Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:
Pezzuto A, Demofonte I, Parisella FR, et al. **Eczema-like cutaneous lesions in idiopathic pulmonary fibrosis: a shared Th2-driven pathway?** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2026.3718

Submitted: 7-09-2025
Accepted: 11-06-2026

Eczema-like cutaneous lesions in idiopathic pulmonary fibrosis: a shared Th2-driven pathway?

Aldo Pezzuto,[1] Ilaria Demofonte,[2] Francesca Romana Parisella,[3] Fabiola Luzi,[4] Gabriella De Marco,[5] Antonella Tammaro[6]

[1]Unit of Pulmonology, Department of Cardiovascular and Respiratory Sciences, Sant'Andrea Hospital, Sapienza University, Rome, Italy; [2]Unit of Dermatology of Dermatology, Department of Medical and Cardiovascular Science, Sapienza Medical School of Rome, Italy; [3]Department of Medicine, University of Queensland, Brisbane, Australia; [4]Plastic and Reconstructive Surgery, San Gallicano Dermatologic Institute IRCCS, Rome, Italy; [5]Department of Dermatology, Sant'Andrea General Hospital, Sapienza University of Rome, Italy; [6]Department of Health Sciences, Magna Graecia University, Catanzaro, Italy

Correspondence: Antonella Tammaro, Department of Health Sciences, University "Magna Graecia" of Catanzaro, Viale Europa, 88100, Catanzaro, Italy. E-mail: tammaroantonella@gmail.com

Key words: idiopathic pulmonary fibrosis, Th2 inflammation, atopic eczema, cytokines, immune dysregulation.

Contributions: all authors contributed to the preparation of this manuscript and all authors agree with the content of the manuscript. Aldo Pezzuto: data curation, writing, editing, supervision. Ilaria Demofonte: writing, data curation, review and editing. Francesca Romana Parisella: data curation. Fabiola Luzi: data curation. Gabriella De Marco: data curation. Antonella Tammaro: validation, supervision.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: the study was conducted in accordance with institutional guidelines and approved by the Ethics Committee of Sant'Andrea Hospital, Sapienza University of Rome, Italy (Ethics Committee consent form 273).

Patient consent for publication: the patient provided informed consent for publication.

Availability of data and materials: the data that support the findings of this study are available on request from the corresponding author.

Acknowledgments: the authors would like to thank the multidisciplinary team involved in the care of the patient, whose collaboration was essential for the diagnosis and management of this case.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process: no use of artificial intelligence.

Dear Editor,

Idiopathic pulmonary fibrosis (IPF) is the most frequent form of idiopathic interstitial pneumonia, characterized by a progressive course and poor prognosis, with a median survival of 3-5 years after diagnosis. Its pathogenesis is driven by chronic epithelial injury with both innate and adaptive immune activation, ultimately leading to irreversible fibrogenesis [1,2]. At the molecular level, key mediators include the *Transforming Growth Factor-β1* (TGF-β1) pathway, Th2 cytokines (IL-4, IL-13), M2 macrophage activation, and the MUC5B promoter polymorphism [3-5].

In parallel, Atopic Eczema is a chronic inflammatory skin disorder characterized by Th2-immune predominance, epidermal barrier dysfunction, and hyper-reactive immune responses. In this setting as well, IL-4 and IL-13 play a pivotal role, triggering inflammatory cascades, eosinophilia, and IgE hyperproduction [6].

Although no direct pathogenetic link between IPF and eczema has been established, the convergence of Th2-driven immunological pathways suggests a shared background of immune dysregulation, raising the possibility of a clinical association between the two diseases, as illustrated in the following case.

We report the case of a 72-year-old woman with chronic oxygen-dependent IPF, multiple cardiovascular comorbidities (arterial hypertension, paroxysmal atrial fibrillation), and antifibrotic therapy with nintedanib. Over recent years, she experienced recurrent episodes of respiratory failure, with HRCT findings consistent with advanced-stage IPF.

In July 2025, she presented to the Emergency Department with worsening dyspnoea (NYHA class III–IV). Laboratory tests revealed increased creatinine (2.5 mg/dl), increased BUN (90 mg/dl), hyponatremia (129 mmol/l), and elevated BNP (1500 pg/ml) C reactive protein was increased (15 mg/dl). High resolution computed tomography, HRCT, confirmed advanced IPF, without pleural effusion or mediastinal lymphadenopathy (Figure 1).

The cardio-respiratory parameters were the following: respiratory rate 30/minute, heart rate 110/minute and by blood arterial haemogas-analysis the rate PaO2/FiO2 was 150 indicating respiratory distress.

A treatment by high flow nasal cannula oxygen, HFNC, was begun with calculated FiO2 90% along with a high intravenous steroid dose, methyl-prednisolone 80 mg. Moreover, diuretic and aerosol therapy with bronchodilators was also prepared. A sputum analysis revealed the presence of S.aureus, therefore a treatment with teicoplanin was started. Progressively the patient responded to the therapy, leading to a stepdown of the same, with a weaning from high flows. The patient resumed anti-fibrotic therapy with nintedanib 150 mg a day. Subsequent radiological examinations showed substantial stability of the fibrotic condition with a

reduction in the oedematous component. There was therefore a gradual improvement in clinical symptoms, including dyspnoea at rest.

Five days after hospital admission, the patient developed intense facial pruritus with diffuse erythema and exudative papules, particularly in the zygomatic and periorbital regions. Dermatological examination revealed diffuse erythema with excoriations in the malar region and fine frontonasal desquamation, without evidence of secondary infection. The patient had no previous history of atopic dermatitis, eczema, asthma, allergic rhinitis, or other documented atopic disorders. Intravenous corticosteroid therapy was initiated one day after the onset of the skin eruption, minimizing the possibility that the initial clinical presentation was modified by systemic steroid administration. Total serum IgE measured during the dermatological evaluation was 115 kU/L.

Histopathological examination of a lesional skin biopsy performed on hematoxylin-eosin–stained sections showed perivascular lymphocytic infiltrate with eosinophils and intraepidermal spongiosis, consistent with an atopic-like eczema pattern. No histological features suggestive of other specific inflammatory dermatoses were identified.

Although these findings supported the diagnosis of eczema-like dermatitis, a complete distinction from certain drug-induced eruptions could not be established on histopathological grounds alone, and clinicopathological correlation was therefore considered essential.

Therapeutic management included topical corticosteroids, barrier emollients, and continued monitoring of antifibrotic therapy.

Although the literature does not report a direct or systematic association between IPF and cutaneous disorders, several dermatological manifestations have been described in patients with idiopathic pulmonary hypertension or in the context of chronic respiratory complications:

- Peripheral cyanosis: frequent, due to chronic hypoxemia and reduced oxygen saturation [7];
- Livedo reticularis: observed in patients with low cardiac output and advanced IPF [8];
- Acrocyanosis and Raynaud-like lesions: related to hypoxemia and peripheral vascular dysfunction [9];
- Peripheral edema with tense and shiny skin: reflecting right heart failure [10];
- Cutaneous telangiectasias or angiomas: occasionally reported, nonspecific but found in chronic pulmonary hypertension [11].

These dermatological features, while not specific to IPF itself, reflect the systemic involvement of the disease, chronic hypoxemia, and its cardiovascular complications.

Alongside the importance of oxygen therapy and controlling flare-ups in interstitial lung diseases, the present case highlights how a patient with IPF may develop eczema-like cutaneous lesions, which may be interpreted either as an atopic manifestation unmasked or as

the cutaneous counterpart of a Th2-driven immune dysregulation shared between the lung and the skin.

In IPF, TGF-β1 acts as the central profibrotic mediator, while IL-4 and IL-13 promote M2 macrophage polarization and collagen deposition [5]. In eczema, the same cytokines sustain skin inflammation, eosinophilia, and increased IgE levels, in association with epithelial mediators such as TSLP, periostin, and galectins [6,12].

An alternative explanation that deserves consideration is a drug-related cutaneous reaction. Although gastrointestinal adverse events are the most commonly reported side effects of nintedanib, cutaneous adverse reactions, including skin rash, have also been described in the literature [13]. In the present case, the temporal relationship appears less supportive of a direct nintedanib-induced eruption because the lesions developed during treatment interruption and before drug reintroduction. Nevertheless, a contributory role of nintedanib cannot be completely excluded and should be acknowledged as a potential confounding factor.

The occurrence of dermatological manifestations in IPF could therefore be interpreted in two contexts:

1. Clinical signs related to chronic hypoxemia or cardiovascular complications (cyanosis, livedo, edema).
2. Eczema-like inflammatory lesions potentially linked to a shared Th2-driven immunological polarization.

In conclusion, although a definitive pathogenetic connection between idiopathic pulmonary fibrosis and atopic eczema has not yet been demonstrated, the present report highlights the occurrence of atopic-like eczema manifestations in a patient with advanced IPF. This observation should be regarded as a preliminary and hypothesis-generating clinical finding rather than evidence of a pathogenetic association. While the coexistence of these conditions may reflect overlapping Th2-mediated immune pathways involving IL-4 and IL-13 signalling, alternative explanations, including drug-related mechanisms, cannot be excluded. Recognition of such cutaneous manifestations requires a multidisciplinary approach and underscores the need for further clinical and translational studies to elucidate whether this observation represents a true biological association or a coincidental finding, as well as to better define the pathogenetic, clinical, and diagnostic framework potentially linking the two diseases.

References

1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;198:e44-68.
2. Harari S, Caminati A. Idiopathic pulmonary fibrosis: from clinical trials to real-life experiences. Eur Respir Rev 2015;24:420-7.
3. Singh P, Guin D, Pattnaik B, Kukreti R. Mapping the genetic architecture of idiopathic pulmonary fibrosis: Meta-analysis and epidemiological evidence of case-control studies. Gene 2024;895:147993. Erratum in: Gene 2025;941:149223.
4. Drakopanagiotakis F, Wujak L, Wygrecka M, Markart P. Biomarkers in idiopathic pulmonary fibrosis. Matrix Biol 2018;68-69:404-21.
5. Montero P, Milara J, Roger I, Cortijo J. Role of JAK/STAT in interstitial lung diseases; molecular and cellular mechanisms. Int J Mol Sci 2021;22:6211.
6. Mandlik DS, Mandlik SK. Atopic dermatitis: new insight into the etiology, pathogenesis, diagnosis and novel treatment strategies. Immunopharmacol Immunotoxicol 2021;43:105-25.
7. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
8. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62:D42-50.
9. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573-619.
10. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. BMJ 2018;360:j5492.
11. Sitbon O, Morrell N. Pathways in pulmonary arterial hypertension: the future is here. Eur Respir Rev 2012;21:321-7.
12. Dubin C, Del Duca E, Guttman-Yassky E. The IL-4, IL-13 and IL-31 pathways in atopic dermatitis. Expert Rev Clin Immunol 2021;17:835-52.

13. Provenzani A, Leonardi Vinci D, Alaimo M, et al. Real-world insights into safety, tolerability, and predictive factors of adverse drug reactions in treating idiopathic pulmonary fibrosis with pirfenidone and nintedanib. Ther Adv Drug Saf 2025;16:20420986251341645.

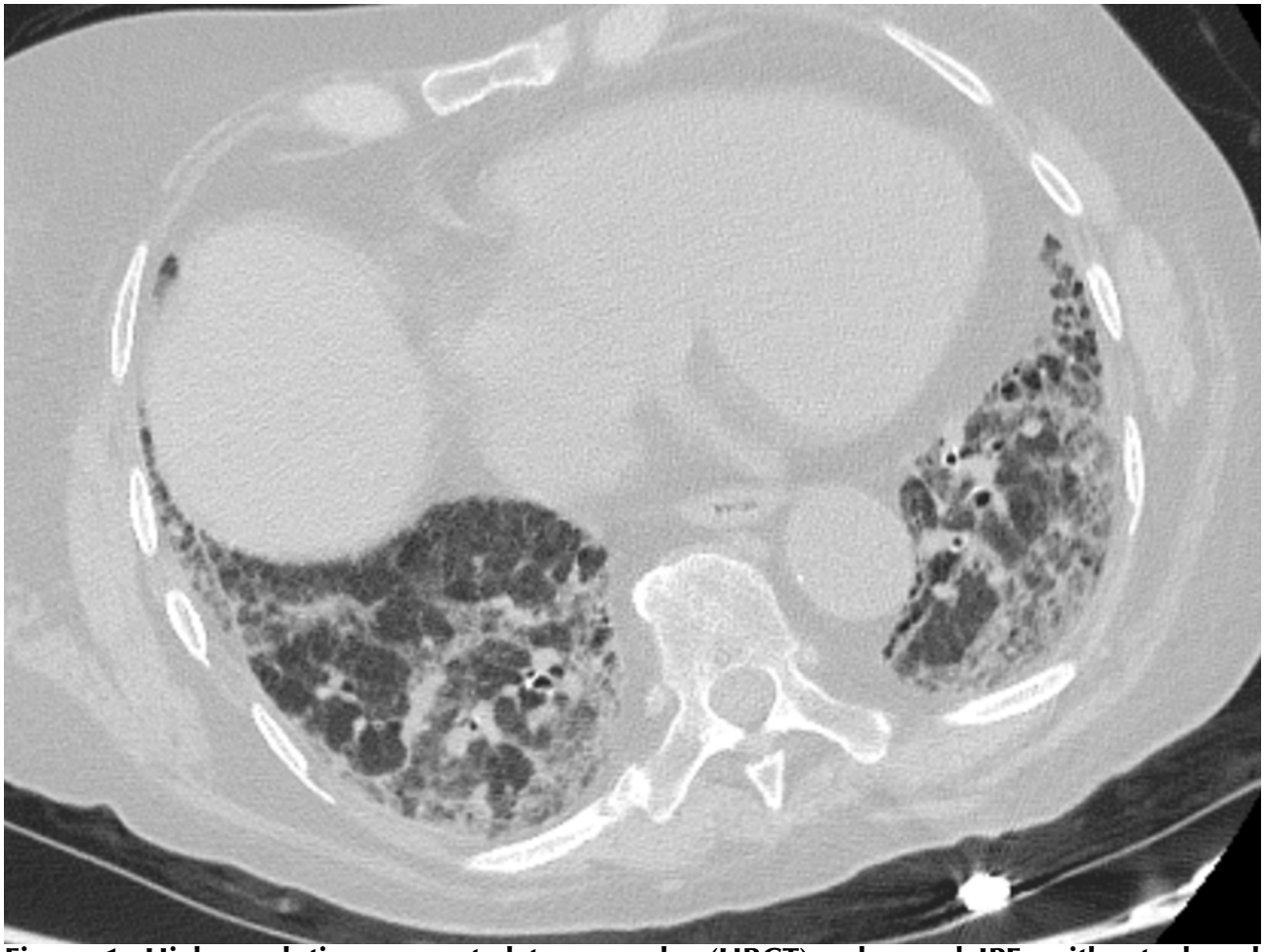

Figure 1. High resolution computed tomography (HRCT): advanced IPF, without pleural effusion or mediastinal lymphadenopathy.