A novel presentation of minocycline-induced nail discoloration: A case report

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Abstract. Minocycline, a tetracycline antibiotic used to treat acne and rosacea, is known to cause nail discoloration, typically as blue-gray pigmentation. However, other unique manifestations are less frequently reported. A 19-year-old male with acne developed a unique 'snow mountain nail' after one month of minocycline treatment. The patient's nails showed blue-gray pigmentation near the nail bed, along with bright white changes at the free edge and parallel white stripes on the nail bed, forming a distinctive dual-color pattern. After the discontinuation of minocycline, the treatment plan was also adjusted. After 2 months, the pigmentation was significantly reduced. After 2 years the nails had returned to normal and there were no residual pigmented spots. The 'snow mountain nail' phenomenon introduces a novel clinical presentation of minocycline-induced pigmentation. It may be proposed that minocycline forms chelates with iron, which accumulate in the nail cuticle, causing discoloration. The bright white stripes may result from changes in the blood supply or inflammation in the nail bed. This case expands the understanding of minocycline-induced nail discoloration, emphasizing the importance of early recognition and management of this side effect to minimize its cosmetic and psychological impact. The present findings offer new insights into its pathogenesis and diagnostic significance.

Introduction

Nail discoloration is an abnormal change in nail (toenail) color that can provide important clues to potential systemic and skin diseases. The causes of nail discoloration are mainly divided into internal factors and external factors, including infection, systemic disease, trauma and drug influence. White nail is the most common nail discoloration; white nail can be divided into true white nail, white spot and false white nail (1). It is caused by the change of the structure of the nail substance itself, the pathological change of the nail bed, and the superficial invasion and dissemination of fungi. Blue nail beds can be caused by cyanosis, hereditary acrotelangiectasia, antimalarial drugs, argyria and glomus tumors, and the use of systemic drugs can also cause blue nails (2).

Minocycline is a tetracycline antibiotic commonly used to treat acne and rosacea. Common side effects of minocycline associated with pigment include the following: Minocycline may affect the development of bones and teeth in children, causing teeth to turn yellow or brown. There have been numerous reports of patients taking minocycline for a period of time and their nails changed from the normal light color to gray or blue (2).

Pigmentation caused by minocycline can be divided into five types, among which the 'blue nail' phenomenon caused by minocycline is considered to be type II pigmentation (3). However, in this case, the report of minocycline-related tinea is significantly different from the traditional type II pigmentation, which is manifested as a snowy mountain of nail bed changes, i.e., the unique clinical characteristics of blue gray pigmentation and bright white nail bed changes, providing new phenotypic characteristics for minocycline-related nail bed pigment changes and contributing to further research on its pathogenesis and clinical diagnosis.

Case report

In July 2022, a 19-year-old male presented to the Department of Dermatology with facial acne vulgaris, featuring hyperplastic nasal scars, atrophic scars and persistent papular lesions. The patient took minocycline, a medication prescribed by the attending physician, twice a day at 50 mg each time, totaling 100 mg per day, and maintained this dosage for 1 month. During the 1-month treatment, the patient's nails developed a unique appearance, 'snow mountain nails' (Fig. 1), with a blue-gray pigmentation near the nail bed. There was also a distinct bright white nail change at the free end, where parallel bright white stripes were visible on the nail bed, complementing the blue-gray area to form a unique bicolor change. It is worth noting that the patient did not have abnormal

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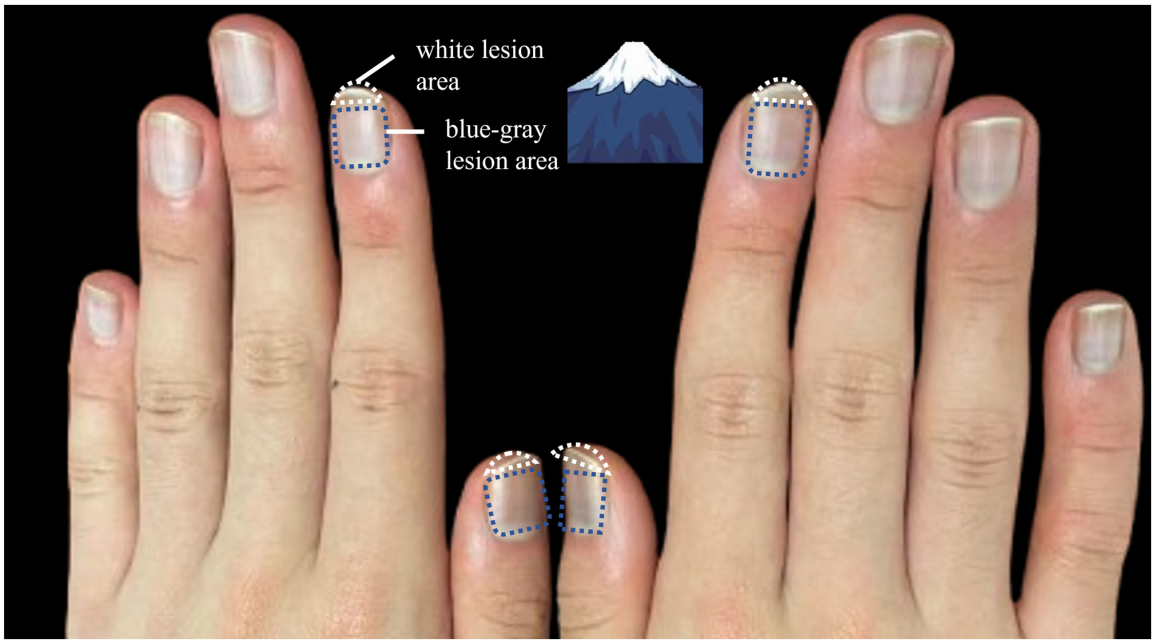

Figure 1. The patient's nail appearance on both hands. The 'snow mountain nail' is characterized by blue-gray pigmentation near the root of the nail bed, accompanied by a distinct bright white nail change at the free end. In addition, bright white stripes arranged in parallel are seen on the nail bed, which complement the blue-gray areas and form a unique dual color. The white area represents the white lesion of the nail, while the blue area corresponds to the blue-gray lesion. These areas respectively correspond to the white summit and the blue gray body of a snow mountain. It is important to note that the thumbs and index fingers indicated by the arrows in the figure are shown for demonstration purposes only. The same 'snow mountain nail' phenomenon was observed on the other fingers as well. There was no change in color on the patient's toes, which may be due to the relatively slow growth rate of the toenail.

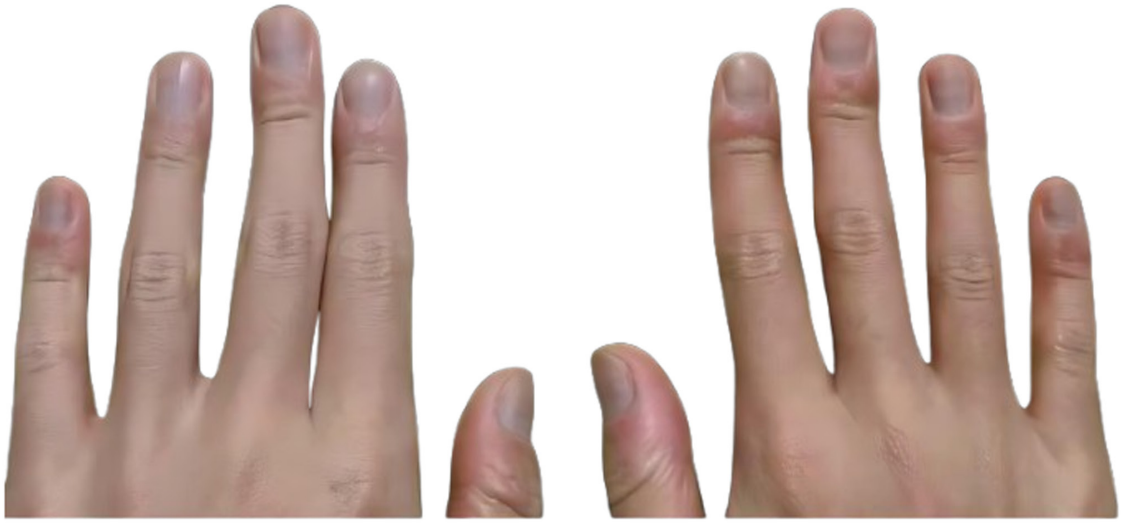

Figure 2. At 2 years post-discontinuation of the medication, the patient's nails returned to a more normal state, but there was still a slight residual pigment at the proximal end. This may be due to the slow degradation of the minocycline-iron complexes. The redness and swelling above the knuckles indicate the persistence of local inflammatory activity

pigmentation of the skin, teeth or toenails during the course of the disease. When white nails appeared at the free end of the nail, the treatment plan was adjusted. Minocycline was discontinued, and the patient was instructed by the attending physician to take isotretinoin soft capsules orally twice a day at a dose of 10 mg to treat the acne. The abnormal nail appearance did not improve until 2 months after the initial medication was stopped. Biochemical tests and complete blood count analyses conducted before and after minocycline treatment revealed an abnormal elevation in plateletcrit at 2 weeks post-administration, increasing from 0.256 to 0.303% (reference range: 0.108-0.303%). All other results were within the normal ranges. Routine blood tests were performed using the Sysmex XN-10 automatic hematology analyzer (Sysmex Corporation). Biochemistry tests were conducted with the Abbott Alinity C automatic biochemistry analyzer (Abbott). Dry biochemistry tests were carried out using the Ortho Vitros 5600 automatic biochemistry and immunoassay analyzer (QuidelOrtho Corporation). The patient was followed up every 2 weeks, where a physical examination was conducted.

Throughout the follow-up period, the dosage of isotretinoin was adjusted based on the patient's facial acne condition and nail status. At 2 months after discontinuation of the medication, the color of the nail had gradually improved: The blue-gray pigmentation range of the nail bed was obviously reduced and the color changed from dark to light. The free end of the bright white nail was gradually blurred, but certain residual color changes were still observed. At 2 years post-discontinuation of the medication, the patient's nail color improved, with the bluish-gray and white tones gradually disappearing, but the nails still did not regain their normal appearance. The patient has been consistently taking isotretinoin for acne treatment ever since. The periungual erythema and swelling of the right hand may be associated with a chronic low-grade inflammatory response triggered by the deposition of minocycline-iron chelate complexes (Fig. 2).

Discussion

Blue-gray nail pigmentation is affected by a variety of factors, such as infectious factors, including green nail syndrome caused by bacterial infection, which can be identified by direct fungal microscopy or positive culture, and lesions usually start at the nail margin and gradually expand to the entire nail (4). If *Pseudomonas aeruginosa* is detected in nail culture, green nail syndrome caused by bacterial infection can be diagnosed. Furthermore, nail discoloration also requires a differential diagnosis with other causes. For example, mechanical injury may lead to subungual bleeding (appearing bluish-black), while prolonged exposure to chemicals may directly cause nail discoloration (5).

Systemic diseases such as liver disease can cause white nails. One study found that 82% of patients with 'alcohol, necrosis and cholangitis' cirrhosis had a red or brown distal nail bed that included <20% of the total nail length, kidney failure leading to half nails, cardiovascular disease leading to pale nails, and in addition, nail bed edema in lymphedema (1). Pale nail bed in severe anemia, scar changes after whole-skin electron beam irradiation and selenium deficiency can also cause obvious leukonychia (6). Drug reactions from long-term medication use can turn nails yellow or black (7). The most common genetic factor is autosomal dominant inheritance; for example, patients with congenital leukonychia typically have milky white nails (1).

Minocycline, as a broad-spectrum antibiotic, is commonly used to treat bacterial infections, particularly those associated with acne and chlamydia. However, some side effects may occur with the use of minocycline, among which pigmentation and nail discoloration are the more common skin and appearance changes. Long-term use of minocycline can cause pigmentation of nails, skin and sclera without affecting function. Discontinuation is one of the treatments for blue nails. In one study, it was found that nail pigmentation can be resolved after discontinuation of oral minocycline and the resolution time varies from 1 month to 3 years (2). In the 2024 treatment guidelines for common acne, it is stated that oral minocycline is a commonly used medication for treating moderate to severe acne and the patient in this case does not fall into the prohibited population category (8). During the 16-week treatment period for inflammatory skin lesions associated with rosacea, the treatment success rate for the 40 mg dose of minocycline was 66%, which was significantly higher than the 11.5% in the placebo group, and it also demonstrated a significant advantage in reducing the number of inflammatory lesions (9). Compared to tetracycline, minocycline has a stronger antibacterial effect (10).

There are five types of pigmentation caused by minocycline: Type I develops blue-black discoloration in previously inflamed areas, such as acne secondary scarring; Type II skin has blue-gray pigmentation in normal areas; Type III is a rare diffuse mud-brown pigmentation, aggravated in sun-exposed areas; Type IV appears with bluish-gray spots on the scarred area of the back; and Type V is associated with hyperpigmentation and subcutaneous involvement and is considered a progression of Types I and II to subcutaneous infiltration. The 'blue nail' phenomenon caused by minocycline is considered type II pigmentation. The incidence of type II and III pigmentation increases with the cumulative dose of minocycline (3). The minocycline-associated nail pigmentation reported in the present case showed significant differences from traditional type II pigmentation. In addition to the blue-gray pigmentation of the nail bed, the presentation was also uniquely accompanied by a bright white change of the free end of the nail and the cross-distribution of bright white stripes on the nail bed, and with the blue-gray area near the nail root, it exhibited a sharp two-color contrast. This unique nail manifestation not only enriches the scope of the clinical phenotype of minocycline-associated pigmentation, but also provides new ideas and research directions for further exploration of its pathogenesis and diagnostic value.

The blue-gray pigmentation effect of minocycline is mainly related to its metabolic process *in vivo* and its interaction with tissues. It usually occurs in patients taking high doses and using it for a longer period of time. Minocycline itself can be deposited in the basal layer of the skin by chelating with iron to form a stable complex, and minocycline can also affect melanin production in the skin or interact directly with the melanin synthesis mechanism, resulting in increased local pigmentation. The chelation of minocycline with iron may accumulate within the cuticle of the nail, and due to the high protein and metal ions in the nail, the binding of minocycline with these components may cause nail discoloration. In one study, it was reported that patient who used minocycline for a long time may have blue or gray pigmentation of their skin (11). The metabolism of minocycline in the body may cause the drug to bind to metal ions in the skin, causing this type of pigmentation change. A patient who had taken minocycline for 4 years also experienced diffuse blue-gray pigmentation on the face and ears (12). This pigmentation may occur not only in the skin, but discoloration of the nails may also be observed, another one of the more common side effects of minocycline. After taking minocycline for several months, the patient developed a significant discoloration of the nails, which changed from a normal light color to gray or blue. Masuyama *et al* (13) found that after 10 weeks of minocycline use, a patient's nail bed turned grayish-blue and its thickness increased to 9 mm. This phenomenon is usually associated with the accumulation of drugs. A 66-year-old male patient had persistent blue-gray discoloration of the nails during the treatment of rosacea with minocycline for 22 years (3). This

blue nail was likely to be misdiagnosed as a change in nail bed color related to heart disease, and further cardiac-related tests were needed (3). It may take several months for the nail color to recover after stopping the drug. Long-term use of minocycline may lead to pigmentation when the cumulative dose exceeds the threshold of 100 grams (3). This pigmentation is dose-dependent and a daily dose of 100 mg for patients falls within the low-dose range, which may also be one of the reasons for the regression of 'snow mountain nail'. In addition to the blue-gray pigmentation near the nail base of the nail bed, there is also a significant bright white nail change at the free end. This comprehensive nail change provides a new clinical feature for drug-induced nail lesions, and its pathogenesis and diagnostic significance need to be further studied. The formation of white stripes on the nail plate may be due to the indirect effect of minocycline on the local blood supply or inflammation of the nail bed during the anti-inflammatory treatment of acne, which leads to a color change of the nail plate (13). The formation and deposition of iron-minocycline chelates may affect the normal function of nail bed keratinocytes, including keratin production and metabolism, making nails look pale. In addition, the long-term use of minocycline may reactively interfere with local melanin production and distribution, or it may be a rare manifestation related to individual differences or local environmental factors such as light exposure, inflammation and metabolic status. In the present case, the clinical manifestations improved markedly following discontinuation of minocycline, supporting the hypothesis that the occurrence of 'snow mountain nails' represents an adverse reaction associated with minocycline therapy. However, the persistent bluish discoloration at the proximal nail bed is likely attributable to the slow degradation of minocycline-iron complexes deposited within the keratinized layer and superficial dermis, resulting in residual blue-gray pigmentation. Under these circumstances, the coexistence of proximal bluish pigmentation and distal whitish striations did not resolve after drug withdrawal or improved circulation, thereby excluding hypoperfusion or systemic hypoxemia as potential underlying mechanisms. This observation may further indicate the persistence of local inflammatory activity, which could account for the erythematous swelling observed over the dorsal aspect of the interphalangeal joints.

In conclusion, side effects of minocycline, a common antibiotic used to treat acne, include pigmentation of the nails and other areas, but are generally reversible. To the best of our knowledge, the present study reports the first case of a 'snow mountain nail' characterized by blue-gray pigmentation near the root of the nail accompanied by bright white changes at the free end and parallel bright white stripes, which was different from the blue pigmentation caused by minocycline reported in the past. Although it was only a single case report, the clinical manifestations of this case were relatively important, and this is highly likely to be a new type of minocycline-based disease. Therefore, the present case was reported for reference. This clinical manifestation not only expands the phenotype spectrum of minocycline-associated pigmentation, but also provides a new clue for clinicians to monitor drug-related pigmentation during minocycline use. It provides an important reference for further study on the pathogenesis and diagnostic value of drug-related nail lesions.

It was further confirmed that minocycline-induced nail discoloration was improvable by withdrawal of minocycline and detailed follow-up observation. The nail changes gradually returned to normal after drug withdrawal, suggesting that this phenomenon was an adverse reaction caused by minocycline. Case observations in the literature suggest that such pigment alterations may involve the chelation of minocycline and iron and their interference with melanin production and metabolism, and are closely related to inter-individual differences or local inflammatory states. The report of this case not only provides important clues for the diagnosis and differential diagnosis of minocycline-related hyperpigmentation, but also highlights the importance of focusing on hyperpigmentation of parts such as nails during minocycline treatment. Future studies can further explore the pathogenesis, diagnostic criteria and application value of 'snow mountain nail' in the monitoring of adverse drug reactions.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

As the attending physician for this patient, LS was the first to observe the 'Snow Mountain Nail' phenomenon. KL performed a literature review and revised and supplemented the manuscript. YTQ conducted the biopsy and initially analyzed the medical record data. WJZ was responsible for the language editing of the article. YTQ and WJZ confirm the authenticity of all the raw data. KL, WJZ, YTQ and LS were involved in the conception of the study and the interpretation of the data, and have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of case information and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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