Pirfenidone-Induced Dose-Dependent Phototoxicity – A Distinct Drug Reaction

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Sir,

Pirfenidone is a novel drug with anti-fibrotic and anti-inflammatory properties used in the treatment of idiopathic lung fibrosis.[1] Herein, we report a case of pirfenidone-induced phototoxicity.

A 70-year-old male presented with hyperpigmented itchy skin lesions involving the face, forearms, and thighs for 10 days. His skin lesions were associated with photosensitivity, swelling of face, redness, and watering of eyes. History revealed that he was a recently diagnosed case of idiopathic pulmonary fibrosis and was started on treatment with pirfenidone 200mg two tablets thrice daily. Two months later the dose of pirfenidone was stepped-up to 200 mg three tablets thrice daily. One month after dose increment, the patient started developing itching and redness involving the photoexposed areas.

Cutaneous examination revealed hyperpigmentation with erythematous borders involving the face, "v"area of neck, forearms, dorsum of hands, upper back, thighs, and legs. There was a clear cut demarcation between the photoexposed and nonphotoexposed areas [Figures 1 and 2]. Examination of palms, soles, oral cavity, and genitalia did not reveal any abnormality. Routine hematological and biochemical investigations were within normal limits. Antinuclear antibody by immunofluorescence method was negative. Histopathological examination revealed epidermis exhibiting hyperkeratosis, parakeratosis, and large subcorneal clefting with extensive epidermal necrosis. There was also subepidermal blister formation containing fibrin and mixed inflammatory infiltrate. Dermis showed lichenoidinfiltrate composed of lymphocytes, plasma cells, occasional eosinophils, and neutrophils [Figures 3 and 4]. Naranjo algorithm showed a score of 6 with probable association of drug with the reaction. A diagnosis of pirfenidone-induced phototoxic drug reaction was entertained based on the distinct photodistributed skin lesions and extensive epidermal necrosis with dermal inflammatory infiltrate in histopthology.

Photosensitivity following drug intake occurs in two different patterns: phototoxicity and photoallergy. Phototoxicity is a nonimmunologic reaction following absorption of ultraviolet radiation by drug metabolites. On the contrary, photoallergic reaction is a cell-mediated immune reaction occurring in a sensitized host. Clinically phototoxic reaction mimics sunburn with sharp delineation to the sun exposed areas, whereas photoallergic reaction mimics eczema and it involves nonphotoexposed skin as well. Other patterns described in drug-induced photosensitivity include lichenoid skin lesions, pseudoporphyria, pellagra reaction, and photoonycholysis.[2]

Pirfenidone is an anti-fibrotic agent approved for treatment of idiopathic lung fibrosis. It inhibits transforming growth factor (TGF) -β stimulated collagen production by reducing fibroblast proliferation and production of fibrogenic mediators. Anti-inflammatory action is attributed to its inhibition of inflammatory cytokines like tumor necrosis factor-α, interleukin-1, and production of anti-inflammatory cytokine interleukin-10.[1]

In a study by Taniguchi *et al.* photosensitivity was the major adverse event observed in 51% of the patients in the high-dose group and 53% in low-dose group.[3] Apart from phototoxicity; pirfenidone-induced photoallergy and photoleucomelanoderma have been reported.[1,4]

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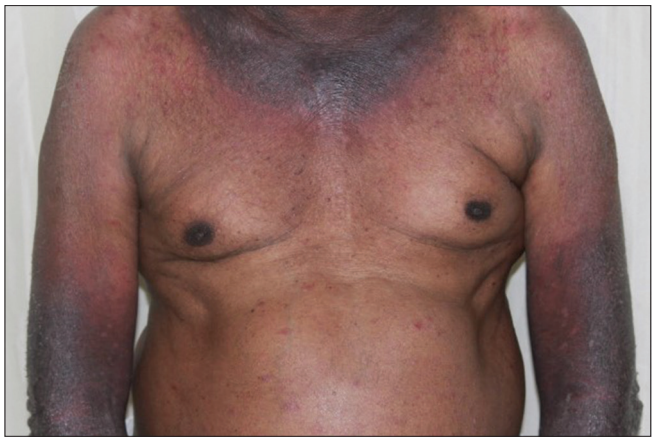

Figure 1: Hyperpigmentation with erythematous borders involving the "v"area of neck, forearms

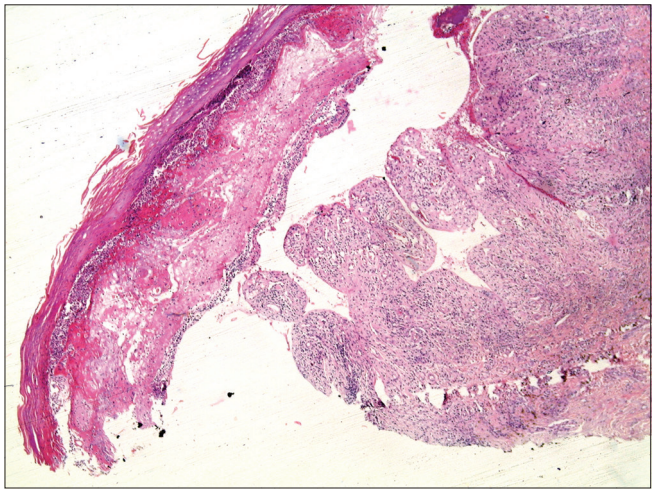

Figure 3: Epidermis with hyperkeratosis, parakeratosis, subcorneal clefting, extensive epidermal necrosis, and subepidermal blister formation with fibrin and mixed inflammatory infiltrate. Dermis showing inflammatory infiltrate composed of lymphocytes, plasma cells, occasional eosinophils, and neutrophils [H&E 100×]

Seto *et al.* in their study assessed the photosafety of pirfenidone and concluded that there was production of singlet oxygen and superoxide radicals from drug metabolites of pirfenidone on exposure to sunlight pointing to its phototoxic potential. The study also showed that phototoxicity testing using high doses of pirfenidone in rats caused photosensitivity compared to low doses, pointing to the factthat phototoxic reaction parallels concentration of drug levels in skin.[5] Likewise in the present case skin lesions appeared after increment of the dose.

Diagnosis in drug induced photosensitivity can be established with histopathological examination, phototesting in case of phototoxic reaction, and photopatch testing in photoallergic reaction. Guillén *et al.* reported a similar case, where they conducted phototesting which showed a reduced minimal erythema dose and an aberrant response to ultraviolet A starting from 2 J/cm^2.[6] In our case, histopathology revealed a picture consistent with phototoxic reaction, however phototesting was not done.

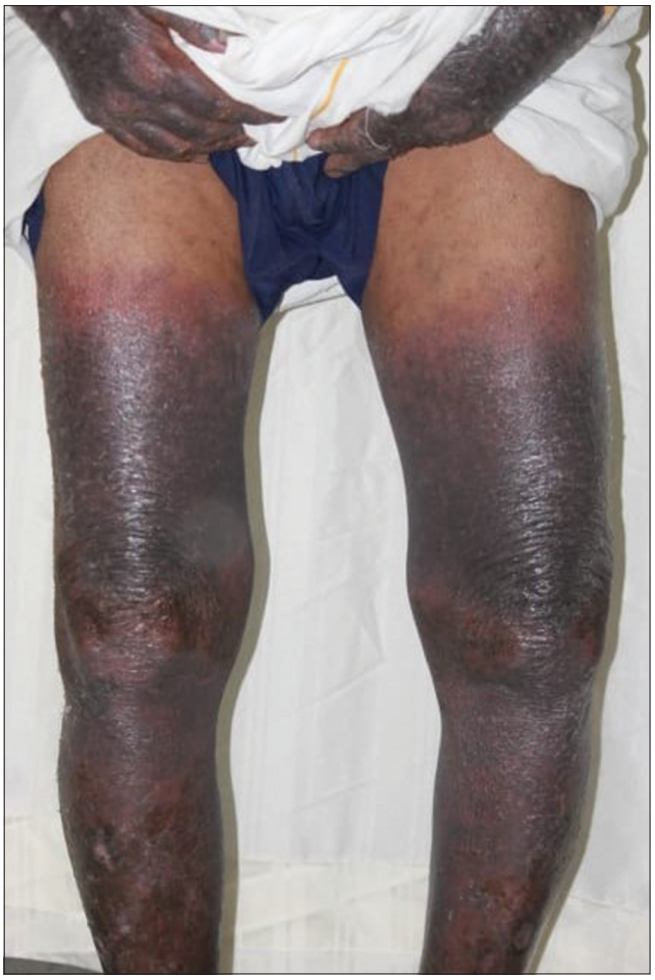

Figure 2: Hyperpigmentation with erythematous borders involving thighs and legs

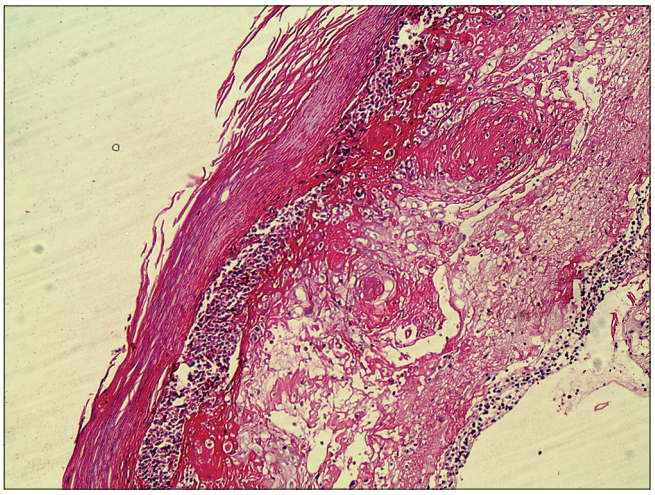

Figure 4: Closer view showing keratinocyte necrosis and inflammatory cells in epidermis [H&E 400×]

Treatment options include photoprotection, broad spectrum sunscreens, short course of steroids, and dose reduction

or stopping of drug. With resolution of skin lesions reintroduction of the drug can be attempted with low doses. However in photoallergic reactions drug reintroduction should be avoided.[7,8] The present case was treated with short course of steroids, sunscreens, and stopping of the drug with improvement of skin lesions. The present case is highlighted for the distinct side effect profile of a new therapeutic agent.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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