ONLINE FIRST

Gefitinib-Induced Paronychia
Response to Autologous Platelet-Rich Plasma

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Background: Paronychia has been reported in as many as 10% of patients treated with gefitinib. Although conservative management and treatment with topical or systemic antibiotics are beneficial, no effective method exists for intractable cases. Platelet-rich plasma (PRP) consists of a high concentration of platelets that promote wound healing through chemotaxis, cell proliferation, angiogenesis, and tissue remodeling.

Observations: We herein report a refractory case of gefitinib-induced paronychia successfully treated with autologous PRP. A 68-year-old woman who had been diagnosed as having lung adenocarcinoma with multiple bone and brain metastases initiated gefitinib therapy at an oral dose of 250 mg/d. After 1 month, multiple paronychia with periungual granulation appeared on the nail fold of the first, second, and third toenails of both feet. Because the paronychia recurred repeatedly despite use of a topical antibiotic, topical corticosteroid, and short-term systemic antibiotic, she started PRP treatment. After 3 months, the lesion showed marked improvement with minimal pain or discharge.

Conclusion: This case highlights the therapeutic challenges of using PRP to promote tissue repair in intractable gefitinib-induced paronychia and merits further investigation.


GEFITINIB IS A NEWER CHEMOTHERAPEUTIC AGENT THAT INHIBITS TYROSINE KINASE ACTIVITY OF EPIDERMAL GROWTH FACTOR RECEPTOR, THUS PROHIBITING THE INDUCTION OF CELL PROLIFERATION, MIGRATION, AND ANGIOGENESIS.1,2 Gefitinib-induced paronychia has been reported in as many as 10% of patients receiving gefitinib therapy.3-6 Although wet dressings, cushioning of the affected areas, topical or systemic antibiotics, and pain control are beneficial, no effective treatment has been documented for intractable cases.1

We herein report a recalcitrant case of gefitinib-induced paronychia successfully treated with autologous platelet-rich plasma (PRP). Platelet-rich plasma, consists of a high concentration of platelets and growth factors and promotes wound healing by influencing chemotaxis, cell proliferation, angiogenesis, and tissue remodeling.7-9 This case highlights the therapeutic challenges of using PRP to promote tissue repair in intractable gefitinib-induced paronychia and merits further investigation.

REPORT OF A CASE

A 68-year-old woman was diagnosed as having adenocarcinoma of the lung with multiple bone and brain metastases. The cancer progressed despite the chemotherapy with gemcitabine hydrochloride and cisplatin. Four months after the first administration of chemotherapy, gefitinib therapy at an oral dose of 250 mg/d was initiated. One month later, multiple paronychia with periungual granulation appeared on the nail fold of the first, second, and third toenails of both feet (Figure 1). Short-term systemic antibiotic treatment with cefuroxime axetil for 5 days, wet dressings, and topical antibiotic therapy were started. Although the swelling, pain, and amount of discharge showed mild improvement with the oral antibiotics, the paronychia became aggravated repeatedly after the discontinuation of the antibiotic therapy. The patient received intermittent short-term oral administration of cefuroxime or cefradine for 1 year, but aggravation of the paronychia was observed once or twice a month. Doxycycline monohydrate therapy, at a dose of

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200 mg/d, was initiated for 2 months, but the result was less satisfactory than with cephalosporins. Furthermore, periungual inflammation worsened in the use of topical desoximetasone (desoxymethasone). Unsuccessful attempts to treat the patient’s gefitinib-induced paronychia led to the initiation of topical autologous PRP therapy.

The technique for obtaining PRP has been previously described by Na et al. Twenty milliliters of the patient’s venous blood was drawn in a syringe prefilled with 3mL anticoagulant solution (anticoagulant citrate dextrose solution formula A; Baxter Healthcare Corp). The blood was centrifuged at 160 g for 10 minutes. After the first spin, the bottom concentrate of red blood cells was discarded and the supernatant was centrifuged again at 400 g for another 10 minutes. Next, the resulting pellet of platelets was mixed with 3mL supernatant to produce 3 mL of PRP. To release the growth factors contained in platelets, the PRP was frozen in liquid nitrogen and thawed at room temperature. Three milliliters of PRP was distributed equally into 10 syringes and provided to the patient. Afterwards, the resulting platelet lysate was stored at −20°C and thawed at room temperature 30 minutes before administration. The patient applied 0.3 mL of PRP daily to the wound at home. The wound was occluded with an adhesive tape after PRP application.

One month after the start of the PRP treatment, the wound showed much improvement with minimal to no pain or discharge (Figure 2). The PRP treatment was continued for 3 months, while the edema and granulation tissue gradually subsided without any exacerbation (Figure 3). After 3 months of PRP treatment, gefitinib therapy was discontinued owing to the tumor’s poor response to the chemotherapeutic agent.

**COMMENT**

Autologous PRP is a portion of the plasma containing a high concentration of platelets and growth factors. Several studies have reported the effectiveness of autologous PRP in the treatment of acute wounds and non-healing chronic wounds. Because of its potential to enhance wound healing, autologous PRP is widely used for implantation and bone regeneration in dentistry, oral-maxillofacial surgery, and orthopedic surgery and for soft tissue wound healing in plastic surgery.

Gefitinib-induced paronychia involving the great toes is often the first sign, usually starting at 4 to 8 weeks after the initiation of the treatment. To prevent gefitinib-induced paronychia, friction and pressure on the nail fold.
must be minimized as much as possible. Wearing comfortable-sized shoes, cushioning appropriate areas, and applying wet dressings once the signs and symptoms of paronychia appear are recommended for relief of symptoms. Although gefitinib-induced paronychia does not involve an infectious cause, the risk for secondary infection is increased because of the defective skin barrier in the lesion, thus explaining the use of topical antibiotics.19 Topical corticosteroids have been prescribed in severe cases of periungual inflammation, but their efficacy is still unclear.5

Systemic antistreptococcal therapy can be used if secondary infection is suspected, but the response has been insignificant.19,20 In 2 cases where cultures of the periungual abscesses yielded Staphylococcus aureus, a favorable response was seen with minocycline hydrochloride use, but the paronychia persisted.5,9 Only with the discontinuation of gefitinib therapy did the paronychia improve. Furthermore, a case report has shown rapid and successful treatment of paronychia induced by cetuximab, an epidermal growth factor receptor inhibitory monoclonal antibody, with use of doxycycline monohydrate, 100 mg for 6 weeks.20 However, paronychia in this patient was refractory to doxycycline treatment, with even with a higher dose and longer treatment period.

Because paronychia can mimic the clinical presentation of an ingrown nail, surgical treatments including partial nail bed excision and total nail extraction with destruction of nail matrix have been performed with little benefit and have led to permanent nail loss.10 Large granulomatous papules have been reported to be successfully treated with electrodesiccation.5

Although most of the treatments of gefitinib-induced paronychia mentioned in this report are mainly conservative in that they focus on symptomatic relief or prevention and treatment of secondary bacterial infection, PRP directly affects wound-healing mechanisms. Platelet-rich plasma contains growth factors such as platelet-derived growth factor, transforming growth factor β1, vascular endothelial growth factor, and insulin-like growth factor 1. As a result, PRP enhances wound-healing mechanisms such as chemotaxis, cell proliferation, angiogenesis, and extra-cellular matrix deposition and remodeling.8,9 Moreover, these growth factors have been reported to enhance human mesenchymal stem cell proliferation and differentiation into various cell types, including fibroblasts, endothelial cells, adipocytes, and osteocytes.21,22

Compared with systemic antibiotic therapy, with which long-term use causes problems with resistance, topical PRP treatment can be used continuously for a long period. Therefore, PRP may be a good treatment modality for long-term and maintenance therapy in those patients taking gefitinib for months to years. In addition, autologous PRP is easy to obtain and can be prepared at a low cost. Moreover, only a slight decline in the level of growth factors was found when PRP was stored at −20°C for 10 days.23 Thus, PRP treatment can be used in an outpatient setting, and patients can apply the PRP themselves at home if it is stored in household refrigerator. Finally, because autologous PRP is derived from the patient’s own blood, it does not carry any risk of allergic reaction. Because PRP is made in liquid, an occlusive material such as an adhesive bandage was used to enhance its absorption.

We report the successful treatment of gefitinib-induced paronychia with autologous PRP. This newer chemotherapeutic agent is becoming more prevalent in its use against malignant neoplasms, and the adverse effects involving the nail often lead to discontinuation of the therapy. Therefore, dermatologists must manage gefitinib-induced paronychia properly. Autologous PRP consists of abundant growth factors that can help wound healing and restoration of tissue. Platelet-rich plasma is easy to obtain at a low cost without the risk of allergic reaction. This case highlights the therapeutic success of using autologous PRP to promote tissue repair in intractable gefitinib-induced paronychia and merits further research.

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