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Pirfenidone-induced photosensitivity confirmed by pathological phototest

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is an idiopathic interstitial progressive fibrotic lung disease and the most lethal of all interstitial lung diseases. Pirfenidone is a novel antifibrotic and anti-inflammatory agent which reduces decline in lung function and prolongs progression-free survival. It has a favourable benefit-risk profile and is generally well tolerated. However gastrointestinal events, photosensitivity reactions and rash are the most common adverse events.

Objective: We report a 71-year-old man with 1 week history of erythematous partially pruritic lesions on both sides of the neck and the back of the hands limited to sun exposed areas. He had been diagnosed with IPF and was being treated with pirfenidone (Esbriet) for 8 months. We suspected a photosensitivity reaction caused by pirfenidone.

Methods: A phototest and a punch biopsy were performed.

Results: The phototest had a pathological result. The minimal erythema dose was decreased, presenting with erythema and edema starting from 7 mJ/cm^2 of UVB and an aberrant response to UVA starting from 2 J/cm^2. Histopathological examination revealed spongiotic acute dermatitis with focal presence of necrotic keratinocytes. The patient was diagnosed with pirfenidone-induced photosensitivity and treated with high potency topical steroid leading to the resolution of the lesions, without the need for discontinuation of the drug.

Conclusion: To our Knowledge, this is the first pirfenidone-induced photosensitivity reported case confirmed by pathological phototest. Patient education and photoprotection advice are essential for prevention.

1. Introduction

Idiopathic pulmonary fibrosis is an idiopathic interstitial progressive fibrotic lung disease and the most lethal of all interstitial lung diseases. It is characterised by progressive dyspnoea and irreversible loss of lung function, with a median survival off 20% at 5 years [1,2].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is a novel orally available antifibrotic and anti-inflammatory agent which reduces decline in lung function, reduces the proportion of patients with a 10% or more FVC (forced vital capacity) decrement by 30% compared with placebo, reduces risk of death or disease progression by 26% and prolongs progression-free survival [1]. It inhibits the activity of transforming growth factor (TGF) β and tumour necrosis factor (TNF) α, reduces fibroblast proliferation and collagen synthesis [1,2].

2. Case report

A 71-year-old man presented with a 1 week history of erythematous partially pruritic lesions on both sides of the neck and the back of the hands. His medical history was significant for idiopathic pulmonary fibrosis which was being treated with pirfenidone (Esbriet) since October 2015. He was also receiving treatment with acenocoumarol, telmisartan and inhaled tiotropium bromide. Physical examination revealed erythematous lesions affecting both sides of the neck and the back of the hands (Fig. 1). It was noticeable that lesions were limited to sun exposed areas. Residual hyperpigmentation was observed on the pinnae. The patient admitted a previous exaggerated solar burn 2 months ago on a cloudy day. We suspected a photosensitivity reaction caused by pirfenidone.

A phototest and a punch biopsy were performed. The phototest had a pathological result. He had Fitzpatrick skin type 2. The immediate reading was negative but after 24 h the minimal erythema dose was decreased, presenting with erythema and edema starting from 7 mJ/cm^2 of UVB and an aberrant response to UVA starting from 2 J/cm^2 (Fig. 2(a)). Histopathological examination revealed spongiotic acute dermatitis with focal presence of necrotic keratinocytes (Fig. 2(b) and

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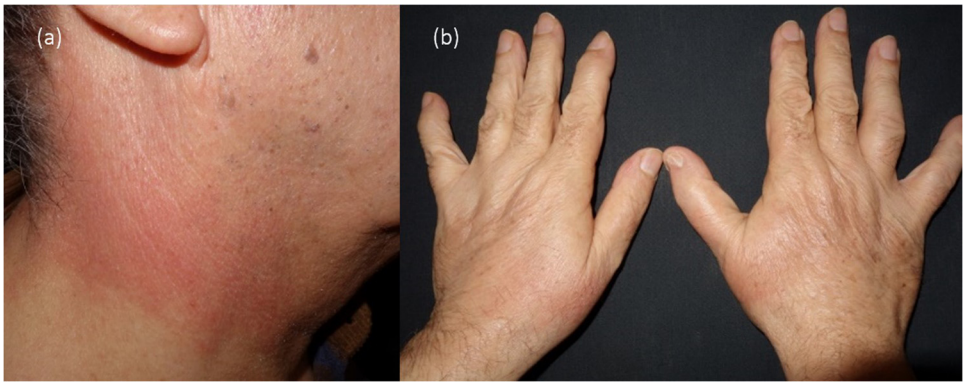

Fig. 1. Erythema on both sides of the neck (a) and the back of the hands (b) limited to sun exposed areas.

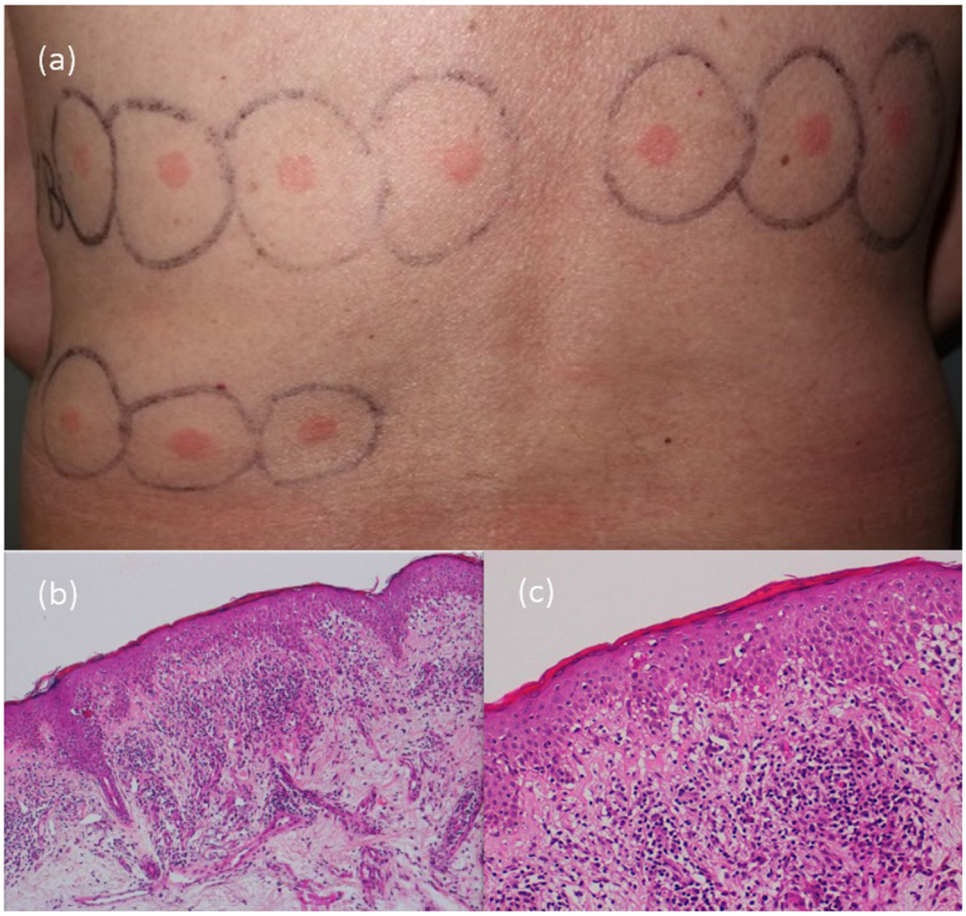

Fig. 2. (a) Phototest on the back. Reading after 24 h: minimal erythema dose decreased, erythema and edema starting from 7 mJ/cm^2 of UVB and an aberrant response to UVA starting from 2 J/cm^2. (b) H-E 40x (c) H-E100 × . Spongiotic acute dermatitis with focal presence of necrotic keratinocytes.

(c)).

These results were consistent with the diagnosis of pirfenidone-induced photosensitivity and treatment with high potency topical steroid was started.

3. Discussion

Pirfenidone has a favourable benefit-risk profile and is generally well tolerated. However higher incidence of dermatological, gastrointestinal and neurological adverse events have been reported in patients treated with pirfenidone vs placebo: nausea 36% vs 17%, vomiting 14% vs 4%, dyspepsia 19% vs 7%, diarrhea 18% vs 14%, anorexia 11% vs 3%, dizziness and fatigue 18% vs 10%, rash 32% vs 12% photosensitivity 12% vs 2%. Liver enzyme elevation in ALT (alanine aminotransferase) and AST (aspartate aminotransferase) of more than three times the upper limit of normal occur in 4% of patients. Consequently liver function tests should be conducted prior to the initiation of treatment and at 1–3 monthly intervals thereafter. Nearly all patients experience a treatment adverse event, most of which are mild to moderate [3,4].

Gastrointestinal and skin-related events are the most common adverse events and several studies have shown they led to treatment discontinuation in 1.7% and 2.3% pirfenidone-treated patients, respectively. They have a tendency to occur early in the course of treatment and decrease over time [5].

Skin reactions are the most commonly reported adverse effects and

the major reason for discontinuation or dose reduction of Pirfenidone. They can manifest as photosensitivity reactions in 12.2% and rash in 32.2% of pirfenidone-treated patients. Clinical manifestation consist of an erythematous with edema or as a phototoxic burn-like skin rash, occurring on sun-exposed body areas.

The pirfenidone-induced photosensitivity is thought to be phototoxic and due to the ability of the Pirfenidone in skin to absorb UVB and UVA, therefore proportional to the intensity of sunlight exposure and drug concentration. This is thought to generate reactive oxygen species and lipid peroxidation, leading to a phototoxic reaction.

Treatment consists of avoiding sun-exposure and concurrent photosensitising medications. In cases of rash or mild to moderate photosensitivity reaction that does not spontaneously resolve, pirfenidone dose should be reduced to one capsule (267 mg) three times a day for 7 days. If it persists more than 7 days, therapy should be discontinued for 15 days or until symptom resolution. In cases of severe photosensitivity reaction, therapy should be discontinued and replaced with prednisone 30 mg/day for 7–10 days. Once the skins clears, pirfenidone may be slowly re-introduced. If rash is likely to be due to an allergic reaction, pirfenidone should be permanently discontinued [5,6].

Recommendations for prevention and management of photosensitivity include avoidance of sun exposure, especially at mid-day, during seasonal high UV periods and a few hours after pirfenidone administration. Indirect sunlight as well as intense artificial light sources should also be avoided. It is mandatory the application of a broad-spectrum SPF50 sunscreen with both UVA and UVB protection. UVA component can penetrate clouds, clothing and car windows. Appropiate clothing is recommended, such as wide-brimmed hats, sunglasses, long-sleeve shirts, and trousers and gloves for driving and outdoor activities [2,5].

Decisions on disease management should always be made in conjunction with the patient, who should be informed of potential drug side-effects. The balance between quality of life and efficacy benefits of continued treatment should be considered. Previous studies have demonstrated a favourable long-term safety up to 8 years and they are currently ongoing [5].

4. Conclusion

This is the first pirfenidone-induced photosensitivity reported case confirmed by pathologic phototest. Our aim by presenting this case is to increase awareness and surveillance of clinicians for photo-distributed erythematous eruptions of patients on pirfenidone therapy. Patient education and photo protection advice are essential for prevention.

The underlying mechanism of pirfenidone in most photosensitivity reactions is likely to be phototoxic. It differs from a photoallergic rash which presents as a generalized eruption including unexposed areas and it is a contraindication to re-introduction of pirfenidone.

Nevertheless further studies are required to clarify the mechanism of photosensitivity and provide evidence-based guidelines for management of this entity.

Conflict of interest

Any of the authors report any conflict of interest that could influence them regarding this manuscript.

Financial disclosures

Any of the authors have any financial relationship regarding this manuscript or any financial conflict of interest.

References

[1] P.W. Noble, C. Albera, W.Z. Bradford, U. Costabel, M.K. Glassberg, D. Kardatzke, T.E. King Jr, L. Lancaster, S.A. Sahn, J. Szwarcberg, D. Valeyre, R.M. du Bois, Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials, Lancet 377 (2011) 1760–1769, https://doi.org/10.1016/S0140-6736(11)60405-4.

[2] E. Papakonstantinou, A. Prasse, V. Schacht, A. Kapp, U. Raap, Pirfenidone-induced severe phototoxic reaction in a patient with idiopathic lung fibrosis, J. Eur. Acad. Dermatol. Venereol. (March) (2016), https://doi.org/10.1111/jdv.13657.

[3] A. Lara, M. Schwarz, Pirfenidone: is it tolerable? BMJ Open Respir. Res. 3 (2016) e000124, , https://doi.org/10.1136/bmjresp-2015-000124.

[4] O. Hilberg, U. Simonsen, R. du Bois, E. Bendstrup, Pirfenidone: significant treatment effects in idiopathic pulmonary fibrosis, Clin. Respir. J. 6 (2012) 131–143, https://doi.org/10.1111/j.1752-699X.2012.00302.x.

[5] U. Costabel, E. Bendstrup, V. Cottin, P. Dewint, J.J. Egan, J. Ferguson, R. Groves, P.M. Hellstro¨m, M. Kreuter, T.M. Maher, M. Molina-Molina, K. Nordlind, A. Sarafidis, C. Vancheri, Pirfenidone in idiopathic pulmonary fibrosis: expert panel discussion on the management of drug-related adverse events, Adv. Ther. 31 (2014) 375–391, https://doi.org/10.1007/s12325-014-0112-1.

[6] C. Jiang, H. Huang, J. Liu, Y. Wang, Z. Lu, Z. Xu, Adverse events of pirfenidone for the treatment of pulmonary fibrosis: a meta-analysis of randomized controlled trials, PLoS One 7 (10) (2012) e47024, , https://doi.org/10.1371/journal.pone.0047024.