Anti-PD1 following Ipilimumab for mucosal melanoma: durable tumor response associated with severe hypothyroidism and rhabdomyolysis.

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Running title: Anti-PD1 is associated with autoimmune-related adverse events

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Abstract:

Treatment with fully human monoclonal antibodies against programmed death 1 (anti-PD1) have demonstrated great promise for the treatment of a number of advanced malignancies. While inflammatory adverse events have been well-described with anti-Cytotoxic T-Lymphocyte Antigen (CTLA4) therapy, experience with the range of adverse effects of anti-PD1 remains comparatively limited. Here, we report a patient with advanced mucosal melanoma who received four doses of MK-3475, a fully human monoclonal antibody against PD1, and experienced a durable near complete response, but developed severe hypothyroidism, rhabdomyolysis and acute kidney injury. To our knowledge, this is the first case reported of a patient with advanced mucosal melanoma who responded to anti-PD1 therapy. With the promising antitumor effects of anti-PD1 in a wide array of tumors, we expect an increasing number of patients to be exposed to anti-PD1 therapies. Recognition of infrequent presentations of adverse events such as elevated CK levels and thyroid disorders in patients who receive anti-PD1 therapy is important.
Introduction:

Immunotherapy has emerged as a promising therapeutic method for patients with metastatic melanoma. In clinical studies, monoclonal antibodies targeting immune checkpoint proteins have elicited long-lasting anti-cancer response (1-4). In 2011, the US FDA approved the use of Ipilimumab, a CTLA4 monoclonal antibody for treatment of metastatic melanoma. Monoclonal antibodies against the programmed death 1 receptor (PD1) and its ligand (PD-L1), the second-generation immunomodulatory antibodies, demonstrated significant durable benefits in patients with metastatic melanoma (4-6). However, our knowledge is very limited regarding the efficacy of immunotherapy for patients with metastatic mucosal melanoma, and the efficacy of anti-PD1 therapy for this melanoma subtype is unknown. Inflammatory adverse events have been well-described in patients who received anti-CTLA4 therapy (7). In phase I anti-PD1 clinical trials, adverse events such as pulmonary disorder (pneumonitis), renal disorders (acute renal failure and tubulointerstitial nephritis), hepatic disorders (ALT and AST elevations), gastrointestinal disorders (colitis and diarrhea), skin disorders (rash, vitiligo and pruritus), and endocrinopathies (hypothyroidism, hyperthyroidism, hypophysitis, and adrenal insufficiency) were observed with limited detail regarding the timeframe for the onset of these adverse events.

Case presentation:

A 46 year old man with advanced mucosal melanoma was enrolled in the clinical trial of MK-3475 (Merck), a fully human monoclonal antibody against programmed death 1 (PD1), at a dose of 10 mg/kg of body weight, given intravenously every three weeks. Four years ago, he was diagnosed with mucosal melanoma following a history of prolonged sinus complaints. He underwent maxillectomy, septectomy and dacryocystorhinostomy followed by 60 Gray (Gy) in 30 fraction via intensity-modulated radiation therapy (IMRT) technique to the surgical bed. Subsequently, lung and spinal metastases developed, which were resistant to treatments with
temozolomide and ipilimumab therapies. Four months prior to initiation of MK-3475 therapy, he received one course of 30 Gray in 10 fractions radiotherapy to cervical vertebrae 6-thoracic vertebrae 1 (C6-T1), which involved radiation exposure to parts of the thyroid gland. During MK-3475 therapy, he had thyroid function tests (TFTs) routinely as per the clinical trial protocol. During the first fifteen weeks of anti-PD1 therapy (5 doses), he had normal TFTs and remained active. Upon presentation to the clinic for evaluation prior to his sixth dose of MK-3475, he complained of significant myalgias, tender muscles, and fatigue. He was hospitalized following laboratory results that were significant for elevated transaminases: aspartate transaminase (AST) 858 units per liter (reference range: 10-50), and alanine aminotransferase (ALT) 289 units per liter (reference range: 10-50) (Figure 1). The levels of alkaline phosphatase, bilirubin and gamma-glutamyl transferase in the blood were normal but the level of creatine kinase (CK) was significantly elevated at 30980 units per liter (reference range, 55-170) (Figure 1), supporting the diagnosis for rhabdomyolysis rather than hepatic injury. After aggressive hydration, rhabdomyolysis improved but not resolved. Acute renal injury developed subsequently with his serum creatinine level increased from baseline 0.9-1.1 to 1.4-1.6 mg per deciliter (reference range: 0.7-1.3). Over the course of a week, he complained of progressing signs and symptoms of hypothyroidism including fatigue, weight gain, constipation, dry skin and bradycardia. Further laboratory testing revealed severe hypothyroidism; TSH was 145 and peaked at 187.82 mIU per liter (reference range 0.5-5) (Figure 1) with undetectable free thyroxine. Adrenal insufficiency was ruled out by a random blood cortisol level of 9 mcg per deciliter (reference range: 6-24). Given his young age and no history of heart disease, levothyroxine 150 mcg (=1.6 mcg per kilogram body weight) daily was started. His TFTs, CK level and renal function normalized with levothyroxine replacement; TSH returned to normal within 22 weeks after initiating hormone replacement.
Discussion:

PD1 is an immune-checkpoint receptor that negatively regulates T cell activation (8). Anti-PD1 antibody induces durable responses in patients with advanced solid tumors (3, 6). The current patient with mucosal melanoma, a rare form of melanoma, had an initial near complete response to MK-3475 therapy (Figure 2) and has remained in remission for 14 months after discontinuing treatment. Our understanding of immunotherapy efficacy in patients with mucosal melanoma is inadequate. A recent study showed that in patients with mucosal melanoma the overall response rate to ipilimumab therapy is low (9). Here, we report the first case of a patient with metastatic mucosal melanoma who experienced a durable response to anti-PD1 treatment following CTLA4 blockade. Our findings provide insight for immunotherapy efficacy in patients with mucosal melanoma as well as inform future drug development. Severe hypothyroidism is likely associated with the MK-3475 therapy or a combined effect of ipilimumab followed by MK-3475. It is unlikely that this is a sole effect of ipilimumab since time to onset of ipilimumab-related endocrinopathies including thyroiditis is usually between 7 to 20 weeks of initial ipilimumab therapy (10, 11). This patient remained euthyroid for 43 weeks after completing ipilimumab. Radiation-induced hypothyroidism is usually subclinical (12) but whether radiation precipitates immunotherapy-related autoimmunity is unknown. His rhabdomyolysis could be a consequence of hypothyroidism or autoimmune-related myositis. The patient did not receive any glucocorticoid treatment. Since normalization of TFTs by levothyroxine replacement was associated with normalization of his CK, it is likely that his rhabdomyolysis is directly associated with the severe and acute onset of hypothyroidism. Nonetheless, given the nature of inflammatory adverse events associated with anti-PD1 therapy, autoimmune myositis and hepatitis cannot be excluded. The association of hypothyroidism with rhabdomyolysis and acute renal injury has been reported (13); this female patient was presented with weakness, anorexia, dysuria, and typical signs of severe hypothyroidism including hypothermia, hoarse voice and
metal status change. She also had a long history of Hashimoto thyroiditis but stopped thyroid hormone replacement several years prior to her presentation. The relatively mild signs of hypothyroidism in our case correlate well with its nature of rapid onset. Both patients had remarkably high TSH and very low T4, elevated CK, creatinine, and aminotransferase. Replacement with levothyroxine corrected the biochemical abnormalities in both cases. Prior to beginning levothyroxine replacement, it is important to rule out adrenal insufficiency that is a relatively common adverse event in patients receiving immunotherapy, as levothyroxine may trigger adrenal crisis in patients with uncorrected adrenal insufficiency (14). The initial dose of levothyroxine depends on the age and heart condition of the patient. In young patients without heart disease such as in this case, the average replacement dose of T4 is approximately 1.6 mcg/kg body weight daily, but the range of required doses is broad. For further levothyroxine dose titration, TSH and free T4 should be measured 4-6 weeks after the initiation of levothyroxine replacement. In older patients or patients with coronary artery disease, levothyroxine should be started at a low dose, usually 12.5 to 25 mcg daily and increased slowly, 12.5 to 25 mcg every 4-6 weeks. The rapid development of severe hypothyroidism and the unusual manifestation of hypothyroidism presenting as rhabdomyolysis underscore the importance of thyroid function tests in all patients on immune checkpoint blockade, the range of clinical presentations, as well as clinical recognition of the wide variety of autoimmune-related adverse effects. Thyroid function tests before each ipilimumab infusion are included in the ipilimumab package insert. Here, we recommend that all patients on anti-PD1 therapy should have their TSH and free T4 checked before each dose of anti-PD1 and be screened for the clinical manifestations of hypothyroidism and myositis. Blood CK level should be measured if the patient develops symptoms and signs of myositis such as myalgias.
References:


Figure Legends

Figure 1. Changes in TSH, CK and ALT levels before and after MK-3475 therapy. The trends of serum levels of TSH (Normal range: 0.5-5 mIU/L), CK (normal range: 55-170 U/L) and ALT (normal range: 10-50 U/L) were plotted. Time 0 represents the first dose of MK-3475. Time for ipilimumab treatment and radiation therapy are indicated as well. Ipi: ipilimumab.

Figure 2. Tumor response to anti-PD1 immunotherapy. The images of chest CT before, 2 and 14 months after initiation of MK-3475 therapy.
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