EJMA

DOI: 10.14744/ejma.2023.47966
EJMA 2023;3(3):149–151

Case Report

Myastenic Syndrome Diagnosed After Treatment of Small Cell Lung Cancer with Atezolizumab (PDL-1 Inhibitor)

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Abstract

Immune checkpoint inhibitors have been increasingly used for many type of solid tumor, first line treatment of small cell lung cancer (SCLC) with chemotherapy combination with atezolizumab is one of them. Although usually well tolerated, autoimmune related side effects can be seen.We report of autoimmune myasetnia gravis that occured after treatment of atezolizumab, an anti-programmed-death (anti-PD-1) monoclonal antibody.

Our patient is 71 year old woman with extensive stage small cell lung cancer receiving chemotherapy combined with atezolizumab. Although good oncological response to treatment after 8 cycle of atezolizumab, myastenia gravis was occured. This automimmune neurological syndrome is likely associated with atezolizumab treatment, patient had no any neurological disorder before. Symptoms were partially responded after steroid, piridostigmine and iv-ig therapy.

The number of the patient that treated with immunotherapy will increase in the future so it should be important to know the adverse effects management of immunotherapy.

Keywords: Myastenia gravis, atezolizumab, immunotherapy

Cite This Article: *Öven BB, Türkmen İ, Geyikoğlu İ, Çelik S, Çağlar LA. Myastenic Syndrome Diagnosed After Treatment of Small Cell Lung Cancer with Atezolizumab (PDL-1 Inhibitor). EJMA 2023;3(3):149–151.*

Small cell lung cancer (SCLC) is characterized by rapidly progressing tumor with poor survival.[1] Immunotherapy is a novel approach that targets patient's own immune system to enhance antitumoral response. Immune checkpoint inhibitors(CPI), are available and had modest activity for SCLC.[2] The antiPDL-1 antibody atezolizumab with combination of carboplatin and etoposide in the first line treatment of SCLC improve survival nearly 2 months.[2] CPI related neurological side effects are rare but they can be lethal.[3] They manifest in dose dependent manner within 3-12months of initiation of theraphy with incidence of ≥grade 3 adverse effect was <1%.[4] After nivolumumab therapy myastenic crisis was reported in melanoma patient.[3] Immune mediated toxicities, paraneoplastic disorders such as Lambert-Eaton myasthenic syndrome(LEMS) resulting from reactivation of immune system are elicited by blockage of immune checkpoints.[5] In the differantial diagnosis cranial metastasis and paraneoplastic syndromes should be thought.[3] In the case of myastenia gravis CPI should be witheld, systemic corticosteroid, and pyridostigmine should be initiated.[4] We report the case of a 71 year-old woman in whom myasthenic syndrome was developed after immunotherapy treatment for SCLC. The number of the patient

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Submitted Date: August 19, 2022 **Revision Date:** August 19, 2022 **Accepted Date:** July 19, 2023 **Available Online Date:** March 28, 2024

that treated with immunotherapy will increase in the future so it should be important to know the adverse effects management of immunotherapy.[6]

Case Report

71 year-old woman was presented with supraclavivular lymph node metastasis.PET-CT revealed multiple bone, liver, mediastinal lymph nodes metastasis and right hiler mass. cranial MR showed clivus metastasis. SCLC with synaptophysin, chromogranin and TTF-1 positivity was diagnosed by biopsy from the supraclavicular lymph node. There was past medical history of hypertension, and colon cancer operation 20 years ago. There was neither history of autoimmune disorders nor corticosteroid dependence. She had 60 package year of smoking history. Standart carboplatin AUC5, etoposide(100mg/m^2) and atezolizumab(1200mg/m^2) and zoledronic acid 4 mg were started for every 3 weeks after paliative bone and cranial radiotherapy were performed. Atezolizumab maintenance for every 3 weeks was followed by 4 cycles of chemotherapy. Becuse of transaminse elevation (AST/ALT:255/212) atezolizumab was stopped during 8th cycle. Cholestasis tests, hepatitis markers (HbsAg, antiHCV, anti-HBc Igm, antiCMV), autoimmune hepatitis markers (ANA, ASMA, antiLKM) were negative, abdominal USG was normal. Immunotherapy related hepatitis was considered and methylprednisolone 1mg/kg was started. Over the 1 week, transaminases returned normal but she had compliant of jaw pain, progressively increased dysphagia both for liquid and solid. bilateral ptosis, lower limb muscle weaknesss. Gastroscopy was normal, thoraco- abdominal CT and nasopharyngealMR were normal and tumor had good oncological response except stabile sclerotic bone metastasis. Otolaryngologist revealed disappearance of gag reflex, mechanical ventilation was achieved with entubation because of hypercapnic respiratory failure then tracheostomy was performed. MRI of the brain showed stabile clivus metastasis without any cranial nerve invasion; biochemical and cytological examination of lumbar puncture were normal. Repetitive nerve stimulation test was undiagnostic. Paraneoplastic panel including anti-Hu, anti-Ri, anti-Yo, antivoltage-gated potassium and calcium channel antibodies,acetylcholine receptor antibody were negative, but anti-titin antibody was positive. Myastenic symptoms developed during the 24th week of atezolizumab treatment (after 8th cycle) and decreased after steroid, piridostigmine and ivig treatment after 2 months. She was extubated, swallowing and muscle weakness were gradually improved and she is still internalized for palliative rehabilitation care unit for 3 months after the start of steroid therapy without lung cancer exacerberation.

Discussion

Immunotherapy is increasingly used in solid tumor with better quality of life, lower side effect and longer survival compared to chemotherapy. Adverse effects are related with immunotherapy are different from the systemic chemotherapy.[7] Neurological adverse effects under anti-PDL-1 treatment were reported as nearly 10% with 0.1-15% of grade 3-4.[6] Although rare, they may lead to fatal consequences so it is important to diagose and treat early. [8] Differantial diagnosis should always be performed because neurological symptoms can be related with infectious, paraneoplastic, vascular, toxic or metabolic causes. [6] Cerebrospinal fluid examination with cytology, culture or biochemical analysis support metastasis, infection or inflammatory mediated disease, cranial MRI can exclude new metastasis.[6]

Myastenia gravis is one of the neurological autoimmune syndrome characterized with proximal muscle weakness, ptosis, respiratory failure with involvement of respiratory muscle[6] is seen during therapy with CPland 6.1%with anti-PD1antibodies.[7] In addition to the clinical presentation, the repetetive nerve stimulation test, autoimmune antibody support the diagnosis of myastenic syndrome. In our case, only anti-titin antibody was positive that is similar to the pembrolizumab induced myastenia gravis in treatment of lung adenocarcinoma.[9] This antibody is generally positive in thymoma and late onset myastenia gravis and combined with poor prognosis.[10]

This syndrome was reported during treatment with nivolumumab both for melanoma, SCLC and squamous cell lung cancer.[7] Although myastenia gravis related with anti-CTLA-4 or anti-PD1 have been reported, this case is noteworthy because it is the first reported to be related with atezolizumab, anti-PDL-1 antibody was used for SCLC. No eligible study related with neurological adverse effects of atezolizumab have been found in the literature. Abdel-Rahman and et al evaluated neurological toxicity of immunotherapy among 18 trials and 17 case reports of cancer patients.[8] Among 22 patients with neurological toxicity, only one had SCLC and none of them was taken atezolizumab.[8]

It was difficult to differantiate etiology as paraneoplastic syndrome or immune adverse effect. Because the onset of this syndrome developed after SCLC received nearly complete response clinically after atezolizumab therapy (6 months later), unlike paraneoplastic syndrome. Because later usually starts before diagnosis of malign disease and generally patient has symptom relief while primary disease was improved with therapy. Early recognition and can reverse the neurological symptoms within 6-12 weeks. [6] In our case the respiratory and proximal muscle weak-

ness reversed after 2 months. Sysytemic myastenia gravis can potentially life threatening syndrome with respiratory muscle involvement.[6] It is difficult to predict whether continuation of immunotherapy may cause progression of myastenia gravis or not. Our patient also had radiologically nearly complete response to atezolizumab for 3 months without therapy. It is important to keep in mind that unexpected immune related adverse effects can be seen during treatment with CPI. Clinical suspicion and early treatment of this life-threatening adverse effect are important because autoimmune antibodies are not always clinically positive for differantial diagnosis.

Disclosures

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – B.B.Ö., İ.T., İ.G., L.A.Ç.; Design – İ.T., İ.G., L.A.Ç.; Supervision – B.B.Ö., S.Ç.; Materials – İ.T., B.B.Ö.; Data collection and/or processing – İ.T., İ.G., S.Ç., Analysis and/or interpretation – B.B.Ö., S.Ç., İ.T., İ.G.; Literature search – İ.T., İ.G.; Writing – İ.T., İ.G.; Critical review – B.B.Ö., S.Ç.

References

1. Tsoukalas N, Fatorou E. Advanced Small Cell Lung Cancer (SCLC): New Challenges and New Expectations. Annals of Translational Medicine, 2018.
2. Armstrong SA, Liu SV.Immune Checkpoint Inhibitors in Small Cell Lung Cancer: A Partially Realized Potential.Adv Ther. 2019 Jun 17.
3. Heinzerling L, Goldinger SM.A review of serious adverse effects under treatment with checkpoint inhibitors. Curr Opin Oncol 2017 ;29:136-144.
4. Trinh S, Le A, Gowani S, La-Beck NM.Management of Immune-Related Adverse Events Associated with Immune Checkpoint Inhibitor Therapy: a Minireview of Current Clinical Guidelines. Asia Pac J Oncol Nurs 2019;6:154-160.
5. Majem M, Rudin CM. Small-cell lung cancer in the era of immunotherapy. Transl Lung Cancer Res 2017;6(Suppl 1):S67-S70.
6. Astaras C, de Micheli R, Moura B, Hundsberger T, Hottinger AF.Neurological Adverse Events Associated with Immune Checkpoint Inhibitors: Diagnosis and Management.Curr Neurol Neurosci Rep. 2018 ;18:3.
7. Nakatani Y, Tanaka N, Enami T, Minami S, Okazaki T, Komuta K. Lambert-Eaton Myasthenic Syndrome Caused by Nivolumab in a Patient with Squamous Cell Lung Cancer.Case Rep Neurol. 2018 ;10:346-352.
8. Eltobgy M, Oweira H, Petrausch U, Helbling D, Schmidt J, Mehrabi A, et al. Immune-related neurological toxicities among solid tumor patients treated with immune checkpoint inhibitors: a systematic review.Expert Rev Neurother. 2017 ;17:725-736.
9. Onda A, Miyagawa S, Takahashi N, Gochi M, Takagi M, Nishino I, et al.Pembrolizumab-induced Ocular Myasthenia Gravis with Anti-titin Antibody and Necrotizing Myopathy. Intern Med 2019;58:1635-1638.
10. Chen XJ, Qiao J, Xiao BG, Lu CZ.The significance of titin antibodies in myasthenia gravis--correlation with thymoma and severity of myasthenia gravis.J Neurol 2004 ;251:1006-11.