An image case report of a complex pirfenidone skin rash in a patient with idiopathic pulmonary fibrosis

Apostolos Sarivalasis, Olga Papaefthymiou, Bernard Egger

SUMMARY

Idiopathic pulmonary fibrosis (IPF) is a progressive fatal pulmonary condition of unknown origin. Recent data demonstrated that old established treatments were either ineffective or deleterious. Novel therapies are needed to treat this disease. One of such treatments is Pirfenidone, an oral anti-fibrotic agent with considerable impact on IPF disease progression. Dosage titration is needed until the target dose of 2403 mg/day is reached.

The main toxicities of Pirfenidone can occur to any dosage level and consist of gastrointestinal toxicity, photosensitivity rash and but also other forms of rash rendering differential diagnosis of skin toxicity from other common dermatitis challenging. This article illustrates using photographic material the difficulties, possible pitfalls, proposed medical treatment and clinical evolution of a case of skin toxicity developed during Pirfenidone treatment in a patient suffering from IPF.

We believe that because of the increasing frequency of Pirfenidone treatment prescription, physicians are often going to encounter this drug-related toxicities. Therefore an image-backed report of skin toxicity presentation, evolution and medical treatment can help physicians managing IPF patients recognize and treat this drug-related toxicity.

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CASE REPORT

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ABSTRACT

Introduction: Recent data on idiopathic pulmonary fibrosis treatment options suggest that old established treatments are either ineffective or deleterious. One novel treatment is pirfenidone, an oral anti-fibrotic agent. This treatment is often limited by skin toxicity. This case report provided a daily photographic guide of the eruption and recovery of pirfenidone skin toxicity, along with the prescribed treatment and alternative diagnoses to be ruled out. **Case Report:** A 59-year-old Caucasian male patient was admitted for Pirfenidone treatment titration and rehabilitation after an idiopathic pulmonary fibrosis exacerbation. The patient did not experience any gastrointestinal toxicity but a facial skin pruritic and tender rash developed 48 h after drug's target dose reached. The patient had only one hour limited sun exposure during his transfer to our unit. Due to skin eruption topography corresponding to the concomitant continuous positive airway pressure treatment pressure points a differential diagnosis was to

be investigated. The rash evolution prompted local dermatological treatment and a temporary pirfenidone treatment discontinuation. After skin toxicity resolved the treatment was resumed without relapse of the skin rash. **Conclusion:** This case report provides images of a pirfenidone skin rash. It points out the fact that only limited time light exposure is sufficient for the development of skin toxicity and that the primary therapeutic consists on timely discontinuation of treatment.

Keywords: Idiopathic pulmonary fibrosis, Pirfenidone, Skin rash

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with insidious clinical evolution characterized by progressive lung function decline, respiratory failure and death. The median survival of patient ranges between 2 to 5 years [1, 2]. The etiology of IPF remains unknown while its accurate diagnosis based on specific criteria is paramount. The treatment of IPF to date is palliative with oxygen supply, rehabilitation and vaccination against pneumococcus and influenza. Recent data suggest older treatment options to be deleterious or ineffective in slowing disease progression [3, 4]. Randomized data suggest pirfenidone to slow IPF functional decline [5–9]. This oral agent requires dose titration over two weeks

and is associated with gastrointestinal and skin-related toxicities notably photosensitivity rash [10–12].

This case report is the first to describe with images the evolution of pirfenidone the facial and scalp skin rash in a Caucasian patient. It provides tangible material for the timely recognition of this drug related side effect to any physician encountering patients on this treatment. It describes the diagnostic procedure, along with potential differential diagnosis, highlighting the short sunlight exposure needed for triggering a photosensitivity reaction. The effective treatment is explained encompassing current, toxicity related, treatment adaptation guidelines and local dermatological treatment options. As described discontinuation is the main measure for rapid rash recovery.

CASE REPORT

A 59-year-old Caucasian male patient with a history of obstructive sleep apnea and hypoxemic respiratory failure due to idiopathic pulmonary fibrosis was admitted for respiratory rehabilitation and Pirfenidone treatment monitoring.

The patient presented a rapid degradation of dyspnea and a sharp decline in his physical activity after admission in a tertiary hospital for acute respiratory failure on February 2014. After immunological and infectiological workout with negative bronchoalveolar lavage (BAL) an exacerbation of the known idiopathic pulmonary fibrosis was diagnosed. A corticosteroid treatment was initiated at a dose of 1 mg/kg along with oxygen at 1 Lt/min. The corticosteroids were tapered due to a negative benefit to harm ratio with the advent of psychiatric toxicity in the form of delirium episodes and disease control failure. Pirfenidone treatment was indicated [2]. At the time pirfenidone was introduced the patient was oxygen dependant, presented a mMRC 3 dyspnea and had lost 250 ml on FEV₁ since February 2014 his pulmonary function showed a forced expiratory volume at 1 second (FEV₁) at 43%, a forced vital capacity (FVC) at 41% and a total lung capacity (TLC) at 40% of note the diffusing capacity of carbon monoxide (DLCO) was not available due to poor maneuver tolerability.

The patient received his first dose of Pirfenidone 267 mg on day 1 after the exclusion of liver function test (LFT) abnormalities. Dose titration progressed according to protocol without side effect until day-16, the day following the patient admission to our unit. At this time the patient was since 48 hours on the 2403 mg/day target dosage. The patient first noticed a well-demarcated erythematous plaque on his forehead and cheeks with nasolabial folds involvement in a mask-like distribution without pruritus or desquamation (Figure 1).

Our differential diagnosis included seborrheic dermatitis, contact dermatitis and pirfenidone skin toxicity. Indeed the patient had discontinued his continuous positive airway pressure (CPAP) treatment

during three weeks prior his admission and used his CPAP facial mask the night before the facial eruption occurred. Because the weather on the admission day was cloudy and there was not any recent treatment change the skin toxicity hypothesis was at first ruled out but was not formerly excluded. In the absence of history compatible with episodes of seborrheic dermatitis and because the need of an emergency etiologic treatment in this setting is relative we first ordered a discontinuation strategy withholding the CPAP treatment without pirfenidone dosage change pursuing the contact dermatitis hypothesis. Our strategy was backed by the finding that the rash distribution pattern was consistent with the CPAP facial mask margins. Nevertheless after 48 hour the eruption evolved with desquamation, invalidating face pruritus, tenderness and spread to the cheeks and front. (Figure 2A–C) In addition, pruritus scalp desquamative lesions without alopecia appeared (Figure 3).

This evolution mandated an emergent dermatological consultation on day-20. The retained diagnosis was a photosensitivity rash compatible with the pirfenidone photosensitivity/ toxicity possibly due to the late dose escalation and to discreet sunlight exposure during the patient transit for admission. We concluded to a grade 2 photosensitivity adverse event (lack of the body surface extension criteria for grade II toxicity but presence of tenderness) according to CTCAE v.4.03. The pirfenidone treatment was suspended for one week and a local treatment and sunlight eviction were prescribed according to the dermatologist advice. Although several treatment options exist [13], the prescribed facial treatment consisted of Fusidic acid/ betamethasone valerate 20:1 mg cream for 5 days 2 application daily and pimecrolimus 1% rescue treatment 1–2 times/day if persistent rash. The scalp eruption was treated with mometasone scalp lotion once/day.

Interestingly in this case only the patient face and scalp were affected by the skin rash while other sun-exposed parts like hands and sternum were not affected. This comes in contrast with other case reports showing essentially hand and ear located photosensitivity reactions.

A week later the facial skin eruption, tenderness and pruritus have completely resolved with no need of pimecrolimus rescue treatment (Figure 4A–B). The same evolution was observed in the scalp desquamative lesions. Of note no rash flare was observed as we resumed CPAP treatment 48 hours after local treatment initiation. Pirfenidone treatment was re-introduced, according to the established guidance [13], at the first level of titration on day 27 after LFT were found normal, with no skin toxicity relapse.

DISCUSSION

Pirfenidone is an oral immunosuppressant with both antifibrotic and anti-inflammatory properties.

Figure 1: Discrete bilateral nasolabial folds eruption on day-16.

Figure 2(A–C): Desquamative tender pruritic eruption spread to the cheeks and front on day-18.

Pirfenidone's regulatory effect on TGF- β and TNF- α inhibits collagen synthesis and fibroblast proliferation. The result is a reduction of idiopathic pulmonary fibrosis disease progression .

The recommended daily dose is three 267 mg capsules three times a day with food for a total of 2403 mg/day. The posology requires dose titration over two weeks: 1st

Figure 3: Scalp desquamative lesions without alopecia on day-18.

Figure 4 (A, B): Complete skin recovery on day-21.

week 1 cap , 3 times/day; 2nd week 2 caps, 3 times/day; from day-15 onwards 3 caps, 3 times/day. Pirfenidone's primary route of metabolism is via CYP1A2 so vigilance is needed for potential drug interactions. Its primary metabolite, 5-carboxy-pirfenidone is predominantly excreted via the urine.

Treatment with pirfenidone can be complicated gastrointestinal and skin-related events notably photosensitivity rash according to the CAPACITY trial results [7]. Both side effects are treated according to the symptom severity. Skin reactions are best treated with active avoidance of sunlight exposure and sunscreens. When established the primary treatment consist of treatment discontinuation. In severe cases dermatological local treatment can be applied. Treatment can be resumed after side effect resolution [13].

This case illustrates potential pitfall to be avoided during pirfenidone's treatment. The rash can be triggered even with minimal sun exposure and needs to be differentiated from other dermatological conditions. A high level of suspicion is needed for gastrointestinal, laboratory and skin toxicities for every patient on Pirfenidone. The differential diagnosis procedure should

not delay diagnosis and management especially in this palliative setting, fragile population of patients.

CONCLUSION

This case report provides images of a pirfenidone skin rash. It points out the fact that only limited time light exposure is sufficient for the development of skin toxicity and that the primary therapeutic consists on timely discontinuation of treatment.

LIST OF ABBREVIATIONS

IPF: Idiopathic pulmonary fibrosis
TGF- β : transforming growth factor beta
TNF- α : tumor necrosis factor alpha
mMRC : modified Medical Research Council
BAL : Bronchoalveolar Lavage
FEV₁ : Forced expiratory volume 1 sec
FVC : Forced vital capacity
TLC : Total lung capacity
DLCO: diffusing capacity of the lung for carbon monoxide
LFT : Liver function tests
CPAP : Continuous positive airway pressure
CTCAE : Common Terminology Criteria for Adverse Events

CONSENT

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

Author Contributions

Apostolos Sarivalasis – Substantial contributions to conception and design, Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Olga Papaefthymiou – Substantial contributions to conception and design, Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Bernard Egger – Substantial contributions to conception and design, Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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