Pirfenidone Induced Photosensitive Rash in Idiopathic Pulmonary Fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a gradually worsening interstitial lung disease ordinarily managed with anti-fibrotic agents such as pirfenidone, which has been shown to slow the disease progression but may be linked with adverse effects such as gastrointestinal intolerance and cutaneous reactions. Awareness of photosensitivity as a potential side effect is essential to ensure treatment adherence as well as patient safety. We report the case of a 63-year-old gentleman with moderately severe IPF who was started on oral pirfenidone and consequently developed a widespread erythematous rash within one month, initially affecting sun-exposed areas before becoming more generalised. Dermatological assessment suggested a photosensitive reaction, and the patient was acknowledged as lack of awareness regarding sun-protection measures. Pirfenidone was quickly discontinued, and he was started on oral and topical corticosteroids alongside counselling on strict sun protection. Skin biopsy was performed and histopathological findings were persistent with photosensitive dermatitis. The rash resolved gradually over two to three weeks without residual changes, and there was no recurrence on follow-up with continuous adherence to sun-protective measures. This case highlights the importance of being familiar with pirfenidone-induced photosensitivity and highlighting preventive advice when initiating therapy.

KEY WORDS

Antifibrotic therapy, Idiopathic pulmonary fibrosis (IPF), Phototoxic dermatitis, Pirfenidone

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a serious long term progressive disease that is generally incurable; however treatment aims at slowing the progression of fibrosis by use of anti-fibrotic therapy such as Nintedanib and Pirfenidone.[1] Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an orally active molecule which employs anti-fibrotic, anti-inflammatory, and antioxidant effects by hindering cytokine TGF-b and collagen synthesis. Pirfenidone has known phototoxicity as an adverse effect, which is thought to be mediated through generation of reactive oxygen species when the drug comes in contact with ultraviolet radiation.[2]

In this report, we intend to present a case of Pirfenidone induced cutaneous photosensitivity reaction which developed after one month of starting Pirfenidone in IPF, highlighting the importance of careful monitoring during the course of therapy. Appropriate sun protection measures seems to be paramount in all subjects taking pirfenidone.

CASE REPORT

A 63-year-old gentleman with a known history of moderate to severe idiopathic pulmonary fibrosis was commenced on pirfenidone for 4 weeks duration. He was urgently referred to our center from a GP service with complains of a widespread painful purpuric rash and desquamation for 5 days duration. The rash was localised circumferentially to the photo-exposed areas of extremities, V-area of neck and the face. There were sharp cut-offs to the photoprotected areas and there was no involvement of conjunctival or mucosal surfaces. The patient declined history of exposure to external sunlight, recent travel or holidays and was not using tanning beds.

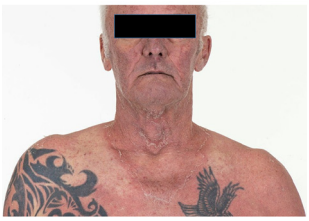

Figure 1. Clinical photograph showing erythematous rash over the face and neck in a photosensitive distribution.

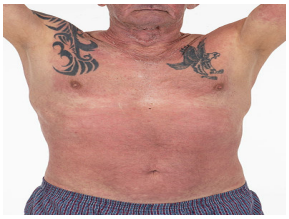

Figure 2. Clinical photograph showing diffuse erythematous rash over the chest and neck involving sun-exposed areas.

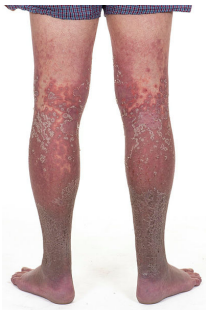

Figure 3. Bilateral lower limbs showing erythematous plaques with scaling and desquamation predominantly over photoexposed areas.

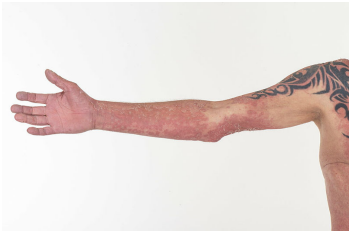

Figure 4. Upper limb showing erythematous rash with scaling in a photosensitive distribution.

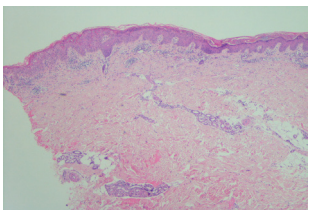

Figure 5. Histopathological image (10X) showing epidermal changes with mild hyperkeratosis and dermal inflammatory infiltrate.

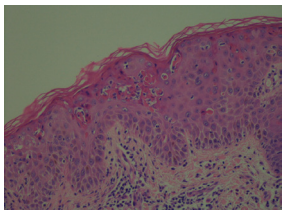

Figure 6. Higher magnification (40X) showing spongiosis, dyskeratotic keratinocytes, and perivascular inflammatory infiltrate consistent with phototoxic dermatitis.

The gentleman's past history included treatment with Nintedanib from tertiary respiratory center at Guy's hospital but was eventually discontinued due to its significant gastrointestinal side effects. Pirfenidone was then commenced to halt the process of fibrosis. Also, the patient was not aware of sun-protection measures.

Upon examination, the patient was haemodynamically stable with skin showing purpuric eruptions keeping with photosensitive eczema with grade III erythema and there was complete sparing of Wilkinson's triangle.

Skin biopsies were obtained for histopathological analysis which suggested mild hyperkeratosis with parakeratosis, spongiosis, dyskeratotic keratinocytes in the epidermis. Dermal findings included edema within the papillary dermis with perivascular lymphocytes and mild eosinophils. The overall picture in the context of clinical history suggested a phototoxic reaction. Based on the temporal association between Pirfenidone commencement and onset of rash, histopathological analysis, a diagnosis of Pirfenidone induced cutaneous phototoxic reaction was made.

Management included immediate cessation of Pirfenidone, a five day course of oral. Prednisolone 40 mg along with oral Lansoprazole and a 2 week courses of topical clobetasone to the face and neck and clobetasol propionate to the extremities, chest and back. Sun-protection were advised.

The patient showed gradual improvement and rash resolved over 2 to 3 weeks with no residual skin changes. On clinical follow-up, the patient was stable and showed no recurrence of photosensitive reactions with ongoing sun protection measures. He was advised sun protection measures to be continued further.

DISCUSSION

Idiopathic Pulmonary Fibrosis (IPF) is a chronic condition characterized by disrupted lung architecture, scarred thickened alveolar walls requiring life long medical therapies like immunosuppressants until 2014, however, European Medicine Agency in 2011 and US FDA in 2014 approved Pirfenidone and Nintedanib for IPF which has shown to reduce lung function decline and improve mortality rates.[3,5]

However, in some cases, medication changes become necessary due to poor response and adverse side effects.[4] Despite having qualities to reduce the progression of disease in IPF and generally considered safe, it has been associated with adverse effects such as rash and photo-sensitivity.[5] Although the mechanisms of Pirfenidone-induced photo-toxicity have not been fully known yet, Pirfenidone acts as photosensitiser which absorbs UV light and releases ROS which causes photo-toxic reactions in skin and eyes.6 While lower doses causes negligible reactions, higher dose cause serious effects.[6]

Similar cases have been reported. Nazeen Bano et. al. reported a case on pirferidone for 6 months, after dose reduction, rashes appeared within 2 days in sun exposed areas.[7] Another study from Gaikwad et al. reported new onset of rashes in photo exposed areas after dose escalation where the patient was on Pirfenidone for 5 months.[8] Augustin et al. stated rashes developed on sun exposed area after two months initiation of Pirfenidone, which is quite similar to our case.[9] Clinical evidence from a study named CAPACITY study indicated that Pirfenidone treatment is associated with dermatological reactions, specifically affecting 32% with rashes and 12% with photo-sensitivity.[10]

In contrast to the above mentioned studies, in our patient the rash appeared quite early within the first four weeks of therapy. The exact rationale for this could be higher ultraviolet exposure during the therapy which might have triggered the cutaneous response; however it cannot be clearly quantified.

This case highlights careful monitoring after medication changes along with strict advices to be given with medications which are already known to have photo-aggravating potential as pirfenidone in this case. Early recognition of drug induced complications and immediate measures like discontinuation prevents the serious outcomes and also gives the chance to carefully reintroduce the medicine after complication settles down.

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