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CASE REPORT

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# Pneumonitis and multiple pneumonial infections under combined immune-checkpoint inhibition

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**Abstract**

The introduction of immune checkpoint inhibitors and targeted therapies has revolutionized melanoma treatment. The downside are immune-mediated adverse events which are frequent and require close patient management. We report a case of severe immune-mediated hepatitis and pneumonitis under combined immune-checkpoint inhibitor therapy requiring immunosuppressive therapy. Under immunosuppressive therapy, however, a series of opportunistic infections occurred. It can be challenging to distinguish the signs of immune-mediated adverse events of checkpoint inhibitors and pathogen-mediated inflammation due to overlaps in clinical and laboratory findings. This case has the goal to rise awareness for infectious complications during immunosuppressive therapy needed to address immune-mediated adverse events of checkpoint inhibitors.

**KEYWORDS**

immune-checkpoint inhibition, immune-related adverse events, pneumonia, pneumonitis

## INTRODUCTION

The prevalence of malignant melanoma is increasing with no signs for a reversed trend especially in predominantly caucasian populations.[1] Meanwhile, targeted therapies as well as immunotherapies have broadened therapeutic options for patients.[2] A growing number of patients also with co-morbidities takes advantage of these novel therapies today. However, especially in the context of immune-checkpoint inhibitors (CPI), a significant proportion of patients develops immune-related adverse events (irAE).[3,4] Together with diverse co-morbidities this makes the treatment challenging and requires specific clinical expertise. Treatment options depend on the type and severity of irAEs. While endocrine irAE are usually irreversible and require life-long hormone substitution, others like hepatitis, pneumonitis and colitis are treated with immunosuppressants.[5] Prednisolon, mycophenolate or infliximab are the most important anti-inflammatory treatment options.[6] However, immunosuppressive therapies bear the risk of infectious diseases, including opportunistic infections. Herein, we present a case of simultaneous pneumonial infection with *Pneumocystis jiroveci*, *Legionella pneumophila*, *Escherichia coli*, *Staphylococcus aureus* and herpes simplex virus (HSV) following CPI and immunosuppression due to irAEs. Furthermore, we discuss the diagnostic and therapeutic challenges in such situations.

## CASE REPORT

A 55-year-old patient received the diagnosis of malignant melanoma of nodular type and 7,1 mm tumour thickness (BRAF wt, c-kit wt, NRAS Q61K mutant) 20 months ago. Because of micrometastasis in the sentinel lymph node, adjuvant immunotherapy with nivolumab 240 mg was started. After 8 months a progress with bone and cerebral metastases was observed and combined CPI therapy with additional ipilimumab as well as radiotherapy were introduced. After four cycles of ipilimumab/nivolumab (3 and 1 mg/kg body weight) the patient developed an immune-mediated hepatitis Common Terminology Criteria for Adverse Events (CTCAE) 3 which was treated with 120 mg prednisolone at its maximum.

Meanwhile, dry cough in the morning, increasing weakness and shortness of breath occurred. Fever was not observed. Blood analysis revealed a slight elevation of CRP at 2,4 mg/dL (reference: <0.5 mg/dL) and normal levels of leucocytes. Suspecting an immune-mediated pneumonitis, lung function tests were conducted revealing a moderate reduction of carbon monoxide (CO) diffusion capacity (3,62 mmol/(min + kPa); reference: 9.23 mmol/(min + kPa)) and slight hypoxaemia ($PaO_2$ 70.49 mmHg; reference: 77.93 mmHg). Computed tomography (CT) scans showed basal bipulmonary infiltrations and ground glass opacity (Figure 1), suggesting pneumonitis caused by CPI. The patient was hospitalized and received prednisolone intravenously. Shortly thereafter, the patient developed severe hypoxaemia ($PaO_2$ 53.79 mmHg; reference: 77.93 mmHg) requiring nasal oxygen application and an increase in body temperature. Simultaneously, an increase in leucocyte count (13.10 G/L; reference: 4.0–9.0 G/L) and CRP 3.2 mg/dL (reference: <0.5 mg/dL) was detected. Bronchoscopy including bronchoalveolar lavage was performed and a biopsy was taken. Hereby, histology did not indicate speed of melanoma cells and polymerase chain reaction (PCR) tests as well as cultures for pathogens were performed (Table 1).

*Pneumocystis jiroveci*-PCR was positive indicating a *pneumocystis jiroveci* pneumonia. Since the patient suffered from terminal renal insufficiency requiring haemodialyses three times weekly, cotrimaxazol was

**TABLE 1** Results from bronchoalveolar lavage.

| Bronchoalveolar lavage | Result |
|---|---|
| *Pneumocystis jiroveci* PCR | Positive |
| *Chlamydophila pneumoniae* PCR | Negative |
| *Mycoplasma pneumoniae* PCR | Negative |
| Legionella spp. PCR | Positive |
| Legionella culture | |
| *Legionella pneumophila* | Positive |
| Anaerobic culture | |
| *Escherichia coli* | Positive |
| *Staphylococcus aureus* | |
| Adenovirus PCR | Negative |
| Cytomegalovirus PCR | Negative |
| Herpes simplex virus 1/2 DNA quant. PCR | Positive (12 750 Geq/ml) |
| Influenza A/B PCR | Negative |
| Metapneumovirus PCR | Negative |
| Parainfluenza PCR | Negative |
| Rhinovirus PCR | Negative |
| RSV PCR | Negative |
| SARS CoV-2 PCR | Negative |

Abbreviation: PCR, polymerase chain reaction.

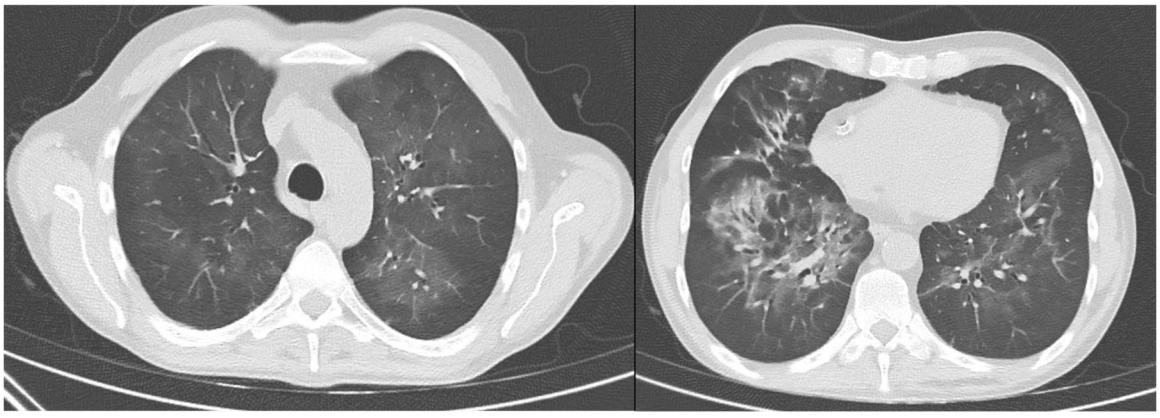

**FIGURE 1** Axial computed tomography scans of the chest. On the left the middle and on the right the lower part of the lungs are depicted. Ground glass opacities are visible all over the lungs and right basal pulmonary infiltrations are emphasized.

administered intravenously on the days of haemodialyses before and after dialysis (12 and 6 ampoules of Cotrimoxazol 480 mg respectively). *Legionella pneumophila* (serotype 2–14) was also detected by PCR and in bacterial culture, hence additional intravenous therapy with levofloxacin (500 and 750 mg intravenously on the first day followed by 250 mg every 24 h) was started. On top of that, the anaerobic culture was positive for *Escherichia coli* as well as *Staphylococcus aureus* and *HSV 1/2* DNA was detected in the material from bronchoalveolar lavage. Accounting for these pathogens, the patient received additional antibiotic and antiviral treatment with ampicillin/sulbactam and aciclovir at the recommended dose. A systemic HSV infection was excluded by negative HSV-PCRs performed from peripheral blood. *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*-PCR from bronchoalveolar lavage were negative. Despite the necessity to temporarily apply oxygen via face mask because of respiratory insufficiency, the patient recovered well. CO diffusion capacity normalized and immunosuppressive therapy with prednisolon was tapered and finally stopped.

While pathogens were well controlled with the above treatments, the patients melanoma recurred after 3 months with cutaneous and multiple new cerebral metastases requiring palliative radiotherapy.

## DISCUSSION

Hepatitis and pneumonitis are two frequent irAE under CPI.[3] Like all irAE, they are more common in patients receiving combined CPI therapy compared to patients treated with PD-1 inhibitors only.[7] Typically, the onset of immune-mediated hepatitis occurs earlier during CPI therapy compared to pneumonitis.[4] Clinical symptoms, imaging and laboratory exams aid the diagnosis of irAEs. However, results are not specific and may be similar to findings in patients with underlying infections. The timing of onset of symptoms as well as initial exams were indicative of immunotherapy-related pneumonitis triggering systemic glucocorticoid therapy.

Since pulmonary condition did not improve, bronchoscopy was swiftly indicated to aim for direct detection of potential pathogens. These analyses should not only cover diagnostics for microbial, viral and other infectious diseases, but also histology of tissue samples to exclude metastatic spreading of tumour cells. Combined treatment with antimicrobials, oxygen and anti-inflammatory therapy led to a recovery of our patient. It is possible, however impossible to proof, if both, immune-related pneumonitis and inflammation caused by pathogens were responsible for the course of the disease in our patient.

The first-line therapy to treat irAE are glucocorticoids.[6] Depending on the type of irAE duration of therapy varies with shorter treatment periods of corticosteroid therapy for hepatitis e.g. in comparison to severe pneumonitis.[8] Long-term steroid therapy is immunosuppressive by nature making infectious diseases more likely.[9] Especially patients with additional co-morbities are suspectible to opportunistic infections. Our patient suffered from chronic terminal renal insufficiency and received haemodialyses three times weekly additionally increasing his risk for opportunistic infections. In general, the ESCMID Study Group for Infections in Compromised Hosts recommends an anti-pneumocystis prophylaxis for patients with CPI-induced irAE when an anti-inflammatory treatment with 20 mg prednisolone or more over at least 4 weeks is planned,[9] which was not the case here. Further recommendations include a pre-therapeutic screening for chronic infections such as latent tuberculosis and hepatitis B/C,[9] which were all negative in our patient. Apart from immunosuppression because of an irAE (immunotherapy infection due to immunosuppression, ITI-IS), there are reports that infections occur more frequently under CPI, independent of an immunosuppressive treatment.[10] It is hypothesized that a dysbalance of the immune system caused by immunotherapy may lead to an increased risk for infections.[10] This case represents an ITI-IS because of preceding immunosuppressive therapy with prednisolone due to immune-mediated hepatitis, however, simultaneously combined CPI therapy might have further increased the risk for developing multiple opportunistic infections.

### AUTHOR CONTRIBUTIONS

**Kristine E. Mayer**: Conceptualization; writing—original draft; visualization. **Thomas Gan**: Conceptualization; writing—original draft. **Jochen Gaa**: Visualization; writing—review and editing. **Tilo Biedermann**: Writing—review and editing. **Christian Posch**: Conceptualization; writing—review and editing.

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### DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

## ETHICS STATEMENT

All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details (including photographs) for publication.

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