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CASE REPORT

Varicella–zoster virus hepatitis in polymyositis

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Abstract A 31-year-old woman had recurrent mild flare-ups of polymyositis for years. Fourteen days after low-dose methotrexate was added in an attempt to taper the corticosteroid, she began to feel abdominal and lower back pain, followed by generalized pustulosis, severe liver dysfunction, and disseminated intravascular coagulation. On the diagnosis of varicella–zoster virus (VZV) hepatitis, acyclovir, immune globulin and plasmapheresis were given with a favorable outcome. Physicians should be aware that VZV infection could complicate severe hepatitis in immuno-suppressed patients.

Keywords Varicella–zoster virus · Hepatitis · Polymyositis · Corticosteroids · Methotrexate

Introduction

Varicella–zoster virus (VZV) is well known as the cause of chickenpox in cases of primary infection and herpes zoster in cases of reactivation. In immuno-compromised hosts, however, VZV infection occasionally is accompanied by complications such as pneumonia, encephalitis, and hepatitis, especially in primary infection [1]. Furthermore, a second episode of primary VZV infection has been suggested not to be uncommon in immuno-compromised individuals [2, 3]. VZV hepatitis is a rare complication but once it occurs, the outcome may be fatal [1]. We describe herein a severe case of VZV hepatitis that occurred during the treatment of polymyositis (PM) with prednisolone (PSL) and methotrexate (MTX). The liver injury aggravated rapidly until the prothrombin time fell to less than 40% of normal, however, administration of acyclovir (ACV) was started on the day she developed generalized pustulosis followed by immune globulin and plasmapheresis, and this treatment resulted in complete recovery.

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Case report

A 31-year-old woman had been treated for PM from the age of 13. Initial treatment for the PM with 60 mg/day PSL was effective, however, she had to continue taking 12.5–20 mg/day PSL thereafter, because of the fluctuation of serum creatine kinase (CK) level. In June 2004, low-dose MTX (7.5 mg/week) was added to 20 mg/day PSL to taper the dose of corticosteroids. Fourteen days later, after she had taken the last capsule of MTX for the third week, she visited our emergency room with a 2-day history of increasing abdominal and lower back pain, and was hospitalized immediately. She had no past history of chickenpox. Two weeks prior to the admission, however, she visited a pediatrician to take a physical examination of her child, where she possibly contacted with the disease.

Upon admission, small pustules were scattered over the hands and face, bowel sounds were increased, and mild muscle weakness was detected in the proximal regions of the extremities. Laboratory tests revealed elevated levels of liver enzymes (AST 230 U/l, ALT 242 U/l, LDH 707 U/l, γ-GTP 47 U/l), lymphopenia (WBC 8,500 μl^{-1}, Neu 88.0%, Ly 5.0%), and low total protein (6.5 g/dl) and immunoglobulin levels (IgG 615 mg/dl, IgM 59 mg/dl,

IgA 130 mg/dl). CK (207 U/l) and myoglobin (77 ng/ml) were slightly elevated, but did not differ greatly from her usual state. Serum creatinine was normal. HBs antigen, anti-HCV antibody, and IgM anti-CMV antibody were negative. IgG anti-CMV antibody was positive. Echography and computed tomography of her abdomen showed no particular findings. At this time, we considered that the liver injury was most likely caused by MTX, and stopped giving MTX thereafter, while PSL was continued at 20 mg/day.

However, the patient developed generalized pustulosis on the second day of hospitalization and the Tzanck test was positive (Fig. 1). VZV DNA in the vesicles was at 5,200,000 copies/ml. Serum VZV-IgG and IgM antibodies were not detected initially, but later, both became positive by the 12th day, indicating a primary infection by VZV (Fig. 2). From the second day, 750 mg/day ACV was given on the diagnosis of VZV hepatitis, but liver injury developed further and was complicated by disseminated intravascular coagulation. On the fourth day, ACV was increased to 1,500 mg/day and 5 g/day VZV immune globulin was also given for 3 days. On the fifth day, AST elevated as high as 4,795 U/l, and prothrombin time was prolonged to less than 40% normal activity. Although encephalopathy was not observed, rapidly progressive liver injury and low prothrombin time suggested a poor prognosis, plasmapheresis was therefore conducted from the seventh day. After 2 weeks of these intensive managements, she recovered fully and was able to be discharged from the hospital.

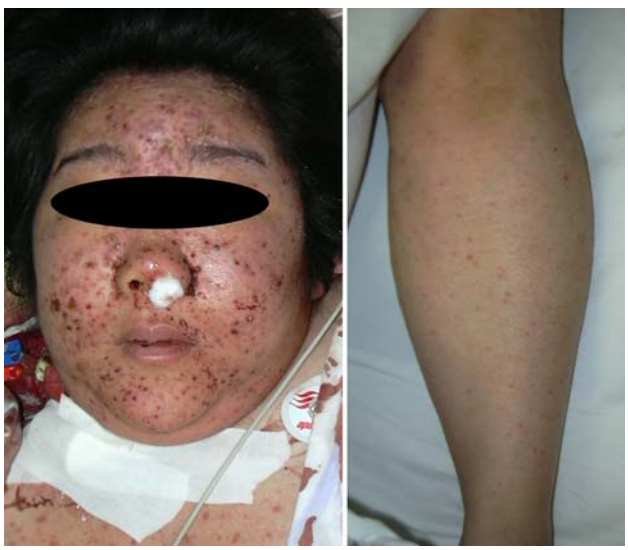

Fig. 1 Generalized pustulosis on the face (*left panel*) and leg (*right panel*) on the fifth hospital day

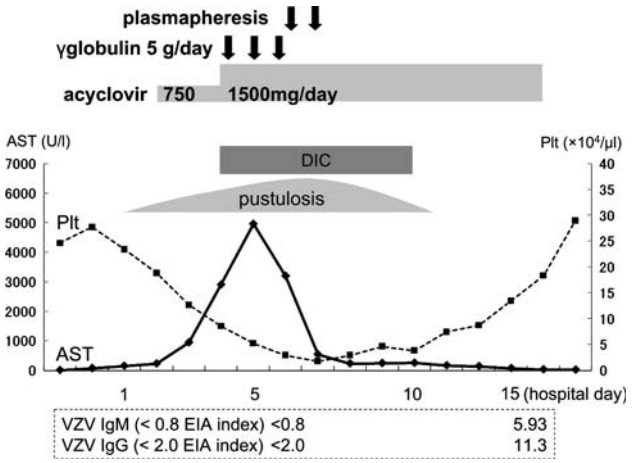

Fig. 2 Clinical course during hospitalization. *AST* aspartic aminotransferase, *DIC* disseminated intravascular coagulation, *Plt* platelet

Discussion

Viral infections and drugs should be taken into account as a cause of acute liver injury in this case. Although MTX was initially suspected as a causative agent, further elevation of liver enzymes after quitting the drug suggested the presence of other causes. Because there was no other possibly hepatotoxic drug in her medication, viral hepatitis was mostly suspected. HBV is one of the major causes of acute hepatitis, as we reported previously a case of fulminant hepatitis which resulted from reactivation of HBV in an asymptomatic carrier during the course of low-dose MTX therapy for rheumatoid arthritis (RA) [4]. In the present case, however, serological tests for HBV as well as HCV were negative. Finally, the appearance of generalized pustulosis on the second hospital day enabled us to make a correct diagnosis of VZV hepatitis.

Disseminated varicella infections in immuno-suppressed hosts are rare, but highly relevant because of both the severe clinical features and the associated high mortality rate [5]. Most of the reported cases of disseminated varicella are transplant recipients or patients with acquired immunodeficiency syndrome. However, in the English literature we found ten cases of connective tissue diseases (CTDs) with disseminated varicella infections (Table 1), including six with RA [6–11], and one each with systemic lupus erythematosus [12], PM [13], Wegener's granulomatosis [14], and microscopic polyangiitis [15]. The sole case of PM was a 66-year-old man with a 3-year history of taking 5 mg/day PSL. He complicated with varicella encephalitis, and ACV, immune globulin and high-dose PSL (80 mg/day) were given with favorable outcome. Two cases of VZV hepatitis were associated with RA. One of them was a 32-year-old man who developed pneumonitis and hepatitis during anti-TNFα therapy (infliximab), and ACV was given successfully [9]. The other was a 70-year-old woman who had been

Table 1 Disseminated varicella zoster virus (VZV) infection complicated in the course of connective tissue diseases (CTDs; reported cases in English literature)

	First author (ref)	Age	Sex	IgG level, the number of Ly	Connective tissue disease		VZV infection				
					Diagnosis	immuno-suppressant	Occurrence of VZV infection after diagnosis of CTD	Primary infection or reactivation	Complication	Treatment of VZV	Outcome
1	Toyoda [13]	66	M	ND	PM	PSL 5 mg/day	3 years	Reactibation	Encephalitis	ACV IVIG	Recovered
2	Lefond [14]	54	M	ND	WG	PSL 80 mg/day CPA 150 mg/day	5 months	ND	Encephalitis Pneumonia	ND	Died
3	Krishnaswamy [6]	78	M	Ly 600 ml^{-1}	RA (Felty's syndrome)	HCQ 400 mg/day G-CSF, PSL	15 years	ND	ND	ACV	Recovered
4	Jarrett [7]	76	F	ND	RA	PSL 10 mg/day MTX 10 mg/week	Unknown	Reactibation	Fasciitis	ACV	Recovered
5	Yamane [8]	70	F	IgG 883 mg/dl CD4 Ly 206 μl^{-1}	RA, IP	Corticosteroid CYA	15 years	ND	Pneumonia Hepatitis	ND	Died
6	Matsumoto [15]	60	F	ND	MPA	PSL 45 mg/day mPSL pulse CPA 50 mg/day	4 months	Reactibation	Encephalitis	ACV IVIG	Recovered
7	Sekiguchi [12]	31	F	ND	SLE	PSL 20 mg/day	20 years	Reactibation	Encephalitis	ACV IVIG	Recovered
8	Vonkeman [9]	32	M	ND	RA	Infliximab	ND	Primary infection	Pneumonia Hepatitis	ACV	Recovered
9	Kinder [10]	ND	ND	ND	RA	MTX	ND	ND	ND	ND	Died
10	Agarwal [11]	65	M	IgG normal CD4 Ly 2,250 μl^{-1} CD8 Ly 1,048 μl^{-1}	RA	PSL 0.15 mg/(kg day) MTX 10 mg/week	13 weeks	Reactibation	Pneumonia	ACV	Recovered
11	Present case	31	F	IgG 615 mg/dl Ly 425 μl^{-1}	PM	PSL 20 mg/day MTX 7.5 mg/week	18 years	Primary infection	Hepatitis	ACV IVIG Plasmapheresis	Recovered

CPA cyclophosphamide, *CYA* ciclosporine, *G-CSF* granulocyte-colony stimulating factor, *HCQ* hydroxychloroquine, *IP* interstitial pneumonia, *IVIG* intravenous immunoglobulin, *Ly* lymphocyte, *MPA* microscopic polyangiitis, *mPSL* methylprednisolone, *MTX* methotrexate, *PM* polymyositis, *PSL* prednisolone, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *WG* Wegener's granulomatosis, *ND* not described

treated with corticosteroids and ciclosporin A. Because she had no vesicular rash, a diagnosis of disseminated VZV was not established until post-mortem examination [8]. Among the findings described in these cases, including age, sex, underlying CTD, laboratory data, each therapeutic agent for the CTD, we detected no particular risk factors, to cause severe complications. However, all of the cases had been given some immuno-suppressive agents such as corticosteroids, cyclophosphamide, ciclosporin, hydroxychloroquine, MTX, or infliximab; it is reasonable to consider these therapies for the CTDs to be the primary risk factor.

In addition to PSL, the possible contribution of MTX to the severe hepatitis of the present case might not be neglected, although it was introduced only 2 weeks before the onset of the VZV infection. The average incubation period for varicella infections is about 2 weeks [16]. After the entry of VZV, the virus undergoes replication in regional lymph nodes, which is followed by a primary viremic phase and then the virus undergoes replication in the liver and spleen. After the replication in the reticuloendothelial system, a secondary viremia occurs and skin lesions appear about 2 weeks after the entry of VZV. During this critical period, our patient was taking MTX until the day of admission. MTX has been demonstrated to interfere with clonal expansion and differentiation of naïve cells into effector and memory CD8 T cells [17].

In a recent retrospective study on 156 patients with polymyositis/dermatomyositis (DM), 18 (11.5%) patients were found in medical records who developed opportunistic infections [18]. Higher doses of corticosteroids, lymphopenia, and lower serum total protein levels were significantly more frequent in the group of PM/DM patients with opportunistic infections than those without. Our case had all of these risk factors. On the other hand, primary infection of VZV in adults has higher risk of complications compared to that in children [19]. Also, primary infection of VZV has been reported to show more severe courses than reinfection in transplant recipients [2, 20]. Given the above discussion, it can be recognized that the present case had multiple risk factors such as use of corticosteroid (with MTX), adult primary infection, lymphopenia, and low serum total protein.

The early diagnosis of disseminated VZV hepatitis is usually difficult because of the delayed appearance of characteristic skin lesions. A report of a series of ten patients of visceral VZV infection after bone marrow transplantation revealed that abdominal pain was the most common symptom with moderately to profoundly elevated aminotransferases or pancreatic enzymes [21]. The pain was reported to be epigastric, occasionally involving the right upper quadrant or radiating to the back, and importantly, preceded the eruption of the vesicular rash by 4–10 days. The abdominal pain is thought to be caused by the stretching of Glisson's capsule secondary to hepatitis, pancreatitis, gastritis, or neuropathy. Previous reports on autopsies of disseminated VZV infection revealed extensive involvement of bowel, liver, pancreas, spleen, and terminal esophagus [22, 23].

Mortality of disseminated VZV infection was reported to be about 50% in patients after bone marrow transplantation [21]. Even in our review of patients with CTDs (Table 1), three out of ten patients died. To improve the mortality, early administration of ACV is essential. Anderson et al. [23] described a fatal case of VZV hepatitis in an immuno-competent adult, in whom ACV therapy was begun 3 days after the appearance of the skin lesions. They discussed that ACV should be started within 24 h of the skin manifestation. In our case, the pustulosis appeared on the third day after the onset of the lower back pain, which enabled us to make a diagnosis and administration of ACV during a window of opportunity, leading to good prognosis, despite the complication of severe hepatitis and disseminated intravascular coagulation. In addition to ACV, we administered immune globulin because of the severe complication and the low serum IgG level, which might contribute to the good prognosis in our patient. Plasmapheresis was aimed to relieve the patient from the progressive liver injury according to the regimen for fulminant hepatitis, however it might also have possible effect on reducing the circulating viral load [24].

In conclusion, physicians must be aware of the possibility of VZV hepatitis when examining patients with abdominal pain of uncertain etiology accompanying liver dysfunction, which usually precedes the vesicular skin eruption. Delayed start of ACV could be fatal especially in immuno-suppressed patients.

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