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Case Report

Progressive Exertional Dyspnea and Fatigue in an Oncology-Patient

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Abstract

Background: Progressive fatigue even further dyspnea are common between oncology patients; however the development of these symptoms in a patient who has been treated with some of the new immune checkpoint inhibitors must make us thinking of a possible adverse event of these drugs.

Case Report: We report a case of a 78-year-old man with a history of ischemic heart disease, who presented with fatigue, elevated myocardial enzymes and atrioventricular block in the electrocardiogram. He had been diagnosed of lung cancer and included in a clinical study with combination therapy of ipilimumab and nivolumab. Further investigation during hospitalization revealed also neuromuscular, thyroid and neurological affectation. Also we started immunosuppressive therapy, the patient died fewer days after diagnosis.

Conclusion: We report a case of myocarditis due to new immune checkpoint inhibitors use for cancer treatment. Although this type of toxicity has yet been reported, we still lack of a score risk to predict high risk patients or genetic predisposing. Since an early diagnosis and prompt treatment could prevent the fast development we encourage medical practitioners to retain a high degree of suspicion.

Keywords: Dyspnea; Lung cancer; Atrioventricular block; Nivolumab; Ipilimumab; Myocarditis

Introduction

We present a case of a suspected myocarditis and multiorganic toxicity due to immune checkpoint inhibitors used in cancer treatment. Some cases have been reported in the literature although the peculiarity of this one was the multiorganic and simultaneously affectation.

We are attending the striking development of cancer treatment, which allows patients in the most astonishing cases to the complete resolution of the disease. However, to get the aim many trials and surveillance studies must been performance. The release of biological targeted medications has passed over the feared chemo resistance to conventional drugs. But we need to balance even though the prognosis is often very poor, a detailed assessment of the advantages and disadvantages taking into account the patient and family's preferences.

However we could think that more specific treatment would lead us to less aggressive adverse events, but that's not the case with immune checkpoint inhibition drugs.

Case Report

A 78-year-old male, ex-smoker, who had a history of ischemic heart disease 10 years ago, with preserved ejection fraction, was diagnosed in June, 2016 of a non-small cell lung cancer (squamous cell carcinoma disseminated to liver without any remarkable molecular profiling). He was proposed to take part in a clinical essay that evaluate the answer to nivolumab 3mg/kg every 2 weeks associated to ipilimumab 1 mg/kg every 6 weeks; beginning the above mentioned treatment five months later and receiving the first dose of nivolumab on November 24th.

Patients whose tumors do not contain a driver mutation or do not have ≥50 percent expression of Programmed Death-Ligand 1 (PD-L1), or when such information is unknown, combination therapy using a platinum-based doublet is generally recommended. This approach has been associated with an improved survival, which was independent of histology, performance status, and age [1].

Ipilimumab (an anti-CTLA-4 antibody) and nivolumab (an anti-PD-1 monoclonal antibody) have been used for metastatic melanoma with promising results, so this combination is under investigation in other metastatic histologies [2,3].

After two weeks of drugs administration he came to the emergency department for shortness of breath of approximately a week of evolution. An initial workup revealed a prolongation of 250ms of the PR interval, minimal leukocytosis and neutrophilia, according with an elevation of C-Reactive Protein (CRP) and a persistent raised troponin I around 3-4 μg/L (normal level, <0.017). A transthoracic echocardiography showed no interesting finding as well as a chest and abdominal CT scan that revealed a doubtful tumoral wall-aorta infiltration.

Within the first hours the patient presented abrupt respiratory insufficiency and a high degree atrioventricular block, including some complete block episodes as we can observe in figure 1, so he was taken to the intensive care unit where a permanent pacemaker was

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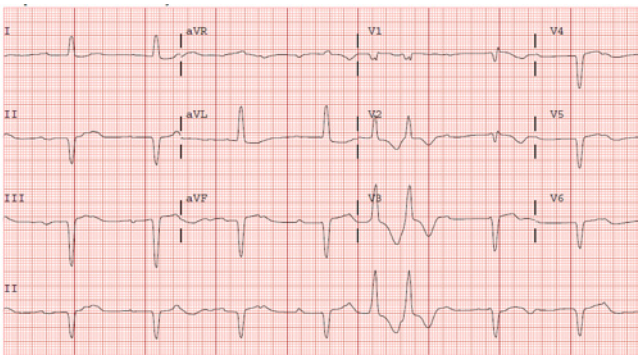

Figure 1: Complete atrioventricular block with 2 ventricular premature beats.

implanted. Although pneumonitis and myocarditis were suspected they could not be proved due to the impossibility to collect a histological sample. Serial echocardiograms revealed no changes with respect to the first one.

Considering the dramatically situation, we decided the patient not candidate to endotracheal -intubation, according to oncologists and the patient's family so empirically we began treatment with high-doses glucocorticoids (1 mg per kilogram per day), completing finally 5 days [4]. He was also diagnosed of hyperthyroidism and polyneuropathy and after eight days in the intensive care unit finally died of cardiac arrest. Histological study was not requested according to family's desire.

Discussion

Although we suspected pulmonary and myocardial toxicity due to the clinical development we could not prove them. The presence of a normal left eyection fraction and normal left filling pressures beside severe respiratory insufficiency tough to diuretics is uncommon in fulminant myocarditis. For this reason we thought about the possibility of pneumonitis which explains the current clinical problem.

On the literature pneumonitis is more common than myocarditis (3-5 % versus 1% only in nivolumab-treated patients) [5,6]. In the limited reported cases (risk of less than 1% with the combined treatment) a common finding is conduction delays and persistent elevation of myocardial biomarkers [7].

No matter what the immune-related adverse event was, the common approach includes immediately treatment withdrawal, glucocorticoids and other immune-modulatory medications in steroid-refractory cases with very diverse results [5].

Conclusion

New therapies for cancer treatment are on continuous development, even though clinical trials and studies report all the adverse reactions, such others drugs is when they become of general use when we really discover its full action's spectrum. We must investigate any new symptoms in this type of patients because in most of the cases a quick suspension could relieve these symptoms. On the other hand is only a matter of time that cancer therapy will be approached to biological targeted medications taking into account DNA peculiarities of each patient minimizing adverse events. In the main time maybe we must consider patients with a cardiovascular history as high risk for drugs with cardiovascular adverse reactions described.

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