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An Unprecedented Case of Myasthenia Gravis Induced by Binimetinib

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Abstract

Low-grade serous ovarian cancer, representing 10% of all ovarian cancer diagnoses, is renown for its poor response rate to chemotherapy, despite its indolent course. The MILO study is an international, randomized phase III trial comparing binimetinib, a targeted agent, to standard chemotherapy in patients diagnosed with low-grade serous ovarian cancer. This oral drug is designed to down-regulate cancer cell proliferation and survival through the inhibition of MEK-1 and MEK-2, involved in the RAS/RAF/MEK/ERK signal cascade. We present the case of a 77-year-old female started on binimetinib in November 2014, in a clinical trial context. She developed head drop syndrome correlating exactly with the administration of this drug. The clinical presentation, evolution and electrodiagnostic studies were compatible with myasthenia gravis. Anti-acetylcholine receptor antibodies were not detected. Improvement was noted immediately after the MEK inhibitor was withdrawn.

Keywords: Myasthenia gravis; MEK-inhibitor; Binimetinib; Ovarian cancer; MAPK pathway; Dropped head syndrome

Introduction

The addition of pyridostigmine and prednisone consolidated the clinical recovery until her baseline state was reached. MEK inhibitors have been reported to cause myopathy, but this is to our knowledge the first description of drug-induced MG arising from binimetinib. MG is a rare autoimmune disease with an estimated prevalence of 10-20 per 100,000. The neuromuscular junction is attacked by autoantibodies directed against the nicotinic AChR, producing symptoms of fatigable muscle weakness. Certain drugs have been reported to induce or exacerbate MG including penicillamine, chloroquine and quinidine. Inhibitors of the MEK signaling pathway can be added to this list. We reached an era where novel therapies may revolutionize cancer management. Optimizing the prevention and treatment of the potential adverse events is of key importance.

Case Report

Low-grade serous ovarian cancer (LGSOC), representing 10% of serous epithelial ovarian cancer diagnoses, is a challenging disease with poor response to chemotherapy. The disease disproportionately affects younger patients, and response to treatment is less than 4% in recurrent disease. This has led to the search for novel therapies to treat this difficult condition, and trials are underway using a variety of both cytotoxic and targeted agents. Here we present the case of a patient treated on a clinical trial with binimetinib, a MEK inhibitor first approved for use in advanced melanoma. MEK inhibition acts on the mitogen-activated protein kinase (MAPK) pathway, which is involved in cancer cell proliferation, differentiation, migration, survival and angiogenesis, and is upregulated in up to 30% of human cancers [1]. We present the case of a 77-year-old female with LGSOC treated with binimetinib who presented with symptoms of myasthenia gravis (MG) secondary to binimetinib exposure. Myasthenia gravis (MG) is an uncommon autoimmune disease with an estimated prevalence of 10-20 per 100,000 [2]. In MG, the neuromuscular junction is attacked by autoantibodies directed against the nicotinic acetylcholine receptor, producing characteristic muscular fatigability [3]. To our knowledge, this case describing myasthenia gravis induced by an inhibitor of the MEK signalling pathway is unprecedented.

This patient diagnosed with recurrent low-grade serous ovarian cancer commenced treatment with binimetinib in November 2014 in a clinical trial context. She presented four weeks later with an isolated dropped head syndrome indolently progressing since the trial drug was introduced. She had no ocular, bulbar or appendicular muscle weakness on physical examination. Fatigability was observed in the cervical musculature: repetitive neck flexion and extension emphasized this hallmark of neuromuscular junction disease. The neurological examination was otherwise unremarkable. Electrodiagnostic testing comporting needle electromyography (EMG) of the four extremities and paraspinal muscles, as well as extensive nerve conduction studies, were globally unremarkable. Myopathic features were absent. MRI of the cervical spine did not show edema in the cervical paraspinal muscles, and laboratory (including CK) and EMG testing were normal, all of which suggest the absence of inflammatory myositis. Thoracic CT Scan was unremarkable, without evidence of thymoma. Single fiber EMG (SFEMG) studies were markedly abnormal and confirmed the presence of impaired neuromuscular transmission, consistent with myasthenia gravis (increased jitter of 190 μs, with 44% abnormal pairs, and 22% blocking). Laboratory investigation showed normal CK, TSH, serum lactate, electrolytes, and ESR. Acetylcholine receptor antibodies were not detected. Binimetinib was discontinued and symptoms began improving within a few days with further gradual improvement with the addition of pyridostigmine 60 mg BID. Symptoms resolved completely with the addition of prednisone at a dose of 10 mg daily.

Discussion

Dropped head syndrome, an uncommon neurologic presentation, has been linked to various neurological disorders including MG. Focal

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myopathy is the most frequently reported aetiology [4]. Case series described cases of myositis secondary to MEK inhibitor exposure presenting with a dropped head [5]. The abnormal SFEMG and marked improvement after the introduction of pyridostigmine confirmed the diagnosis of MG. Drug-induced MG has been linked to numerous medications such as penicillamine, diphenylhydantoin, chloroquine, quinidine, trimethadone, and procainamide [6,7], as well as ipilimumab [8], but to our knowledge this is the first case reported in association with a MEK inhibitor. Generally, development of drug-induced MG is a contraindication to re-exposure to that particular medication. However, this is not so straightforward given the marked anti-cancer effects of novel targeted agents and immunotherapy. While the trial using binimetinib in LGSOC was stopped due to futility, these agents have shown promising results in other cancers, including BRAF-mutant melanoma. Thus, it is conceivable that a similar situation could arise in a patient with melanoma, in which MEK inhibition is likely to have significant therapeutic benefit. MG could reach a stable state for a prolonged period after the adequate regimen of pyridostigmine and prednisone is determined for a given patient. On the other hand, progressive metastatic melanoma is lethal without treatment. The risks and benefits must be weighed accordingly. In the case of our patient, prior to study cessation, we continued the MEK inhibitor after the first episode of dropped head, at a reduced dose. Her symptoms recurred, so we modified the doses of pyridostigmine and prednisone until she completely recovered again. She discontinued the trial because of tumor progression, but the myasthenia was controlled throughout the entire time she spent in that trial because of a rapid diagnosis and management.

While the MAPK-pathway targeted agents, including inhibitors or BRAF and MEK, are not typically viewed as immunomodulatory agents, there is increasing evidence for the role of the MAPK pathway in mediating immune evasion of tumour neoantigens. MAPK pathway inhibition may enhance anti-tumour immunity by increasing T-cell immune priming and reducing secretion of immunosuppressive cytokines [1]. This is illustrated by the increased severity of autoimmune side effects observed with the combination of immune checkpoint inhibitors and BRAF-inhibitors [9]. Thus, inhibition of MEK may have led to T-cell mediated autoimmunity affecting the neuromuscular junction, as suggested by the lack of acetylcholine receptor antibodies and the marked response to immunosuppression with prednisone.

Conclusion

In an era where targeted therapies will be prescribed more frequently for various cancers, it is important to recognize the presence of new neurologic symptoms in order to expedite diagnosis and intervention. Neurological complications of novel cancer therapies are rare but may be serious or life threatening. Thus, awareness of the potential autoimmune complications of immunological and non-immunological therapies is also important for patient safety. Furthermore, the increased application of targeted agents for oncologic and non-oncologic disease, including use in combination with immune stimulating agents, we need to adapt and optimize the treatment of neurologic conditions such as MG, which may result. Novel therapies will be employed more frequently outside of strict and regulated clinical trials context, letting more latitude to the judgment of the treating physician. The understanding of the pathophysiological mechanisms underlying central and peripheral nervous system adverse events is key, as we deal with a critical balance: cancer survival versus neurologic sequelae.

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