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Case Report

Myasthenia Gravis Secondary to Pembrolizumab

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Abstract

In recent years, the development of anti-cancer target drugs therapy has been increasing significantly. In this context, a new monoclonal antibody group, which inhibits the programmed cell death 1 receptor, has emerged as an effective frontline of treatment of certain neoplasms. Prembrolizumab, a humanized monoclonal antibody, is a standard option for the treatment of advanced and metastatic malignancies like multiple myeloma. However, clinical research has uncovered diverse, unpredictable and serious immune related adverse events that raise concerns regarding its safety. Here, we will describe the case of an oncology patient with a suspected myasthenia gravis after receiving pembrolizumab 200 mg every 3 weeks.

Keywords: Myasthenia Gravis; Pembrolizumab; Programmed Cell Death 1 Receptor

Introduction

The development of drugs that inhibit immune control points has given a new approach to antineoplastic therapies. The programmed death 1 receptor (PD-1) adjusts in a negative manner immune activity of T cells through its interaction with transmembrane ligands PD-L1 and PD-L2 which are present in certain cell lines. In normal physiological conditions, the main function of PD-1 is to inhibit activity of cells to avoid an overstimulation of immune response in peripheral tissues and to prevent tissue damage mediated by the immune system (SI) [1,2]. Certain types of tumors overexpress PD-L1/PD-L2 as an escape route to immune response, thus blocking this interaction is an interesting pharmaceutical point. Pembrolizumab (PBZ), a humanized monoclonal antibody, joins and inhibits, in a selective manner, PD-1 and, in this manner, it promotes immune and anti tumor response of T cells. However, as IPCIs block these routes, overstimulation of SI may generate inflammatory reactions known as adverse events related to the immune system (irAEs) such as myasthenia gravis (MG) [3,4].

MG is a disease characterized by the abnormal production of auto-antibody that affect the neuromuscular junction destroying acetylcholine receptors, which is clinically seen as a progressive weakness in the striated muscles [5].

Case Presentation

Below we present a 79-year-old male, with high blood pressure, dyslipidemia, stroke and malignant melanoma (MM) under treatment with PBZ IV 200 mg every 3 weeks, who has been seen in Emergency on December 17, 2017 as he has had right palpebral ptosis, diplopia and dysarthria for 72 hours. He was admitted for observation and indicated to take meprednisone VC 60 mg/day which reverted the current condition. A MRI of head and blood test were made with erythrocyte sedimentation rate of 33 (Normal rate:

0-20mm/h) and no other features with respect to previous clinical condition of the patient. This is understood as a likely inflammatory myositis. As he had good evolution he was discharged 72 hours later to be followed up by Oncology. Medication prescribed after discharge: enalapril 10mg/day, atorvastatin 10mg/day, ranitidine 300 mg/day, acetylsalicylic acid 100mg/day and meprednisone 60mg/day.

Ten days after discharge from hospital, he was seen in Emergency again as he had reduced vital capacity and dropped head syndrome, it was decided to carry out an orotracheal intubation and to hospitalize the patient. Consultation with Ophtalmology, Oncology and Neurology was carried out.

The situation was understood as suspicion of secondary MG due to the use of PBZ. It was decided to stop the third administration of the drug and a blood analysis is requested to check antibody against acetylcholine receptors (ACRA) and a positive result was obtained, which confirms MG. Some days later five cycles of gamma globulin IV (3.000 mg/day + hydrocortisone IV 100 mg/day) and pyridostigmine SNG (240 mg/day), the last of which was stopped due to improper response.

There is also pneumonia Klebsiella pneumoniae carbapenemasa (KPC) after 15 days of having been admitted. An antibiotic scheme was started: colistin IV 150 mg/day, meropenem IV 3 gr/day and vancomycin IV 2gr/day, but evolution was not good due to secondary progressive kidney failure to colistin injury. There was a conversation with the family and it was decided not to continue with invasive procedures, as comfort was prioritized. The patient died after one month. The Pharmacy Service received and analyzed the RAM, stating the cause of Naranjo algorithm with a probable result. This case has been notified to the corresponding Pharmacy Surveillance Center.

Discussion and Conclusion

The use of IPCIs offers an innovative strategy for the treatment of certain tumors. PBZ is a monoclonal antibody approved for treatment of unresectable metastatic MM and as adjuvant in tumors of non- small lung cells and, although their prospect the appearance of IrAEs is seen, there is no reference as to events or exacerbation of MG [6]. As opposed to the reports of events related to MG due to PBZ, they have increased during the last period in spite of the fact that there is little evidence available. The first fatal case of induced MG due to PBZ is described by Zimmer and col [4] and it took place in a multicenter and retrospective study which assessed safety of the anti PD-1 treatment in 496 patients treated with nivolumab or PBZ, in which a 69-year-old oncology patient developed respiratory distress, ptosis and diplopía after the third intake of PBZ. She received corticosteroids treatment IV in high doses (methylprednisolone 1gr/day) with subsequent tapering VO of 60mg/day, pyridostigmine VO 60mg/day and five cycles of plasmapheresis without a good response, consequently losing their capacity to move freely, talk and swallow and he died four months after he was admitted. This patient had a negative blood análisis for AARA and was, therefore, diagnosed as seronegative MG. Unlike this case, our patient presented symptoms compatible with MG after the second intake IV of PBZ and was treated with a pharmacological scheme of lower dose of corticosteroids, a greater dose of pyridostigmine (which was later stopped due to bad clinical tolerance) and there was no other plasmapheresis. Another point regarding the patient presented by Zimmer and col. lies in the fact that serology for MG was positive for AARA and the cause is not described to be the patient. In our case, the Pharmacy Service attributed the cause based on the Naranjo algorithm with probable result.

In light of the foregoing, it is recommendable to have a prior and current pharmaceutical background of patients that could give useful information to differentiate causes of medication, interaction and/or adverse effects in order to have a better description of the pathophysiological condition. An electronic medical record included in the health system could be a good option for the improvement of an ongoing follow up of risks and benefits related to the PBZ therapy at the time of indicating it as treatment given the type of seriousness of irAEs that may be related to their use.

Conflict of Interest

The author states he has no conflict of interest.

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