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【 CASE REPORT 】

Atypical, Levetiracetam-induced Hypersensitivity Syndrome Complicated by Fulminant Liver Failure in a Patient Undergoing Hemodialysis

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Abstract:
A 59-year-old man undergoing hemodialysis was administered levetiracetam, after which he developed a systemic rash, high fever, severe liver dysfunction, and leukocytopenia with reactivation of human herpes virus 6. Atypical drug-induced hypersensitivity (DIHS) was diagnosed, and prednisolone was administered at 60 mg/day. However, liver failure rapidly progressed, and the patient died 12 days following treatment. Despite the rarity of DIHS with concomitant fulminant liver failure from levetiracetam and sufficient clearance thereof by hemodialysis, our case suggests that this syndrome may still ensue, resulting in mortality, even in hemodialysis patients. Although no treatment has yet been established, strict monitoring and aggressive treatment may be required.

Key words: levetiracetam, drug induced hypersensitivity, hemodialysis

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Introduction

Drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is the most severe presentation among severe cutaneous adverse reactions (SCARs). Its clinical manifestations are highly variable and may affect multiple organs (1). Although the pathogenesis of this syndrome is not fully understood, human herpes virus 6 (HHV-6) reactivation has been detected in the majority of patients (2), and it is speculated that complex interactions between herpesvirus reactivation, culprit drugs, and immune reactions thereto are pivotal for the pathogenesis of this syndrome (3).

The most frequent causative agents are anticonvulsants (4), and the liver is most commonly involved (5). The clinical course of DIHS/DRESS among patients undergoing hemodialysis (HD) is not well described, and there are almost no reports describing DIHS/DRESS complicated by fulminant liver failure among patients undergoing HD.

We herein report a rare case of fatal DIHS/DRESS, complicated by fulminant liver failure, induced by levetiracetam (LEV), in a patient undergoing HD.

Case Report

A 59-year-old man with aphasia was admitted to our hospital. His medical history included hypertension and chronic kidney disease due to nephrosclerosis, and he had been maintained on HD for two years. He had no history of allergies. His family history was unremarkable. He denied recent changes in medication prior to admission.

Upon an examination, his vital signs were as follows: Glasgow Coma Scale E4V3M6, SpO_2 99% (room air); respiratory rate, 10 breaths/min; blood pressure, 203/106 mmHg; and pulse rate, 78 beats/min. His height and body weight

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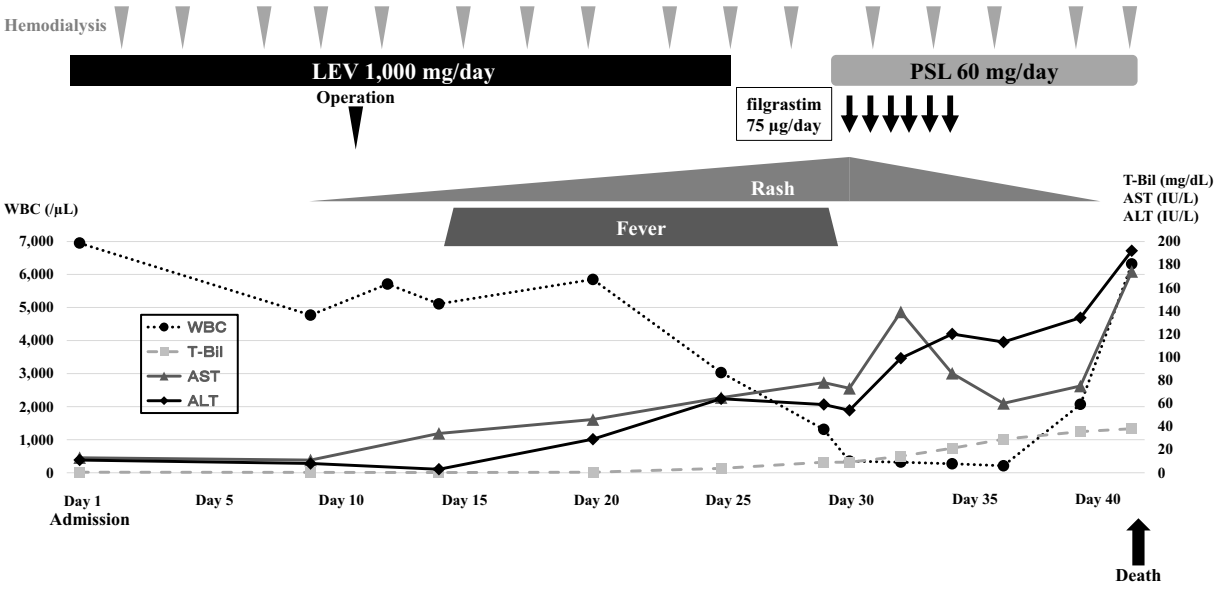

Figure 1. Clinical course of the patient. No improvement of liver failure was achieved despite treatment with prednisolone. Liver failure was aggravated, and the patient died on day 43. AST: aspartate aminotransferase, ALT: alanine aminotransferase, LEV: levetiracetam, PSL: prednisolone, T-Bil: total bilirubin, WBC: white blood cells

were 158 cm and 56.6 kg respectively. Aphasia was observed. Physical examinations were otherwise unremarkable.

Laboratory data were within acceptable limits for patients undergoing hemodialysis. Non-contrast computed tomography (CT) and magnetic resonance imaging (MRI) revealed a mass covering the left temporal lobe. Based on these findings, a brain tumor was suspected, so he was admitted for neurosurgery.

The clinical course of the patient is provided in Fig. 1. Considering the location of the tumor, the patient was at high risk of seizure development, therefore prophylactic oral levetiracetam (LEV) was commenced on day 1 of admission. The dose of LEV was 500 mg in the morning and evening (total 1,000 mg/day) considering the sufficient clearance of LEV by HD. The evening dose was administered after HD on an HD day. HD was performed 3 times a week from day 2 with an APS®-18 EA dialyzer (polyarylethersulfone, membrane surface area 1.8 m^2; Asahi Kasei Medical, Tokyo, Japan). The blood flow and dialysate flow rates were 200 mL/min and 500 mL/min, respectively.

LEV administration along with HD was followed by the emergence of small rashes on the abdomen, back, face, and bilateral legs on day 9. The small rashes were treated with topical steroids, and the patient underwent craniotomy for tumor resection on day 11. The operation was performed and completed successfully. Histopathology of the resected tumor revealed a meningioma. Postoperatively, aphasia gradually improved with rehabilitation. However, the systemic rash worsened, and a remittent fever of up to 39°C was observed beginning on day 15. There were no signs of infection, and blood culture was negative. We suspected an allergic reaction to the dialyzer used upon hemodialysis and changed the material; however, the fever continued. In addition, a progressive decline in the liver function, jaundice, leukocytopenia, and eosinophilia were observed beginning on day 25.

Laboratory findings at that time are described in Table 1. There was no evidence of autoimmune hepatitis, viral hepatitis, Epstein-Barr virus infection, or cytomegalovirus activation. Repeat blood culture at that time was negative, and cranial to abdominal non-contrast CT revealed lymphadenopathy in the cervical, mediastinal, and inguinal regions in the absence of malignancy. In addition, reactivation of HHV-6 was observed. Based on these findings (rash, fever >38.5° C, liver abnormalities, leukocyte abnormalities with eosinophilia, lymphadenopathy, and HHV-6 reactivation), we suspected atypical DIHS based on criteria from the Japanese Research Committee on Severe Cutaneous Adverse Reactions (JSCAR) (2).

Because there were no new drugs administered other than LEV after admission, LEV was deemed the culprit medication and was accordingly discontinued. Oral prednisolone was commenced at 60 mg/day (≒1 mg/kg/day) along with subcutaneous filgrastim injection at 75 μg/day.

Despite the immediate resolution of the fever and gradual improvement of leukocytopenia and rash, his liver dysfunction and severe jaundice progressed in severity. The overall condition of the patient worsened rapidly, and he subsequently became comatose. The patient's family did not consent to the administration of further aggressive treatment, so we decided to provide palliative care. HD was terminated on day 41, and the patient died on day 43. Consent for an autopsy was obtained from the patient's son, which was conducted following the events.

Upon the autopsy, each organ was noted to be icteric, and macroscopic cholestasis was observed in the cross section of

Table 1. Laboratory Data.

Blood count			
WBC (/μL)	1,310	Cl (mEq/L)	97
Neut (/μL)	118	Ca (mg/dL)	8.1
Eos (/μL)	970	P (mg/dL)	2.1
RBC ($\times10^4$/μL)	235	NH^3 (μg/dL)	57
Hb (g/dL)	7.3	CRP (mg/dL)	2.29
Platelets ($\times10^4$/μL)	28.1	RF	-
Coagulation test		ANA	-
PT-INR	1.14	IgG (mg/dL)	621
Biochemical & Serological test		IgA (mg/dL)	156
Total protein (g/dL)	4.7	IgM (mg/dL)	27
Albumin (g/dL)	2.3	HBs Ag	-
T-Bil (mg/dL)	9.1	HCV Ab	-
D-Bil (mg/dL)	7.3	TSH (μIU/mL)	0.62
ALP (IU/L)	818	FT3 (pg/mL)	<1.5
AST (IU/L)	78	FT4 (ng/dL)	0.75
ALT (IU/L)	59	Ferritin (ng/mL)	786.7
LDH (IU/L)	274	EBV-VCA-IgG	160
γ-GTP (IU/L)	395	EBV-VCA-IgM	<10
ChE (IU/L)	117	EBV-EBNA	40
BUN (mg/dL)	65.5	CMV antigenemia assay	-
Cr (mg/dL)	13.8	anti-mitochondria M2 Ab	-
Na (mEq/L)	135	HHV-6 DNA (copy/mL)	220
K (mEq/L)	4.1		

WBC: white blood cell, Neut: neutrophils, Eos: eosinophils, RBC: red blood cell, Hb: hemoglobin, PT-INR: prothrombin time international normalized ratio, T-Bil: total bilirubin, D-Bil: direct bilirubin, ALP: alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, GTP: glutamyl transpeptidase, ChE: cholinesterase, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, RF: rheumatoid factor, ANA: antinuclear antibody, Ig: immunoglobulin, HBsAg: hepatitis B surface antigen HCVAb: hepatitis C antibody, TSH: thyroid stimulating hormone, FT3:free triiodothyronine, FT4: free tetraiodothyronine, EBV: Epstein-Barr virus. VCA: virus capsid antigen, EBNA: EBV nuclear antigen, CMV: cytomegalovirus, HHV: human herpes virus

the liver (Fig. 2). A microscopic evaluation of the liver revealed intrahepatic cholestasis, which was compatible with drug-induced liver injury, without features of acute hepatitis or sepsis (Fig. 3a, b). There were no remarkable findings that could have led to failure of other organs. Therefore, we concluded that the patient developed had multiple organ system failure secondary to acute fulminant liver injury from atypical DIHS on a background of chronic kidney disease from hypertensive nephrosclerosis, eventually leading to mortality.

Discussion

We encountered a lethal case of atypical DIHS in a patient on LEV, despite undergoing HD. Although prednisolone was administered, the patient's condition deteriorated rapidly, resulting in death. There are almost no reports of cases similar to this one; therefore, we believe that our case provides valuable clinical information relevant to future

Figure 2. Cross section of the liver. The liver was discolored and yellowish; cholestasis was macroscopically observable as small green dots over the entire surface of the liver.

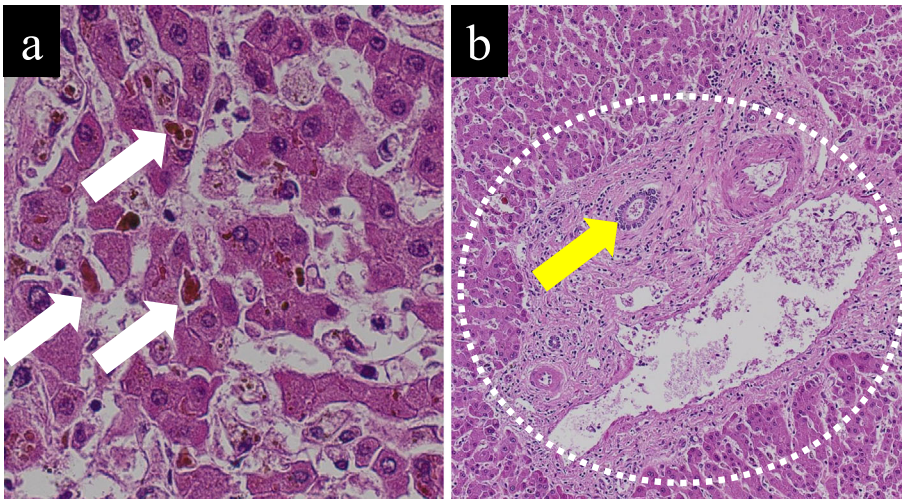

Figure 3. A microscopic evaluation of the liver. (a) The cholestatic type liver injury was observed; cholestasis in bile canaliculi were observed (arrows) [Hematoxylin and Eosin (H&E) staining ×400]. (b) Features of acute hepatitis and sepsis were absent; the lobular structure of the liver was well preserved. Inflammatory infiltration of lymphocytes around the portal triad were unremarkable (dotted line). Cholestasis was absent at the interlobular bile duct level (yellow arrow) (H&E staining ×100).

Table 2. Diagnostic Criteria for Drug Induced Hypersensitivity Syndrome (DIHS) by the Japanese Research Committee on SCAR (JSCAR).

1. Maculopapular rash developing>3 weeks after starting with a limited number of drugs
2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug
3. Fever (>38ºC)
4. Liver abnormalities (alanine aminotransferase>100 U/L)
5. Leukocyte abnormalities (at least one present)
   a. Leukocytosis (>11×10^9 L-1)
   b. Atypical lymphocytosis (>5%)
   c. Eosinophilia (>1.5×10^9 L-1)
6. Lymphadenopathy
7. Human herpesvirus 6 reactivation

The diagnosis is confirmed by the presence of all seven (typical DIHS) or of at least five of seven (atypical DIHS) criteria above.

Table 3. Diagnostic Criteria for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) by the RegiSCAR.

Score	-1	0	1	2
Fever ≥38.5 (core) or >38ºC (axillary)	N	Y		
Enlarged lymph nodes (>1 cm size, at least 2 sites)		N/U	Y	
Eosinophilia		N/U	700-1,499/μL 10-19.9% (if leukopenia)	≥1,500/μL ≥20% (if leukopenia)
Atypical lymphocytes		N/U	Y	
Skin invlovement				
-Rash extent (%BSA)		N/U	>50%	
-Rash suggesting DRESS (≥2 of facial edema, purpura, infiltration, desquamation)	N	U	Y	
-Biopsy suggesting DRESS	N	Y/U		
Organ involvement		N/U	1 organ	≥2 organs
Resolution>15 days	N	Y		
Evaluation of other potential causes			Y	
-Serology for HAV/HBV/HCV; blood culture			(None positive and	
-Antinuclear antibody; Chlamydia/Mycoplasma			at least 3 negative)	
Total score <2: Excluded, 2-3: Possible, 4-5: Probable, ≥6, Definite				

N: no, Y: yes, U: unknown, BSA: body surface area

similar cases.

DIHS and DRESS were diagnosed according to the JSCAR criteria (2) and the RegiSCAR criteria (6), respectively (Table 2, 3). Both DIHS and DRESS are in the same disease category as the most severe form of SCARs, and DIHS is a more severe form of DRESS that can only be diagnosed upon documented reactivation of HHV-6. Given that our case partially met the DRESS and DIHS criteria, along with severe clinical manifestations and HHV-6 reactivation, we diagnosed the patient with atypical DIHS.

In a retrospective observational study of 52 patients with DIHS/DRESS, the latent period from the administration of the culprit drug to the occurrence of symptoms was 16 days (interquartile range, 9-27 days). Major clinical manifestations of DIHS/DRESS were skin involvement (100%), visceral involvement (85%), a high fever (79%), eosinophilia (57.7%), and lymphadenopathy (50%) (5). Consistent with the above clinical features, the latent period from the LEV commencement to the occurrence of each symptom was 9-25 days, and rash, eosinophilia, visceral (hepatic) involvement, a high fever, and lymphadenopathy were observed in our case. In addition to these typical clinical manifestations, our patient developed fulminant liver failure, and an autopsy revealed severe cholestatic liver injury.

The patterns of liver injury in DIHS/DRESS are diverse, including cholestatic, hepatocellular, and mixed types. Sulfonamides, antiepileptic drugs, and allopurinol have been reported as major causative agents of liver injury in DIHS/DRESS (7). Regarding the severity of liver failure in DIHS/DRESS patients, a study comparing liver failure due to Stevens-Johnson syndrome/toxic epidermal necrolysis with DIHS/DRESS reported more severe and prolonged liver damage associated with cholestatic liver injury in DIHS/DRESS. This study also described the poor efficacy of systemic corticosteroids for either recovery from liver injury or diminution of mortality in DIHS/DRESS (8). Aggressive

treatment may be required in severe liver failure; however, a treatment strategy for this situation has not yet been established (9). Although few patients undergo liver transplantation, the prognosis of this syndrome is poor, with a relatively high mortality rate (approximately 50%) (10). Furthermore, a case of fulminant liver failure due to recurrence of DRESS following liver transplantation has been reported (11). Other treatments include intravenous immunoglobulin (IVIG), cyclosporine, cyclophosphamide, mycophenolate mofetil, and plasma apheresis (12, 13); however, the efficacy of these treatments has been reported only in a limited number of patients and has not been verified in a larger population. Considering these findings, fulminant liver failure induced by DRESS/DIHS appears to be a life-threatening condition without any established treatment. In our case, although the additional treatment options included IVIG, another type of immunosuppressant, or liver transplantation, above and over systemic corticosteroid administration, whether or not the patient's life could be saved was unclear.

LEV, which was the culprit drug in our case, is a major antiepileptic drug affecting presynaptic SV2A receptors. LEV is neither bound to plasma protein nor metabolized in the liver, being mainly excreted in the urine. The efficacy, tolerability, and safety of LEV are well established (14). Furthermore, there are no established treatments for the prevention of perioperative seizure in patients undergoing supratentorial craniotomy for non-traumatic pathology (15). However, the efficacy and safety of prophylactic LEV have been reported recently (16, 17). In addition to well-known culprit medications (carbamazepine, phenytoin, phenobarbital, zonisamide, lamotrigine, mexiletine, dapsone, sulfasalazine, minocycline, allopurinol, and vancomycin), LEV has been reported as an emerging antiepileptic drug that is potent in causing DIHS/DRESS (18). In a previous study, 9 of 89 patients diagnosed with DIHS/DRESS were administered LEV. In addition, there have been a few case reports of DIHS/DRESS associated with severe liver failure (19-21) or isolated severe liver failure (22). Furthermore, reports on such patients receiving HD are scarce, and to our knowledge, this is the first case report of LEV-induced DRESS/DIHS complicated by fulminant liver failure in a patient dependent on HD. Regarding LEV pharmacokinetics among patients undergoing intermittent hemodialysis, the volume distribution of LEV and the intradialytic elimination half-life are reported to be 0.48 L/kg and 31 h, respectively. HD removes nearly 85% of serum LEV (23), and the potential risk of underdosing of LEV in HD patients has been reported (24, 25). We suspect that the accumulation of LEV itself did not contribute to the development of DIHS/DRESS in our case. Although we were unable to measure the serum concentration of LEV, the increase in the serum LEV level during each HD session may have contributed to the development of the syndrome. Complex interactions between herpesvirus infection, antiviral immune reactions, and drug-specific immune responses may induce DIHD/DRESS (26). Both CD4+ and CD8+ T cells contribute to the development of DIHS/DRESS. CD4+ T cells elicit drug-specific allergic reactions, and the subsequent activation of herpesvirus-specific CD8+ T cells induces tissue damage (1). Although the pathogenesis of this syndrome remains largely unclear, LEV-induced DIHS/DRESS can occur even in patients undergoing HD who have sufficient clearance of LEV.

Although further studies are warranted to clarify the clinical features and establish an appropriate treatment strategy, we must be aware of the potential for DRESS/DIHS to develop in the context of LEV administration, even among patients on HD. This syndrome can be lethal, so we must observe patients strictly and not hesitate to provide aggressive treatment upon rapid patient deterioration.

Conclusion

Although extremely rare, physicians should be aware of the possibility of DIHS/DRESS development induced by LEV, even in patients on HD. Concomitant fulminant liver failure is a life-threatening condition, so we must monitor patients closely and provide aggressive treatment if their condition deteriorates rapidly.

Consent for the publication of this case report was obtained from the patient's son.

The authors state that they have no Conflict of Interest (COI).

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