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Blue-grey hyperpigmentation in acne after vandetanib therapy and doxycycline use: A case report

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Abstract

Vandetanib is an oral tyrosine kinase inhibitor with cutaneous adverse effects that include the development of acne. We present a patient who underwent vandetanib therapy for stage IV medullary thyroid cancer in conjunction with the use of doxycycline for acne that developed. After vandetanib use, blue-grey pigmentation developed in the acne on his face, chest, back, and arms, which darkened after the use of doxycycline. We review the literature to report that this blue-grey hyperpigmentation was likely vandetanib-induced but may have been the result of both drugs being used in combination.

Keywords

Blue hyperpigmentation, blue discoloration, vandetanib, doxycycline, tyrosine kinase inhibitor

Introduction

Vandetanib (4-anilinoquinazoline) is an orally administered medication used for the treatment of malignant neoplasms, primarily advanced medullary thyroid cancer that cannot be surgically cured. It acts to selectively inhibit various receptor tyrosine kinases (RTKs), notably vascular endothelial growth factor receptor 2 (VEGFR2) and epidermal growth factor receptor (EGFR) which are often overexpressed in thyroid cancers. RTK inhibition reduces tumour angiogenesis, metastasis, and cellular proliferation.[1] Cutaneous adverse effects (AEs) associated with vandetanib therapy are well reported and seen in up to 46.1% of patients.[2] Among these, blue-grey hyperpigmentation has been reported in the literature.[3]

Vandetanib-induced acneiform eruption is regularly treated by dermatologists. Doxycycline is a member of the tetracycline class of antibiotics that also includes minocycline. Doxycycline prevents acne through a bacteriostatic mechanism by binding to the 30S ribosomal subunit of *Cutibacterium acnes*.[4] Cutaneous AEs of doxycycline include photosensitivity and brown discoloration of the nails, teeth, and within acne scars. Blue-grey discoloration due to doxycycline has been scarcely reported in the literature and is unlikely to result from clinical doses.[5] However, minocycline is known to cause stage I minocycline-induced pigmentation (MIP), which can appear blue-grey in colour, often affecting and scars.[6] Here, we present a patient who developed blue-grey hyperpigmentation after being administered vandetanib, which darkened after being administered oral doxycycline.

Case report

A 45-year-old male presented to a dermatology clinic with an eruption present from the waist upwards following the use of vandetanib for stage IV medullary thyroid cancer. His only other medication was hydromorphone. Clinical examination revealed aggressive papulopustular acne with a slight blue discoloration present on the head, chest, back, and arms. The patient was prescribed 100 mg oral doxycycline daily in addition to a 10% benzoyl peroxide wash. The patient reported that this eruption developed several weeks after starting vandetanib therapy and was pruritic and painful with occasional bleeding. After 3 months of treatment, a follow-up clinical examination revealed a dramatic improvement in the acne while the blue-grey hyperpigmentation persisted and darkened (Figure 1). After 6 months of treatment, the acne completely resolved on the body and began fading from

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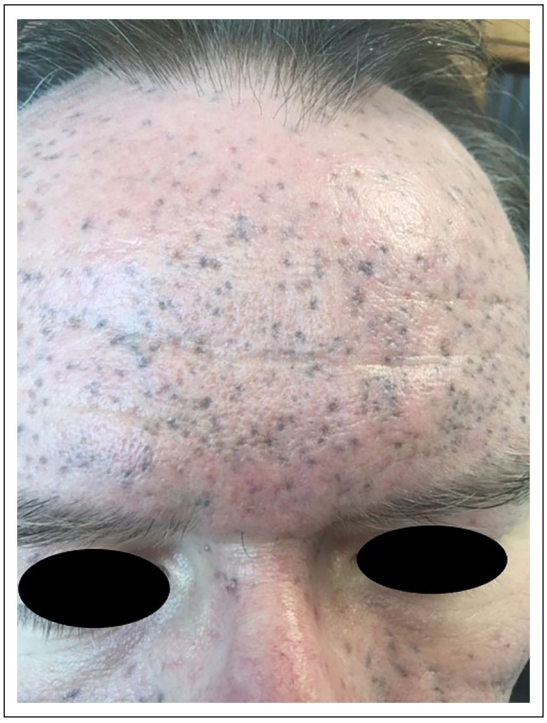

Figure 1. Multiple blue macules distributed over the forehead and cheeks corresponding to areas of previous acne in a patient on vandetanib and doxycycline.

the face. After 8 months, vandetanib and doxycycline were discontinued due to cancer progression. Blue-grey hyperpigmentation continued to fade on the face and body. No histology was obtained because it was not felt to influence patient management. Unfortunately, the patient died of his medullary thyroid cancer shortly after his last appointment.

Discussion

Blue-grey hyperpigmentation induced by vandetanib therapy has been reported within the literature. During a study conducted on 63 participants on vandetanib, Giacchero et al. found that the incidence of blue-grey hyperpigmentation was 12%. Vandetanib also caused folliculitis in 49% of participants, photosensitivity in 23%, dry skin in 13%, and paronychia in 7%.[3] Kong et al.[7] reported blue-grey hyperpigmentation appearing on the face of a 49-year-old woman and on the anterior neck of a 59-year old woman, both of whom underwent vandetanib therapy. Sibaud and Robert[8] determined that blue-grey macules appeared in upwards of 20% of patients reported in the literature who underwent vandetanib therapy. Negulescu et al.[9] reported a 42-year-old patient who underwent vandetanib therapy developing dusty blue-grey hyperpigmentation over the face and dorsal aspects of the hands and the neck.

Several mechanisms exist through which vandetanib may form blue macules on the facial skin. Vandentinib is thought to induce blue-grey hyperpigmentation through its inhibition of the autophosphorylation of the transporter ABCG2. This causes intracellular accumulation of porphyrin, leading to photosensitization and blue-grey hyperpigmentation after exposure to UV-A.[3] However, this mechanism is unlikely in our case report as it does not account for the blue discolouration exhibited in non-photoexposed areas. A direct deposit of the drug, its metabolites, a drug-melanin complex or hemosiderin in the skin is more likely. Biopsy staining of a similar case of vantentanib-induced blue-grey hyperpigmentation detected iron, suggesting the presence of hemosiderin deposits.[7] Successful resolution of blue-grey hyperpigmentation with Q-switched alexandrite laser therapy also suggests a direct deposit of vandetanib.[10]

Although the appearance of blue-grey hyperpigmentation in our case report likely resulted from vandetanib therapy, the possibility of its manifestation being due to doxycycline cannot be eliminated as it darkened after doxycycline initiation. While rare, doxycycline-induced blue-grey pigmentation has been reported in a patient on a super-pharmacologic dose due to a direct deposit of the drug in the skin and the over-activation of melanocytes.[11] Other instances of doxycycline-induced blue discoloration due to pharmacological doses have been reported in nail beds and ventral surfaces of the hands and legs. These instances were thought to arise from free radical formation after UV-A exposure and direct deposit of a doxycycline-iron/calcium complex on lesions.[5,6] Minocycline, a structurally similar tetracycline to doxycycline, is also reported to cause blue-grey discoloration (type I MIP).[6] However, type I MIP is thought to occur through local pigment deposits by macrophages, a different mechanism than seen in doxycycline-induced pigmentation.[6]

We postulate, based on the literature describing the cutaneous AEs of both vandetanib and doxycycline, that vandetanib was the likely cause of the blue-grey hyperpigmentation in our patient. Vandetanib-induced blue-grey hyperpigmentation with similar distribution patterns exhibited by our patient has been cited several times in literature, whereas doxycycline-induced pigmentation is rare within clinical doses. Giacchero et al.[3] reported that among their participants with vandetanib-induced blue-grey hyperpigmentation, only 42% were concurrently being administered doxycycline, further reaffirming our postulation. However, there exists a possibility that the two drugs interact in vivo, causing the darkening of our patients' blue-grey hyperpigmentation.

It is important that clinicians are aware of the risks of cutaneous adverse effects when administering vandetanib for the treatment of malignant neoplasms. Our patient who underwent vandetanib therapy developed blue-grey discolouration on the face, neck, and back in acne lesions that persisted after the acne resolved. This was likely a result of the direct deposit of vandetanib and its metabolites on the skin and not the doxycycline the patient was simultaneously administered. Because of the clinical worsening of blue-grey

hyperpigmentation after the addition of doxycycline and the inability to exclude an unknown mechanism of action, it would be reasonable to caution patients of adverse effects and recommend limiting sun exposure, as this may worsen pigmentation. Additional research must be conducted to determine the safety and potential adverse effects of vandetanib therapy and doxycycline taken in conjunction.

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Informed consent

The patient's family provided consent for publication of the case report and image.

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