Blue-gray discoloration of the skin after levofloxacin exposure in a 44-year-old man with pulmonary tuberculosis

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Introduction

Human tuberculosis (TB) is primarily caused by Mycobacterium tuberculosis. Pulmonary disease occurs in 70-90% of the patients being the most commonly affected sites. The standard therapeutic regimen for TB as recommended by World Health Organization (WHO), consists of two months of the intensive phase, and four months of the continuation phase. The intensive-phase drugs include isoniazid (H) 5 mg/kg, rifampin (R) 10 mg/kg, ethambutol (E) 15 mg/kg, and pyrazinamide (Z) 25 mg/kg. Then isoniazid and rifampin are continued for the next four months. In the cases of resistance to isoniazid, treatment with a combination of rifampin, ethambutol, pyrazinamide, and a quinolone antibiotic such as levofloxacin (Lfx) is performed for a total of six months [1-3]. Drug-induced hepatitis is the most well-known complication of anti-TB treatment. Other adverse events include anorexia, vomiting, abdominal pain, peripheral neuropathy, thrombocytopenia, renal reactions, and skin rashes [4]. Here, we reported a rare complication of levofloxacin which was used as a second-line agent for TB treatment.

Case presentation

A 44-year-old male presented to our infectious disease clinic with blue-gray discoloration of the skin on August 15th, 2022. He claimed that the skin color change initiated about 20 days after levofloxacin usage as a second-line treatment for Tuberculosis. He reported pruritus and scaling on the affected skin. His past medical history included ischemic heart disease (IHD), diabetes mellitus (DM), and pulmonary tuberculosis which was diagnosed on February 22nd, 2022. Her drug history included metformin 500mg twice daily, empagliflozin 25mg/ linagliptin 5mg daily, aspirin 80mg daily, nitroglycerin 2.6 mg twice daily, rifampin 600mg/d, pyrazinamide 2gr/d, ethambutol 800mg/d, and levofloxacin 750mg/d. He was diagnosed with pulmonary tuberculosis based on positive culture from a broncho-alveolar lavage specimen. His symptoms were cough, hemoptysis, fever, weight loss, and dyspnea. Chest computed tomography (CT) scan revealed consolidation in basal segments of the lower lobe of the right lung along with bronchiectasis (Figure 1). He underwent bronchoscopy and a specimen of broncho-alveolar lavage was obtained for diagnostic evaluations including smear and culture. When TB diagnosis was confirmed by culture, he was started on first-line agents (isoniazid 300mg/d, rifampin 600mg/d, ethambutol 800mg/d, and pyrazinamide 2gr/d). After two months of the intensive phase, the continuation phase was started with isoniazid and rifampin until the infection was recognized as isoniazid-resistant TB according to the drug susceptibility testing (DST) findings. Therefore, isoniazid was replaced with levofloxacin. After 20 days he developed blue-gray discoloration of the skin and came back to our infectious disease clinic.

On physical examination, vital signs were stable. Blue-gray discoloration of the skin with fine scaling was observed on the face, forearms, legs, and abdomen. We also detected, alopecia areata with ophiasis pattern (Figures 2 &3). Examination of the respiratory and cardiovascular systems was within normal limits.

Since levofloxacin was the only drug started a short time before the initiation of skin discoloration, it was

considered the culprit drug. Therefore, all medications, including levofloxacin, were discontinued. The sputum sample was sent to check the resistance to rifampin by the Gene Expert method. In this experiment, Mycobacterium tuberculosis sensitive to rifampin was reported. During hospitalization, following the discontinuation of drugs (including levofloxacin), edema of the limbs and scaling were resolved, and the hyperpigmentation became lighter. With the possibility of a drug complication to levofloxacin and due to drug resistance to isoniazid, a 4-drug treatment regimen was started with isoniazid, rifampin, pyrazinamide, and ethambutol, and the patient was discharged from the hospital after tolerating the drug regimen.

The patient was followed up 6 weeks after the discontinuation of levofloxacin. The blue-gray pigmentation was observed with a much lower intensity, and an almost complete resolution was observed after 6 months (Figure 4).

Discussion

Drug-induced skin reactions are one of the most commonly observed adverse effects of drugs. Skin reactions could be induced by almost any type of drug, but some drugs including antiepileptics, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs) are more frequently reported to be associated with these reactions. Cutaneous drug reactions could be mild and self-limiting or severe and life-threatening, including photosensitivity, pigmentary disorders, alopecia, fixed drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), vasculitis, etc [5, 6]. Fluoroquinolones are a widely used group of antibiotics. The third generation of quinolones like levofloxacin act against gram-positive, gram-negative, and atypical agents, and is one of the second-line treatments of TB. Fluoroquinolones have an acceptable safety profile. Gastrointestinal and neurologic complications are among the most common adverse effects. In contrast, cutaneous adverse reactions are relatively rare. TEN, hypersensitivity reactions, drug reaction with eosinophilia and systemic symptoms (DRESS), leukocytoclastic vasculitis, and fixed drug eruption have been associated with levofloxacin exposure [7, 8].

Lorente et al [9] reported a 71-year-old male who developed blue-gray pigmentation on limbs and trunk after two months of exposure to levofloxacin Skin biopsy was taken and showed hemosiderin-like deposits in macrophages and myoepithelial cells and fibroblasts in the superficial and deep dermis. Redondo et al [10] reported a 72-year-old man who had been receiving levofloxacin for several months and dark discoloration of the legs appeared a few weeks after exposure to the drug. Skin biopsy revealed brown granular cytoplasm in macrophages and confirmed the diagnosis. Connors et al [11] introduced a 58-year-old male with brown-gray hyperpigmentation 20 days after initiation of levofloxacin. In contrast to the previous reports, skin discoloration was in a photosensitive distribution. Similarly, pefloxacin, another member of the fluoroquinolone Family, was reported to be associated with skin hyperpigmentation in the legs [12].

In our case, the resolution of skin changes after discontinuation of the culprit drug and the timing association between levofloxacin exposure and the onset of the skin changes confirmed the causality of levofloxacin. Therefore, we did not take a skin biopsy from our patient. The specific feature of our patient was developing alopecia. As far as we know no previous article reported alopecia in association with levofloxacin or other quinolones. Three well-known types of drug-related alopecia are anagen effluvium (caused by cytotoxic chemotherapy drugs), telogen effluvium, and idiopathic androgenic alopecia (caused by drugs with androgen activity) [13]. In our patient, we detected alopecia areata with ophiasis pattern which did not fit any of the mentioned types.

The approach to resistance to isoniazid for TB treatment depends on the time of detection of resistance. Isoniazid-resistant TB (Hr-TB) treatment is expected to be started if either of the following circumstances applies [14]:

1) Hr-TB is confirmed and rifampicin resistance ruled out before TB treatment is started – in such cases, the 6-month course of (H)REZ-Lfx regimen is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be introduced. Should DST results taken at the start eventually show susceptibility to isoniazid, then levofloxacin is stopped and the patient continues treatment in order to complete a 2HREZ/4HR regimen.

2) Hr-TB is discovered after the start of treatment with the 2HREZ/4HR regimen (this includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance while on first-line treatment) – in such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance has been excluded, a full 6-month course of (H)REZ-Lfx is given. The duration is driven by the need to give levofloxacin for 6 months.

All medicines in this regimen are to be used daily for 6 months. When fixed-dose combination formulations are used, isoniazid is included but is not obligatory for the regimen. If levofloxacin cannot be used because there is fluoroquinolone resistance or intolerance or other contraindications to the use of fluoroquinolone, then 6(H)REZ may be prescribed daily for 6 months.

In the present case, considering the existing conditions and the lack of knowledge of resistance to rifampin at the beginning of the treatment, the challenge was the possibility of developing resistance to rifampin during the period of time that isoniazid was used. So he was asked on two occasions for a gene expert experiment, which confirmed the sensitivity to rifampin. Since during the hospitalization following the discontinuation of the drugs, the edema of the limbs and scaling disappeared, and the hyperpigmentation became less, these symptoms were attributed to drug side effects, and since these symptoms occurred after the initiation of levofloxacin, this drug is the first defendant that was abandoned from the treatment regimen.

We conclude that skin discoloration could be a potential adverse effect of levofloxacin which resolves gradually after discontinuation of the drug. Clinicians should be aware of this potential complication for appropriate diagnosis and treatment.

Ethics approval and consent to participate

Approval was not needed by the local Clinical Research Ethics Committee for case reports.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of interests

The authors declare that they have no competing interests.

Data availability statement

Data is available if requested

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Authors' contributions

BS conceived the idea to report the case. ZF was responsible for data collection. DM drafted the manuscript. BS and ZF commented on the manuscript. All authors read and approved the final manuscript.

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References

1. Migliori GB, Wu SJ, Matteelli A, Zenner D, Goletti D, Ahmedov S, Al-Abri S, Allen DM, Balcells ME, Garcia-Basteiro AL, Cambau E. Clinical standards for the diagnosis, treatment and prevention of TB infection. The International Journal of Tuberculosis and Lung Disease. 2022 Mar 1;26(3):190-205.
2. World Health Organization, Stop TB Initiative (World Health Organization). Treatment of tuberculosis: guidelines. World Health Organization; 2010.

3. Jeong YJ, Lee KS. Pulmonary tuberculosis: up-to-date imaging and management. AJR Am J Roentgenol. 2008 Sep 1;191(3):834-44.
4. Kim HY, Cho JG, Akkerman OW, Padanilam X, Seaworth B, Alffenaar JW. Anti-Tuberculosis Drugs and Adverse Events. Essential Tuberculosis. 2021:121-9.
5. Mockenhaupt M. Epidemiology of cutaneous adverse drug reactions. Adverse Cutaneous Drug Eruptions. 2012;97:1-7.
6. García RM, Molina SC. Drug-induced hyperpigmentation: review and case series. The Journal of the American Board of Family Medicine. 2019 Jul 1;32(4):628-38.
7. Lode H, Rubinstein E. Adverse effects. Quinolone antimicrobial agents. 2003 Aug 12:405-19.
8. Baggio D, Ananda-Rajah MR. Fluoroquinolone antibiotics and adverse events. Australian prescriber. 2021 Oct;44(5):161.
9. Lorente M, Ballano A, Juanes A, Pastor MA, Cuevas J. Blue-Gray Pigmentation in Trunk and Extremities in a 71-Year-Old Man.JAMA Dermatol. 2013;149(9):1111–1112.
10. Redondo RG, Molero VM, Fuentes AM, de Eusebio Murillo E. Le vofloxacin-Induced Hyperpi gmentation.
11. Connors TM, Restrepo A, Dao Jr H. Brown-gray hyperpigmentation in a photosensitive distribution after levofloxacin exposure. Dermatology Online Journal. 2018;24(7)
12. Le Cleach L, Chosidow O, Peytavin G, Berry JP, Boisnic S, Le Charpentier Y, Herson S, Frances C. Blue-black pigmentation of the legs associated with pefloxacin therapy. Archives of dermatology. 1995 Jul 1;131(7):856-7.
13. Llau ME, Viraben R, Montastruc JL. Drug-induced alopecia: review of the literature. Therapie. 1995 Mar 1;50(2):145-50.
14. World Health Organization. WHO operational handbook on tuberculosis. module 4: Treatment-drug-resistant tuberculosis treatment, 2022 update. World Health Organization; 2022 Dec 15.

Figure legend

Figure 1: Chest computed tomography (CT) scan of the patient showing a consolidation in basal segments of the lower lobe of the right lung along with bronchiectasis.

Figures 2 &3: Blue-gray discoloration of the skin on the face, forearms, legs, and abdomen along with alopecia areata with ophiasis pattern.

Figure 4: Resolution of the skin discoloration after six months.