〈Case Report〉

Severe thrombocytopenia and maculopapular erythema-induced by regorafenib in a patient with advanced gastrointestinal stromal tumor

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ABSTRACT A 28-year-old Japanese male was diagnosed with a gastrointestinal stromal tumor and multiple liver metastases at 23 years of age underwent gastrectomy and partial hepatectomy. At 27 year of age, multiple liver metastases and peritoneal dissemination were observed and the patient was switched to sunitinib. Approximately, one year later, the liver metastases worsened, and the patient was switched to regorafenib. Fatigue and palmar-plantar erythrodysesthesia syndrome occurred seven days after starting regorafenib, and thrombocytopenia occurred nine days later. Eleven days later, small erythema with fever and erythematous papules appeared throughout the body; therefore regorafenib was discontinued, and oral administration of steroids was initiated accordingly. After 17 days, platelets count decreased to 14,000/μL, prompting platelet transfusion. Maculopapular erythema was diagnosed based on the skin findings and histopathological examination. Oral and topical steroids were initiated and the maculopapular eruption gradually improved. A drug hypersensitivity reaction to regorafenib was diagnosed and treatment was discontinued, after which the patient entered a clinical trial for a new drug. We encountered a case of marked thrombocytopenia and maculopapular erythema during the early stages of regorafenib treatment. Regorafenib occasionally causes serious adverse events; therefore, careful observation and prompt treatment are necessary.

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Key words：Regorafenib, Thrombocytopenia, Cutaneous adverse reactions, Maculopapular erythema, Gastrointestinal stromal tumor

INTRODUCTION

Regorafenib is a multityrosine kinase inhibitor that inhibits the activity of kinases involved in angiogenesis (VEGFR1, VEGFR2, VEGFR3, and TIE2), the tumor microenvironment (PDGFRβ, FGFR), and tumorigenesis (KIT, RET, RAF-

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1, BRAF)[1]. Regorafenib is approved for unresectable advanced or recurrent colorectal cancer, gastrointestinal stromal tumors (GISTs) and unresectable hepatocellular carcinoma that progress after chemotherapy [2-4].

Regorafenib is an effective drug; however, adverse events occur in > 90% of patients, and 10%-25% discontinue treatment due to adverse events[2, 4]. Cutaneous adverse reactions such as palmar-plantar erythrodysesthesia syndrome are common; however, fatal reactions, such as liver failure, hemorrhage, thrombosis, and gastrointestinal perforation, have also been reported[2, 3].

Herein, we report a case of advanced GIST in which regorafenib treatment was discontinued owing to severe regorafenib-induced thrombocytopenia and generalized maculopapular erythema.

CASE REPORT

A 28-year-old Japanese male who was diagnosed with GIST and multiple liver metastases at 23 years of age underwent gastrectomy and partial hepatectomy. Imatinib was administered as postoperative adjuvant chemotherapy. At 27 years of age, multiple liver metastases and peritoneal dissemination were observed and the patient was switched to sunitinib (50 mg/day), which was administered orally for the first four weeks, off for two weeks, and repeated. Due to neutropenia, thrombocytopenia, malaise, and palmar-plantar erythrodysesthesia syndrome, the dose was reduced to 37.5 mg/day after the seventh course. Abdominal computed tomography revealed exacerbation of the liver metastasis, and the patient was switched to regorafenib. Fatigue and palmar-plantar erythrodysesthesia syndrome occurred seven days after starting regorafenib, and thrombocytopenia occurred nine days later (Fig. 1). Eleven days later, small erythema and erythematous papules with fever developed extensively on the face, trunk, and

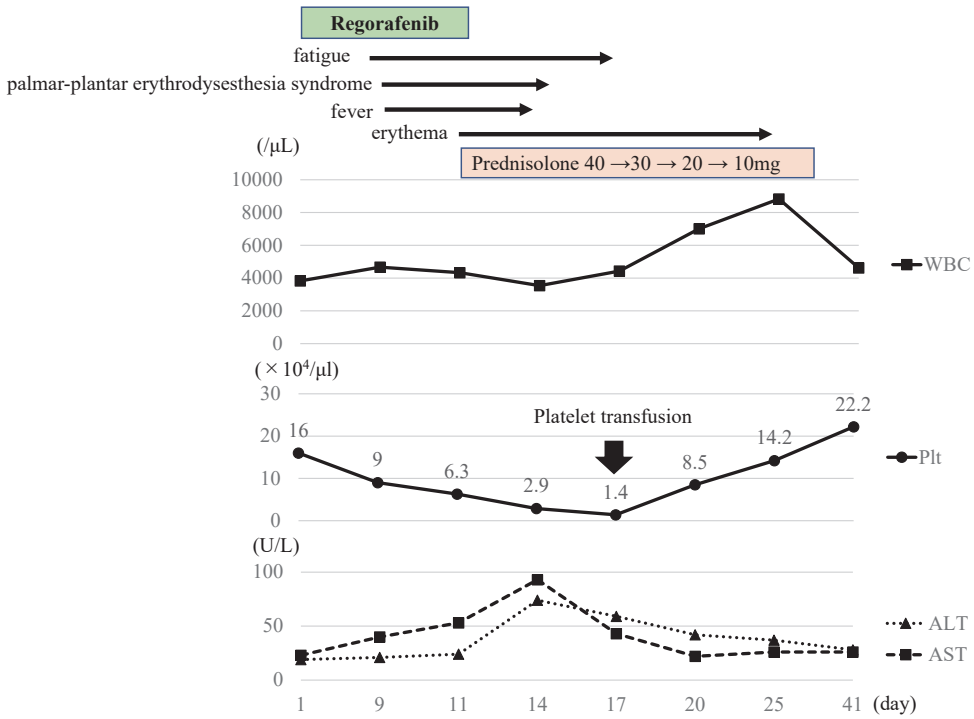

Fig. 1. Clinical symptoms and laboratory findings after initiating regorafenib.

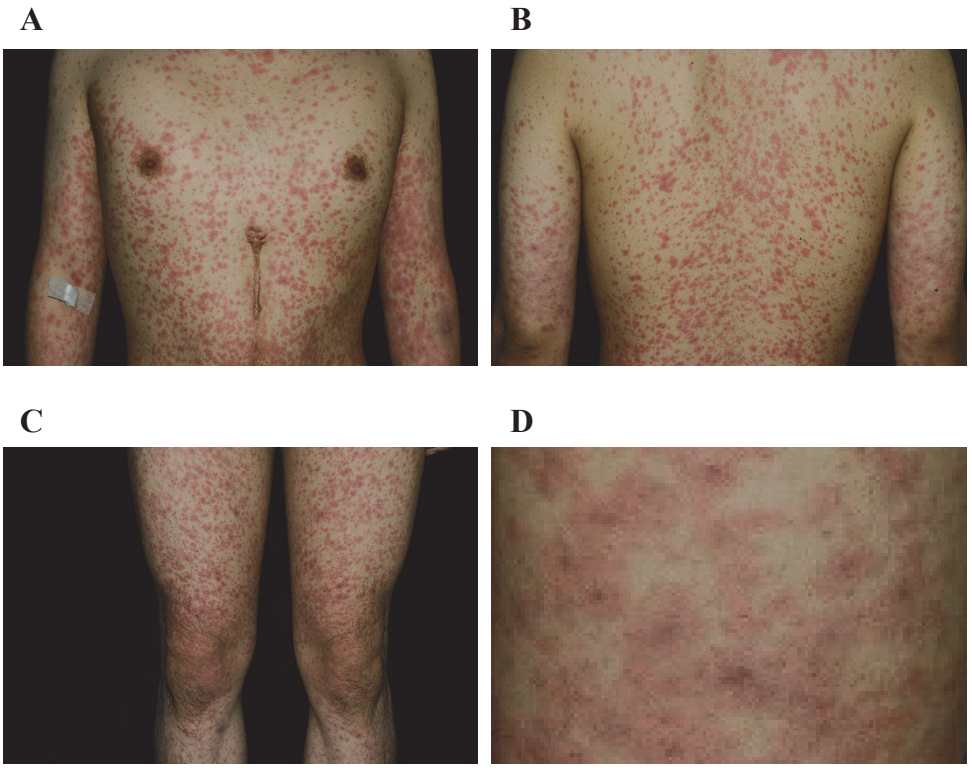

Fig. 2. Macroscopic skin findings.
Small erythema and erythematous papules are distributed symmetrically throughout the body, in a disseminated pattern. (A) Chest/abdomen, (B) back, (C) lower extremity, and (D) raised atypical target-like erythema in extremities.

extremities (Fig. 2A-C). Raised, atypical target-like erythema was observed in the extremities (Fig. 2D). Erythema was observed in the mouth and tongue, and fever and malaise were prominent in the patient. Regorafenib-induced erythema multiforme drug eruption was suspected, regorafenib was discontinued, and oral steroids were initiated. Laboratory investigations revealed no increase in white blood cell and eosinophil counts and no atypical lymphocytes. The liver dysfunction was mild. Viral testing revealed no cytomegalovirus or human herpesvirus 6 reactivations. Skin biopsy revealed perivascular lymphocytic infiltration in the superficial dermis (Fig. 3A) and vacuolar degeneration at the dermoepidermal junction (Fig. 3B). No necrosis of epidermal cells was observed. A small number of eosinophils was observed in the superficial dermis (Fig.3C). Maculopapular erythema (ME) was diagnosed based on clinical and histopathological findings, and mild nosebleed occurred after 15 days. Seventeen days later, platelet count decreased to 14,000/μL, prompting platelet transfusion. The patient experienced no complications other than mild epistaxis. Erythema gradually improved and it was relieved after 14 days. The steroids were tapered and discontinued. The patient was clinically diagnosed with regorafenib-induced thrombocytopenia and hypersensitivity. After discontinuing treatment, he entered a new drug clinical trial and has since participated in several clinical trials.

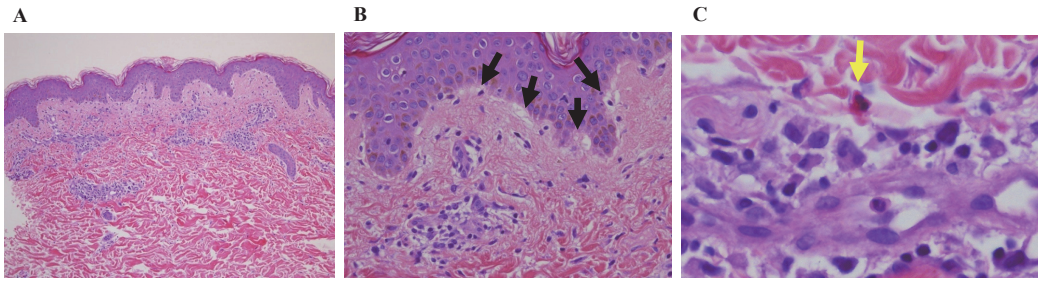

Fig. 3. Skin biopsy findings.

(A) Perivascular lymphocyte infiltration is observed in the superficial dermal layer. (B) Vacuolar degeneration (black arrows) is observed in the dermoepidermal junction, and no necrosis of the epidermal cells is observed. (C) A small number of eosinophils (yellow arrow) are observed in the superficial dermis.

DISCUSSION

Regorafenib has been approved for unresectable advanced or recurrent colorectal cancer, GISTs, and unresectable hepatocellular carcinoma that progress after chemotherapy. Regorafenib was administered orally at a dose of 160 mg once daily, with 3 weeks of continuous on/one- week off as one cycle; this cycle was repeated accordingly. In a global phase III clinical study (GIST-Regorafenib in Progressive Disease [GRID]) involving patients with unresectable or metastatic GISTs that progressed after cancer chemotherapy, the primary endpoint of progression-free survival was the superiority of the regorafenib group over the placebo group[3].

Adverse events from regorafenib occurred in 93%-100% of patients, with the most common including fatigue, palmar-plantar erythrodysesthesia syndrome, diarrhea, decreased appetite, dysphonia, hypertension, mucositis, rash, and nausea. Serious side effects included toxic epidermal necrolysis, Stevens-Johnson syndrome (SJS), erythema multiforme (EM), liver failure, hemorrhage, thromboembolism (myocardial ischemia and myocardial infarction), hypertensive crisis, reversible posterior leukoencephalopathy, gastrointestinal perforation, and thrombocytopenia[2-4]. In our case, fatigue, palmar-plantar erythrodysesthesia syndrome, thrombocytopenia, fever (39℃), thrombocytopenia, and maculopapular erythema were observed after regorafenib treatment. The platelets counts were 90,000/μL on day 9 and 63,000/μL on day 11, and regorafenib was discontinued. Although regorafenib was discontinued, epistaxis occurred on day 15, with a platelet count of 14,000/μL on day 17, prompting platelet transfusion (Fig. 1). In the GIST GRID study, thrombocytopenia occurred in of 8/132 patients (6.1%) and it was of grade 3 in 3 patients (2.3%).

Regorafenib-induced cutaneous adverse reactions were the most frequent in patients with palmar-plantar erythrodysesthesia syndrome. In the GRID trial, palmar-plantar erythrodysesthesia syndrome was 86/132 (65.2%) and 11/12 (91.7%) patients were Japanese.

Other serious skin disorders include SJS and EM. There have been no reports of SJS or EM in the GRID trials. Our patient was initially suspected to have EM but was diagnosed with maculopapular erythema based on skin and biopsy findings. Maculopapular erythema spread throughout the body, and high fever was also observed. It gradually improved with oral steroids, and the erythema disappeared in 14 days.

A search for regorafenib-induced skin disorders such as SJS and EM, revealed six cases[5-10](Table

Table 1. Cutaneous adverse reactions of regorafenib

Reference	Age, years	Sex	Type of cancer	Dose (mg)	Diagnosis	Days from regorafenib	Site of rash	Systemic steroid	Duration (days)	Regorafenib readministration	Status
Mii Y, *et al*. 2014	47	Female	Colon	160	EM	12	Face, trunk, limb, oral mucositis	Ointment	25	None	Deceased
Mihara Y, *et al*. 2015	55	Male	Rectum	160	SJS	9	Palm, nasal mucosa, perianal mucositis	+	23	None	Deceased
Muranaka T, *et al*. 2016	62	Female	Colon	unknown	SJS	12	Entire body, eye, oral,pubic mucositis	Steroid pulse	Unknown	None	Deceased
Matsunaga M, *et al*. 2017	29	Male	Cecum	unknown	EM	14	Trunk, limb	+	Unknown	Dose reduction	Unknown
Tashiro K, *et al*. 2019	62	Female	Colon	160	EM	14	Entire body	+	14	Dose reduction +steroid	Alive
García-Gutiérrez I, *et al*. 2019	58	Female	HCC	160	ME	16	Entire body	+	1	Desensitization	Alive
Present case	28	Male	GIST	160	ME *	11	Entire body	+	14	None	Alive

EM, erythema multiforme; SJS, Stevens-Johnson syndrome; ME, maculopapular exanthema; *ME, maculopapular erythema; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma

1). There were two males and four females with an average age of 51.5 years, two with SJS, three with EM, and one with maculopapular exanthema (ME). The time from the start of regorafenib to onset was 9-16 days (mean 12.8 days), and two patients with SJS and one with EM experienced mucosal eruption. Treatment included topical steroids in one case and systemic steroids in other cases. The time till eruption disappearance was 14-25 days (mean 15.8 days). The dose was reduced and re-administered in two cases of EM, and desensitization therapy was performed in one case of ME. In particular, hyposensitization therapy, in collaboration with an allergist, is considered effective[10]. In our case, re-administration of regorafenib at a reduced dose was considered; however, on account of severe thrombocytopenia and drug-related eruptions, the patient wished to participate in a clinical trial of a new drug.

Recently, associations between trough levels of regorafenib and its metabolites and adverse events have been reported. In the CORRECT trial for colorectal cancer, it was reported that adverse events such as palmar-plantar erythrodysesthesia syndrome, hypertension, and fatigue were more frequent among Japanese participants than among other nationals[11]. Regorafenib was dose-modified in 75% of patients due to adverse events. Regorafenib is converted to the active metabolites, N-oxide (M2) and N-oxide/N-desmethyl (M5). In the monitoring of regorafenib and its metabolites, the area under the curve (AUC; 0 -24 h) for regorafenib and metabolic enzymes (M2, M5) was measured, and significant differences were observed between Japanese and non-Japanese patients[11]. The maximum differences in the values of regorafenib, M2, and M5 were 6.9-, 14.3-, and 76.8-fold, respectively. Therefore, attention should be devoted to individual differences in AUC for regorafenib, M2, and M5. Regarding the relationship between blood concentration, therapeutic efficacy, and adverse events, it has been reported that in patients with low trough concentrations of regorafenib, efficacy is low, whereas patients with high trough concentrations of M5 exhibit strong skin toxicity[12]. Other studies have also reported associations between regorafenib concentrations and increased total bilirubin and thrombocytopenia[13] and between trough levels of M5 and hypertension and severe skin eruptions[14]. Although there are studies on genetic

polymorphisms of regorafenib metabolic enzymes, transporters and adverse events, no clear correlation has been observed[13, 14]. This patient also had severe thrombocytopenia and skin disorders from the early stages of treatment, and it is possible that the blood level of regorafenib was high. These studies suggest that hypertension, thrombocytopenia, severe skin eruptions, and blood trough measurements are indicators of regorafenib control.

Regorafenib is a third-line treatment for GIST, and there is no other effective treatment if it has to be continued due to adverse events. In the absence of therapeutic agents, regorafenib desensitization or reduced-dose re-dosing are treatment options. Although regorafenib is an effective drug, it may cause serious adverse effects. Regular outpatient visits and prompt responses to adverse events are important.

CONFLICT OF INTEREST STATEMENT

No author of this manuscript has any conflicts of interest to be disclosed.

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