New approaches and consequences for elderly cancer patients with focus on melanoma

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Chapter 8e

Rapid granulomatosis with polyangiitis induced by immune checkpoint inhibitiont

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Introduction

There is a rise in the use of immune potentiating drugs in oncology. The immune checkpoint modulators ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, and nivolumab and pembrolizumab, anti-programmed cell death 1 (PD-1) antibodies, have demonstrated survival benefit in metastatic melanoma. Potential drawbacks of anti-CTLA-4 and anti-PD-1 are their immune potentiating side effects. CTLA-4, a key negative regulator of T cell activation, binds to CD80/CD86 on the surface of antigen-presenting cells (APCs). This interaction dampens the costimulatory "second signal" of T cell activation mediated via interaction between CD80/CD86 on APCs and CD28 on T cells. Thus, by blocking the action of CTLA-4, ipilimumab promotes stimulation and potentiation of T-cell activation. Also, PD-1 belongs to the CD28/CTLA-4 family of negative regulator of T cell activation, which serves to protect against autoimmune diseases [1]. However, cancer cells can co-opt the PD-1 pathway to escape immune surveillance. Therefore, blockade of either CTLA-4 or PD-1 pathway has become an attractive target in cancer therapy.

Case report

We treated a 56-year-old woman with metastatic melanoma successfully with 4 courses of 3 mg/kg ipilimumab. During ipilimumab treatment she reported mild arthralgia. Unfortunately, six months later she had progressive melanoma and treatment with 850 mg/m^2 dacarbazine every 3 weeks was initiated. The disease progressed further after 2 courses and dacarbazine was discontinued. At that time, pembrolizumab became available in the setting of a Named Patient Program. She was included after giving informed consent. One week after her first infusion of 2 mg/kg pembrolizumab she had high grade fever without signs of infection. She developed purpura on her feet and arthritis of hands, elbows and ankles. A chest X-ray revealed stable pulmonary nodular lesions (Figure 1A) and her urine sediment was normal. She was diagnosed as having serum sickness based on the presence of arthritis, high-grade fever and cutaneous vasculitis and was treated with 40 mg prednisone once daily. Under this regimen she developed progressive dyspnea and a repeated chest X-ray 1 week later showed diffuse infiltrates (Figure 1B). Complement C3 and C4 levels were normal and her skin biopsy showed vasculitis without immunoglobulin or complement deposition. Repeated urinalysis showed a massive number of dysmorphic erythrocytes and proteinuria. She was tested positive for proteinase 3 anti-neutrophil cytoplasmic antibodies (PR3-ANCA). In retrospect, a spare serum sample revealed already a low titer shortly before start of pembrolizumab. Oral cyclophosphamide, 150 mg once daily, and pulse methyl prednisone induced rapid resolution of symptoms.

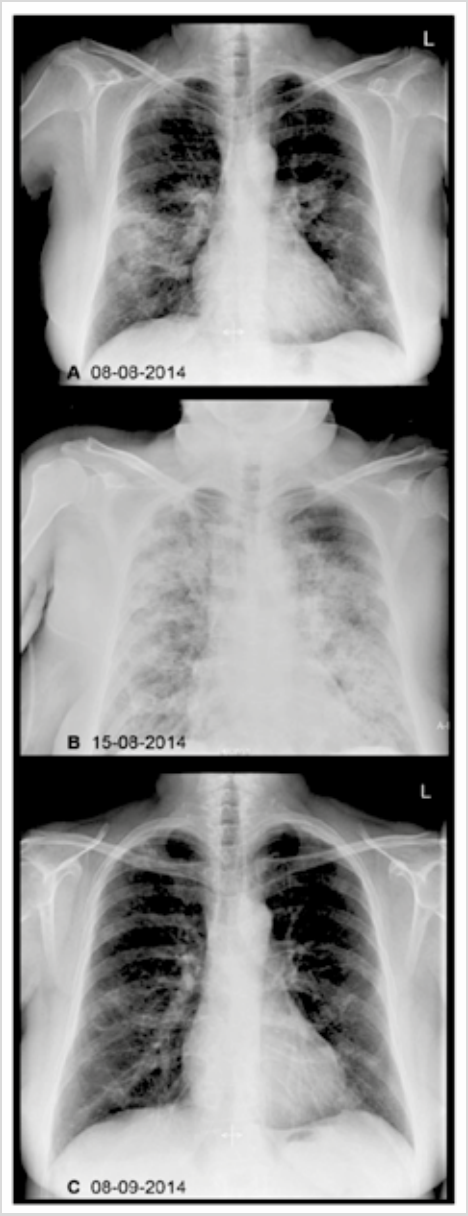

Figure 1: Radiological examinations.
(A) Bilateral pulmonary lesions in a patient with progressive metastatic melanoma, **(B)** Progression of the pulmonary lesions after initiation of pembrolizumab, **(C)** Improvement after 3 weeks high dose steroids and cyclophosphamide.

Discussion

This is the first report on the development of GPA after sequential immune checkpoint inhibition with ipilimumab and pembrolizumab, as well as the first report of vasculitis observed after pembrolizumab treatment. Intriguing is that this life-threatening condition suddenly arose shortly after a single dose of pembrolizumab. In retrospect, the pre-existing pulmonary nodular anomalies might have been subclinical GPA.

Interestingly, aberrant expression of PD-1 on T-helper cells in GPA is reported to be of importance in the pathophysiology of GPA [2]. Genome-wide association studies revealed an associated between GPA and polymorphic variants in genes encoding PR3 and its main inhibitor α1 antitrypsin [3]. However, also polymorphisms in *PDCD1*, the gene encoding PD-1, and the *CLTA4* gene are reported to play a role in patients with GPA [4].

After ipilimumab treatment, several forms of vasculitis, including large vessel vasculitis have been reported [5–7]. The present case developed arthralgia during ipilimumab treatment, which in retrospect might be considered as symptoms preceding GPA. Abatacept, a functional counterpart of ipilimumab, is composed of a modified Fc-region of IgG1 and the ligand-binding domain of CTLA-4, which leads to CD80/86 inhibition on APCs. Of interest is an open-label trial in 20 GPA patients treated with abatacept that reported disease improvement in 18 patients (90%) [8].

Based on our findings, one could hypothesize that ipilimumab induced PR3-ANCA production, which set the stage for the development of GPA that was rapidly unleashed by pembrolizumab treatment. Together with existing data on PD-1 polymorphism in GPA and on aberrant expression of PD-1 on T-helper cells in GPA, this report highlights the important role of PD-1 in the development of GPA.

References

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