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Case Report

Varicella with rapidly progressive hepatitis presenting with multiple hepatic nodules in a child with acute leukemia

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ABSTRACT

Abdominal pain may precede the characteristic varicella skin lesions in immunocompromised patients with visceral varicella. The absence of skin lesions may delay timely diagnosis and treatment of varicella for those patients. Furthermore, abdominal imaging findings to provide information to diagnose visceral varicella have rarely been reported. Varicella was diagnosed in a 5-year-old boy with acute lymphoblastic leukemia complaining of fever and abdominal pain followed by papulovesicular skin lesions. Later, the patient was found to have rapidly progressive acute hepatitis, and abdominal computed tomography showed multiple hypodense hepatic nodules. The patient was treated with intravenous acyclovir, intravenous immunoglobulin, and empirical antibiotic and antifungal therapy. However, his fever and abdominal pain persisted, and a laparoscopic liver biopsy was performed to differentiate other causes of the persisting symptoms. Eventually, the patient was diagnosed with visceral varicella based on histopathologic findings. In conclusion, visceral varicella should be considered in immunocompromised patients with abdominal pain and multiple hypodense hepatic nodules on abdominal imaging studies. However, bacteria, fungi, and tuberculosis can produce similar imaging findings; therefore, a biopsy may be necessary in patients not responding to antiviral therapy.

1. Introduction

Hepatitis with elevated serum aspartate transaminase (AST) levels, exceeding two times the normal upper limit, occurs in 3.4% of immunocompetent children with varicella, and life-threatening hepatitis rarely occurs [1]. However, visceral varicella occurs more frequently in immunocompromised patients, including recipients of chemotherapy and hematopoietic cell transplantation (HCT), compared to immunocompetent patients [2–5]. Fulminant hepatitis caused by the varicella-zoster virus (VZV) in immunocompromised patients results in high mortality [5–7]; however, early antiviral therapy for patients with visceral varicella improves the prognosis [5]. Most immunocompromised patients with visceral varicella complain of abdominal discomfort before they develop the characteristic varicella skin lesions [2,5]; therefore, evaluation of a patient's abdominal pain may be performed prior to the diagnosis and treatment of visceral varicella. Abdominal imaging findings helpful for diagnosing visceral varicella have rarely been reported. We performed an abdominal computed tomography (CT) scan to investigate the evidence of internal organ involvement in a boy with underlying acute lymphoblastic leukemia (ALL), who had varicella with rapidly progressive hepatitis. The abdominal CT findings could not differentiate visceral varicella from hepatic abscesses caused by a bacterial infection, hepatosplenic candidiasis, or miliary tuberculosis. A laparoscopic liver biopsy was performed, and the patient was accurately diagnosed with visceral varicella.

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2. Case report

A 5-year-old boy was admitted to our hospital complaining of abdominal pain lasting 3 days and a fever that developed that morning. One month before this admission, the child had been diagnosed with standard risk ALL at our hospital. He had received remission induction chemotherapy with vincristine, daunorubicin, L-asparaginase, and oral prednisolone and was discharged from the hospital in complete remission 3 days prior to this admission. His abdominal pain developed on the day of discharge from the hospital, and fever occurred in the morning of this admission. A few papular lesions were observed on his scalp, and papulovesicular skin lesions spread to his face and trunk by hospital day 2. He was diagnosed with varicella, and was started on intravenous acyclovir therapy (10 mg/kg three times a day). He had received vaccination against varicella (SuduVax®, Green Cross Corporation, Yongin, Korea) when 1 year old, and had no previous history of varicella or herpes zoster. However, his serological status against VZV was not determined at the time of ALL diagnosis.

On admission, hepatosplenomegaly was not present, and blood tests revealed a white blood cell count of 3250/mm^3 (neutrophils 79%, lymphocytes 19%), hemoglobin of 8.7 g/dL, platelet count of 196,000/mm^3, AST of 238 U/L, alanine transaminase of 189 U/L, and C-reactive protein of 0.20 mg/dL (Table 1). He received empirical antibiotic therapy including piperacillin/tazobactam and isepamicin. On hospital day 4, his fever, which had resolved on hospital day 2, recurred. Hepatomegaly was noted on physical examination, and laboratory results showed rapid aggravation of hepatitis (Table 1). He was diagnosed with visceral varicella, and a total of 1 g/kg of intravenous immunoglobulin (IVIG) was administered for 3 days. The results of blood tests for VZV, which were performed on admission, were reported as follows on hospital day 4: positive qualitative polymerase chain reaction (PCR), positive IgG, and negative IgM. Serologic tests for hepatitis A, B, and C were negative, and blood and urine cultures performed on admission were negative. On hospital day 7, crusts were observed on his skin; however, his fever persisted with aggravation of hepatomegaly. An abdominal CT scan was performed to evaluate the cause of hepatomegaly and rapidly progressive hepatitis, and the CT scan revealed diffuse gastric mucosal hypertrophy, hepatomegaly, and multiple hypodense hepatic nodules (Fig. 1A). The nodules showed no rim enhancement after administration of intravenous contrast material. He received an additional 1 g/kg of IVIG during 3 days, for a total of 2 g/kg given during 6 days, to treat the persisting fever.

On hospital day 11, his fever resolved, and all the skin lesions had crusted. However, his abdominal pain and hepatomegaly persisted, and fever recurred on hospital day 13. Although the patient had received oral fluconazole (3 mg/kg once a day) prophylaxis, due to neutropenia that had occurred during prior chemotherapy, up till 10 days before this admission, he was started on intravenous fluconazole (6 mg/kg once a day) therapy on hospital day 13 based on the abdominal CT findings, which could not rule out the possibility of hepatosplenic candidiasis. Serum galactomannan was positive on hospital day 11 while receiving piperacillin/tazobactam. Cefepime was substituted for piperacillin/tazobactam on hospital day 15, and serum galactomannan level became negative on hospital day 18. Therefore, we ruled out hepatic involvement of invasive aspergillosis.

In spite of empirical antifungal therapy, the patient experienced recurrent fever and severe abdominal pain with persistent hepatomegaly. Acyclovir-resistant VZV infection was considered because his symptoms persisted despite prolonged acyclovir therapy. In order to clarify the cause of persistent fever with hepatomegaly, he underwent laparoscopic liver biopsy on hospital day 21, which revealed several yellowish nodules with central necrosis on the hepatic surface (Fig. 2). Histopathologic findings of lymphoplasmacytic infiltration of the portal and perivascular areas were reported 5 days later, and the VZV PCR test was positive in the biopsied liver tissue without any evidence of bacterial or fungal infections. His fever resolved on hospital day 22 and abdominal pain resolved on hospital day 23. Intravenous acyclovir therapy was continued for 30 days instead of alternative antiviral therapy. However, hepatomegaly and positive VZV PCR in the serum persisted.

The patient was discharged from the hospital with oral valacyclovir therapy (20 mg/kg three times a day), with a plan to maintain oral antiviral medication for 1 year for suppression of VZV reactivation. The abdominal CT scan on discharge from the hospital showed no improvement of hepatic nodules; however, follow-up imaging done 1 month after discharge from the hospital showed resolution of the nodules (Fig. 1B). Seven months following discharge from the hospital, the patient has not experienced

Table 1
Laboratory results during hospitalization.

	HD #1	HD #4	HD #7	HD #11	HD #21	HD #30
WBC count (/mm^3)	3250	4150	2490	6600	5140	3040
Neutrophils (%)	79	72	41	47	43	56
Lymphocytes (%)	19	21	43	40	48	58
Monocytes (%)	2	6	9	5	8	14
Hemoglobin (g/dL)	8.7	10.9	8.5	7.7	10.1	9.8
Platelet count (/mm^3)	196,000	105,000	113,000	98,000	283,000	269,000
AST (U/L)	238	2013	320	129	68	46
ALT (U/L)	189	1351	531	177	56	34
ALP (U/L)		366	546	511		
γ-GTP (U/L)		567	763	691		
LDH (U/L)	1347	5350	2815	1371		
Total bilirubin (mg/dL)	1.01	1.11	2.10	1.24	0.60	0.41
Direct bilirubin (mg/dL)		0.48	1.55	0.84		
PT INR	1.15	1.39	1.18	1.15	1.05	1.04
aPTT (sec)	51.9	39.0	46.1	34.6	25.7	27.4
FDP (μg/mL)	3.4	35.4		33.9	18.6	15.5
D-dimer (mg/L)	1.05	12.07		8.70	4.76	4.25
Fibrinogen (mg/dL)	82	120		225	311	218
Antithrombin III (%)	32.3	51.8		93.9	92.1	93.2

HD: hospital day, WBC: white blood cell, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, LDH: lactate dehydrogenase, PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time, FDP: fibrin degradation product.