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Case Report

Internal Medicine Section

Pirfenidone Induced Dress Syndrome Post COVID-19 Infection- An Unusual Case Report

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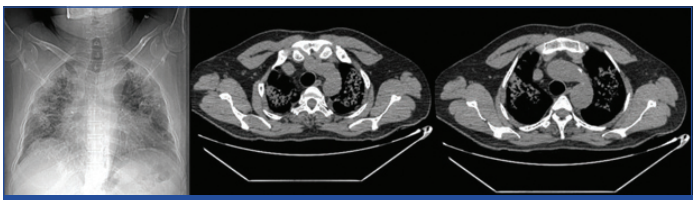
ABSTRACT

Drug Reaction, Eosinophilia and Systemic Symptoms (DRESS) is an idiosyncratic drug reaction characterised by extensive skin rash, fever, lymphadenopathy and internal organ involvement. Since, eosinophilia may or may not always be present, the condition is now more preferably called Drug-Induced Hypersensitivity Syndrome (DIHS). The authors here report a case of DRESS syndrome, secondary to pirfenidone, an antifibrotic given to the patient for post Coronavirus Disease-2019 (COVID-19) fibrosis. The 51-years-old male patient, presented with multiple pus-filled erythematous lesions, three months after the initiation of pirfenidone. Laboratory results showed deranged liver and renal functioning, along with reactive Dengue Nonstructural protein 1(NS 1) antigen. He showed significant improvement in the dermatological lesions and multisystem laboratory involvement with tapering doses of steroids.

Keywords: Coronavirus disease-2019 fibrosis, Drug induced hypersensitivity syndrome, Naranjo criteria, RegiSCAR

CASE REPORT

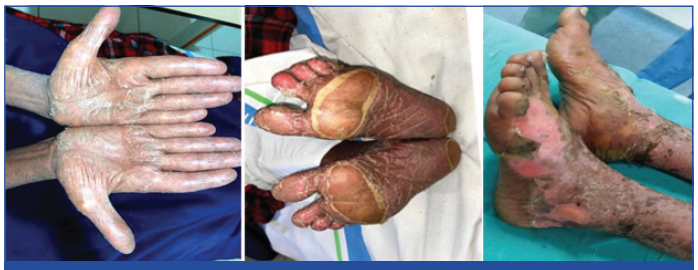
A 51-year-old hypertensive male patient presented with high-grade fever, generalised weakness and anorexia of five days duration. He had a strong positive contact history with COVID-19 patients, as he was working as a social worker during the pandemic. Chest imaging High Resolution Computed Tomography (HRCT) showed multiple ground-glass opacities with diffuse irregular consolidation in bilateral lung fields [Table/Fig-1]. Though, his Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) for COVID-19 was negative, but in view of strong clinical suspicion with classical radiological evidence, he was managed on the lines of COVID-19 infection using remdesevir for five days and steroids. He required 6-8 litres of oxygen during the stay, which was gradually tapered to 2 litres.



[Table/Fig-1]: (Left) Chest X-ray showing diffuse irregular consolidations in bilateral upper lobes of the lungs; (Center and Right) High Resolution Computed Tomography (HRCT) images showing ground glass opacities with irregular interlobular and intralobular septal thickening with tractional bronchiectasis.

After two weeks of uneventful hospital stay, he was discharged on home-based oxygen therapy and oral steroids in tapering doses, which eventually was omitted over next four weeks. As he had persistent hypoxia requiring home oxygen treatment and his HRCT showed changes of post COVID-19 fibrosis, he was prescribed an antifibrotic agent, pirfenidone 600 mg/day. He was lost to follow-up thereafter. After three months of discharge, he presented with complains of multiple erythematous lesions over the face, trunk and extremities [Table/Fig-2]. These appeared about 20 days back and gradually progressed to large, fluid and pus-filled bullous lesions, which would rupture spontaneously. He told that he continued pirfenidone since he was first released from hospital. He was readmitted for the evaluation.

During the first admission, the Liver Function Test (LFT) was within normal limits. However, during the readmission, it was significantly deranged, with raised liver enzymes, hyperbilirubinaemia, and raised



[Table/Fig-2]: Local site involvement on the palms, soles and feet.

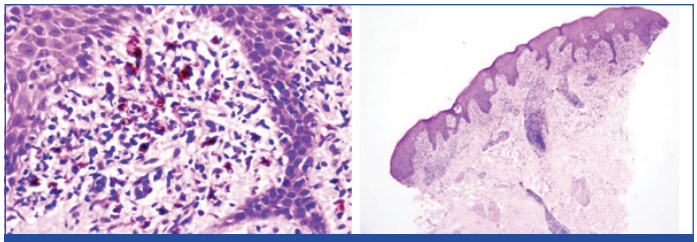
creatinine levels [Table/Fig-3]. Human Immunodeficiency Virus and viral hepatitis were ruled out and Antinuclear Antibody (ANA) panel was negative.

A possibility of Adverse Drug Reaction (ADR) leading to DRESS syndrome was considered. The patient was taking only steroids and pirfenidone, so pirfenidone was suspected to cause DRESS syndrome. However, in view of long-term steroids, a possibility of sepsis was also considered. As per the dermatologist's advice, a skin biopsy from left forearm was performed from the lesion, and stained with Haematoxylin and Eosin (H&E) stain. The biopsy showed changes of atopic dermatitis favouring a drug induced reaction [Table/Fig-4]. The Naranjo score was 6 implying a probable diagnosis of ADR, due to pirfenidone causing DRESS [1]. Using the RegiSCAR criteria [2], a provisional diagnosis of DRESS syndrome was considered (skin eruption, fever >38ºC, visceral organ involvement-altered liver and renal function tests with eosinophilia).

Thus, pirfenidone was discontinued and injectable dexamethasone was given for three days, which later was switched to oral prednisolone. Broad spectrum antibiotics (Meropenem 1 gm intravenously three times/day) was started. Topical beclomethasone and paraffin creams were advised. After discontinuation of pirfenidone, the skin lesions started to improve over next two days. On day four of admission, he started to have fever spikes (Injection (Inj.) Meropenem 1 gm iv was ongoing, platelet count was reduced (1,71,000/µL to 1,64,000/µL). Dengue NS1 antigen was reactive. Malarial serology was negative. Dengue hepatitis was considered, but the resolution of the LFT coincided with the improvement in the skin lesions. Blood cultures showed *Acinetobacter baumanii* and *Candida* species for which antibiotics were continued according to sensitivity reports.

Test	Normal range	On first admission	On readmission	On discharge (day 7)	On 1 month follow-up	On 2 month follow-up	On 3 months follow-up
TLC (x1000/µL)	4-10	14.3	26.3	9.7	7.1	4.6	11.5
Platelets (x1000/µL)	150-410	524	171	391	291	212	384
Differential counts (in %): (N/L/E/M/B)	N:40-80 L:20-40 E:2-6 M:2-8 B:0-1	84/12/1/3/0	39/10/20/2/0	75/18/1/6/0	80/15/1/4/0	61/31/2/6/0	90/5/1/4/0
ALT (IU/mL)	16-63	111	217	349	46	42	20
AST (IU/mL)	15-37	29	129	223	21	12	16
Total bilirubin (mg%)	0.2-1.0	0.73	6.77	5.36	0.68	0.53	0.52
Direct bilirubin (mg%)	0.0-0.2	0.20	5.77	4.91	0.31	0.19	0.14
Creatinine (mg%)	0.8-1.3	0.98	1.72	1.38	1.31	0.85	0.87
LDH (IU/mL)	85-227	320	756	Not done	Not done	Not done	Not done
Albumin (gm%)	3.4-5.0	2.6	1.8	2.8	2.7	3.5	2.3
Blood culture				*Acinetobacter baumanii* and *Candida* spp.		No growths isolated	
Dengue NS1 antigen			Reactive				
Malarial serology			Negative for *Plasmodium falciparum* and *Plasmodium vivax*				

[Table/Fig-3]: Laboratory investigations.
TLC: Total leucocyte count; ALT: Alanine transaminase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; NS1: Nonstructural protein 1



[Table/Fig-4]: Skin biopsy with H&E staining (Left: 40x and right: 4x magnification) (Left): Microphotograph shows moderate oedema in the superficial dermis with moderate to intense lymphohistiocytic infiltrate causing focal degeneration of basal layer of epidermis with prominent pigmentary incontinence. (Right): Microphotograph shows irregular acanthosis with mild spongiosis and a moderate perivascular and periadnexal lymphocytic infiltrate in the superficial dermis.

On follow-up, with tapering doses of oral prednisolone, he showed good recovery in both clinical and in laboratory parameters. The skin lesions regressed on subsequent follow-ups and were completely normalised over the next three months.

DISCUSSION

'False negative' results of COVID-19 RT-PCR, despite having a high clinical suspicion can be attributed to simple errors such as sampling errors. Also, each patient may be at a different stage of the disease spectrum when tested initially, hence giving a variable, and often unreliable result.

In patients of DRESS, there is a significant lowering of the proinflammatory cytokines viz., Tumour Necrosis Factor (TNF)-∝, interferon gamma and interleukins 6, 12 [3]. Various cases of DRESS syndrome have been reported with a variety of aetiologies, the most common one being drug-induced including anticonvulsant (carbamezipine), antibiotics (particularly beta-lactams), antiretrovirals and allopurinol [4]. Other aetiologies include DRESS in association with the reactivation of Human Herpes Virus (HHV-6), as reported by Ichiche M et al., and also according to Lens S et al., approximately 50% of the reported cases of DRESS with hepatic involvement resulted in death or liver transplantation [5,6].

Pirfenidone is being increasingly used for Idiopathic Pulmonary Fibrosis (IPF) as an antifibrotic agent especially for patients with mild to moderate disease, along with other anti-fibrotic drug like nintedanib. The latter is also effective in systemic sclerosis-related Interstitial Lung Disease (ILD), as well as non IPF ILD. Considering their anti-fibrotic, anti-inflammatory, oxygen radical scavenger effects [7], these drugs have been increasin gly used presuming their benefit in post COVID-19 fibrosis, especially after the first wave of COVID-19 [8].

Pirfenidone has been attributed to a variety of adverse effects like gastrointestinal (nausea, dyspepsia), neurological (insomnia, anxiety) and dermatological (rash, photosensitivity) [9]. However, what is lesser known is the rare and unusual side-effects of these drugs. DRESS/DIHS is one of the very rare adverse effects of pirfenidone, which was first reported in 2018 in Japan in a patient in whom pirfenidone was given for treatment of IPF [10]. However, to the best of our knowledge, this is the first case of pirfenidone induced DRESS syndrome being reported in a patient with post COVID-19 fibrosis, complicated with dengue co-infection, along with positive Widal titers.

CONCLUSION(S)

During the current times of the pandemic, with pirfenidone being prescribed widely and routinely, such a rare and serious adverse effect should be kept in mind, and the drug should be prescribed cautiously with regular routine follow-up and looking out for such an ADR. Patients and their relatives should be counselled about possible serious adverse reactions of pirfenadone. Further, phase IV post marketing surveillance of the drug should be conducted, keeping in mind the current explosion in the aforementioned drug usage.

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