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RESPIRATORY CASE REPORTS

A Rare Side Effect of Pirfenidone: Lichenoid Actinic Keratosis and Lichenoid Actinic Mucositis

Pirfenidon'un Nadir Bir Yan Etkisi: Likenoid Aktinik Keratoz ve Likenoid Aktinik Mukozit

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Abstract

Pirfenidone is one of two approved treatments for Idiopathic pulmonary fibrosis (IPF), the most common side effects of which are related to the skin and the gastrointestinal tract. Although these side effects are well tolerated, it may at times be necessary to discontinue the drug. We present here a case with rare side effects of pirfenidone treatment, lichenoid actinic mucositis and lichenoid actinic keratosis. A 72-year-old male patient with complaints of dyspnea and dry cough was diagnosed with IPF with typical radiological findings, and was followed up for three years. The patient was considered stable under pirfenidone treatment, however, skin lesions were observed on the scalp and lip at the third-year follow-up, a biopsy of which revealed the presence of lichenoid actinic mucositis and lichenoid actinic keratosis. The lesions regressed upon the cessation of pirfenidone, but returned after the reinitiation of treatment, and the precancerous nature of the lesions spurred a change of treatment to nintedanib.

Keywords: *Actinic Keratosis, Drug Side Effects, Idiopathic Pulmonary Fibrosis, Pirfenidone.*

Öz

Pirfenidon, İdiopatik pulmoner fibrozis (IPF) için onaylanmış iki tedaviden biridir. Pirfenidonun en yaygın yan etkileri cilt ve gastrointestinal sistem ile ilgilidir. Yan etkiler iyi tolere edilse de zaman zaman ilacın kesilmesi gerekebilir. Bu olgu sunumunda pirfenidon tedavisinin nadir görülen bir yan etkisi olan likenoid aktinik mukozit ve likenoid aktinik keratoz bildirilmiştir. Nefes darlığı ve kuru öksürük şikayetleri ile başvuran 72 yaşındaki erkek hasta, tipik radyolojik bulgularla İPF tanısı almış ve 3 yıldır takip edilmektedir. Pirfenidon tedavisi altında stabil olarak değerlendirilen hastanın üçüncü yıl kontrolünde saçlı deri ve dudakta deri lezyonları görüldü. Bu lezyonların biyopsisi likenoid aktinik mukozit ve likenoid aktinik keratoz varlığını ortaya koydu. Bu lezyonlar, pirfenidonun kesilmesi üzerine gerileme gösterdi; ancak tedavinin yeniden başlatılmasından sonra lezyonlar tekrarladı ve lezyonların premalign doğası nedeniyle tedaviye nintedanib olarak devam edildi.

Anahtar Kelimeler: *Aktinik Keratoz, İlaç Yan Etkileri, İdiopatik Pulmoner Fibrozis, Pirfenidon.*

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Idiopathic pulmonary fibrosis (IPF) is characterized by progressive fibrosis, and is a chronic, non-curable disease with an unknown etiology that has a worse prognosis than many cancers (1). The antifibrotic agents used for the treatment of IPF in recent years have been shown to prevent the progression of pulmonary fibrosis, to slow the worsening of pulmonary function tests and disease progression, and to reduce the frequency of attacks and hospitalizations (2). Pirfenidone is one of two currently approved treatments for IPF, the most common side effects of which are related to the skin (rash 26.2%, photosensitivity 9.3%) and the gastrointestinal tract (16-32%) (3,4). Although the side effects are well tolerated, it may be necessary to discontinue the drug at times. We present here a case with rare side effects of pirfenidone treatment – lichenoid actinic mucositis and lichenoid actinic keratosis.

CASE

A 72-year-old male patient was evaluated at an outpatient clinic for complaints of dry cough and shortness of breath. The patient had a smoking history of 30 pack-years and had quit smoking 15 years earlier. While he had no known comorbidities, a physical examination revealed bibasilar crepitant rales in auscultation and clubbing of the fingers.

A chest x-ray requested for an initial evaluation revealed a prominent reticular appearance in the middle and lower zones. High-resolution computed tomography (HRCT) revealed findings consistent with the usual interstitial pneumonia (IUP) pattern and increased reticular densities in the lower zones of both lung parenchyma, traction bronchiectasis and prominent honeycomb appearances. Collagen tissue markers for possible rheumatological involvement were requested and were found to be negative. A mild limitation was observed in the pulmonary function test (PFT); and forced vital capacity (FVC), forced expiratory volume (FEV1%), FEV1/FVC ratio and carbon monoxide diffusion capacity (DLCO) were 72%, 78%, 83% and 88% respectively. The patient walked 450 meters in a 6-minute walking test (6MWT), during which no desaturation was present, and the Borg scale scores were 0 at the beginning and 1 at the end of the test. Echocardiography (ECHO) findings were considered stable, with an ejection fraction of 60% and systolic pulmonary arterial pressure (sPAB) of 30 mmHg.

The patient was evaluated by the interstitial lung multidisciplinary council of the hospital for a diagnosis of idiopathic pulmonary fibrosis (IPF). With other diagnoses being unlikely based on the radiological findings, negative rheumatological markers and patient history, the diagnosis of IPF was confirmed, and antifibrotic treatment was initiated.

The patient was placed on a pirfenidone regimen with an initial dosage of 200 mg QID, and a weekly dosage titration plan along with liver enzyme control up to a maximum dosage of 2400 mg/day. The patient was started on a proton pump inhibitor to counter the gastrointestinal side effects and sun protection was recommended. A three-monthly follow-up plan that included chest X-ray, routine laboratory testing and PFT; and a six-monthly 6MWT and annual HRCT were recommended to the patient for disease control. The patient was considered stable for the following 3 years (Table 1).

At the third-year evaluation, the patient complained of dark-colored lesions on the lips and scalp that were considered macular (Figure 1). A biopsy was performed in accordance with a dermatology consultation, and the pathology report defined the lesions as lichenoid actinic mucositis and lichenoid actinic keratosis. Local treatment was started for the lesions and the antifibrotic treatment was halted as the mentioned lesions were considered precarious. The lesions were observed to have regressed after 1 month, and pirfenidone was initiated with the original 200 mg QID dosage titration (Figure 2). As the lesions reappeared in the third-week control, the pirfenidone treatment was discontinued again as the lesions were considered a drug side effect. Regression in the lesions was observed during the first-month control, and the antifibrotic regimen was changed to nintedanib. As of the time of this report, the patient had been evaluated at the third monthly follow-up under nintedanib and has demonstrated good drug tolerance.

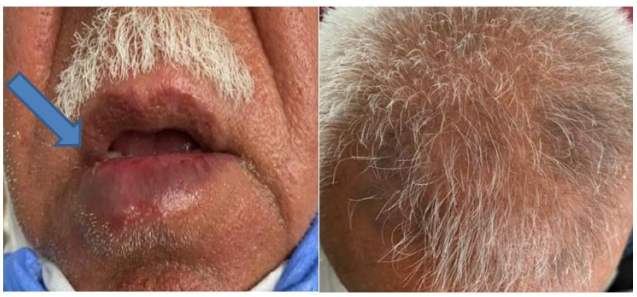

Figure 1: White-colored lesions on the lower lip (right) and dark-colored lesions on the scalp

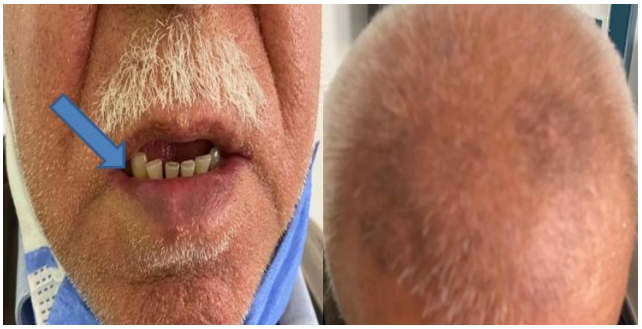

Figure 2: Lesion regression after the discontinuation of pirfenidone

Table 1: Patient Follow-up Parameters

		Diagnosis	3rd Month	6th Month	1st year	2nd year	3rd year
FVC (%)		72	73	69	74	63	63
DLCO (%)		88	77	73	77	82	79
6MWT (m)		450		420	400	450	380
ECHO	sPAP (mmHg)	30			35	35	45
	EF (%)	60			60	60	55

FVC: Forced Vital Capacity, DLCO: Diffusion Capacity of Carbon Monoxide, 6MWT: Six Minute Walking Test, ECHO: Echocardiography, sPAP: Systolic Pulmonary Arterial Pressure, EF: Ejection Fraction

DISCUSSION

The 2015 update of the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association treatment guidelines identified pirfenidone as one of only two novel agents conditionally recommended for the treatment of IPF (1).

Pirfenidone is prescribed in doses of 2400–2403 mg/day in mild and moderate cases with FVC and DLCO values of 50% and 30%, respectively. While the mechanism of action is not entirely understood, it is assumed to work by blocking the TGF-b pathway, thus reducing fibroblast growth and differentiation into myofibroblasts, according to an in vitro research (2). Photosensitivity is a common side effect of pirfenidone with a reported incidence in 12% of patients taking pirfenidone versus 2% of patients taking a placebo (3–5). The reported cases of severe photosensitizing drug eruptions caused by pirfenidone were attributed to its phototoxic effect and its ability to absorb UVA and UVB light. The absorption of UV light by pirfenidone in the skin leads to the development of lipid peroxidation and reactive oxygen species, resulting in skin lesions with clinical characteristics similar to sunburn (5). Such developments tend to occur early in treatment and settle over time (3). If the rash persists for more than 15 days, the treatment dose should be reduced and the drug should be stopped. Once the symptoms subside, the drug can be slowly reintroduced (6). There have been no studies to date associating actinic mucositis, actinic keratosis or squamous dysplasia with pirfenidone.

Actinic keratosis is the most common premalignant skin disease in the white population, and is caused by ultraviolet radiation exposure. It remains one of the most common reasons for dermatologist visits (7–9).

The tumor suppressor gene p53 and telomerase, located on chromosome 17p132, are two mutation sites of particular interest in the formation of actinic keratosis. It has been suggested that people with actinic keratosis lesions have a 10.2% chance of developing squamous cell carcinoma within 10 years (10). Avoiding direct sun exposure, wearing long sleeves, wearing hats and using wide-spectrum sunscreens with proper UVB and UVA protection are currently recommended for patients under pirfenidone treatment. For those who develop side effects, the treatment can be stopped and low-dose re-treatment can be started, or local systemic steroid drugs can be used. The drug treatment should be stopped in patients who do not respond, as was the case with the patient covered in this case report.

CONCLUSION

When starting a patient on pirfenidone therapy, they should be informed about the drug's potential to cause skin cancer when exposed to light. Due to the risk of malignancy, treatment must be stopped if actinic keratosis is detected.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - B.A.Ö., T.Ş.Ö., E.S.A., K.E., B.A.; Planning and Design - B.A.Ö., T.Ş.Ö., E.S.A., K.E., B.A.; Supervision - B.A.Ö., T.Ş.Ö., E.S.A., K.E., B.A.; Funding -; Materials -; Data Collection and/or Processing - E.S.A., B.A.; Analysis and/or Interpretation - B.A.Ö., T.Ş.Ö., K.E.; Literature Review - E.S.A., B.A.; Writing - B.A.Ö., K.E.; Critical Review - B.A.Ö., K.E.

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