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Case report

Organizing pneumonia following treatment with pembrolizumab for metastatic malignant melanoma – A case report

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ABSTRACT

Pembrolizumab is a monoclonal antibody against the programmed cell death 1 (PD-1) receptor, and is widely used for the treatment of various malignancies, most commonly malignant melanoma. Here we report the first documented and pathology proven case of Organizing Pneumonia complicating treatment with Pembrolizumab. This was a man who presented with a dense lung consolidation four months following treatment with Pembrolizumab. A thorough microbiological workup was negative and his findings did not improve with broad spectrum anti-microbial treatment. Transbronchial biopsy revealed organizing pneumonia, and treatment with cortico-steroids resulted in complete resolution of clinical and radiological disease.

This report highlights the importance of recognizing immune related adverse events, specifically pulmonary inflammation, in patients receiving treatment with novel immune-modulating agents.

Pembrolizumab is a monoclonal antibody against the programmed cell death 1 (PD-1) receptor, and is widely used for the treatment of various malignancies, most commonly malignant melanoma. Here we report the first documented case of Organizing Pneumonia complicating treatment with Pembrolizumab.

1. Case report

A 73 year old patient was admitted to our hospital due to non-resolving pneumonia. He complained of progressive shortness of breath and fever (38.5 °C) that started ten days prior to his admission. Chest x-ray showed the presence of an alveolar infiltrate in the right upper lung field. He was treated with oral ciprofloxacin and cefuroxime, for suspected pneumonia.

Past medical history was significant for recurrent metastatic melanoma which had been initially diagnosed on his forearm more than 30 years ago and was treated by local excision. Recurrent metastatic disease was diagnosed 8 years prior to his admission, and was treated with recurrent local excision, axillary lymph node dissection, partial liver resection, local radiotherapy and whole cell tumor vaccines. Recently an adrenal mass was identified on PET-CT. He was given three courses of ipilimumab, but was switched to pembrolizumab four months prior to his admission due to disease progression. The last dose of treatment with pembrolizumab was two weeks prior to his admission. No known lung metastasis were evident. Other past medical conditions were ischemic heart disease, hypertension, hypercholesterolemia, benign prostatic hyperplasia and depression. Chronic medications included bisoprolol, atorvastatin, valsartan, hydrochlorothiazide, esomeprazole, ezetimibe, mianserin, risperidone, lorazepam, tamsulosine, escitalopram and aspirin. None of these has been started recently.

On examination the patient was febrile with a temperature of 38.2, in no obvious respiratory distress and with an oxygen saturation of 93% while breathing ambient air. He had decreased breath sounds over the right lung with coarse crackles.

Laboratory workup was unremarkable aside from hyponatremia (128 mmole/L). Chest CT revealed a new large consolidation in the right upper lobe, with air-bronchogram (Fig. 1).

The patient was started on intravenous cefuroxime and ciprofloxacin, which was later changed to piperacillin/tazobactam due to persistent fever andh no improvement of his symptoms. Blood cultures, serum CMV and EBV PCR, urinary testing for Legionella and Pneumococcal antigens and throat PCR-swabs for mycoplasma and respiratory viral antigens were all negative.

Flexible bronchoscopy was performed, and cytopathologic and microbiologic analysis were negative for infectious causes. Transbronchial biopsies demonstrated organizing pneumonia (Fig. 2). He was consequently started on treatment with high dose

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corticosteroids (I.V. hydrocortisone 100mg TID) with prompt resolution of his fever and marked improvement of his shortness of breath. Repeat chest CT was done 12 weeks after his admission showing marked improvement of his lung infiltrates (Fig. 3).

2. Discussion

Discovered in 1992, programmed death receptor 1 (PD-1) is a member of the B7-CD28 superfamily [1]. It is expressed on activated T ($CD8^+$ and $CD4^+$) cells, B cells, monocytes, natural killer T-cells and antigen-presenting cells (APC). Inflammation-induced cytokines produced as a result of infection or tumor formation induce the expression of programmed death receptor ligand 1 (PD-L1) on various cell types, and programmed death receptor ligand 2 (PD-L2) on APC. The PD-1/PD-L1/PD-L2 interaction negatively affects the function of T and B cells, leading to decreased cytokine production and antibody formation, thereby inhibiting autoimmunity, anti-tumor and anti-infectious immunity [2].

Pembrolizumab (previously known as MK-3475 and lambrolizumab) is a humanized IgG-4 monoclonal antibody against PD-1. This blockade enhances the functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection [3]. It is the first anti–PD-1 agent to be approved by the US Food and Drug Administration (FDA) for the treatment of melanoma. It is approved for patients with metastatic melanoma who have failed Ipilimumab treatment and, if *BRAF* mutation positive, also for patients who have failed treatment with a BRAF inhibitor [4]. It is also currently approved for use in melanoma in several additional countries, including recent approval in the European Union [2].

Survival results reported to date in melanoma following this treatment are highly encouraging [5,6] and further investigation in other malignancies is currently ongoing (e.g. in advanced non-small cell lung cancer) [7]. However, this agent is not free from toxicity and the novel mechanism of action of pembrolizumab is associated with a risk of side effects. These immune-related adverse events are reversible and easily manageable in most cases [8]. However, some of them can be potentially life-threatening and their diagnosis and treatment require experience and the involvement of not only oncologists but also other specialties such as pulmonologists and endocrinologists.

The most frequently reported side effects in the KEYNOTE-002 trial (phase 2 trial of pembrolizumab including 540 patients)

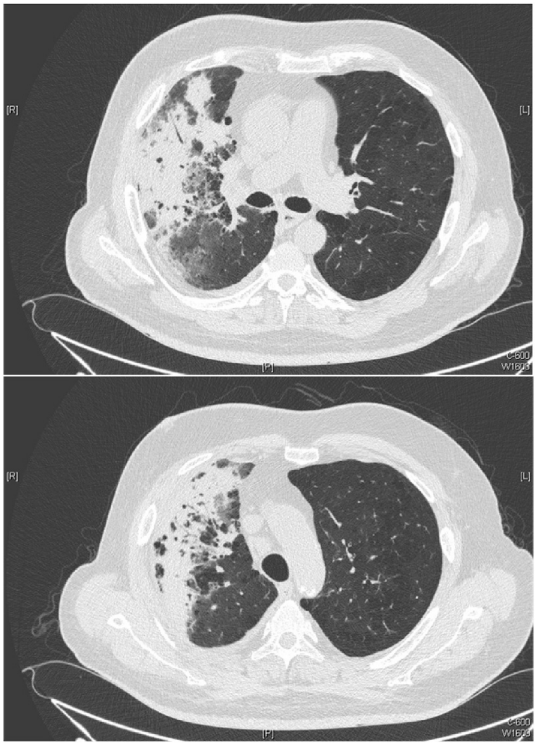

Fig. 1. Chest CT at presentation showing a large right upper lobe alveolar infiltrate with air bronchogram.

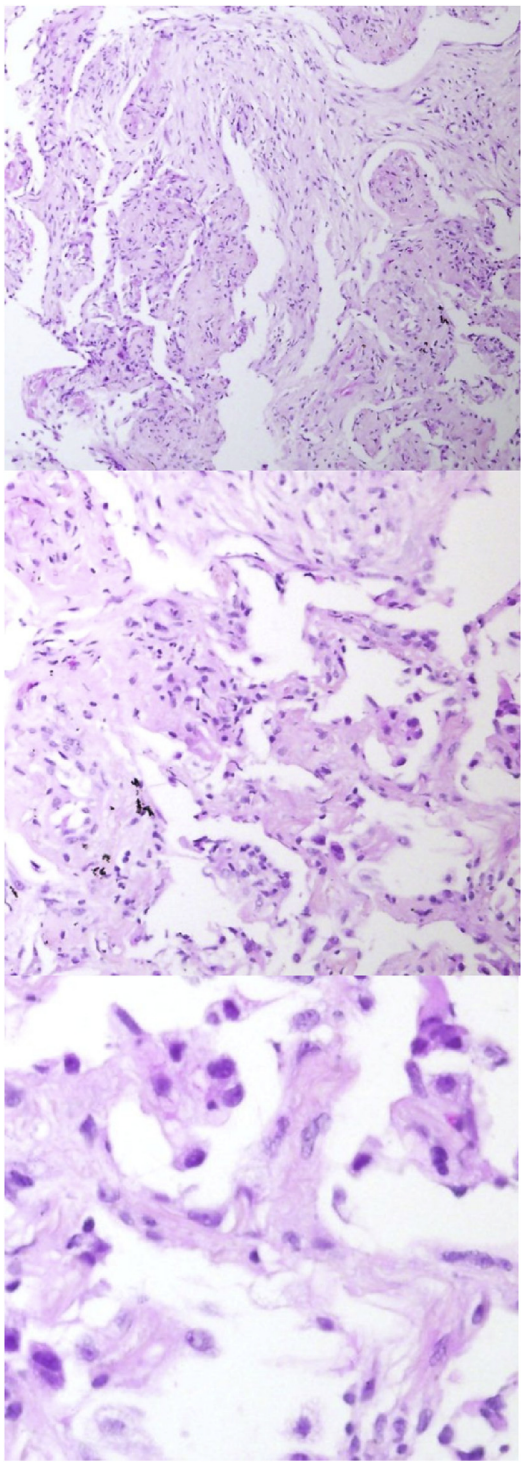

Fig. 2. A, B, C: Lung parenchyma with thickened alveolar septa and mild chronic inflammation, consistent with organizing pneumonia. Hematoxylin and eosin stain; magnification ×100, ×200 and ×400 respectively.

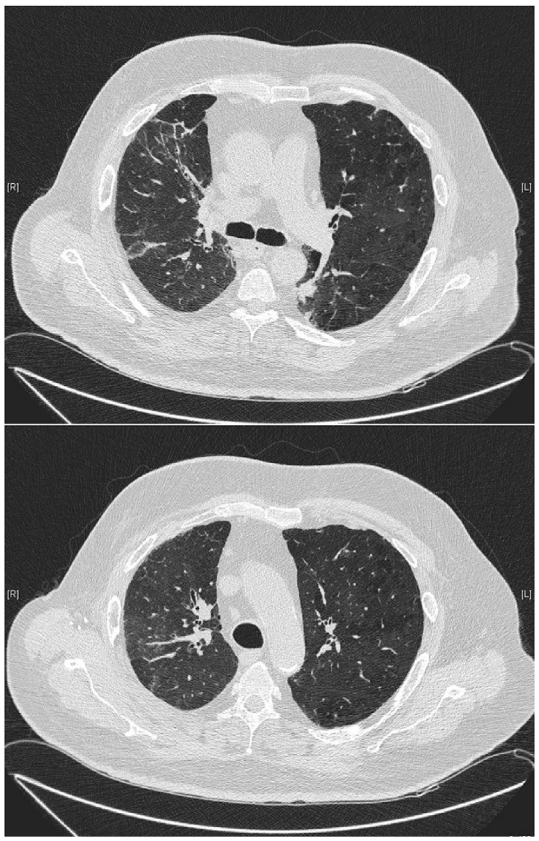

Fig. 3. Chest CT following three months of steroid treatment showing resolution of the RUL infiltrate.

were fatigue (30%), pruritus (21%), diarrhea (20%), myalgia (12%), aspartate aminotransferase (AST) increase (10%), nausea (10%), headache (10%) and asthenia (10%). The most common grade 3–4 treatment related side effects reported were hypopituitarism, colitis, diarrhoea, decreased appetite, hyponatremia, and pneumonitis (about 1% of patients each) [6]. Other immune-related adverse events of pembrolizumab reported subsequently in the literature are skin reactions (in up to 42% of patients) [9,10], uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, adrenal insufficiency, myasthenic syndrome, optic neuritis, and rhabdomyolysis. These are usually mild and in general are managed with corticosteroids and when essential, interruption of treatment [15].

The prevalence of pneumonitis secondary to anti-PD-1 therapy is variable and may be as high as 4% [10,12–14], however data is lacking regarding the definition of pneumonitis used, and tissue confirmed diagnosis. Most cases reported are mild in nature. Workup for these patients includes chest imaging, yet there are no characteristic radiographic findings that will rule in or rule out pneumonitis. In patients with pulmonary metastases or cardiopulmonary comorbidities, evaluation can be particularly challenging. Tumor progression (e.g. lymphangitic spread), pseudoprogression (i.e. inflammation of an existing metastasis), exacerbations of chronic obstructive pulmonary disease, congestive heart failure, diffuse alveolar hemorrhage, and pulmonary embolism are often possible confounding diagnoses [13].

Organizing pneumonia is a known manifestation of drug induced lung injury. It is a histopathologic reaction to a nonspecific inflammatory insult and can occur after exposure to a number of drugs including many anti neoplastic agents. Symptoms may include nonproductive cough and shortness of breath with bilateral crackles. Imaging shows patchy airspace infiltrates, peribronchial or subpleural in location, with air trapping. The histopathologic changes seen in organizing pneumonia include intraluminal buds of granulation tissue with preserved lung architecture [16].

In this paper we report the first biopsy-proven case of organizing pneumonia in a patient treated with pembrolizumab. Our patient presented with signs of lung inflammation while extensive microbiologic workup did not reveal any evidence of active pulmonary infection. His prompt clinical response to corticosteroid treatment is also suggestive of an inflammatory process.

There has been one report of organizing pneumonia in a patient receiving ipilimumab (a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocker) [11] which our patient had received previously, however his symptoms and lung findings began four months after he had stopped this treatment with no pulmonary symptoms, and began treatment with pembrolizumab.

This report highlights the importance of recognizing immune related adverse events, specifically pulmonary inflammation, in patients receiving treatment with novel immune-modulating agents.

Authors contribution

Patient follow up, data collection and manuscript drafting – RK, ML, AA, UL, NB and ZGF.

Pathology interpretation – TN.

Radiology interpretation – EMB.

Conflicts of interest

All authors declare no conflict of interest regarding this publication.

References

[1] Y. Ishida, Y. Agata, K. Shibahara, T. Honjo, Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death, EMBO J. 11 (1992) 3887–3895.
[2] L. Khoja, M.O. Butler, S.P. Kang, et al., Pembrolizumab, J. Immunother. Cancer 3 (2015) 36.
[3] S.S. Kumar, C.M. McNeil, Pembrolizumab for the treatment of melanoma, Expert Rev. Clin. Pharmacol. 8 (5) (2015) 515–527.
[4] T. Rajakulendran, D.N. Adam, Spotlight on pembrolizumab in the treatment of advanced melanoma, Drug Des. Dev. Ther. 9 (2015) 2883–2886.
[5] C. Robert, J. Schachter, G.V. Long, et al., Pembrolizumab versus ipilimumab in advanced melanoma, N. Engl. J. Med. 372 (2015) 2521–2532.
[6] A. Ribas, I. Puzanov, R. Dummer, et al., Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial, Lancet Oncol. 16 (2015) 908–918.
[7] E.B. Garon, N.A. Rizvi, R. Hui, et al., Pembrolizumab for the treatment of non–small-cell lung cancer, N. Engl. J. Med. 372 (2015) 2018–2028.
[8] J. Martin-Liberal, T. Kordbacheh, J. Larkin, Safety of pembrolizumab for the treatment of melanoma, Expert Opin. Drug Saf. 14 (6) (2015) 957–964.
[9] M. Sanlorenzo, I. Vujic, A. Daud, et al., Pembrolizumab cutaneous adverse events and their association with disease progression, JAMA Dermatol 151 (11) (2015) 1206–1212.
[10] O. Hamid, C. Robert, A. Daud, et al., Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma, N. Engl. J. Med. 369 (2) (2013) 134–144.
[11] I.Z. Barjaktarevic, N. Qadir, A. Suri, et al., Organizing pneumonia as a side effect of ipilimumab treatment of melanoma, Chest 143 (3) (2013) 858–861.
[12] C. Robert, G.V. Long, B. Brady, et al., Nivolumab in previously untreated melanoma without BRAF mutation, N. Engl. J. Med. 372 (2015) 320–330.
[13] S.L. Topalian, F.S. Hodi, J.R. Brahmer, et al., Safety, activity, and immune correlates of anti-PD-1 antibody in cancer, N. Engl. J. Med. 366 (2012) 2443–2454.
[14] C. Robert, A. Ribas, J.D. Wolchok, et al., Anti-programmed-death receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial, Lancet 384 (2014) 1109–1117.
[15] M.A. Postow, Managing Immune Checkpoint-blocking Antibody Side Effects, ASCO EDUCATIONAL BOOK, 2015.
[16] R. Prasad, P. Gupta, A. Singh, N. Goel, Drug induced pulmonary parenchymal disease, Drug Discov. Ther. 8 (6) (2014) 232–237.