

## Unseiin, a Kampo medicine, Reduces the Severity and Manifestations of Skin Toxicities Induced by Cetuximab: A Case Report

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### ABSTRACT

Cetuximab is an effective drug used to treat patients with recurrent or metastatic head and neck squamous cell carcinoma. Skin toxicities such as paronychia and skin exsiccation are common adverse events caused by cetuximab. Skin toxicities may cause significant physical and psychosocial discomfort. The goal of managing skin toxicities is to minimize the detrimental effects on quality of life and continue the treatment. In one patient, skin toxicities became severe, up to grade 2, during treatment. The pain induced by paronychia and skin exsiccation made daily life difficult. Ten days after starting Unseiin, symptoms and finger findings resolved significantly. The patient could resume daily activities. No adverse effects induced by Unseiin were observed during treatment. Unseiin was effective on paronychia and skin exsiccation in this case and may contribute to successful treatment of skin toxicities induced by cetuximab.

**Key words** cetuximab; epidermal growth factor receptor inhibitor; Kampo medicine; paronychia skin toxicities

Cetuximab (Cmab) is an effective drug for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).<sup>1, 2</sup> Skin toxicities such as paronychia and skin exsiccation are adverse events that are more commonly associated with Cmab than anti-cancer agents such as platinum-based drugs, taxanes, and fluoropyrimidine-based formulations which have been used in patients with HNSCC.<sup>3–5</sup> Skin toxicities are seen in approximately 80% of patients treated with Cmab.<sup>6–8</sup> However, paronychia and skin fissures often cause severe, intolerable pain in the fingers and toes, although

they are rarely life-threatening.<sup>9–11</sup> These adverse events make it impossible to perform daily life activities such as grasping something and walking. When these adverse events are severe, quality of life (QOL) is impaired because of pain and discomfort.<sup>12</sup> This leads to loss of motivation and treatment compliance. Unless properly managed, they can result in dose reduction and discontinuation of treatment, which occurs in approximately 15–25% of patients.<sup>13, 14</sup> Cmab should be continued if it has a confirmed therapeutic effect. It is reported that the management such as topical corticosteroids or oral tetracyclines have been used for the treatment of skin toxicities.<sup>15</sup> However, definitive management for skin toxicities induced by Cmab has not been established yet. Therefore, effective management of these skin toxicities is required to maximize treatment efficacy and maintain QOL.

### PATIENT REPORT

The patient was a 64-year-old man. He had previously received treatment for hypopharyngeal HNSCC (stage cT1N2bM0) consisting of cisplatin-based concomitant chemoradiotherapy and bilateral neck dissection. Lymph node metastasis was found in the left neck 37 months after these treatments. Intravenous Cmab and carboplatin once weekly were planned as maintenance chemotherapy. The patient's past medical history included heart failure and coronary atherosclerosis.

Initial carboplatin dosage based on the Calvert method was only approximately 300 mg. The initial dosage of Cmab was 400 mg/m<sup>2</sup>. The Cmab dosage after initial administration was 250 mg/m<sup>2</sup> once a week. His other medications included minocycline 100 mg/day and a moisturizer to reduce the severity of skin toxicity at the same time as the start of initial dosage of Cmab (day 1). A grade 1 acneiform rash was found 5 days after the initial Cmab dose. Cmab-induced skin toxicity was evaluated and graded using the Common Toxicity Criteria for Adverse Events version 4.0 by the same medical oncologist throughout treatment. Table 1 shows that skin toxicity included rash acneiform, skin pain, and subcutaneous tissue disorders, that is, others, specifically paronychia and skin fissures.

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Abbreviations: AD, atopic dermatitis; ADL, activities of daily livings; Cmab, cetuximab; EGFR, epidermal growth factor receptor inhibitor; HNSCC, head and neck squamous cell carcinoma; QOL, quality of life

**Table 1. Grading skin toxicities associated with EGFR inhibitors according to NCI-CTC AE version 4.0**

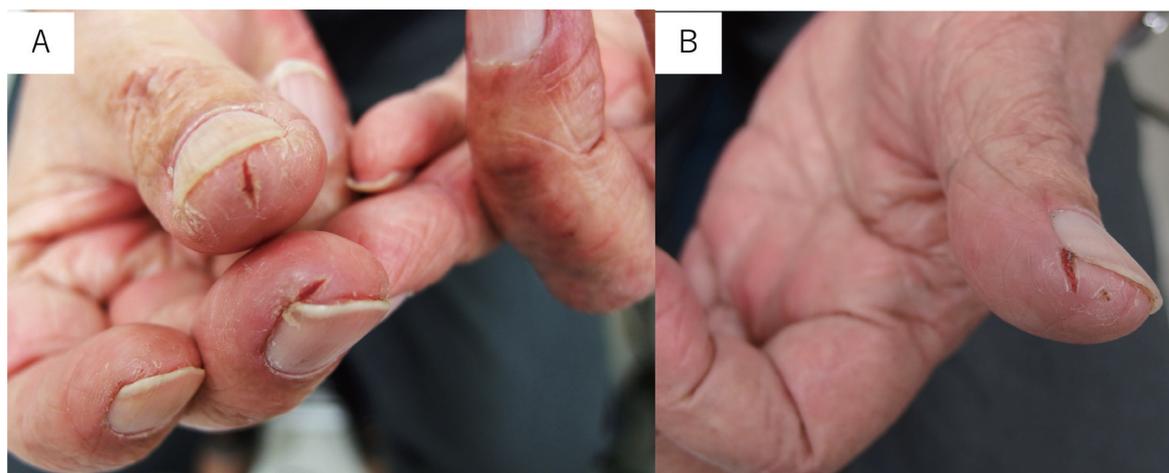
Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash acneiform	Papules and/or pustules covering <10% BSA which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	death
Skin pain	Mild pain	Moderate pain; limiting instrumental ADLs	Severe pain; limiting self-care ADLs	–	–
Skin and subcutaneous tissue disorders, and others specifically paronychia and skin fissures	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADLs	Life-threatening consequences; urgent intervention indicated	Death

BSA, body surface area.

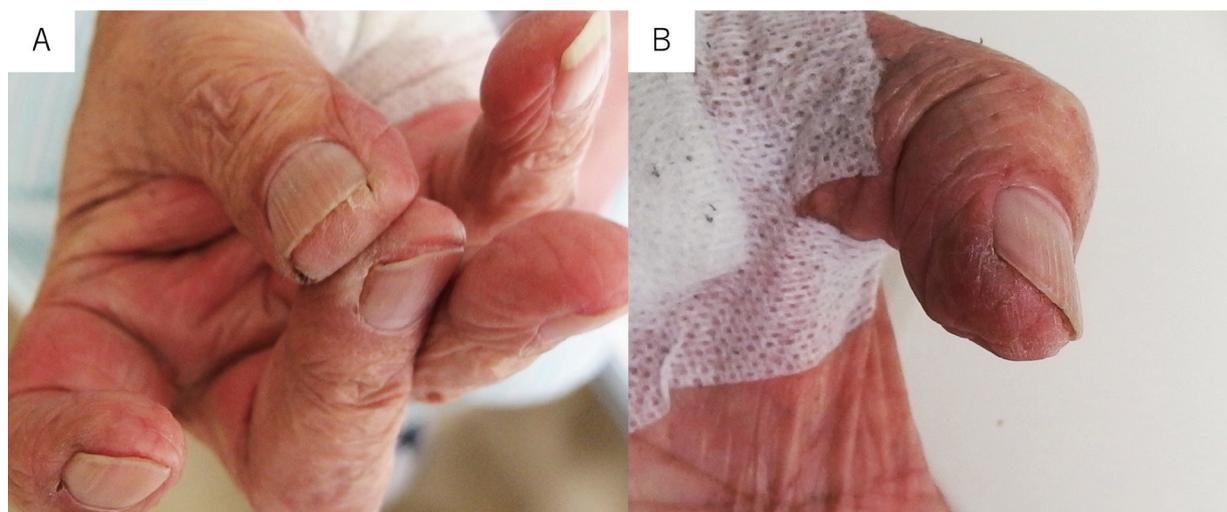
A steroid was started for topical use to manage skin toxicity since acneiform rash was found (day 5). Paronychia and skin fissures caused by skin exsiccation on several fingers were found one day after the second Cmab dose (day 9). These skin toxicities became severe, up to grade 2, before the third Cmab dose (Fig. 1). Subsequently, finger pain progressed to grade 3, which made it difficult to hold chopsticks and pencils as part of daily life activities. In addition to the initial management for skin toxicities, a Japanese traditional medicine (Kampo) called Unseiin was prescribed at 2.5 g three times daily when the third Cmab dose was started (day 22). At 10 days after starting Unseiin, symptoms and findings in the fingers resolved significantly (Fig. 2). The patient could resume daily activities. Cmab was continued with no exacerbation of these skin toxicities for the third to fifth doses. Two months later, CT showed progression of lymph node metastasis and chemotherapy was discontinued. No adverse effects associated with Unseiin were observed during treatment. The clinical course is shown in Fig. 3.

## DISCUSSION

It has been reported that more than 80% of patients who receive Cmab experience skin toxicity; approximately 25% of patients require treatment interruption or discontinuation.<sup>6–8, 13, 14</sup> The skin toxicities induced by Cmab usually lessen within 1 month after discontinuation.<sup>15, 16</sup> However, occurrence of more severe Cmab-induced skin toxicity is correlated with better treatment response and longer survival in several studies across multiple malignancies.<sup>12, 17, 18</sup> Cmab therapy should be continued if it has a therapeutic effect. Therefore, it is important to manage skin toxicities such as paronychia and skin fissures because treatment interruption and discontinuation due to the severity of skin toxicity should be avoided in order to achieve maximum benefit. In our case, the paronychia and skin fissures had to be improved because of significant pain, functional limitation, and impairment in daily living. Topical corticosteroid and anti-inflammatory dose tetracycline to decrease periungual inflammation and antimicrobial to prevent superinfection are recommended for paronychia.<sup>19–21</sup> Skin fissures and cracks often occur in the fingertips due to significant xerosis.<sup>15</sup> Liquid glues like cyanoacrylate preparations can be used to seal the cracks and



**Fig. 1.** Before treatment with Unseiin. Paronychia and skin fissures caused by skin exsiccation. **A:** Right fingers. **B:** Left fingers.



**Fig. 2.** Ten days after treatment with Unseiin. Significant improvement of skin exsiccation. **A:** Right fingers. **B:** Left fingers.

keep them from worsening.<sup>22–25</sup> Hydrocortisone with moisturizer and prophylactic minocycline 100 mg daily is possible as an effective agent in improving acneiform rash.<sup>15</sup> However, there have been no clear effectiveness patterns for these skin toxicities.<sup>12, 15, 26</sup> In our case, these treatments were less effective. Thus, more effective agents had to be taken into consideration to reduce the discomfort of skin toxicities.

This is the first report showing that Unseiin is effective for skin toxicities induced by Cmab. In our patient, skin toxicity was progressing due to the continuation of Cmab. Unseiin was effective for paronychia and skin fissures; these symptoms of skin toxicities lessened without treatment interruption. Unseiin is used to treat pruritic cutaneous diseases such as eczema and skin eruptions.<sup>27</sup> Four herbal compounds including

Unseiin are effective for inflammatory skin disease such as atopic dermatitis (AD) that involve a skin barrier defect.<sup>28</sup> These four herbal compounds are *Coptis Chinensis*, *Phellodendri Cortex*, *Scutellariae Radix*, *Gardeniae Fructus* which can correct the Th1/Th2 cells balance skewed to Th2 cells.<sup>28</sup>

Cmab inhibits the expression of epidermal growth factor receptor (EGFR) in the skin.<sup>9</sup> Inhibition of EGFR-mediated signaling pathways reduces keratinocyte proliferation by inducing growth arrest and apoptosis, decreasing cell migration, and increasing cell attachment and differentiation.<sup>9, 29</sup> These effects lead to defective barrier function of the skin. Chronic impairment of the skin barrier in conditions like AD leads to direct exposure to antigens and upregulation of Th2 activity, thereby increasing cytokine production.<sup>30</sup>

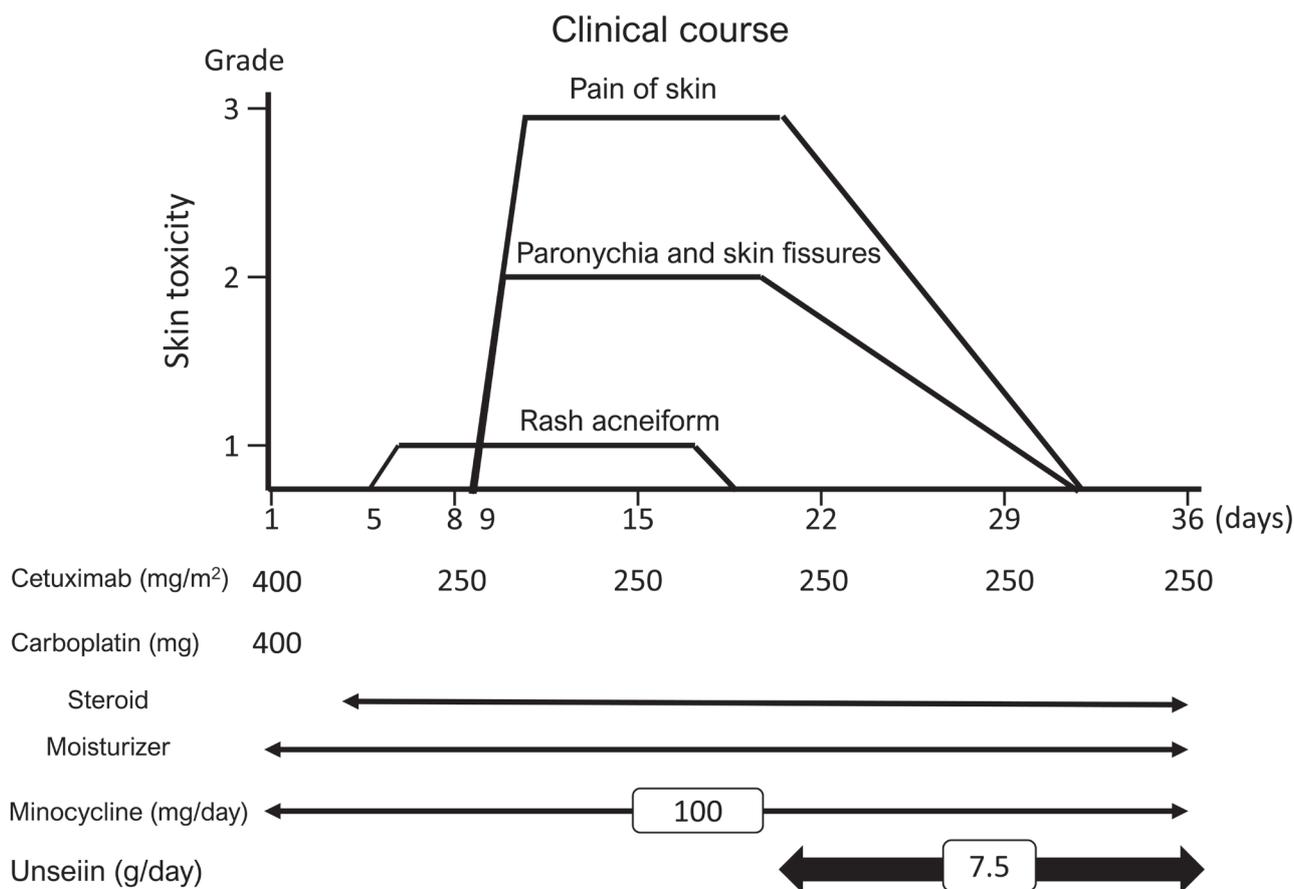


Fig. 3. Clinical course. Cmab could be continued without interruption.

This causes further progression of the skin disorder. Unseiin including four herbal compounds suppresses hypersensitivity reactions associated with Th2 cells. It seems to downregulate Th2 activity and prevent severe dermatitis.

Skin barrier defects cause secondary bacterial infections, which can worsen the symptoms of skin inflammation. Unseiin is composed of eight herbal compounds: *Coptis Chinensis*, *Phellodendri Cortex*, *Scutellariae Radix*, *Gardeniae Fructus*, *Angelicae Radix*, *Cnidii Rhizoma*, *Paeoniae Radix*, and *Rehmanniae Radix*. Several herbal substances are associated with mechanisms that reduce the severity of inflammation and pain. It has been reported that *Coptis Chinensis* and *Angelicae Radix* have antibacterial activities<sup>31</sup> and *Coptis Chinensis* and *Phellodendri Cortex* have anti-inflammatory activity and suppress the production of prostaglandin E2, which induces pain.<sup>32-37</sup> We speculate that these pharmacological actions are effective for reducing symptoms and the severity of skin toxicities caused by Cmab. In this case, chemotherapy was completed because of reduced skin toxicity after

Unseiin was started. Therefore, Unseiin may contribute to successful treatment of skin toxicities induced by Cmab. One limitation is shown in a case report of a patient with head and neck cancer where there is a lack of evidence-based clinical guidelines for management. More data are needed to confirm the positive relationship between skin toxicity and clinical response of Unseiin.

In conclusion, Unseiin was effective for paronychia and skin exsiccation. Further studies are also required to fully understand the biological activity of Unseiin against skin toxicities.

*Consent for publication:* Informed consent was obtained from the patient regarding the publication of the details of this case and associated images.

*The authors declare no conflict of interest.*

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