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Myasthenia gravis during treatment with anti-PD-1 - successful treatment using pirydostygminum – case report and literature review

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Abstract

Background: Against limited effectiveness of known oncological treatment such as chemo- and radiotherapy or surgery, new ways of treatment, such as for example immunotherapy has developed. Usage of immune checkpoint inhibitors (ICPIs), resulting in overactivation of immune system, may significantly raise efficacy of oncological treatment, but simultaneously predispose to occurrence various autoimmune health complications. Adverse actions of the therapy may affect multiple organs and systems, with the presented example of immune-related neurological complication, myasthenia gravis. This relatively rare condition may be severe, life-threatening illness.

Case report: We present a case of 66-year-old male patient diagnosed with a large tumor histopathologically assessed as squamous cell carcinoma. Due to ineffectiveness of implemented chemo- and radiotherapy, he was qualified for anti-PD1 immunotherapy with nivolumab. General treatment tolerance was very good with positive antineoplastic effect. Autoimmune hypothyroidism has emerged, therefore levothyroxine therapy has been implemented. After about a year of using immunotherapy, significant weakness and decrease in muscle strength has appeared, subsequently, immunotherapy-related myasthenia gravis was raised. Improvement in the patient's condition was achieved after initiating pyridostigmine treatment. Cessation of antineoplastic treatment wasn't necessary, what is unusual.

Conclusions:

Undeniably myasthenia gravis may determine serious, life-threatening adverse effect of immunotherapy. Usually requires withdrawal of applied antineoplastic treatment, and should be treated with immunomodulators, immunosuppressants or intravenous immunoglobulins or plasmapheresis, however – as we present- in some cases may be properly cured only with pyridostigmine.

MeSH Keywords: Carcinoma, Non-Small-Cell Lung , Immunotherapy, Myasthenia Gravis, Nivolumab

Abbreviations:

ANA - antinuclear antibodies

CTLA4 - cytotoxic T lymphocyte antigen-4

ICPIs - immune checkpoint inhibitors

irMG – immunotherapy related myasthenia gravis

irAEs - immune related adverse events

nivoMG- nivolumab-induced myasthenia gravis

NCI - National Cancer Institute

NSCLC - non-small cell lung cancer

PD-1 – programmed death 1

PDL-1 - programmed death ligand 1

TCR - T lymphocyte receptor

Background:

Self-defence of the host organism from environment pathogenic factors is provided by immune system, which plays a pivotal role also in performing immunosurveillance of cancerogenesis. Some types of neoplasms are able to escape immunological supervision, increasing their growth potential. This escape effect may be pharmacologically reversed by implementing immunotherapy, what from the other hand takes a risk of bringing adverse effects, which are commonly called immune related adverse events (irAEs)(1) .

Nowadays, most commonly used in immunotherapy are immune checkpoint inhibitors (ICPIs), which are specific antibodies targeted to selected antigens. We can indicate antibodies, that have ability to react with e.g: anti-programmed cell death receptor-1 (anti-PD-1; nivolumab, pembrolizumab), anti-programmed death ligand-1 (anti-PDL1; durvalumab) or anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA4; ipilimumab).

In general, T lymphocyte receptor (TCR) needs to be connected with adequate ligand inherent on presenting cell (APC), subsequently a game of co-stimulatory factors takes place. When CD28 present on T cell binds with its coreceptor CD80/86 (B7-1,2) present on APC, lymphocyte T is activated, whereas when CTLA-4 present on T cell binds with the same coreceptor, inhibition of lymphocyte T overlaps. Tumors have an ability to present inhibitory ligands on their surface – to avoid activation of T cell. ICPIs effectuate the inhibition of inhibitory action of costimulators and ipso facto activate T lymphocytes. PD-1 molecule is a transmembrane glycoprotein, a member of the CD28/CTLA-4/ICOS costimulatory receptor family. Activation of this receptor carries negative signals for regulation lymphocytes T and B(2) . Monoclonal antibodies anti-PD-1 (nivolumab i pembrolizumab) have an ability to block PD-1 molecule. Generally, proteins from the family of receptors mentioned above, are present on lymphocyte T, whereas PD-1 is present on lymphocyte T and activated lymphocyte B.

Bearing in mind mechanism mentioned above, we should be aware of possible hyperactivation of T cells and its clinical features (3) . Nowadays, development of this condition isn't known in details. Presumably ICPIs enhance Th1 and Th17 cell responses and cytokines production, what leads to humoral immunity activation and abnormal function of T-regulatory cells. These phenomenon leads to dysregulation of Treg and Th17 balance, what seems to be important for autoimmune diseases development. ICPIs are also able to stimulate antibody production.

Specific kinds of immune checkpoint inhibitors may induce different types of adverse effects various in their spectrum of organ involvement and severity(4) .

What is interesting, some adverse effects of anti PD-1 are reported to be a positive prognostic factor of good response to implemented treatment(5) (6) .

Adverse actions of immune checkpoint inhibitors may affect multiple organs and systems, such as gastrointestinal tract, endocrine or renal system, liver, pancreas or skin. The frequency of irAEs is mainly dependent on the medications used (7) , whereas individual characteristic of patient is also important (4) . IRAEs may occur with high frequencies of around 30 and 50% in treated with anti-PD-1 and anti-CTLA-4 antibodies and even up to 70–90% in patients treated with combinations of the above (8). Sample summary of group of 496 German patients treated with nivolumab or pembrolizumab (anti-PD1 antibodies) shows, that 27,8 % of subjects developed side-effects of treatment. 8,7% patients suffered because of dermatological changes, where the most common were pruritus, rash, eczema and vitiligo. From gastrointestinal tract complications, which concerned 4,2% of subjects, most frequent were diarrhoea, abdominal pain, xerostomia, coprostitis and colitis. Hepatitis concerned 2,2% of subjects, whereas 1,8% developed pancreatitis. Most common endocrine system disorders were hyper- and hypothyroidism, in some cases with thyroiditis; hypophysitis, diabetes mellitus and adrenal insufficiency; entirely concerned about 6,0% of patients. IrAEs of renal system affected 2 subjects (0,4%), running with nephritis or renal failure (1) . Immune checkpoint inhibitors may induce multiply side effects, not only mentioned above – also ophthalmic (9) , cardiovascular (10) , (11) or hematopoic (12) side effects also are commonly described.

The National Cancer Institute (NCI) in Common Terminology Criteria for Adverse Events (CTCAE) defines 5 grades of severity of a toxicity with stage 1 being asymptomatic or mild, when intervention is no needed, 2 being moderate and with noninvasive intervention indicated, 3 – severe, but not immediately life-threatening, demanding hospitalization, 4 - life-threatening event with urgent need of medical intervention and 5 – adverse effect in the form of death (13) .

In group of subjects treated with a-PD-1 or a-PDL-1 antibodies, the most common neurological adverse effect were headache, estimated for about 3% and myopathy/myalgia (3%). Grade 3 and 4 toxicity were very rare, with myasthenia gravis being the most common one, with the frequency of 1%, but example of grade 5 toxicity MG was noted (14) . In group of subjects treated with a-PD-1 antibodies, general estimated frequency of neurological irAEs was 2,9 (15) to 3,2% (14). Myositis seems to be the most frequent neuromuscular irAEs (16) .

Immunotherapy-related myasthenia gravis is relatively rare adverse effect of implemented drugs, but may be a severe, life-threatening illness. Due to analysis performed by Becquart et al., anti-PD-1 immunotherapy was the most frequent one causing irMG, with melanoma and lung carcinoma being the most often treated neoplasms (17) .

In most cases of myasthenia gravis, that developed due to a-PD1 application, immunotherapy was held (18) or discontinued (19) and immunosuppressive therapy was implemented (19) , (18) , towards only partial response to pyridostygmine (18) .

Case report:

In the course of diagnostics of intensifying cough in a 66-years-old male, with no previous history of autoimmunity, smoking for 40 years about 20 cigarettes a day, an x-ray of the chest was performed. A large tumor of about 12 cm of the mediastinum and the right cavity was found. Histopathological assessment indicated a diagnosis of squamous cell carcinoma, in further rating, classified as at stage T4N2M0.

Due to the tumor inoperability, the patient was qualified for sequential chemo- and radiotherapy. After receiving 3 cycles of chemotherapy (navelbin and cisplatin), the lesion decreased to 6 cm, but it still infiltrated the division of the right lower and intermediate bronchi, and was still adjacent to the superior vena cava and division of the right pulmonary artery. Sequentially proper radiotherapy was applied, however, in the control CT-scanning of the chest, the dissemination of the disease was described with new changes visualised in the right lung apex up to 2,5 cm in size.

In comparison of the progression of the disease, the patient was referred to a center where immunotherapy is used.

During second histopathological block assessment, immunological tests were performed- tumor receptors have shown to be present. The patient was qualified for anti-PD1 immunotherapy.

Drug treatment brought positive results: the main lesion significantly decreased and peripheral lesions in the right lung completely disappeared. However, autoimmune hypothyroidism has emerged and required levothyroxine therapy, which was implemented. Adrenal function remained normal. General tolerance of nivolumab treatment was very good.

After about 12 months of using immunotherapy, a significant weakness and decrease in muscle strength have occurred. The patient was able to left home only for short walks. Due to increasing difficulties with raising his arms, even clothing caused significant fatigue. The patient was admitted to hospital with growing shortness of breath and companion of silence speech. First, adrenal insufficiency and pneumonia were excluded. Because of symptoms mentioned above, myasthenia gravis was suspected. The levels of chosen autoantibodies have been

checked: no antinuclear antibodies (ANA) or myositis panel antibodies were detected, whereas presence of anti-acetylcholinesterase antibodies has confirmed the diagnosis of myasthenia gravis. Pyridostigmine (acetylcholinesterase inhibitor) therapy was initiated.

Significant improvement in the patient's condition was achieved after initiating pyridostigmine treatment. The drug was used in a dose of 60 mg every 4 hours. Symptoms of muscle weakness subsided very quickly (within a dozen or so hours), but the usage of the drug is necessary to be continued. Fortunately, there was no necessity to hold or set aside treatment with anti-PD1. Treatment with glucocorticosteroids or intravenous immunoglobulin supply weren't necessary.

Currently, the patient is in a very good general condition, on anti-PD1 treatment. Further gradual decrease in tumor mass is observed. However, levothyroxine is required for hypothyroidism and pyridostigmine for myasthenia gravis chronically.

Discussion:

Myasthenia gravis, which in general is an autoimmune disease, featuring with localized or generalized muscle weakness, very often with eyes muscles involvement. It's caused by antibodies directed against acetylcholine receptor related proteins in the neuromuscular junction, most commonly antibodies against the acetylcholine receptor (AChR) or a muscle-specific kinase (MuSK). 10 up to 15% of patients remain seronegative. Two peaks of morbidity of MG are observed, with the age of onset under and above the age of 50. In the first group myasthenia gravis is three times more likely to be diagnosed in females, also coexistence of others autoimmune diseases will be more often then. In group of late-onset myasthenia gravis, discreet advantage of male morbidity is noted (20). Due to complications such as respiratory insufficiency or sepsis, in-hospital mortality of MG is estimated for about 6-10%(21).

Myasthenia gravis may also develop during ICPIs treatment (4), but there are significant differences between regular MG and immunotherapy-related myasthenia gravis (irMG). The irMG mortality rate was higher than in group of regular MG and it was estimated for about 29,8-30,4% (22), (23). The most common cause of death in this group was respiratory paralysis (22). In the mortality group, the patients seem to exhibit an earlier onset of irMG symptoms, usually within 4 weeks from the initiation of ICI therapy(21). The presence of anti-MuSK antibodies among patients with irMG was estimated for 5.3% and for 66.7% for anti-AChR antibodies (22), respectively. Due to different authors the presence of antibodies directed to acetylcholine receptor is estimated for about 73% (24) - 83% (25) of patients reported with irMG, depending on performed analysis. Most commonly irMG was related to antineoplastic treatment with anti-PD1 antibodies (89%), only 11% of subjects were treated with anti-CTLA-4 and anti-PDL-1 inhibitors(21). Most typically symptoms occur within 4-6 weeks (22), (23) of treatment initiation, what is estimated as usually at the time between second and third cycle of immunotherapy(22). The peaks of severity usually occur between 1 and 4 weeks (23). There exist reports of exacerbation of MG in patient treated with pembrolizumab (24). irMG has developed with myositis and myocarditis in some cases (19), (10), (16), so cardiac testing should be performed to exclude myocarditis(25). In most cases of myasthenia gravis, that developed due to anti-PD1 application, immunotherapy was held (23) or discontinued(24) and immunosuppressive therapy was implemented (24), (23), towards only partial response to pyridostigmine (18). Generally different ways of nivoMG treatment, such as anticholinesterase inhibitors (pyridostigmine) as symptomatic treatment, immunomodulators or immunosuppressants (glucocorticoids or azathioprine) or intravenous immunoglobulins (IVIG) or plasmapheresis, as a rapid treatment or even thymectomy are available and should be taken under consideration as needed.

The possibility of treatment irMG only with pyridostigmine is not widely known, probably due to often severe, life-threatening course of this complication. We've found only one case describing 75-old woman with nivo-MG treated solely with pyridostigmine with no cessation of oncological medication (17). IrMG develops most frequently after the first and second cycle of infusion of immunological treatment, the definitive myasthenic symptoms in the case of female mentioned above has appeared after fourth application of the drug (17). Considering the time of onset of myasthenia gravis in our patient, which is about 12 months after initiation of treatment with nivolumab and effectiveness of treatment only with pyridostigmine, the example of our patient seems to be quite outstanding. In authors opinion this phenomenon can be linked with specific, not known at this moment, genetic predisposition conditioning of immune system function.

Presented case gives evidence, that in particular situation, adequate treatment nivoMG with pyridostigmine as a monotherapy, may be sufficient and irMG not always should be treated as an indication for cessation of antineoplastic treatment.

Growing number of patients treated with immune checkpoint inhibitors will result in growing number of autoimmune adverse effects. Unified way of reporting of these events will create great opportunity for further analysis. Planned observational studies are needed to collect reliable medical data for indicating the best method for treatment diverse irAEs, such as irMG depending on clinical features of the patient.

Whereas most cases of nivolumab-induced myasthenia gravis (nivoMG) are recognized up to 12 weeks after implementation of anti-PD1 drug, adverse effects of treatment may develop at any time. Considering the above, careful attention of possible adverse effects of medication should be maintained for the whole time of treatment and probably also after its end. Bearing in mind mechanism of action of ICPIs, awareness needs to be raised regarding to the clinical presentation of new, unusual side effects – worth repeating - independently of the time of treatment implementation.

Going further, at the time of decision making of implementation treatment with ICPIs, vigilant analysis of previous autoimmunity history of the patient should be performed. Also implementing of basic laboratory tests assessing current situation, such as antithyroid antibodies or even 21-hydroxylase or anti-acetylcholinesterase receptors autoantibodies is worth considering. In patients predisposed to develop irAEs, also medical supervision should be more organized and intense, hopefully in near future, based on reliable medical analyses summed up in clear recommendations.

Conclusion:

Treatment with immunotherapy may effect in hyperactivation of immune system and subsequently lead to various progressive autoimmune complications. One of the possible neurological side effects, myasthenia gravis, is potentially fatal.

Nivolumab-induced myasthenia gravis usually forces interruption of immunotherapy and undergoes treatment with immunomodulators, immunosuppressants or intravenous immunoglobulins or plasmapheresis, what may interfere with anti-cancer effect. We've presented a case of patient, who developed nivolumab-induced myasthenia gravis, but no cessation of antineoplastic treatment was necessary.

The possibility of treatment irMG only with pyridostigmine is not widely known. In our report we would like to underline the necessity of individualized approach to each patient and treatment of its present complications, as well as to underline the role of continuous observation of the patient cured with immunotherapy regardless of the duration of treatment.

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