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ORIGINAL RESEARCH

A Multidisciplinary Approach to Improve the Management of Immune-Checkpoint Inhibitor-Related Pneumonitis

Monica Valente[1], Maura Colucci[2], Virginia Vegni[3], Valentina Croce[2], Cristiana Bellan[4], Giulia Rossi[1], Giulia Gibilisco[2], Francesco Frongia[2], Raffaella Guazzo[4], Claudia Ghiribelli[5], Elena Bargagli[6], Vinno Savelli[7], Matteo Ravara[2], Tommaso Sani[2], Elena Simonetti[2], Michele Maio[1–3], Luana Calabrò[8,9], Anna Maria Di Giacomo[1–3]

[1]Department of Oncology, Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [2]Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy; [3]NIBIT Foundation Onlus, Siena, Italy; [4]Department of Medical Biotechnology, Pathology Unit, University Hospital of Siena, Siena, Italy; [5]Cardio-Thoracic-Vascular Department, Interventional and Diagnostic Bronchoscopy Unit, University Hospital of Siena, Siena, Italy; [6]Department of Medicine, Surgery and Neurosciences, Respiratory Diseases Unit, University of Siena, Siena, Italy; [7]Department of Medicine, Surgery and Neurosciences, Surgical Oncology Unit, University Hospital of Siena, Siena, Italy; [8]Department of Translational Medicine, University of Ferrara, Ferrara, Italy; [9]Department of Medical Oncology, University Hospital of Ferrara, Ferrara, Italy

Correspondence: Anna Maria Di Giacomo, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy, Tel +39-0577-586336, Fax +39-0577-586303, Email annamaria.digiacomo@unisi.it

Purpose: Treatment with immune-checkpoint inhibitors (ICIs) can be associated with a wide spectrum of immune-related adverse events (irAEs). Among irAEs, immune-mediated pneumonitis (im-PN) is a rare but potentially life-threatening side effect. TPrompt multidisciplinary diagnosis and effective management of im-PN may be essential to avoid severe complications and allowing resumation of therapy.

Patients and Methods: We collected a case series of skin (melanoma, cutaneous squamous cell carcinoma-CSCC), lung, and mesothelioma cancer patients (pts), treated with ICI at the Center for Immuno-Oncology University Hospital of Siena, Italy, and diagnosed with im-PN. Clinical and radiologic data were thoroughly collected, as well as bronchoalveolar lavage (BAL) samples; im-PN was graded using CTCAE v. 5.0. Radiological patterns were reported according to the *F*leischner Society classification.

Results: From January 2014 to February 2023, 1004 patients with melanoma (522), CSCC (42), lung (342) or mesothelioma (98) were treated with ICI (619 monotherapy; 385 combination). Among treated patients, 24 (2%) developed an im-PN and 58% were symptomatic. Im-PN were classified as grades G1 (10) and G2 (14). Prompt steroid treatment led to complete resolution of im-PN in 21 patients, with a median time to resolution of 14 weeks (range: 0.4–51). Twelve patients resumed ICI therapy once fully-recovered and 2 experienced a recurrence that completely resolved with steroids after resumption of treatment. Three radiologic patterns were identified: organizational pneumonia-like (67%), pulmonary eosinophilia (29%), and hypersensitivity pneumonitis (4%). Furthermore, BAL analysis performed in 8 (33%) patients showed an inflammatory lymphocytic infiltrate, predominantly consisting of foam cell-like macrophage infiltrates in 6 cases. Notably, transmission electron microscopy evaluation performed in 2 patients revealed a scenario suggestive of a drug-mediated toxicity.

Conclusion: Im-PN is a rare but challenging side effect of ICI therapy, with variable time of onset and with heterogeneous clinical and radiological presentations. A multidisciplinary assessment is mandatory to optimize the clinical management of im-PN.

Keywords: immunotherapy, immune-checkpoint inhibitors, immune-mediated pneumonitis, cancer

Introduction

Immunotherapy with immune-checkpoint inhibitors (ICI), such as anti-cytotoxic t-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death protein-1 (PD-1) and/or its ligand 1 (PD-L1) monoclonal antibodies, represents the mainstay of cancer treatment for tumors of different histotypes.[1] Treatment with ICI can be associated with immune-mediated (im) toxicities that can potentially involve any organ or tissue; notably, the skin, endocrine system, liver, and gastrointestinal

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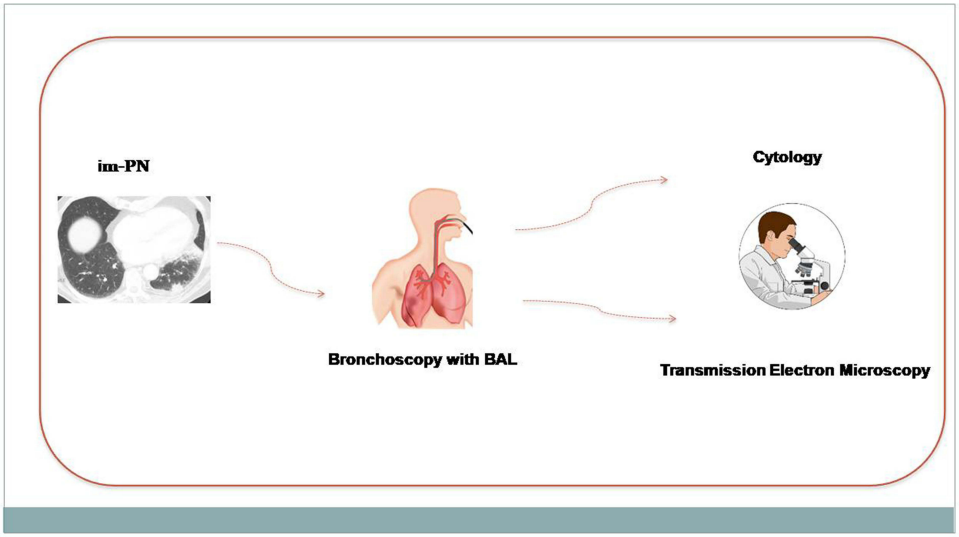
Graphical Abstract



tract are those most involved.[2] Among im-events, lung toxicity with an im-pneumonitis (im-PN) is a rare but challenging event; early clinical trials suggested an incidence of 3–5% with anti-PD-1 antibodies,[3–7] while more recent real-world studies reported a higher incidence (13–19%) of im-PN.[8]

Several potential risk factors predisposing patients to im-PN have been identified; among these are idiopathic interstitial pneumonia, a history of chronic obstructive pulmonary disease, thoracic radiotherapy, exposure to tobacco smoke, and autoimmune disorders.[7] Clinical presentation of im-PN can vary and differs in the severity of onset, with about 50% of symptomatic patients experiencing dyspnea, cough, fever, fatigue, hypoxia, wheezing and/or chest pain.[9] According to the current guidelines, im-PN is graded based on the presence of symptoms and on the amount of radiologic involvement of lung parenchyma. However, the emergence of symptoms is usually associated with a G2–3 im-PN potentially leading to ICI therapy discontinuation, hospitalization, and/or fatal sequelae.

Diagnosis of im-PN could be based on the identification of new or worsening pulmonary infiltrates and/or ground-glass patterns using a high-resolution chest computed tomography (CT) scan as the preferred diagnostic tool. Along this line, Naidoo et al reported five potential distinct radiologic patterns of im-PN by CT scan: ground-glass opacities (GGO), the most frequently observed, organizing pneumonia (OP)-like, hypersensitivity pneumonia (HP), interstitial pneumonia (IP), pulmonary eosinophilia (PEo), and not otherwise specified pneumonitis (NSIP).[10] However, these radiologic patterns are not specific and differential diagnosis includes pulmonary disease progression, pseudo-progression, infectious pneumonia, radiotherapy injury, acute exacerbation of OP disease, or the new coronavirus disease (COVID-19) pneumonia.[11] Despite awareness of the spectrum of radiographic patterns of im-PN to help radiologists accurately detect this clinical entity, the diagnosis of im-PN and its comprehensive management remains challenging for treating physicians, especially in daily practice. Thus, bronchoscopy with transbronchial biopsy and bronchoalveolar lavage (BAL), allowing an in-depth morphologic and histopathologic characterization, are useful approaches to confirm the diagnosis of im-PN and to rule out other etiologies (ie infection, cancer progression).[6]

Once im-PN diagnosis is confirmed, current treatment guidelines recommend corticosteroids as the first specific therapeutic approach, generally leading to clinical improvement within 48–72 hours. However, in steroid refractory im-PN additional immunosuppressive agents, including infliximab, cyclophosphamide, intravenous immunoglobulin, and mycophenolate mofetil, are indicated.[12]

Despite advances in knowledge regarding the comprehensive management of im-PN, in the last decade significant efforts have been devoted to the identification of biomarkers predictive of lung toxicity associated with ICI therapy. However, none of these putative biomarkers has been incorporated into clinical practice as yet.[13]

In light of the considerations above, accurate early diagnosis and management of im-PN within an experienced multidisciplinary team may allow for better risk stratification, close monitoring, and effective therapeutic management. Here, we report on the multidisciplinary management of a large case series of im-PN diagnosed in cancer patients treated with ICI.

Material and Methods

Patients diagnosed with melanoma (MEL), cutaneous squamous cell carcinoma (CSCC), lung cancer (NSCLC) or mesothelioma (MESO), treated with anti-PD-1 monotherapy or ICI combination(s), at the Center for Immuno-Oncology of the University Hospital of Siena, Italy, who developed an im-PN were identified and retrospectively evaluated. For each patient, medical history and concomitant medications were thoroughly collected, as well as clinical (ie im-PN-related symptoms, respiratory rate, oxygen saturation etc) and radiological features of im-PN, time to onset, resolution, and treatment. CT scans were retrospectively reviewed by an internal radiologist, identifying diverse radiological patterns of drug-related pneumonitis, according to the Fleischner Society classification and the National Comprehensive Cancer Network (NCCN) v1.2022 criteria.[14,15] BAL samples or biopsy specimens of patients who underwent bronchoscopy and transbronchial biopsy performed with an endobronchial ultrasound (EBUS) were reviewed by a dedicated pathologist. Im-PNs were graded using the NCI Common Terminology Criteria for Adverse Events Version 5 (NCI-CTCAE v. 5.0).[16]

Statistical Methods

Descriptive statistics were used for patient demographics and characteristics. Time to onset of im-PN was defined as time from first dose of ICI therapy to first occurrence of im-PN-related symptoms or radiologic imaging findings in asymptomatic patients.

Results

From January 2014 to February 2023, 1004 patients with advanced MEL, CSCC, NSCLC and MESO were treated with ICI: 619 patients (62%) received anti-PD1/PD-L1 as monotherapy and 385 (38%) in combination with other immunotherapeutic agents (ie anti-CTLA4, anti-indolamine 2.3-dioxygenase). Among treated patients, 24 (2%) developed an im-PN: 18 MEL, 1 CSCC, 4 NSCLC, and 1 MESO patient. Baseline characteristics of patients diagnosed with im-PN are summarized in Table 1.

Table 1 Baseline Characteristics of Patients Diagnosed with Im-PN

	Patients (n=24)[a]
Sex	
Male	18 (75%)[b]
Female	6 (25%)
Age (years)	69 (41–86)[c]
PS (ECOG)	
0–1	24 (100%)
≥2	0
Baseline lung disease[d]	
Yes	9 (37%)
No	15 (63%)

(*Continued*)

Table 1 (Continued).

	Patients (n=24)[a]
Tumor histotype	
MEL	18 (75%)
CSCC	1 (4%)
NSCLC	4 (16%)
MESO	1 (4%)
Smokers	
Yes	13 (54%)
No	11 (46%)
Smoking exposure[c]	1 pack/y (0.5–5)
Tumour staging[e]	
IIIA-C	5 (21%)
IV	19 (79%)
Thoracic radiotherapy[f]	
Yes	2 (8%)
No	22 (92%)
ICI therapy	
Anti-PD1/PD-L1 monotherapy	14 (58%)
Combination therapy[g]	10 (42%)
BOR[h]	
CR	6 (25%)
PR	4 (17%)
SD	6 (25%)
PD	5 (21%)
Recurrence Free[i]	3 (12%)

Notes: [a]Number of patients diagnosed with im-PN; [b]n (%); [c]median (range). [d]interstitial lung alterations or obstructive lung disease; [e]according to AJCC, 8th edition; [f]concurrent or previous radiotherapy; [g]anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) or anti-indolamine 2.3-dioxygenase (IDO1) monoclonal antibodies; [h]patients treated in metastatic setting; [i]patients treated in adjuvant setting.
Abbreviations: im-PN, immune-mediated pneumonitis; ICI, immune checkpoint inhibitors. PS, performance status according to ECOG scale; MEL, melanoma; CSCC, cutaneous squamous cell carcinoma; NSCLC, non-small cell lung cancer; MESO, mesothelioma; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

The incidence of im-PN was 58% (n=14) and 42% (n=10) in patients receiving ICI monotherapy or combination(s), respectively, with a median time to onset of 46 weeks (wks) [range: 2–312 wks]. Among the 24 patients diagnosed with im-PN, 14 (58%) were symptomatic; the most common reported symptoms were wheezing cough (n=13) and dyspnea (n=9), while fever (n=5) and fatigue (n=2) were unusually described. No significant changes in clinical parameters (ie heart rate, respiratory rate, oxygen saturation etc.) were observed at im-PN diagnosis. According to the NCI-CTCAE v. 5.0, im-PNs were classified as G1 in 10 (42%) patients and G2 in 14 (58%) patients. Fourteen patients (58%) developed additional, any grade, immune-related AEs including: skin rash (25%), lipase (17%) and transaminases (17%) increase, nephritis (8%), colitis (8%), arthritis (4%), hypophysitis (4%), thyroiditis (4%), myositis (4%), and peripheral neuropathy (4%).

Chest CT scans, performed by all patients during ICI therapy and after im-PN diagnosis, were retrospectively reviewed by an internal radiologist who identified 3 different radiologic patterns, according to the Fleischner Society classification of drug-related pneumonitis: OP-like in 16 patients (67%), PEo in 7 patients (29%), and HP in 1 patient (4%). According to NCCN v1.2022 classification, the radiologic lung involvement was identified as G1 in 20 patients (83%), G2 in 3 patients (13%) and G3 in 1 patient (4%). Radiological features and management of im-PN are summarized in Table 2.

Table 2 Radiological Characteristics and Management of Im-PN

	Patients (n=24)[a]
NCCN classification v1.2022	
G1	20 (83%)[b]
G2	3 (13%)
G3	1 (4%)
G4	0
Fleischner Society classification	
OP	16 (67%)
PEo	7 (29%)
HP	1 (4%)
DAD	0
NSIP	0
Starting dose of steroids[c]	
0	2 (8%)
0–1 mg/kg	17 (71%)
1–2 mg/kg	1 (4%)
>2 mg/kg	4 (17%)
Duration of steroid therapy[d]	
<4 wks	3(14%)
4–8 wks	6 (27%)
>8 wks	13(59%)
Outcome	
Total recovery	23 (96%)
Partial recovery	1 (4%)
Rechallenge with ICI	
Yes	12 (50%)
No	12 (50%)

Notes: [a]Treated patients diagnosed with im-PN; [b]n (%); [c]methylprednisolone or equivalent; [d]for patients treated with steroid therapy (n=22).

Abbreviations: NCCN, National Comprehensive Cancer Network v1.2022 criteria; G, grade; OP, organizational pneumonia; PEo, pulmonary eosinophilia; HP, hypersensitivity pneumonitis; DAD, diffuse alveolar damage; NSIP, nonspecific interstitial pneumonitis; ICI.

Among the 24 patients diagnosed with an im-PN, 22 received corticosteroids and prophylactic antibiotic therapy (ie amoxicillin, cephalosporins), while ICI treatment was temporarily discontinued; notably, no patients required additional immunosuppressive therapy. Two asymptomatic patients, classified as G1 im-PN according to the NCI-CTCAE v.5.0, received only symptomatic therapy, also in light of the PEo radiological pattern of im-PN that is usually characterized by transient inflammatory infiltrates leading to a spontaneous resolution.

Treatment with steroids (methylprednisolone or equivalent 0.5–2 mg/kg) led to resolution of im-PN in 21 subjects (95%), with a median time to clinical and/or radiological resolution of 14 wks (range: 0.4–51 wks) (Figure 1); among the 12 patients who restarted ICI therapy, the average time to discontinuation of immunotherapy was 17 wks (range: 7–38).

Bronchoscopy was performed in 8 patients and analysis of BAL samples showed an inflammatory lymphocytic infiltrate, predominantly consisting of foam cell-like macrophages in 6 cases. Among the latter, transmission electron microscopy (TEM) evaluation performed in 2 patients revealed multilamellar bodies, lysosomes, and lipid vacuoles in the alveolar macrophages, a scenario suggestive of a drug-mediated toxicity. Cytology evaluation of BAL and TME in an OP-like im-PN case is reported in Figure 2.

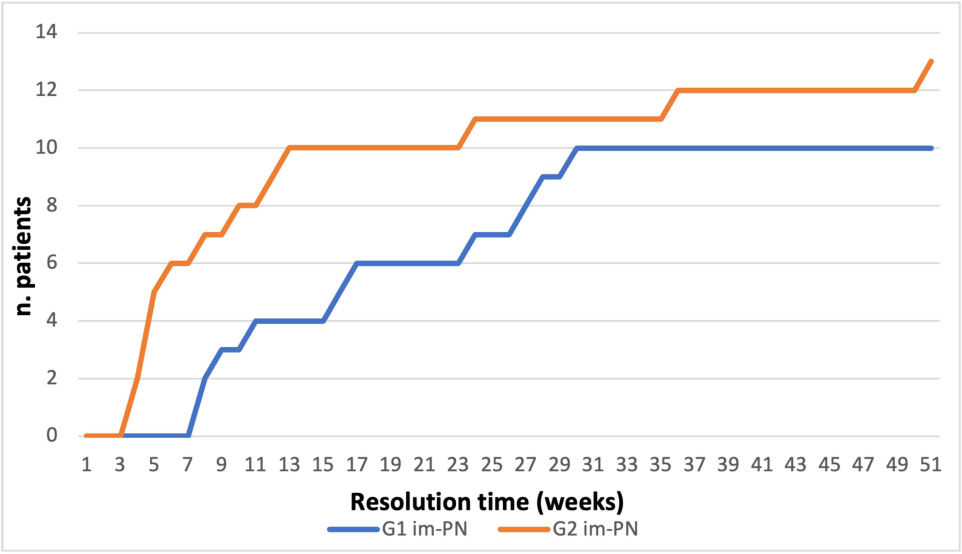


Figure 1 Time of im-PN resolution. Treatment with steroids leading to resolution of G1-2im-PN according to CTCAE v. 5.0 in 95% of subjects, with a median time to resolution of 14 weeks [range: 0.4–51].

At clinical and radiological complete resolution of im-PN, ICI therapy was resumed in 12 patients (50%), showing a recurrence of im-PN only in 2 subjects who presented an OP-like radiological pattern and had been re-treated with ICI combination (ie anti-PD-1 plus anti-CTLA-4) or monotherapy (ie anti-PD-1). Resolution time after im-PN recurrence was longer compared to the first occurrence (median: 17 wks, range: 3–26), and led to permanent discontinuation of ICI treatment. Although ICI therapy was temporarily or permanently discontinued due to im-PN, the majority of patients were relapse-free (60%) or had an ORR (52%) at the time of CT-confirmed im-PN resolution.

Discussion

Im-PN is an uncommon, though potentially life-threatening, immune-mediate adverse event related to ICI therapy. Signs and symptoms of im-PN can be heterogeneous and not specific; thus, an early diagnosis of im-PN should be granted to patients to ensure a faster resolution, avoid its worsening and more severe complications, and eventually allowing for a timely resumption of ICI treatment.

According to the current guidelines, treatment with steroids, based on symptoms and lung parenchyma involvement, should be started promptly in im-PN. However, the severity of symptoms does not always overlap with radiologic and/or histopathologic features of im-PN; thus, handling im-PN within a multidisciplinary team to improve its comprehensive clinical management appears highly recommended. Indeed, in our experience the early radiological identification and concurrent histopathological assessment of patients with asymptomatic im-PN allowed the early-on activation of steroid therapy, likely limiting the im-PN to the observed G1/G2.

Comprehensively, the incidence of im-PN in our experience was lower (2%) compared to that reported in other case series, probably due to the lower number of patients who received combination immunotherapy;[8] however CT scan assessment and follow-up had likely contributed in our study to improve the accuracy of im-PN diagnosis. Along this line, according to the Fleischner Society classification, we identified an OP-like pattern of im-PN in 67% of cases, regardless of patients being symptomatic or asymptomatic. Moreover, the symptomatic OP-like im-PN had a longer resolution time (median: 16 wks, range: 0.4–51) compared to PEo (median: 13 wks, range: 3–30) and to HP (median: 12 wks, range: 0–12) patterns, requiring an extended course of steroid therapy. Furthermore, among the 12 patients (50%) in whom we attempted a rechallenge, only two recurrences of im-PN, with an OP-like pattern, occurred; in this event, as previously reported, recurrent pneumonitis tends to be more durable, though being still responsive to steroid therapy.[17] Notably, despite the prolonged administration of steroids, a favorable clinical outcome was reported in our cohort of patients diagnosed with im-PN since, as previously reported, steroid use did not significantly affect ICI treatment.[18]

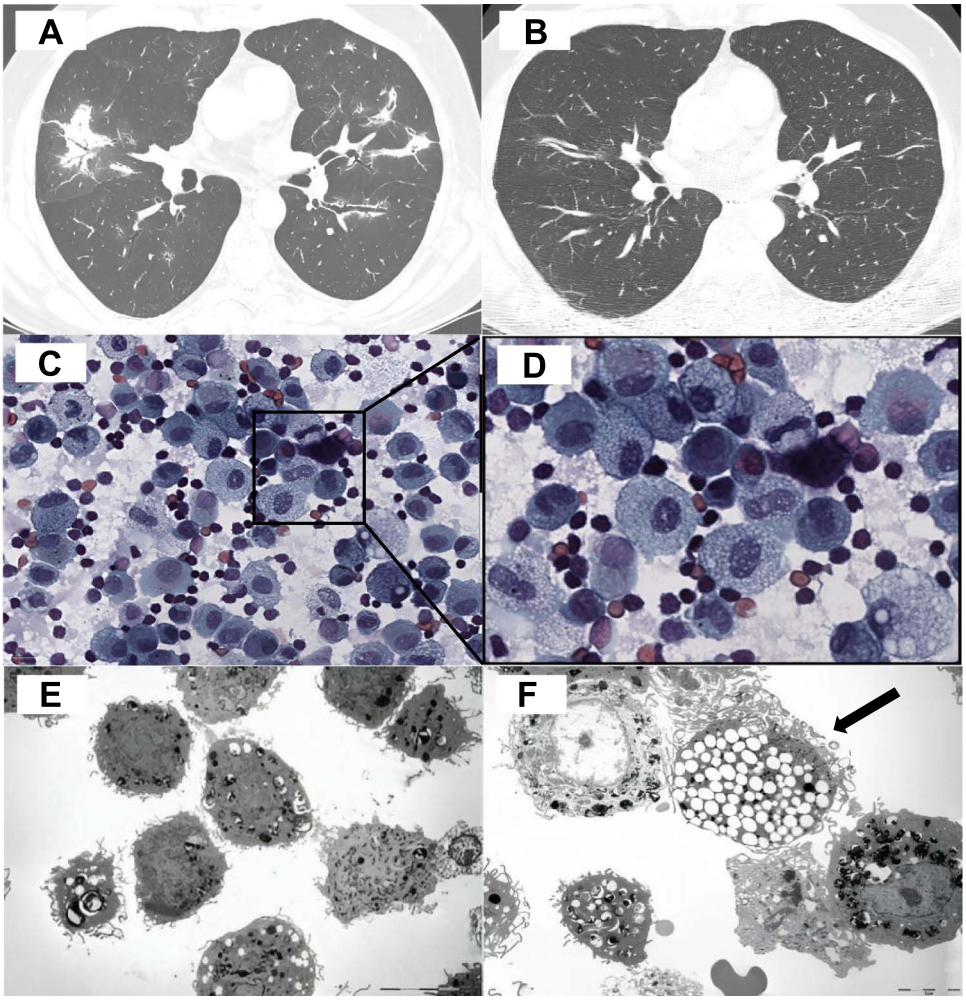


Figure 2 Cytology evaluation of bronchoalveolar lavage and transmission electron microscopy in an OP-like im-PN case. Chest CT scan depicted in MM patient an OP-like pattern of im-PN at diagnosis (panel **A**) and after recovery (panel **B**). Bronchoalveolar lavage sample analysis (panels **C** and **D**) showed an inflammatory lymphocytic infiltrate, predominantly consisting of foam cell-like macrophages characterized by micro- and macro-vacuolization (panel **C**, 40x, papanicolau staining; panel **D**, detail of panel **C**). Transmission electron microscopy evaluation of bronchoalveolar lavage samples revealed multilamellar bodies (panel **E**), lysosomes, and lipid vacuoles in the alveolar macrophages (panel **F**, black arrow), a scenario suggestive of a drug-mediated toxicity.

The results of our case series clearly highlight the importance of a tight collaboration and continuous discussion with a radiologist and pneumologist to better define the diagnostic work-up and treatment of im-PN. Indeed, a prompt diagnosis and appropriate treatment led to low G of im-PN, with a rapid resolution and with a short duration of steroid therapy in a large majority of patients.

Moreover, since radiographic patterns do not necessarily match histopathologic features, it was recently suggested that BAL assessment may offer important diagnostic insights into im-PN by identifying the extent and type of lymphocytic infiltrate.[19,20]

Indeed, a retrospective, observational study of 112 MM patients treated with PD-1 inhibitors alone or combined with anti-CTLA-4 showed an increased CD8+ T cells infiltrate with a reversed CD4+/CD8+ ratio in BAL samples from 5 patients who developed respiratory symptoms due to im-PN.[21] Notably, in our case series, BAL sample analysis, performed in 8 patients (42% asymptomatic), showed an inflammatory lymphocytic infiltrate, predominantly consisting of a foam cell-like macrophage infiltrate. Interestingly, TEM evaluation performed in 2 asymptomatic cases clearly depicted a drug-mediated toxicity, supporting the role of this diagnostic additional tool that merits further investigation.

Based on this comprehensive evidence, and to further support a better diagnosis and management of im-PN, new diagnostic tools such as radiomics assessment may soon help to further improve the accuracy of radiological diagnosis and build predictive models guiding treating physicians to optimize the daily clinical management and monitoring of im-PN.[22]

Limitations

The current study has several limitations, including its retrospective design and small sample size, limiting the extent of interpretation of results. Thus, further studies are needed to improve risk stratification, im-PN diagnosis and treatment.

Conclusion

Im-PN associated with ICI therapy was found to be a rare and challenging side effect, with variable times of onset, and with heterogeneous clinical presentations. A multidisciplinary characterization of im-PN, allowing refinement of the diagnostic algorithm, helps to optimize its clinical management to reduce its severity and the delay in resuming ICI therapy.

Abbreviations

ICI, Immune Checkpoint Inhibitors; irAEs, immune-related Adverse Events; im-PN, immune-mediated Pneumonitis; MEL, Melanoma; SCC, Squamous Cell Carcinoma; NSCLC, No Small Cell Lung Cancer; MESO, Mesothelioma; BAL, Bronchoalveolar Lavage; NCI-CTCAE v 5.0, NCI Common Terminology Criteria for Adverse Events Version 5; G, Grade; wks, weeks; OP, Organizational Pneumoniae; PEo, pulmonary eosinophilia; HP, Hypersensitivity Pneumonitis; IP, Interstitial Pneumonia; NSIP, Not Otherwise Specified Pneumonitis; COVID-19, coronavirus disease; AEs, Adverse Events; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; CTLA-4, Cytotoxic T lymphocyte-associated protein 4; CT, computed tomography; NCCN, National Comprehensive Cancer Network; TEM, Transmission Electron Microscopy; IDO1, indolamine 2,3-dioxygenase.

Ethics Approval and Informed Consent

All patients signed an institutional informed consent for research purposes only and without commercial interests. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and all the data and procedures collected in the study were carried out according to good clinical practice. Based on current national legislation (ItalianLaw Decree n.19/2024), retrospective studies were exempted from review or approval by the ethics committee.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis or interpretation; took part in drafting, revising or critically reviewing the article; and gave final approval of the version to be published.

All authors have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

MV has served as a consultant e/o advisor to Novartis. MM has served as a consultant and/or advisor to Roche, Bristol Myers Squibb, Merck Sharp Dohme, Incyte, AstraZeneca, Amgen, Pierre Fabre, Eli Lilly, GlaxoSmithKline, Sciclone, Sanofi, Alfasigma, Merck Serono, Novartis and iontura; and owns shares in Epigen Therapeutics, Srl. LC has served as consultant and/or advisor to Bristol Myers Squibb, AstraZeneca, Sanofi, Roche, and Merck Sharp Dohme, and has been compensated for educational activities by Bristol Myers Squibb, AstraZeneca and Sanofi. AMDG has served as a consultant and/or advisor to Incyte, Pierre Fabre, GlaxoSmithKline, Bristol Myers Squibb, Merck Sharp Dohme, and Sanofi and has been compensated for

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