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CASE REPORT

소라페닙 치료 간세포암 환자에서 발생한 드레스 증후군 1예

김동균, 이성우, 남화성, 전동섭, 박나래, 남영희, 이수걸, 백양현, 한상영, 이성욱
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A Case of Sorafenib-induced DRESS Syndrome in Hepatocelluar Carcinoma

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Sorafenib is currently the only targeted therapy available for advanced stage hepatocellular carcinoma (HCC). Cutaneous adverse events associated with sorafenib treatment include hand-foot skin reaction, but there has been no report of drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome. Here, we report a case of 72-year-old man with HCC and alcoholic liver cirrhosis who developed skin eruptions, fever, eosinophilia, and deteriorated hepatic and renal function under sorafenib treatment. He has since successfully recovered with conservative care. **(Korean J Gastroenterol 2016;67:337-340)**

Key Words: DRESS syndrome; Sorafenib; Hepatocellular carcinoma

INTRODUCTION

Sorafenib (Nexavar®; Bayer Korea, Seoul, Korea) is a widely-used oral tyrosine kinase inhibitor. It inhibits serine threonine kinases Raf-1, B-Raf; the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3; and platelet-derived growth factor receptor β (PDGFR-β).[1] It is currently approved by the US Food and Drug Administration for the treatment of hepatocellular carcinoma (HCC), metastatic renal cell carcinoma, and thyroid cancer.[2,3]

Sorafenib is associated with a number of adverse effects including fatigue, diarrhea, nausea, and weight loss.[4] Cutaneous manifestations (e.g., hand-foot skin reaction [HFSR], skin eruption, scalp dysesthesia, subungal splinter hemorrhages, alopecia, and body hair loss), mostly mild to moderate in severity, comprise the commonest side-effects.[1,5] There are a few case reports of Stevens-Johnson syndrome (SJS) or drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome.

Here, we present a case of a patient with DRESS syndrome related to sorafenib prescribed to treat HCC.

CASE REPORT

A 72-year-old man was admitted through the emergency room (ER) with a whole body skin rash, onset a day before his visit. He was an alcoholic liver cirrhosis patient and had received transarterial chemoembolization (TACE), radiofrequent ablation, and hepatic wedge resection for treatment of concomitant recurrent multifocal HCC. Because the HCC recurred, he was prescribed sorafenib (Nexavar®) 400 mg

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twice daily. Five days after initiation of sorafenib, he had a mild sense of throat swelling and hoarseness. At 10 days after starting treatment, he developed a whole body rash that started in the lateral part of the right thigh and spread to his whole body.

When he visited the ER, he complained of general weakness, whole body itching, headache, and feeling febrile. He had a fever of over 38°C that had not subsided for more than four days despite antipyretics. His other vital signs were stable.

The complete blood cell test revealed that the white blood cell (WBC) count was 7,730/μL (segmented neutrophil 80.5%, eosinophil 9.7%, lymphocyte 5.0%), and platelet (PLT) count was 64,000/μL (which was markedly decreased compared to the baseline level of 130,000/μL). Serum chemistry findings showed increased levels of creatinine (1.7 mg/dL), total bilirubin (TB)/direct bilirubin (DB) (2.8/1.4 mg/dL), and CRP (6.37 mg/dL), all of which had been within normal limits prior to the event. Serum AST/ ALT levels were not markedly increased (50/14 IU/L). Urinalysis was positive for protein, ketone, WBC, and urobilinogen.

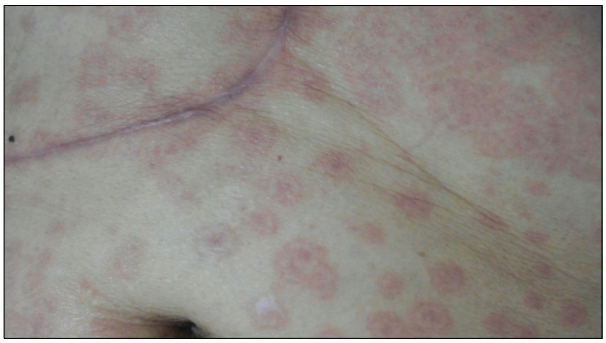

Fig. 1. Abdominal skin lesion at admission. Multiple targetoid and patch-like rash occurred in the lateral part of right thigh and spread to whole body.

We checked blood culture, ascitic fluid analysis and culture, antibodies for cytomegalovirus, Epstein-Barr virus, herpes simplex virus, Korean virus, leptospira and tsutsugamushi, and all were negative.

The skin rashes were multiple erythematous targetoid and patch-like appearance on the chest, abdomen, back, and lower extremities. Peculiar to the upper extremities was a rash with a small dot pattern (Fig. 1).

With the impression of DRESS syndrome, sorafenib was immediately discontinued. We performed conservative care with a topical steroid lotion, antihistamines, antipyretics (acetaminophen), empirical antibiotics, and intravenous fluid therapy. Upon consultation with otolaryngology and ophthalmology, there were not any other severe mucosal lesions in these systems.

The skin lesions, fever, and systemic symptoms such as itching, headache, and general weakness gradually subsided, and consequently, the patient did not need further medications for these discomforts. However, liver function decreased and eosinophilia worsened rapidly. Seven days after the admission, WBC count was 6,770/μL (segmented neutrophil 39.3%, eosinophil 27.9%, lymphocyte 20.8%), and PLT level was 16,000/μL. Serum TB/DB levels increased to 13.5/9.6 mg/dL and AST/ALT was 282/53 IU/L. PT, which had been within normal limits upon admission, was 2.03 in INR, and serum albumin was 2.7 g/dL.

We continued supportive care of his deteriorated hepatic

Table 1. Serial Laboratory Results

	BA 25	AD 1	AD 3	AD 5	AD 7	AD 8	AD 9	AD 11	AD 12	AD 14	AD 16	AD 19	DC 22
WBC (/μL)	4,810	7,730	6,800	6,380	6,650	6,770	5,550	4,950	4,070	2,660	2,840	2,900	5,010
Seg. neutrophil (%)	42.7	80.5	76.2	66.9	48.1	39.3	52.0	51.5	48.2	43.2	37.8	34.8	50.9
Eosinophil (%)	6.4	9.7	12.9	18.0	22.9	27.9	17.0	18.0	12.5	13.9	16.5	14.5	7.2
Platelet (×10^3/μL)	118	64	42	16	24	16	18	39	32	37	38	59	120
PT (INR)	1.05	1.15		1.97	1.99	2.03	1.82		1.67	1.43	1.95	1.50	1.02
Creatinine (mg/dL)	1.3	1.7	2.0	1.8	1.4	1.2	1.1	1.0	1.0		1.0	1.0	1.1
Serum albumin (g/dL)	4.1	3.1		2.8	2.7	2.7	2.8	2.8	2.8	3.1	2.8	2.9	3.6
AST (IU/L)	31	50	109	251	379	282	145	81	49	28	24	30	34
ALT (IU/L)	17	14	21	35	52	53	39	25	21	13	14	10	24
ALP (IU/L)	212	222		159			237	256	219	197	169	169	364
Total bilirubin (mg/dL)	0.9	2.8	4.3	8.6	10.9	13.5	15.6	15.0	12.1	8.9	5.7	4.3	1.6
Direct bilirubin (mg/dL)	0.3	1.4	2.5	5.9	7.8	9.6	10.8	10.4	8.7	6.5	4.5	3.6	1.4
CRP (mg/dL)		6.37		14.43			10.00		8.12		3.78	2.76	0.25

BA, before admission; AD, admission day; DC, discharge day; WBC, white blood cell; Seg., segmented.

function. On the 19th day of hospitalization, although the laboratory findings did not reach baseline, liver function and general condition noticeably improved (WBC 2,900/μL [segmented neutrophil 34.8%, eosinophil 14.5%, lymphocyte 27.6%]), PLT 59,000/μL, serum creatinine 1.0 mg/dL, serum TB/DB 4.3/3.6 mg/dL, AST/ALT 30/10 IU/L, PT (INR) 1.50, serum albumin 2.9 g/dL, CRP 2.76 mg/dL). Table 1 lists the serial laboratory findings. The patient was transferred to a convalescent hospital for further supportive care. When he visited the outpatient department, almost all laboratory findings had normalized or returned to the baseline, and he was in a good physical condition state.

DISCUSSION

Cutaneous adverse events are common with sofafenib treatment. More than 90% of patients experience a skin reaction and 60-70% have HFSR.[3,6] However, delayed cutaneous hypersensitivity reactions, such as erythema multiforme (EM), or severe cutaneous adverse reactions (SCARs), such as SJS, are very rare, although there are some recent reports.[7,8] To the best of our knowledge, the literature does not include reports of toxic epidermal necrolysis (TEN) or DRESS syndrome.

The spectrum of SCARs comprises several disease entities; acute generalized exanthematous pustulosis (AGEP), epidermal necrolysis (TEN, SJS), and DRESS.[9] These conditions are defined mainly by clinical features of visceral organ involvement, hematologic abnormalities, and alterations of vital signs. Specific biological and histological findings are also important considerations.[10]

DRESS syndrome is a distinct, severe, and idiosyncratic reaction to a drug.[11] The clinical manifestations usually appear two to eight weeks after initiation of the causative drug,[12] and include skin lesions (e.g. rash, urticaria, maculopapular eruption, edema, vesicles, pustules, purpura, target lesion, erythroderma), fever, lymphadenopathy, hematologic abnormalities, and deterioration of liver function.[13]

The regiSCAR scoring system is helpful for the diagnosis of DRESS syndrome.[14] When this system was applied to this patient, he scored 6 (fever of 38.9°C at admission, 0; no enlarged lymph nodes, 0; atypical lymphocytes, unknown, 0; eosinophilia, 2; skin involvement $>50\%$ of body surface and suggesting DRESS, 2; increased liver function tests and serum creatinine, 2; resolution ≥ 15 days, 0). Therefore, this patient corresponds to a 'definite case'.

Drugs that can cause DRESS syndrome include anticonvulsants, antidepressants, sulfonamides, antibiotics, anti-inflammatory drugs, anti-hypertensives.[15] A recent systematic review reported 44 drugs associated with 172 DRESS cases reports between January 1997 and May 2009, in PubMed and MEDLINE.[16] Besides sorafenib, the medications that our patient were taking were not in these drug categories. Moreover, he had been taking these medications for at least 20 months without any specific complications.

We did not check autoimmune markers or hepatitis viral markers during admission. Hepatitis B and C markers were checked about eight months before the admission, and were negative. We consider these to be limitations of this case report.

Early recognition and prompt discontinuation of the causative drug is most important in the treatment of DRESS syndrome.[17] Oral corticosteroids are often used in severe cases, although the effectiveness is not evident.[10] Other therapies include cyclosporin, intravenous immunoglobulin, and plasmapheresis.[18,19] In this case, we managed the patient with supportive, symptomatic care, and topical steroid lotion. At the point when we considered oral steroids as the next step in treatment, the patient's clinical manifestations improved. Therefore, we emphasize the importance of cessation of the causative medication.

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