase-antineutrophil cytoplasmic antibody, crescentic glomerulonephritis, mizoribine

Introduction

Sarcoidosis is a common, chronic, multisystem disorder characterized by non-necrotizing epitheloid granulomas and derangement of the normal tissue structure. The reported prevalence of sarcoidosis in the United States and Europe ranges from 10 to 40 cases per 100,000 individuals [1]. Renal involvement is not uncommon and usually manifests as nephrolithiasis, nephrocalcinosis, or tubulointerstitial nephritis [2, 3]. Although rare, an association between sarcoidosis and glomerulonephritis has been suggested. Most reports mention membranous glomerulonephritis, focal segmental glomerulosclerosis or diffuse endocapillary glomerulonephritis. Crescentic glomerulonephritis (CrGN) has been reported in only a few instances [3, 4, 5].

The most common initial treatment for both sarcoidosis and CrGN is corticosteroid therapy; however, steroid-associated adverse events have occurred in a dose-dependent manner, necessitating dose reduction. Mizoribine (MZR) has an immunosuppressive effect equivalent to that of mycophenolate mofetil (MMF) but has lower hepatic toxicity and myelosuppression [6, 7]. MZR is useful for the preemptive treatment of antineutrophil cytoplasmic antibody (ANCA)-associated renal vasculitis patients with a high risk of relapse [8]. We describe a patient with sarcoidosis complicated by myeloperoxidase (MPO)-ANCA-associated CrGN who was successfully treated with MZR not only for urinalysis abnormalities but also for bilateral hilar lymphadenopathy (BHL) enlargement.

Case report

A 57-year-old Japanese woman was referred to our office for evaluation of urinalysis abnormalities in October, 2007. She had schizophrenia and had been diagnosed with sarcoidosis, which was confirmed by biopsy of lower-leg eruption in 2003. At that time, a systemic examination revealed only BHL. Since then, she has visited the office regularly. Around 2005, the urinary sediment showed >5 red blood cells (RBCs) per high-power field (HPF) without proteinuria. In March 2007, the patient had edema of the lower limbs with urinary hematuria and proteinuria, which were more than 2+ on the dipstick. Hence, she was admitted to our hospital for further evaluation in October 2007. On physical examination, her body temperature was 36.6°C, her blood pressure was 140/96 mmHg, and her pulse rate was 60 beats per minute. There was no murmur in her cardiac sounds, and the lungs were clear. Table 1 shows the results of urinalysis, blood biochemistry, hematology, and special investigations. On abdominal examination, no mass was noted. Her lower legs were edematous. There was no notable eruption that suggested sarcoidosis. Laboratory findings were as follows: WBC, 3130/μL; hemoglobin, 12.9 g/dL; platelets, 32.5×10^4/μL; BUN, 17 mg/dL; creatinine, 0.72 mg/dL; and CRP, 2.30 mg/L. The liver function test was normal. Serum calcium was normal. Urinary protein was 3+ on the dipstick, and 40 RBCs were counted per HPF. The serum level of angiotensin-converting enzyme (ACE) was 44.3 IU/L, and the lysozyme level was 12.7 μg/mL; both were elevated. The anti-nuclear antibody (ANA) count was 320x; MPO-ANCA was positive (16 EU), albeit at a relatively low titer. Proteinase3-ANCA, antiglomerular

basement membrane antibody, and anti-double stranded DNA antibody were negative. IgG, IgA and IgM were within the normal range. An ophthalmologic check did not reveal uveitis. A chest radiograph and computed tomography (CT) revealed BHL, which was more enlarged than observed upon the first examination of sarcoidosis in 2003 (Figure 1A and C). The abdominal organs did not show any abnormality. Total-body gallium-67 scintigraphy showed hot lesions on paratracheal nodes in accordance with enlarged BHL. Then we performed kidney biopsy for the evaluation of urinalysis abnormalities. On light-microscopy, although observed glomeruli were only ten in renal biopsy because of obesity, fibrocellular crescents were observed in four of the 10 glomeruli (Figure 2). There was a slight increase in the mesangial matrix but no increase in the number of mesangial cells. In addition, chronic tubulointerstitial nephritis without granulomas accompanied the glomerulonephritis. Immunofluorescence-microscopy did not reveal any glomerular deposits of complement or immunoglobulins. Electron-microscopy electron microscopy showed minor glomerular abnormalities. Therefore, we diagnosed this patient with MPO-ANCA-associated CrGN with sarcoidosis. Her Birmingham vasculitis activity score (BVAS) was 3. Before starting to treat, we performed further evaluation of lung lymph node swelling to rule out malignant disease. Specifically, transbronchial needle aspiration to subcarinal lymph nodes was performed. The pathological changes were compatible with sarcoidosis. Additionally, further work-up of digestive organs was performed; there were not any abnormalities. Therefore, we treated with prednisolone 20 mg/day because of concerns about the side

effects of corticosteroids, especially psychosis. Two weeks after starting steroid therapy, MPO-ANCA had become negative. After that, urinalysis abnormalities were improved, and prednisolone was tapered. However, psychological symptoms such as insomnia and paranoia appeared; it was therefore necessary to reduce the steroid dosage. When prednisolone was tapered to 5 mg/day, urinalysis abnormalities and BHL worsened, although MPO-ANCA remained negative. We additionally treated with mizoribine (MZR) 150 mg/day for these exacerbations. After that, proteinuria and urinary RBCs counts were decreased and there were no abnormal cellular casts in urine. Furthermore, a chest CT revealed that BHL was remarkably improved (Figure 1B and D) in parallel, and levels of MPO-ANCA, ACE, and lysozyme were decreased (Figure 3). Her BVAS was improved from 3 to 0. The serum concentration of MZR three hours after the administration was 1.33 μg/mL. No adverse events related to MZR occurred.

Discussion

To our knowledge, this is the first report of the clinical benefit of MZR in MPO-ANCA-associated CrGN with sarcoidosis not only for urinalysis abnormalities but also for BHL enlargement.

Sarcoidosis is a systemic granulomatous disease of unknown etiology that affects the kidneys in a variety of ways, including hypercalcemia, tubulointerstitial nephritis, granulomatous interstitial nephritis (GIN), and rarely, glomerulonephritis [2, 3]. Although membranous glomerulonephritis, focal segmental glomerulosclerosis or diffuse endocapillary glomerulonephritis IgA nephropathy, and minimal changes in

the extent of disease have been more commonly reported, there have been some cases of CrGN in which MPO-ANCA was positive [3, 4], as in our patients. The changes in titers of ANCA seem to reflect disease activity in 60-70% of ANCA-related vasculitis [9], suggesting that the serum ANCA titer may play an important part in disease diagnosis. Although MPO-ANCA titers and inflammatory findings in clinical parameters were relatively low in our case, laboratory investigations, other than measurement of ANCA, have been found to be of little diagnostic value [10]. In the clinical evaluation of patients with suspected vasculitis and CrGN, it is essential to obtain representative biopsy specimens to confirm the diagnosis. In our case, fibrocellular crescents were observed in four of the 10 glomeruli on light-microscopy, therefore, we diagnosed this case as MPO-ANCA-associated CrGN.

The association between sarcoidosis and MPO-ANCA-associated CrGN is unclear. The inflammatory response in sarcoidosis involves many activated T cells and macrophages with a pattern of cytokine production consistent with a helper T-cell type 1 (Th1) immune response triggered by antigen(s) [11, 12]. However, ANCA-mediated degranulation of neutrophils causes vasculitic damage, Th1 drive granuloma formation in the active phase of ANCA-associated CrGN [13], promote vasculitic damage by several different pathways, and enhance autoantibody production by B cells [14, 15]. Interestingly, CrGN and BHL progressed in parallel with increased sarcoidosis activity in our patients. Thus, the simultaneous occurrence of the two rare diseases may point to a pathological link based on T cell activation.

In general, sarcoidosis shows a good response to steroids but tends to relapse following the tapering

or discontinuation of steroid therapy if the duration or dose of steroid is insufficient [1, 2]. In 20% of adults, GIN has been found to recur during the withdrawal or discontinuation of the steroid [2]. MZR selectively inhibits inosine monophosphate dehydrogenase and guanosine monophosphate synthetase; consequently, it inhibits T cell and B cell proliferation, macrophage activation, and inflammation [6, 7]. The immunosuppressive mechanism of MZR is similar to that of MMF. There have been some reports of the clinical benefit of MMF against sarcoidosis [16, 17], suggesting that these two drugs may have the same mechanism. Compared to other immunosuppressive agents, MZR has few severe adverse effects, such as nephrotoxicity, gonadotoxicity, and myelosuppression [7, 18], and has been reported to exert a clinical benefit in nephrotic syndrome [7], lupus nephritis [18, 19], IgA nephropathy [20], and ANCA-related vasculitis [8]. Recently, Ito et al. reported that MZR was effective for renal sarcoidosis [21]. Although low-dose corticosteroids were maintained during period of treatment in our case, MZR is useful in safely and effectively preventing recurrence during the tapering of steroids in patients not only with ANCA-associated CrGN but also with sarcoidosis.

In conclusion, we showed the therapeutic benefit provided by MZR in a patient with sarcoidosis complicated by MPO-ANCA-associated CrGN not only for urinalysis abnormalities but also for BHL enlargement. More cases will be needed to establish its clinical benefit.

Conflict of interest None.

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Figure legends

Figure 1.

Chest CT scans taken on admission in October, 2007, showing bilateral hilar lymphadenopathy (BHL) (A and B). Chest CT scans taken one year after administration of mizoribine 150mg/day, showing that BHL was remarkably improved (C and D). Arrows indicate the reduced hilar lymph node.

Figure 2.

Light microscopy shows the presence of fibrocellular crescent-shaped glomeruli (A and D, periodic acid–Schiff stain, original magnification x200; B, C, E and F, periodic acid-methenamine-silver stain, B and D, original magnification x200; C and F, original magnification x400). Glanuloma was not found.

Figure 3.

Clinical course. MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, ACE: angiotensin-converting enzyme, uRBC: urinary red blood cells.

Table 1. Laboratory findings at the time of administration

Urinalysis		Peripheral blood		Serology	
Specific gravity	1.012	WBC	3130/μl	CRP	2.30 mg/dl
Protein	(3+) 2.7 g/day	RBC	414x10^4/μl	IgG	1752 mg/dl
Glucose	(－)	Hemoglobin	12.9 g/dl	IgA	274 mg/dl
Occult blood	(3+)	Hematocrit	38.3 %	IgM	64 mg/dl
Sediment		Platelet	32.5x10^4/μl	C3	102 mg/dl
RBC	40/hpf	Chemistry		C4	23 mg/dl
RBC cast	0-1/1	Total protein	6.2 g/dl	CH50	30 U/ml
WBC cast	0-1/1	Albumin	3.3 g/dl	ANA	x320
Hyaline cast	3-6/1	AST	14 IU/l	MPO-ANCA	16 EU
Ccr	77.8 ml/min	ALT	10 IU/l	PR3-ANCA	<3.5 EU
U-Na	54 mEq/l	LDH	247 IU/l	anti-GBM antibody	<10 EU
U-K	15 mEq/l	T-cho	232 mg/dl	Serum ACE	44.3 IU/l
U-Cl	43 mEq/l	Triglyceride	180 mg/dl	Lysozyme	12.7 μg/dl
U-Ca	9.8 mEq/l	BUN	17 mg/dl		
U-iP	23 mEq/l	Creatinine	0.72 mg/dl		
U-Cr	79 mEq/l	Na	141 mEq/l		
U-Vol	1665 ml	K	3.5 mEq/l		
FE Ca	1.6 %	Cl	107 mEq/l		
U-NAG/Cr	14.3 U/g･Cr	Ca	8.9 mg/dl		
U-β2MG	0.20 μg/ml	iP	4.3 mg/dl		

hpf: high power field, β2MG: β2-microglobulin, Ccr: creatinine clearance, WBC: leukocytes, RBC: erythrocytes, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, T-cho: total cholesterol, BUN: blood urea nitrogen, CRP: C-reactive protein, ANA: anti-nuclear antibody, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, PR3-ANCA: Proteinase 3-antineutrophil cytoplasmic antibody, anti-GBM: anti–glomerular basement membrane, ACE: angiotensin-converting enzyme

Figure 1
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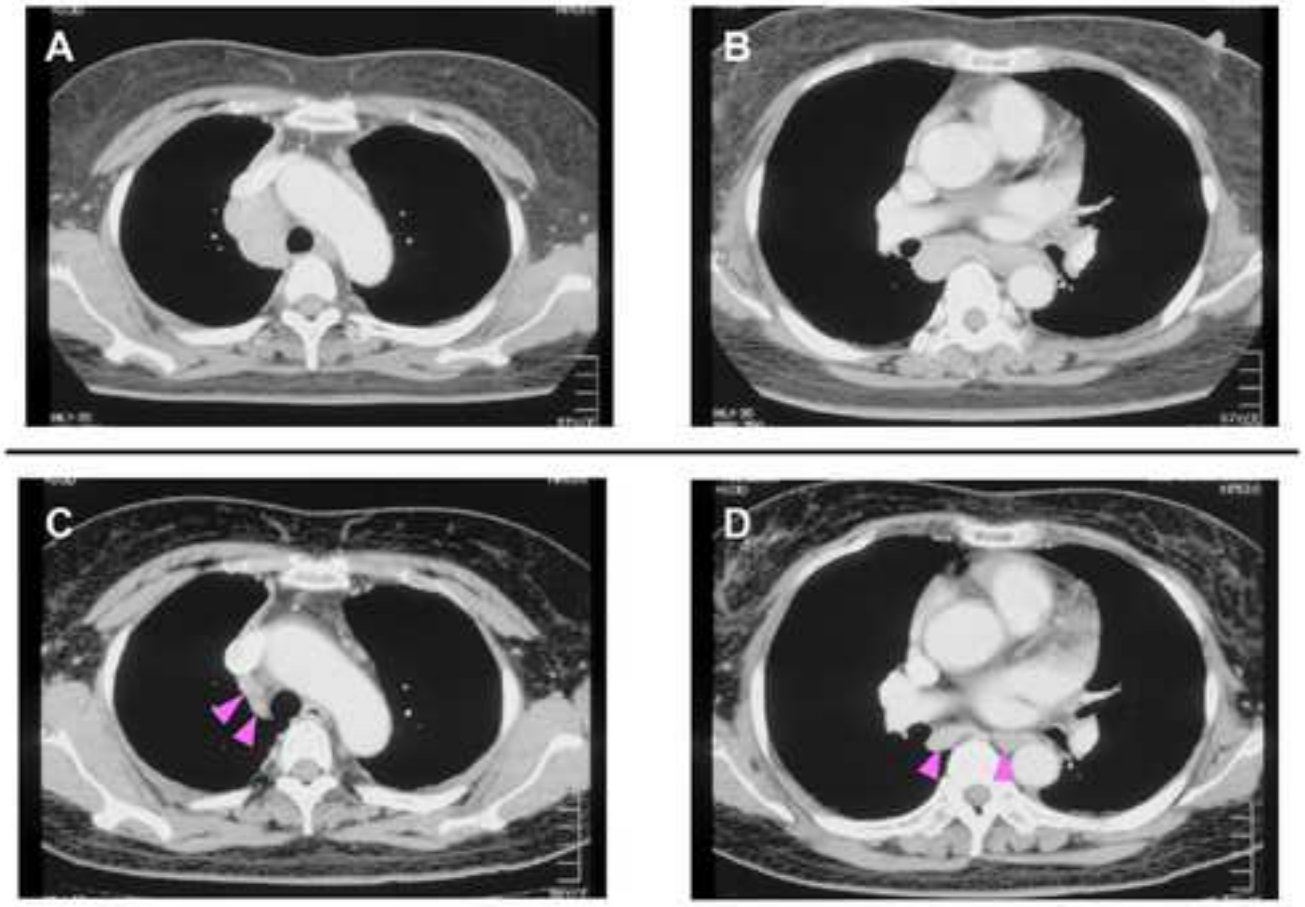

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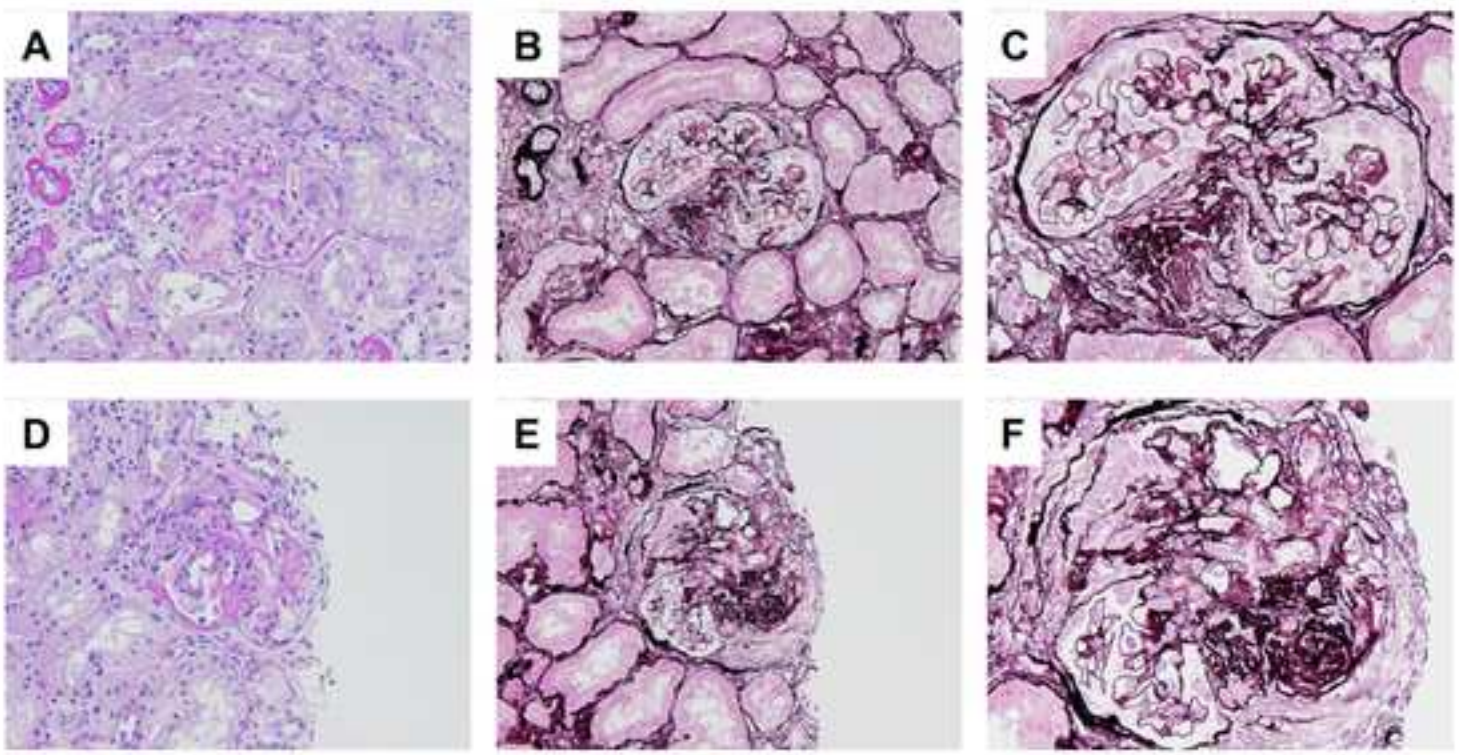

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