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Case report

**A case of refractory cutaneous polyarteritis nodosa with hepatitis B carrier status
successfully treated with tumor necrosis factor alpha blockade**

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Abstract

We describe a refractory cutaneous polyarteritis nodosa (CPAN) patient with hepatitis B (HB) carrier status successfully treated with tumor necrosis factor alpha (TNF- α) blockade, etanercept, and reviewed 5 similar cases. We administered etanercept because of repeated flares despite aggressive therapy. C-reactive protein normalization, prednisolone dose sparing, and absence of any adverse events including HB virus reactivation with nucleotide analogue administration or renal dysfunction have been achieved for 8 months. TNF- α blockade should be considered for intractable CPAN.

Introduction

Polyarteritis nodosa (PAN) is a necrotizing inflammation of medium or small-sized arteries associated with negative results of anti-neutrophil cytoplasmic autoantibodies (ANCA) and often develops secondary to hepatitis B (HB) virus infection [1]. Cutaneous PAN (CPAN) is a chronic and often relapsing cutaneous limited form of necrotizing inflammation involving small or medium-sized arteries without visceral involvement [2]. Some reports suggest that CPAN may represent a distinct subset of classic PAN, and does not progress to PAN [3-5]. Several cases of CPAN with HB carrier status have been reported [6, 7]. However, the relationship between the occurrence of CPAN and HB virus has not

been clarified. Reported treatments of CPAN include non-steroidal anti-inflammatory drugs (NSAIDs) for mild cases, corticosteroids for cases recurring or developing extra-cutaneous symptoms [8], azathioprine, methotrexate, cyclosporine, cyclophosphamide, colchicine, dapsone, chloroquine, pentoxifylline, mycophenolate mofetil, or intravenous immunoglobulin administration [3, 9, 10]. However, some cases of CPAN are resistant to such treatments and experience repeated exacerbations over prolonged periods [8, 11].

Herein, we present a case of refractory CPAN with HB carrier status, which developed seven flares of CPAN during a 7-year period in spite of administration of a variety of immunosuppressants and plasma exchange, successfully treated with tumor necrosis factor alpha (TNF- α) blockade, etanercept and reviewed 4 similar cases of PAN and one of CPAN reported in the literature.

Case report

A 60-year-old woman had been diagnosed as an HB carrier [positive reactions for HB surface antigen (HBsAg) and HB envelope antibodies (HBeAb) and negative results of HB envelope antigen (HBeAg) and HB surface antibodies (HBsAb)] at the age of 30 years. Neither aminotransferase elevation nor any liver abnormalities on ultrasonography were noted at that time. Seven years earlier (June 2004), she had developed fever of 38°C, myalgias, and ankle arthritis with elevated C-reactive protein (CRP) of 11.5 mg/dl. Because the diagnosis was inconclusive, she was referred to our hospital for close examination and

treatment. Physical examination revealed normal blood pressure, arthritis of the metacarpophalangeal joints, and dysesthesia in the dorsum of the feet. Laboratory values were as follows: leukocyte count 8,200/ μ l; hemoglobin 10.1 g/dl; platelet count 375,000/ μ l; aspartate aminotransferase (AST) 14 IU/l; alanine aminotransferase (ALT) 9 IU/l; creatinine 0.52 mg/dl; normal urinalysis; erythrocyte sedimentation rate 77 mm/hour; CRP 11.0 mg/dl; serum IgG 1,170 mg/dl; IgA 233 mg/dl; IgM 152 mg/dl; total functional hemolytic complement (CH50) 48 U/ml (normal 32-47 U/ml); C3 101 mg/dl (normal 65-135 mg/dl); C4 28 mg/dl (normal 13-35 mg/dl); anti-streptolysin O (ASO) titer < 70 IU/ml (normal < 225 IU/ml); positive reactions for HBsAg, HBeAb, and HB core antibodies (HBcAb); and negative results of HBeAg, HBsAb, HB virus DNA, rheumatoid factor, antinuclear antibodies, cryoglobulins, and ANCA for myeloperoxidase and proteinase 3. Tuberculin skin test was negative. Tentative diagnosis was seronegative rheumatoid arthritis (RA). She was treated with 5 mg per day of prednisolone and 150 mg per day of minocycline. The prednisolone was increased to 15 mg daily because of lack of efficacy. One month after starting the treatment (August 2004), purpura, livedo reticularis, and subcutaneous nodules developed on the legs. Nerve conduction velocity tests revealed a peripheral neuropathy pattern. Skin biopsy of the subcutaneous nodule showed vasculitis of small-sized arteries in the dermis and medium-sized arteries in the fatty layer (Fig. 1a, b). Histopathological findings were consistent with the second stage, namely the acute inflammatory stage of Arkin's grading [12]. Because she fulfilled 5 items of the 1990 American College of Rheumatology classification criteria for PAN [13],

livedo reticularis, myalgias, multiple mononeuropathies, presence of HBsAg, and histopathological vasculitis, the diagnosis of PAN was made. She was started on 4 courses of methylprednisolone (mPSL) pulse therapy (500 mg per day of mPSL for 3 days) followed by 50 mg per day of prednisolone, 6 mg per week of methotrexate, and 100 mg per day of lamivudine, which ameliorated her symptoms. However, five months later (March 2005), she developed severe leg myalgias. A left gastrocnemius muscle biopsy showed perivascular lymphocytic infiltration, and a vasculitis flare was confirmed. She was treated with 3 courses of mPSL pulse therapy followed by 50 mg per day of prednisolone, 6 mg per week of methotrexate, and 100 mg per day of cyclosporine (Fig. 2). After these treatments, the symptoms subsided. However, compression fracture of a lumbar vertebra (L2) developed, and administration of sodium risedronate hydrate 2.5 mg daily was initiated. Five years before (June 2006), the vasculitis had flared while tapering the prednisolone dose to 8 mg daily. Symptoms improved by increasing it to 15 mg daily. On the other hand, laboratory examinations revealed AST 90 IU/l, ALT 83 IU/l, and HB virus DNA 5.6 log copy/ml suggesting HB virus reactivation. Adding 10 mg per day of adefovir to lamivudine suppressed the reactivation. Three years before (May 2008), angiography disclosed no aneurysm, stenosis, or occlusion of the renal or celiac arteries. Diagnosis of CPAN was established because of the absence of organ involvement other than skin lesions and peripheral neuropathy. One year before (February 2010), pancytopenia and elevations of AST and ALT were noted. Increase of HB virus DNA was not detected. Adverse effect of methotrexate was suspected and cessation of methotrexate improved these

abnormalities. During the six-year clinical course, CPAN flare occurred five times (March 2005, June 2006, September 2007, May 2008, and March 2010) (Fig. 2). The flares were characterized by the development of myalgias, purpura, and painful subcutaneous nodes in the legs with elevated CRP levels. Every flare was treated by increasing the corticosteroid dose including mPSL pulse therapy. At the sixth flare (June 2010), other treatments were resorted to as follows: administration of tacrolimus (2 mg daily), azathioprine (75 mg daily), colchicine (1.8 mg daily), and cyclophosphamide, plasma exchange, and double filtration plasmapheresis one after the other. Tacrolimus and colchicine were discontinued because of worsening renal function. Azathioprine was stopped because of lack of efficacy. Three courses of 750 mg (15 mg/kg) intravenous cyclophosphamide administration, 6 times plasma exchange, and 3 times double filtration plasmapheresis improved her symptoms. However, six months after these intensive treatments, a seventh flare of CPAN developed in June 2011. From July 2011, 25 mg (0.5 mg/kg) per week of etanercept was started. Such TNF- α blockade dramatically improved the clinical symptoms and laboratory data. CRP decreased to below 0.2 mg/dl consistently. Prednisolone was tapered from 9 to 5 mg daily after stating etanercept. No adverse events including HB virus reactivation or renal dysfunction have been noted for 8 months. This treatment was approved by the ethics committee of our hospital, and the patient provided written informed consent prior to the use of etanercept.

Discussion

Here, we describe a patient with refractory CPAN with HB carrier status successfully treated with etanercept. She experienced seven flares of CPAN during a 7-year period despite aggressive treatment with corticosteroids, methotrexate, cyclosporine, tacrolimus, azathioprine, colchicine, and intravenous cyclophosphamide, plasma exchange, and double filtration plasmapheresis. Finally, TNF- α blockade sufficiently improved the symptoms, with remission maintained for 8 months. HB virus reactivation had not been noted with lamivudine and adefovir co-administration.

During a seven-year clinical course, this case evinced several features consistent with CPAN, namely cutaneous lesions, arthralgias, myalgias, histopathological vasculitis, and absence of hypertension and organ involvement other than peripheral neuropathy [4]. The characteristic cutaneous lesions of CPAN are purpura, livedo reticularis, painful subcutaneous nodules, ulcerations, and infarctions usually arising on the lower extremities [3-5, 8, 11]. Nakamura et al. [4] suggested that the lesions of extra-cutaneous manifestations of CPAN such as peripheral neuropathy, arthralgias, and myalgias are consistent with the area of skin lesions, while classic PAN often has such symptoms in areas unrelated to skin lesions. In this case, the lesions of dysesthesia due to peripheral neuropathy and myalgias were on the feet, corresponding to the lesions of purpura and livedo reticularis. Therefore, the clinical features of this case were consistent with those of CPAN.

Hypersensitivity to minocycline, sulfonamide, streptomycin, penicillin, estrogen, and anti-tuberculous agents, is suggested as a possible cause of CPAN [2]. Díaz-Pérez et al. [14] implicated immunological

mechanisms in CPAN, while Bauza et al. [9] suggested a relation of CPAN not to immunological mechanisms but rather infection with Streptococcus or tubercle bacillus. In this case, these possibilities could be excluded because of the presence of a low titer of ASO and negative result of tuberculin skin test.

HB virus-related PAN represents the most typical form of PAN [1]. On the other hand, the relation between HB virus and CPAN is not clear. Van de Pette et al. [15] reported that HB surface antigen-containing immunocomplexes induced the release by neutrophils of lysosomal enzymes, with the immunocomplexes possibly implicated in the vascular damage. Some cases of CPAN who were also HB virus carriers without any history of hepatitis or HB virus reactivation have been reported, but the relationship between the onset of CPAN and HB virus has not been proved clearly in these cases [6, 7]. Most other reports suggested that HB virus might have little relation to CPAN [3, 4, 8, 9]. In our case, elevation of transaminase or HB virus reactivation was not observed at the onset of CPAN. Therefore, the pathogenesis of CPAN in this case was unknown.

The efficiency of TNF- α blockade for systemic vasculitis has been suggested [16]. In particular, TNF- α plays an important part in the pathogenesis of ANCA-associated vasculitis [17]. However, the role of TNF- α blockade in ANCA-associated vasculitis undergoing remission induction therapy is uncertain [17]. At least, etanercept is not recommended for granulomatosis with polyangiitis in remission on maintenance therapy [18].

On the other hand, successful treatments for childhood PAN with biologic agents have been reported for

unresponsiveness to conventional therapy [19, 20]. Four cases with PAN successfully treated with etanercept were reported (Table 1) [19, 20]. All were children less than 16 years with systemic organ involvement who had received previous conventional therapy for 1 to 9 years before the use of etanercept. Etanercept administration allows corticosteroid dosage reduction, and no adverse events attributable to it have been reported.

In addition, one case of CPAN successfully treated with infliximab was reported (Table 1) [21]. The case was a 14-year-old boy who developed frequent flares. He was administered infliximab because of a lack of response to prednisolone (0.5 mg/kg/day) and prophylactic penicillin administration. Laboratory data showed elevated serum interleukin-1 β , interleukin-6, and TNF- α before infliximab administration, all of which became undetectable after infliximab therapy. Etanercept administration improved the symptoms and showed a corticosteroid sparing effect in this case. CPAN often relapses and some cases need long-term corticosteroid therapy [6, 9]. But long-term corticosteroid use is well known to cause osteoporosis or compression fractures like in this case.

In this case, neither elevation of aminotransferase nor detectable HB virus DNA was noted during eight months' use of etanercept with lamivudine and adefovir co-administration. Recently HB virus reactivation has been reported during TNF- α blockade [22] and prevented by antiviral prophylaxis [23]. TNF- α blockade can cause HB virus reactivation in patients having positive HBsAg because TNF- α inhibits HB virus replication and provokes an HB virus-specific response. Urata et al. [22] reported that the risk of

reactivation of HB virus replication in cases of RA patients with resolved HB was higher in patients who were treated with biologic agents than in those who were not. Lan et al. [23] reported 18 patients with RA with positive HBsAg and HBcAb status treated with TNF- α blockade. Ten patients receiving prophylactic lamivudine did not develop HB virus reactivation, while five of 8 patients without antiviral prophylaxis did. No significant difference in the prevalence of positive HBeAb was observed between patients with and without HB virus reactivation. Hence, antiviral prophylaxis seems to be needed to prevent HB virus reactivation in patients with positive HBsAg during TNF- α blockade.

In conclusion, we reported the first adult case of refractory CPAN with HB virus carrier status successfully treated with etanercept. Further studies are required to confirm the effectiveness and safety of TNF- α blockade in such patients.

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Conflict of interest: None.

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Figure legends

Fig. 1 Histopathology of a subcutaneous node on right leg. Moderate infiltration of neutrophils in lumens and walls of arteries, perivascular infiltration of lymphocytes and histiocytes, and fibrinous deposits were noted in small-sized arteries in dermis (**a**) and in medium-sized artery in fatty layer (**b**). These findings were consistent with the second stage, namely the acute inflammatory stage of Arkin's grading.

a, b Hematoxylin-eosin stain. **a** $\times 200$, **b** $\times 100$

Fig. 2 Clinical course.

mPSL; methylprednisolone, *PSL*; prednisolone, *MTX*; methotrexate, *CyA*; cyclosporine A, *PE*; plasma exchange, *DFPP*; double filtration plasmapheresis, *Tac*; tacrolimus, *AZA*; azathioprine, *IVCY*; intravenous cyclophosphamide