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Case presentation

Eruptive milia and comedones during treatment with dovitinib

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Abstract

Dovitinib (TKI258) is a multi-targeted receptor tyrosine kinase inhibitor currently under clinical trials for a wide variety of cancers. Well-known side effects include nausea, vomiting, diarrhea, and fatigue. To date, there have only been only two reported cases with skin manifestations as a side effect. We report a case of eruptive facial milia and comedones in the setting of dovitinib treatment for metastatic gastrointestinal cancer. This case is unique as the clinical presentation was more rapid in onset and showed an absence of inflammatory lesions. Although the pathogenesis for skin manifestations is presently unknown, we present this case to increase awareness of potentially under-reported cutaneous side effects.

Introduction

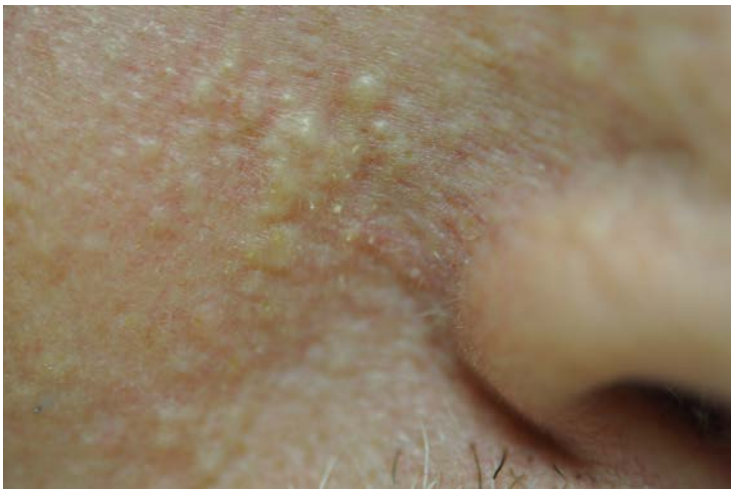
Dovitinib (TKI258) is a multitargeted receptor tyrosine kinase inhibitor. It is known to affect many of the receptors implicated in the tumor growth and angiogenesis in a wide variety of cancers. These receptors include fibroblast growth factor (FGF) receptors 1 to 3, platelet-derived growth factor (PDGF) receptor beta, and vascular endothelial growth factor (VEGF) receptors 1 to 3 [1]. The most common side effects of dovitinib are nausea, vomiting, diarrhea, and fatigue [1, 2]. To date, only two reports have discussed skin manifestations as an adverse effect of dovitinib [3, 4]. We present a case of eruptive facial comedones and milia in the setting of dovitinib use for metastatic gastrointestinal cancer.

Case synopsis

A 63-year-old man with a history of metastatic gastrointestinal cancer presented to the dermatology clinic with a two-week history of new lesions in his bilateral nasolabial folds. He described the lesions as feeling “pebbly” to the touch and noted they were increasing in size and number, but were otherwise asymptomatic. The patient was enrolled in a clinical trial of dovitinib for gastrointestinal cancer one month prior to presentation and his only other medication was fenofibrate, which was initiated one week prior to the growth of the lesions.

Physical examination revealed multiple, skin colored, 2-3mm grouped papules on the nasolabial folds (Figure 1). A 4mm punch biopsy from the left nasolabial fold showed dilated closed follicles filled with keratin (Figure 2). Unfortunately, a CT scan less

than a month later showed continued tumor growth, so the patient was removed from the clinical trial. No new papules have appeared since stopping dovitinib,and the existing lesions improved with the use of a topical retinoid.



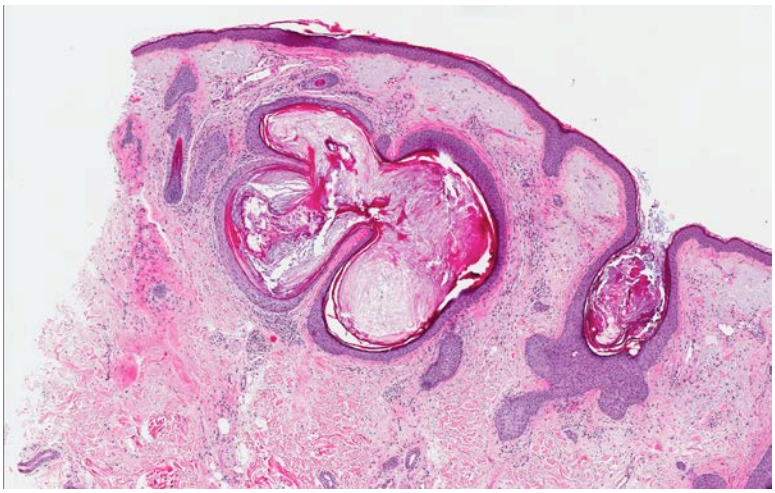


Figure 1. Right nasolabial fold with multiple closed comedones. **Figure 2.** Dilated closed follicles filled with keratin on punch biopsy from the left nasolabial fold

Discussion

Dovitinib is a receptor tyrosine kinase inhibitor currently under investigation for its use in a broad variety of cancers such as colon, breast, melanoma, myeloma, and renal cell carcinoma. It has both anti-tumor and anti-angiogenic effects through inhibition of PDGF, VEGF, and FGF receptors [1, 3]. The most commonly reported adverse effects include nausea, vomiting, diarrhea, and fatigue [1, 2].

There have been few reported adverse effects involving the skin with dovitinib use. One such case involved a patient with metastatic renal cell carcinoma who experienced a fulminant inflammatory acneiform eruption on his back and face after four months of treatment. Unfortunately, this side effect was so intolerable and recalcitrant to treatment that the dovitinib was stopped despite tumor shrinkage [4]. In another case, a man with metastatic adrenal carcinoma developed generalized hyperpigmentation and a comedonal eruption after five months of treatment. He left the clinical trial after eight months of treatment owing to tumor progression [3]. In both cases, the lesions resolved after cessation of treatment [3, 4].

A wide a range of cutaneous reactions are seen with chemotherapeutic medications. Hyperpigmentation is commonly seen with alkylating agents and antimetabolites, whereas depigmentation or hypopigmentation is more common with the kinase inhibitor imatinib. Another common cutaneous manifestation is hand-foot syndrome (HFS) characterized by a sharply delineated palmar and plantar erythema. This unique side effect is seen with 5-fluorouracil, doxorubicin, daunorubicin, and etoposide. The taxanes, vincristine, and vinblastine, elicit erythema that develops on the dorsal aspects of the hands, instead of the palmar aspect [5]. Another hand and foot reaction is seen with sorafenib and sunitib, multikinase inhibitors that block VEGF and PDGF receptors, which is similar to the mechanism of action of dovitinib. In this reaction, areas of trauma and friction on the hands and feet develop hyperkeratotic patches with blistering [6].

Acneiform eruptions have also been reported in patients treated with epidermal growth factor receptor inhibitors and are typically associated with improved patient outcomes [7]. However, these eruptions typically consist of inflammatory, erythematous, monomorphic papules and pustules, as opposed to the non-inflammatory milia and comedones seen in our patient taking dovitinib [8]. BRAF inhibitors are also known to cause a papulopustular reaction [6].

The pathogenesis of milia and comedones secondary to dovitinib is unknown. A tricyclic antidepressant, amineptine, is one of the few medications also known to cause a comedonal eruption with an absence of inflammatory lesions. The pathogenesis is also unknown, but it is hypothesized to be an accumulation of the drug within the sebaceous and eccrine sweat glands [9].

Although the patient was also taking fenofibrate at the time of the eruptive milia and comedones, fenofibrate has not been reported to cause this cutaneous eruption. The most common side effects of fenofibrate are rhinitis, abnormal liver function tests (elevated AST and ALT), and increased CPK. Cutaneous adverse effects of fenofibrate have rarely included urticaria, Stevens-Johnson Syndrome, and toxic epidermal necrolysis [10]. The timing of the facial lesions in this patient suggests a correlation with dovitinib, especially in light of the two other reported patients with similar follicular-based eruptions in the literature.

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