Baseline hyper-eosinophilia: A possible predictor of hyper-progression in a patient with metastatic lung adenocarcinoma treated with pembrolizumab

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Abstract

Immune Checkpoint Inhibitors (ICI) were shown to improve survival in patients with advanced non-small cell lung cancer. Nevertheless, around 10% of treated patients may have an atypical response with disastrous tumor growth and earlier death. Readily available predictors of such response are still unrevealed and desperately needed.

Key Clinical Message

Worsening hyper-eosinophilia before and after immune check point inhibitor as a possible predictor of hyper-progressive disease in metastatic lung adenocarcinoma following treatment with pembrolizumab.

Background

Programmed-death receptor-1 (PD-1) and its ligand (PD-L1) play an important role in tumor cells' mechanism to evade the immune system.[1] Positive expression of these receptors has been associated with improved progression-free survival and overall response in patients treated with anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors (ICIs), and constitute a promising predictive biomarker of response.[2,3]

However, occurrence of an accelerated progression, also termed as hyper-progressive disease (HPD), under these agents have been described in several cancers, suggesting a possible injurious effect of these medications.[4]

The use of predictive factors to determine response before ICI initiation is crucial and is currently under extensive research, especially in patients with metastatic melanoma. Readily available and cost-effective blood markers have the advantage of allowing a quick integration in clinical decision making and help distinguish individuals likely and unlikely to respond to therapy or develop toxicity.[5-7]

We present the case of an 82-year-old male with metastatic lung adenocarcinoma and worsening baseline hyper-eosinophilia, who developed HPD after being treated with pembrolizumab, a PD-1 inhibitor.

Case Report

An 82-year-old man presented on December 1st for work up of recurrent left pleural effusions. A Positron emission tomography-computed tomography (PET-CT) done 3 days later showed an FDG-avid lobulated left lung mass with pleural-based metastatic nodules, mediastinal and left lung hilar metastatic lymph nodes as well as left adrenal involvement (Fig 1). Biopsy of the pleural masses showed a poorly differentiated lung adenocarcinoma, with positive PD-L1 expression in 90% of tumor cells. On December 4th, a peripheral blood count showed white blood cell count (WBC) of 28700/cu.mm, with 17% eosinophils, and an absolute

eosinophil count (AEC) of 4879, consistent with hyper-eosinophilia. Work up for infectious and vasculitic causes of eosinophilia was negative. On December 5th, he received the first dose of pembrolizumab 200 mg.

He presented back on December 15th for worsening dyspnea. Repeat chest CT showed an increase in the left lower lobe consolidation with appearance of multiple bilateral sub-centimetric pulmonary nodules (Fig. 2). Repeat plain radiograph two days later showed complete opacification of the left hemithorax. A therapeutic bronchoscopy resulted in no improvement of the consolidation.

A CT chest was done on December 17th (12 days after Pembrolizumab) for worsening dyspnea, showed further increase in the left lung consolidation and enlargement of the pleural-based masses (Fig. 3). CT-guided biopsy of one of the new masses was positive for adenocarcinoma with PDL-1 positivity in 70% of the cells. A remarkably worsening in his baseline hyper-eosinophilia reaching 5115/cu.mm was also noted. The patient was treated with prednisone 1mg/kg daily for fear from immunotherapy toxicity. He then received his second dose of pembrolizumab 200 mg on December 26th. Of note, his eosinophil count continued to increase progressively to reach 6237/cu.mm, despite his tapered steroid therapy (Figure 4).

A chest CT on January 3rd showed progression of the previously seen metastatic pleural nodules with evidence of lymphangitic spread, multiple new metastatic liver lesions and ill-defined multiple thoracic vertebral lytic lesions, not present on imaging two weeks prior. In view of his rapidly progressing disease, goals of care were agreed to be supportive only, and he passed away two weeks later.

Discussion

ICI have recently revolutionized treatment in oncology, showing evidence of improved survival compared to conventional platinum-based chemotherapy in lung malignancy.[8] However, atypical response to treatment has been reported in up to 10% of cases, leading to a rapid tumor growth rate that is out of proportion compared to the one before therapy initiation. This response to immunotherapy has been termed as HPD. Predictors and biological markers of this fearful disease acceleration remain unknown and desperately needed to prevent both ICI toxicity and/or premature discontinuation of treatment.[9]

Eosinophilia is defined as a peripheral blood AEC greater than 500 cells/cu.mm, and hyper-eosinophilia is the presence of an AEC [?]1500 cells/cu.mm in peripheral blood on two separate occasions at least one month apart or pathologic confirmation of tissue hyper-eosinophilia. It can be seen in allergic, immunologic or infectious processes. Hyper-eosinophilia can also be seen rarely in certain hematologic or neoplastic disorders and has been termed as "paraneoplastic eosinophilia". Eosinophils are hypothesized to have the ability to invade tumor microenvironments, contributing to a better prognosis in certain types of cancers like colorectal and esophageal squamous cell carcinoma. However, contradictory results were also reported in patients with Hodgkin's lymphoma, which question their real role in different malignancies.[5]

The incidence of eosinophilia after ICI therapy has been reported previously and reaches 2.9%,[5] but again with contradictory outcomes, even in cases diagnosed with non-small-cell lung cancer (NSCLC).[5,10] Other routinely available laboratory tests (i.e. baseline serum lactate dehydrogenase and relative lymphocyte count) were also studied and successfully implemented in a predictive model of favorable prognosis in melanoma patients treated with pembrolizumab.[11]

Our case illustrates the early occurrence of HPD within days after pembrolizumab administration, despite the presence of pre-treatment hyper-eosinophilia, a readily available marker that has been previously shown to be associated with an increased overall survival in 616 patients with metastatic melanoma patients treated with pembrolizumab,[7] and another 209 patients treated with ipilimumab, another ICI.[11] It also represents the first case to show worsening hyper-eosinophilia in a patient with NSCLC with subsequent disease hyper-progression, which is contradictory to the results shown after treatment of patients with metastatic melanoma, as discussed earlier.[7,11]

All these heterogenous and sometimes contradictory results raise the question about the possible presence of a certain threshold or peak of eosinophil counts before, during and/or after ICI therapy that must be taken into consideration, and above which, a deleterious effect on host cells or response to immunotherapy

is exerted.[12] Another hypothesis is the possible co-dependence of eosinophils on other factors, not commonly taken into consideration, like in the example of CD8-T cells, to produce an adequate antitumor response, as was demonstrated previously in a mouse model.[13]

In conclusion, the AEC is a potential predictive and readily available factor that can allow immunotherapy treatment guidance in patients with different malignancies. However, taking into consideration the dynamic variation of this count pre and post treatment, along with other possible acting co-factors, can provide a foundation for investigation in future randomized controlled trials.

Author Contribution

SAK and HW were responsible for manuscript writing and literature review. MK and AT were responsible for additional literature review. JAF was responsible for manuscript editing and critical feedback before the final form submission.

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