Panitumumab-Induced Paronychia: A Case Report and a Brief Review of the Literature

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Established Facts

- Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds to the epidermal growth factor receptor.
- Panitumumab is approved for the treatment of refractory metastatic colorectal cancer.

Novel Insights

- Cutaneous reactions, especially nail toxicities, are common adverse effects of epidermal growth factor receptor inhibitors.
- Paronychia is a nail-related adverse effect of panitumumab.

Keywords

Panitumumab · Metastatic colon cancer · Adverse reaction · Nail · Paronychia

Abstract

Panitumumab is a recombinant, fully humanized IgG2 monoclonal antibody targeting the epidermal growth factor receptor (EGFR). Panitumumab is indicated for patients with metastatic colorectal cancer with progressive refractory disease. Targeted therapies are well known to be well tolerated; however, they may induce toxicities that are distinct from those of classical chemotherapeutic agents. For instance, EGFR inhibitors (EGFRIs) are associated with some specific dermatological adverse effects, one of which is nail toxicity. Since panitumumab is fully humanized, unlike most of the other EGFRIs, it has been reported to have reduced incidence

of adverse reactions. Nail-related adverse effects are frequently observed with EGFRIs. A literature search has yielded a list of reviews describing panitumumab-induced nail toxicity. However, as far as we know, there is no case report detailing this adverse effect of panitumumab. Here, we present a case of panitumumab-induced paronychia in a 60-year-old woman with metastatic colon cancer. With this case report, we would like to review the literature and discuss the possible underlying mechanisms of this condition.

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Introduction

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). Panitumumab is approved for

Fig. 1. Erythema and swelling in halluces, accompanied by seropurulent discharge, crusting, and granulation tissue of lateral nail folds.

Fig. 2. Increased erythema and swelling in the halluces on the third month follow-up. Note the artificial staining of the nails due to povidone-iodine soak.

the treatment of refractory metastatic colorectal cancer. When compared with traditional cytotoxic chemotherapies, panitumumab is known to have less side effect profile but better efficacy, since it directly targets cancer cells without affecting normal human cells. On the other hand, molecular targeted therapies have unique dermatological adverse reactions [1, 2]. Nail toxicity is one of the distinctive dermatological adverse effects of targeted therapies, in particular EGFR inhibitors (EGFRIs) [3–9]. Up to now, several case reports have been published about the nail-related adverse reactions of EGFRIs [4, 10–13]. However, a thorough literature search did not reveal any case report illustrating features of nail toxicity of panitumumab, although it has been described extensively in licensing trials and reviews. Here, we present a case of panitumumab-induced paronychia in a 60-year-old woman with metastatic colon cancer. The aim of this case report was to review the literature by highlighting the features of the condition.

Case Report

A 60-year-old woman visited our outpatient clinic with a 4-month history of swelling and redness in her big toes. Her medical history revealed that she was diagnosed with metastatic colon cancer 1 year previously, for which she was receiving panitumumab plus FOLFOX (folinic acid/5-fluorouracil/oxaliplatin) treatment. After the sixth cycle of the therapy, the patient noticed swelling and redness in her big toes, which did not respond to standard paronychia treatment. A dermatological examination demonstrated erythematous and swollen halluces also hemorrhagic crusts on both lateral nail folds, accompanied by a seropurulent discharge on the left side (Fig. 1). Laboratory tests, which included complete blood and differential counts, erythrocyte sedimentation rate, and

C-reactive protein levels, were normal. A wound culture was performed, which did not reveal any pathogens. Since chemotherapeutics are well known with their cutaneous toxicity, we presumed the culprit to be a chemotherapeutic agent as precipitating factor for chronic paronychia. Among the chemotherapeutic drugs, which she was receiving, panitumumab was the most likely causative agent. Based on the history and clinical and laboratory findings, a diagnosis of panitumumab-induced paronychia was established. The patient was prescribed povidone-iodine soak and topical antibacterial cream. However, she had not attended to regular follow-up until she turned up 3 months after the first consultation. On the second visit of the patient, we observed increased erythema and swelling, although seropurulent discharge and hemorrhagic crusts were absent (Fig. 2). She confirmed receiving several courses of oral antibiotics, mainly amoxicillin and clavulanic acid, which only alleviated the discharge. She also informed that her oncologist decided to terminate the panitumumab treatment because of its nail toxicity. The patient was prescribed only topical corticosteroid cream. But, after then, we did not receive any information about the patient.

Discussion

EGFR, which is a member of receptor tyrosine kinase family, mediates a broad spectrum of cellular activities. EGFR plays a central role in cell proliferation, differentiation, apoptosis, and survival, which is the reason why EGFR is strongly associated with development and progression of a myriad of malignancies. It has been shown that EGFR is frequently amplified and/or overexpressed in cancer and increasingly becoming an important therapeutic target in oncology. Currently, EGFRIs are widely used to treat certain types of malignancies, including colorectal, breast, lung, head, and neck cancer. On the other hand, EGFR is physiologically expressed through-

out the whole epithelial tissues. Hence, most important adverse reactions of EGFRIs have been regarded as the cutaneous complications, which are linked with skin, mucous membranes, hair, and nails [3, 5–9, 14].

Nail toxicity is a peculiar cutaneous adverse reaction of EGFRIs. Although the exact incidence is not known, it has been suggested that the incidence of all-grade nail toxicity is 17.2% in patients receiving EGFRIs. Typical nail-related adverse reactions of EGFRIs include paronychia, pyogenic granuloma-like lesions, onycholysis, brittle nails, and pigmentary changes. Nail toxicity may affect any structure of the nail unit. If the nail bed is affected, the resultant finding is onycholysis, while if the matrix is affected, the outcome is brittle nails or nail dyspigmentation. On the other hand, the most common findings of nail toxicity have been reported to be paronychia and pyogenic granuloma-like lesions. Paronychia mostly affects thumbs or halluces and gradually develops within weeks or months after the initiation of the treatment. First signs are erythema, edema, and tenderness, which generally start from the lateral nail folds. This periungual paronychia inflammation slowly progresses into periungual granulation tissue, which mimics ingrown nails [3, 5–9, 11].

The exact mechanism of EGFRi-induced paronychia has not been fully elucidated yet. One theory suggests that periungual skin and nail plate fragility is the triggering factor for the initiation of pathologic inflammatory response in the development of EGFRi-induced paronychia. EGFR physiologically maintains normal skin functions, promoting keratinocyte survival, terminal differentiation of keratinocytes, and suppressing basal keratinocyte differentiation. Thus, inhibition of EGFR activity causes thinning of the stratum corneum, decreased keratinocyte proliferation, and increased apoptosis of epidermal keratinocytes, which means increased desquamation. It is well known that with the accumulation of scales in the nail folds, desquamation may act as a foreign body in the lateral nail groove, leading to inflammation and formation of granulation tissue [8, 11]. One of the noteworthy features of EGFRi-induced paronychia is that the underlying mechanism is inflammatory in nature rather than infectious. Although infection may develop in nonhealing lesions subsequently, infection is not the main culprit in EGFRi-induced paronychia [5, 8, 11].

Up to now, nail toxicity of panitumumab has been reported several times [3–9, 15]. In one of the earliest phase 3 trials of panitumumab in chemotherapy-refractory metastatic colorectal cancer, skin-related toxicities reported to occur in 90% of the patients. Among them, the

incidence of any grade paronychia was 24% and the incidence of grade 3 paronychia was 1% [16]. Nail toxicity of panitumumab was reported to be 30% in a multicenter, phase 2 trial on 300 metastatic colorectal cancer patients [17]. Another phase 3 trial on panitumumab demonstrated that paronychia was one of the most common skin-related toxicities of the drug. Accordingly, the overall incidence of all-grade nail toxicity was 28%, and the incidence of grade 3 nail toxicity was 2% [18]. In 2010, a phase 2, open-label, randomized trial was carried out to evaluate skin toxicities of panitumumab. The study was designed to examine differences between preemptive and reactive skin treatment for specific skin toxicities of the drug. Preemptive treatment covered employment of moisturizers, topical corticosteroid, and the antibacterial doxycycline. The overall incidence of specific skin toxicities of panitumumab was found to be decreased in the preemptive group. Any grade paronychia was observed in 17% of the preemptive group and 36% of the reactive skin treatment group [19].

One of the limitations of this case report was the difficulty in accessing detailed patient history. The patient was reluctant to attend appointments. She received several courses of oral antibiotics and chemotherapeutics. Oral antibiotics, which were mainly amoxicillin and clavulanic acid, were not suspected as the causative factor for chronic paronychia, since she received them after the paronychia had started. The chemotherapy regimen of the patient consisted of not only panitumumab but also 5-fluorouracil and oxaliplatin. On the other hand, a thorough literature search has demonstrated that nail toxicity is not a common adverse effect of 5-fluorouracil and oxaliplatin. Thus, although causality assessment based on Naranjo Algorithm Probability Scale [20] showed that the drug-induced effect of panitumumab in paronychia is possible (score 2), we consider panitumumab as the most likely agent to cause paronychia.

The nail toxicity of panitumumab has been described widely in licensing trials and reviews [3–9, 15–19]. In addition to these reports, we aimed to document this condition with a case report and highlight the importance of nail-related adverse effects of the chemotherapeutics. Since, although nail toxicity is generally regarded as a minor adverse event, it may necessitate discontinuation of the medication. We suggest that cutaneous adverse reactions of EGFRIs appear to be related to pharmacodynamic properties of these agents. The clinical features of EGFRi-induced nail toxicity will be better understood as further case reports are published.

Statement of Ethics

The patient has given consent to publish details and photos of this case.

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Conflict of Interest Statement

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Author Contributions

All the authors fully contributed to preparation of the manuscript.

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