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Evaluation of Cutaneous Drug Reactions due to Pirfenidone: A Histopathological Study and Management of Clinical Findings

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Abstract

Objective: Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrotic, and fatal lung disease associated with the inevitable loss of lung function. Pirfenidone, which has antifibrotic properties and has been used orally in recent years, slows down the progression of the disease and increases survival rates. However, photosensitive skin rash caused by absorbing ultraviolet rays is the most frequently encountered adverse effect in clinical practice.

Methods: Thirteen patients who were treated for IPF in the department of chest diseases between September 2018 and January 2022, used pirfenidone, and applied to the dermatology outpatient clinic due to rash were retrospectively examined. During this period, the number of patients receiving pirfenidone for IPF in chest diseases was fifty-six.

Results: In dermatological examination, scaly plaques on an erythematous background were common in seven patients, whereas lichenoid papules and plaques were dominant in six. In the histopathological evaluation of biopsies taken from the lesional skin area, the findings were consistent with superficial perivascular dermatitis in two, psoriasiform dermatitis in five, and lichenoid reaction pattern in six patients. When photosensitivity reactions occurred, pirfenidone treatment was continued in eleven patients at a reduced dose, and only two patients discontinued pirfenidone and switched to nintedanib therapy.

Conclusion: We aimed to show that photosensitivity reactions can be managed in the majority of patients without discontinuing pirfenidone, which plays a vital role in the treatment of IPF symptom control and survival by reducing the dose, using sun protection, and taking additional protective measures, and to provide further insight to clinicians in this regard.

Keywords: Pirfenidone, idiopathic pulmonary fibrosis, photosensitivity, drug eruption

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an interstitial pneumonia of unknown cause characterized by chronic, progressive fibrosis. The walls of the alveoli in the lungs thicken with scarring in this disease, which is observed mainly in older adults. It causes long-term cough, shortness of breath, fatigue, weakness, loss of appetite, and weight loss, and has a serious course (1). It also causes progressive and permanent damage to the lungs. Oxygen transfer from the lungs thickened by scar tissue to the blood circulation system is reduced, negatively affecting all organs. If left untreated, severe hypoxemic cases develop pulmonary hypertension and right heart failure. The average survival time of patients diagnosed with IPF is 2-5 years (2). The timely diagnosis of IPF is crucial but, unfortunately, is often delayed. Treatment of this disease that causes irreversible damage aims to reduce the patient's symptoms and slow the progression of

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the disease. In recent years, two antifibrotic agents that can slow the progression of IPF have taken their place among the treatment options. Pirfenidone and nintedanib were shown to partially prolong life expectancy and improve quality of life by preventing the progression of fibrosis in the lung when started at an early stage (3). Pirfenidone transforming growth factor-beta has an antifibrotic, anti-inflammatory effect by inhibiting the overexpression of fibroblast growth factor, proliferation and transformation of fibroblasts into myofibroblasts, and collagen synthesis (4,5). This increasingly used agent's most common side effects are related to the skin and gastrointestinal system. The other antifibrotic agent, nintedanib, most commonly causes diarrhea. Cutaneous drug reactions, which are frequently encountered in dermatology practice, can occur in various severities, ranging from asymptomatic to severe clinical manifestations. Although pirfenidone, one of the antifibrotic drugs that has found increasing use in recent years, is well tolerated, it can cause widespread phototoxic and photoallergic reactions on the skin (6). It may be necessary to reduce the dose or change the current treatment, considering the clinical course, lesion severity, and patient tolerance. In the literature, data on skin rash caused by pirfenidone are limited to case reports, and there are few publications with extensive studies on the prognosis. In this article, we aimed to review the skin rash caused by pirfenidone, its clinical course, and its treatment and to provide further insight to clinicians in this regard.

METHODS

Thirteen patients who were treated by the chest diseases department at Necmettin Erbakan University Faculty of Medicine Hospital for IPF between September 2018 and January 2022, used pirfenidone, and applied to the dermatology outpatient clinic due to rash were retrospectively examined. During this period, the number of patients receiving pirfenidone for IPF in chest diseases was 56. The patients' age, gender, clinical findings, time of starting and stopping pirfenidone treatment, lesional skin histopathology findings, skin-specific treatment, and responses were obtained from file records. Forty-four (79%) of 56 patients were male and 12 (21%) were female. Eleven (85%) of the cases with drug reactions were male.

Ethical approval for the study was obtained from the Pharmaceutical and Non-Medical Device Research Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine (decision number: 2020/2429, date: 17.04.2020). Patients with any photosensitive skin disease or a history of photosensitizing drug or non-photosensitizing drug use were not included in the study. The patients did not have any history of chronic inflammatory skin diseases, such as psoriasis and lichen. Informed consent was obtained from all patients participating in the study.

Statistical Analysis

The data were examined using SPSS 22.0 statistical software.

RESULTS

IPF between September 2018 and January 2022 who used pirfenidone and applied to the dermatology outpatient clinic due to rash were retrospectively examined. During this period, the number of patients receiving pirfenidone for IPF in chest diseases was 56. Forty-four (79%) of the 56 patients were male and 12 (21%) were female. Of the 13 patients included in our study, 11 were male (85%), and two were female. Their average age was 78.61 years (range 69-83). The average time from the onset of skin symptoms on pirfenidone for IPF was 5 months (mean: 5.15, minimum: 3, maximum: 12).

The most common site of lesions caused by pirfenidone was the hand in eleven of the patients. Seven patients had lesions on the feet, four on the neck, three on the face, and three on the arms. One patient also had photosensitivity lesions on the trunk, one patient with the lip, and two on the anterior front of the tibia. In dermatological examination, scaly plaques on an erythematous background were common in seven, while lichenoid papules and plaques were dominant in six of our patients (Figure 1,2).

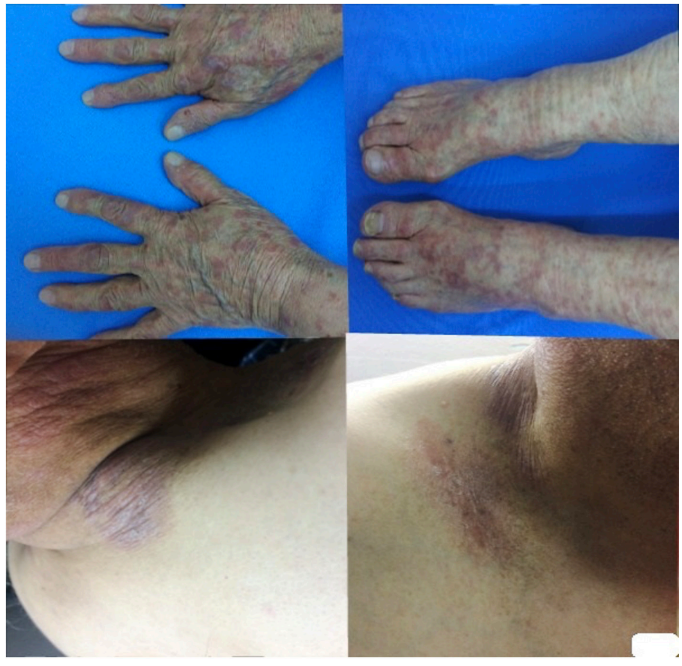

Figure 1. Lichenoid pattern, clinical findings in cutaneous drug reactions due to pirfenidone

In the histopathological evaluation of biopsies taken from the lesional skin area, the findings were consistent with superficial perivascular dermatitis in two, psoriasiform dermatitis in five, and lichenoid reaction pattern in six patients (Figure 3,4). All histopathologies showed necrotic keratinocytes and eosinophil infiltration, consistent with drug eruption. When photosensitivity reactions occurred, pirfenidone treatment was maintained in 11 patients by decreasing the dose, and two patients stopped using pirfenidone and were switched to nintedanib therapy. The two patients who were switched to nintedanib treatment were patients with resistant drug reactions that did not respond to treatments. All patients were treated with topical corticosteroids and antihistamines, and full recovery was observed in six patients within an average of 3.3 weeks (range 2-4), with no recurrence observed. In five patients, a 70-80% recovery was observed in an average of 6.4 weeks (range 4-8), and recurrence was observed within 1 year. In two patients, there was a 60-70% improvement in an average of 9 weeks (between 8-10) and occasional relapses were observed during the 1-year period. Relapse occurred in patients who continued pirfenidone but were controlled with topical corticosteroid and antihistamine treatment. The clinical characteristics of all patients are summarized in Table 1.

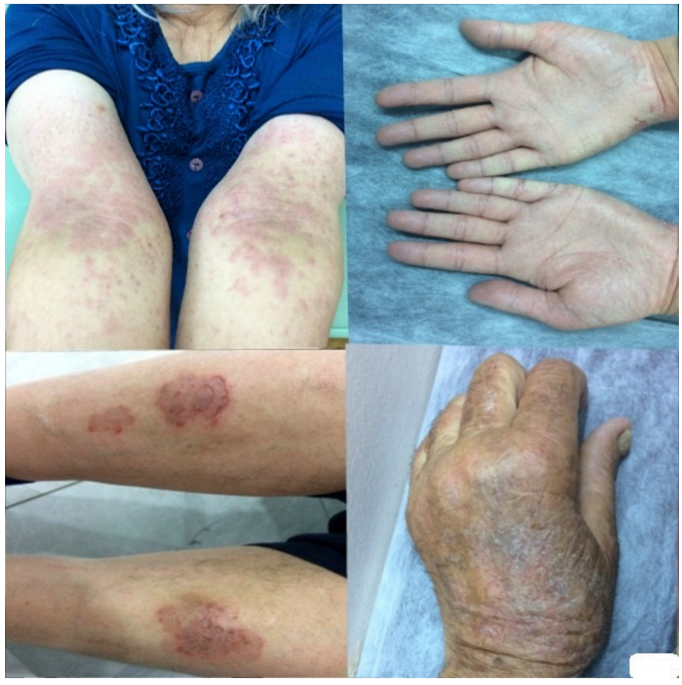

Figure 2. Psoriasiform pattern, clinical findings in cutaneous drug reactions due to pirfenidone

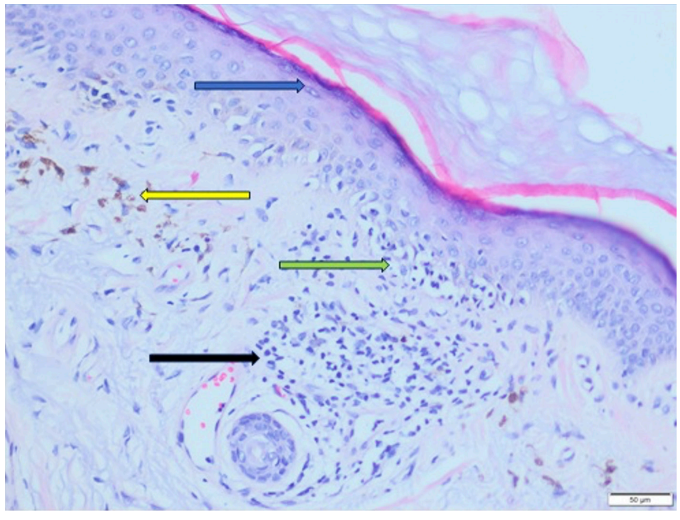

Figure 3. Lichenoid pattern, histopathological findings in cutaneous drug reactions due to pirfenidone

DISCUSSION

The common side effect of pirfenidone is photosensitive rashes, particularly in sun-exposed areas such as the face, neck, hands, and arms. Apart from pirfenidone, low-molecular-weight diuretics, nonsteroidal anti-inflammatory drugs, and antibiotics such as tetracycline-fluoroquinolones-sulfonamide are other essential drugs that can cause photosensitivity (7). Photosensitive drug reactions are divided into two major types: phototoxic and photoallergic. In phototoxic drug reactions, ultraviolet light interacts with the drug or its metabolites on the skin and causes nonimmunological cellular damage with the reactive oxygen molecules formed (8). In photoallergic reactions, ultraviolet rays convert drugs into immunologically active metabolites that stimulate cell-mediated hypersensitivity, causing rash (9). Since all photoallergic chemicals bind to proteins with the formation of free oxygen radicals, there are publications stating that the first step of photoallergic reactions is phototoxicity (10,11). In clinical distinction, early-onset reactions can be evaluated as

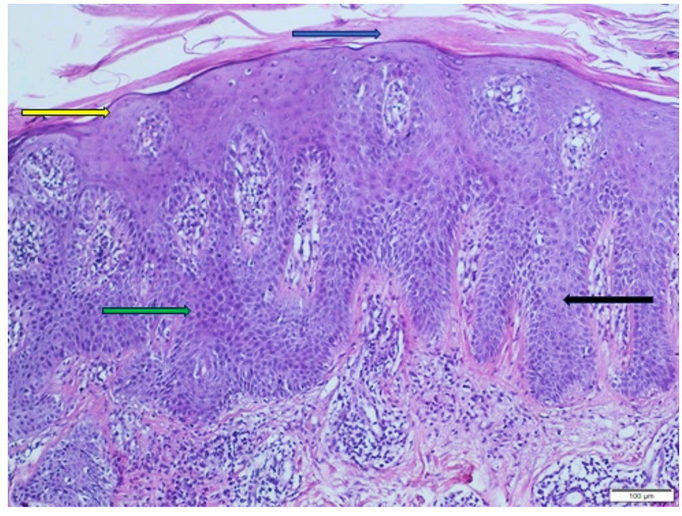

Figure 4. Psoriasiform pattern, histopathological findings in cutaneous drug reactions due to pirfenidone

phototoxic and late-onset reactions as photoallergic. They are very difficult to distinguish clinically and can often be seen together (11). Photoallergic reactions have a more chronic course than phototoxic reactions. In phototoxic reactions, lesions are generally limited to areas exposed to the sun, whereas in photoallergic reactions start primarily in areas exposed to the sun and spread to other regions over time (12).

Rashes were more common in male patients in our study. We attribute this result to the fact that IPF is more common in men. There is a male predominance in studies on the incidence and prevalence of IPF (13). In the literature, the average time between the initiation of pirfenidone and the appearance of skin findings was found to be four months, and in our study, this period was 5 months on average (6).

Table 1. Clinical characteristics of our patients who developed photosensitivity due to pirfenidone use

Age	Gender	Rash onset time	Lesion body location	Lesion characteristics	Histopathology	Treatment	Follow-up
71	M	6th month	Face, neck, tibia anterior face	Squamous plaques on an erythematous base	Psoriasiform dermatitis	The patient discontinued pirfenidone. Nintedanib treatment was started.	Complete cure. No relapse.
83	F	7th month	Bilateral hands and feet	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Complete cure. No relapse.
76	M	3rd month	Bilateral hands and feet	Squamous plaques on an erythematous base	Psoriasiform dermatitis	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.
63	M	4th month	Torso, arm, hand, foot	Squamous plaques on an erythematous base	Psoriasiform dermatitis	Pirfenidone was continued with a reduced dose.	Improved by 60-70%. Needed treatment from time to time.
73	M	3rd month	Face, neck and hands	Widespread erythema, sporadicsquamous plaques on an erythematous base	Superficial perivascular dermatitis	Pirfenidone was continued with a reduced dose.	Complete cure. No relapse.
74	M	4th month	Bilateral feet, arms, hands	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.
71	M	6th month	Neck and hands	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Improved by 60-70%. Needed treatment from time to time.
71	M	12th month	Bilateral hands, lip	Violese lichenoid papules and plaques, lip hyperpigmentation	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.
77	M	4th month	Bilateral hands and feet	Squamous plaques on an erythematous base	Psoriasiform dermatitis	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.
72	M	3rd month	Tibia anterior face	Squamous plaques on an erythematous base	Psoriasiform dermatitis	The patient discontinued pirfenidone. Nintedanib treatment was started.	Complete cure. No relapse.
80	F	7th month	Bilateral hands and feet	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Complete cure. No relapse.
70	M	3rd month	Face, neck and hands	Widespread erythema, sporadicsquamous plaques on an erythematous base	Superficial perivascular dermatitis	Pirfenidone was continued with a reduced dose.	Complete cure. No relapse.
69	M	5th month	Bilateral feet, arms, hands	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.

F: Female, M: Male

In our two patients whose rashes started in the 3rd month of pirfenidone treatment, skin biopsy histopathological evaluation was consistent with superficial perivascular dermatitis. The pirfenidone dose was reduced, and the lesions responded to treatment with no recurrence. This suggests that the reactions were rather phototoxic. Although the lesions started later in most patients with histopathology indicating psoriasiform dermatitis or lichenoid dermatitis, a response rate of 60-80% was obtained from the treatment of rashes while continuing the low-dose pirfenidone, which is more suggestive of a photoallergic reaction. However, we also have two patients with early-onset rash of this character and a complete response to treatment. Therefore, it is almost impossible to make a precise distinction. Phototoxicity is the basis of all reactions observed.

In our study, rashes that occurred due to pirfenidone entirely or largely regressed in all patients after the dose was reduced without the need for discontinuation of the drug. Sun protection methods effectively prevent photosensitivity reactions due to pirfenidone and constitute an essential treatment step. Broad-spectrum sunscreens that provide protection against ultraviolet A and ultraviolet B should be used; exposure should be avoided during hours when the sun's rays are most intense; heavy artificial light sources should be avoided; and protective clothing should be worn as much as possible (14). It is also important to avoid exposure to sunlight for a few hours following pirfenidone intake because of its high blood concentration to prevent the development of reactions (14). The dose should first be reduced in cases of photosensitive reactions, and mild reactions can be controlled by sun protection methods and symptomatic treatment of lesions. Once the symptoms subside and the lesion regress, the dose can be increased slowly. In extremely severe cases that cannot be controlled with simple symptomatic treatment, systemic corticosteroid treatment may be used, and pirfenidone may need to be discontinued.

CONCLUSION

In conclusion, it should be kept in mind that the most common adverse effect of pirfenidone is photosensitive skin rash. The rash can be asymptomatic, self-limiting, and in the form of mild lesions, or it can be chronic, covering large areas and causing severe symptoms that reduce quality of life. The effective treatment of IPF is limited, and photosensitivity drug rash can be controlled without discontinuing pirfenidone, which is important in this regard, by reducing the dose, taking adequate sun protection, and other additional measures (6). Informing the patient in this respect, patient compliance, and the clinician's approach in this situation in light of this information are of great importance.

Footnote

Ethics Committee Approval: Ethical approval for the study was obtained from the Pharmaceutical and Non-Medical Device Research Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine (decision number: 2020/2429, date: 17.04.2020).

Informed Consent: Informed consent was obtained from all patients participating in the study.

Authorship Contributions

Surgical and Medical Practices: S.A.T., S.Y., A.A., A.Z., N.K., P.O., Concept: S.A.T., S.Y., A.Z., Design: S.A.T., S.Y., A.A., A.Z., Data Collection or Processing: S.A.T., S.Y., A.Z., N.K., P.O., Analysis or Interpretation: S.A.T., S.Y., A.A., A.Z., P.O., Literature Search: S.A.T., S.Y., Writing: S.A.T., S.Y.

Conflict of Interest: No conflicts of interest were declared by the authors.

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