Autoimmune Inflammatory Myopathy after Treatment with Ipilimumab

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While human immunity is generally thought to protect against infectious agents, there is also evidence for immune surveillance against neoplastic diseases. Some malignant cells are able to evade or down-regulate this immune response through a variety of chemical mediators, rendering the host response ineffective and leading to poor prognoses. Immune mechanisms seem particularly important in the pathogenesis of malignant melanoma, prompting research into potential immune mediated therapies.

Ipilimumab is a novel humanized monoclonal antibody directed against cytotoxic T lymphocyte antigen 4 (CTLA-4), a T-cell surface molecule involved in down-regulation and suppression of the T cell response to stimuli[1]. Suppression of CTLA-4 may improve immune surveillance and have an antineoplastic effect, and early studies of ipilimumab in patients with various malignancies have been encouraging, demonstrating prolonged time to progression and tumor regression[2,3]. The most commonly reported adverse effects (AE) associated with anti-CTLA-4 treatment are autoimmune in nature, and include dermatitis in approximately 35%[4], and enterocolitis in 10-15%[5,6]. These AE may occur soon after treatment with ipilimumab[7]. Rarely reported AEs include hepatitis, uveitis, and hypophysitis.

The vast majority of immune-related adverse effects (IRAE) respond well to steroids, but preclude further treatment with anti-CTLA-4 therapies. Interestingly, IRAE after ipilimumab treatment are associated with an improved prognosis, and outcome seems to correlate with the grade of AE. Attia and colleagues demonstrated tumor regression in 36% of patients with a grade III or IV IRAE, vs. 5% of those with no IRAE[2]. Beck et al[8] reported similar findings in their series. To date, no neuromuscular IRAE have been associated with ipilimumab.

We are now reporting the first case of autoimmune polymyositis in association with ipilimumab treatment, and discuss potential implications of CTLA-4 in neurologic disease and therapeutics.

Case Report

A 51-year-old woman with a history of metastatic melanoma, status post-chemotherapy and laparotomy for abdominal metastases, was referred from her family physician after presenting with a two week history of progressive bulbar symptoms. She had initially been diagnosed with malignant melanoma two years previously.

She had received two doses of ipilimumab after being enrolled in a trial at another center. She was initially admitted to her local hospital with dysphagia and dysarthria, followed by diffuse weakness, which she attributed to malnourishment from limited oral intake. She reported no fever, rash, fatigueability, diplopia, pain, sensory symptoms, muscle tenderness or sphincter dysfunction.

Neurologic examination was significant for mild diffuse weakness of the facial muscles and severe weakness of neck flexion. She had pronounced dysarthria and pharyngeal weakness. Ocular movements were normal. Motor examination of the extremities showed severe diffuse weakness, scored as MRC 2/5 proximally and distally in the upper and lower extremities. Myotactic reflexes were diminished but present. The plantar responses were flexor. The sensory examination was normal. Functional assessment revealed an inability to sit independently, and she required assistance with ambulation. Examination of the integument and lymph nodes was unremarkable.

Blood work revealed elevation of CK at >5000 U/L. AST (352 U/L) and ALT (646 U/L) were mildly elevated. Renal and hepatic functions were normal. Cerebrospinal fluid parameters were normal, with no evidence of malignant cells.

Nerve conduction studies demonstrated a marked reduction in compound motor action potential amplitudes in the right ulnar, median, peroneal and tibial nerves. Sensory conductions were normal including left median and ulnar sensory nerve action potentials. Compound motor action potential amplitude did not increase with exercise, and repetitive stimulation of the facial and median nerves at 3 Hz revealed no decrement. Needle electrode examination demonstrated spontaneous activity (fibrillations, positive sharp waves) and small amplitude, short duration motor unit potentials with early recruitment in proximal and distal muscle groups in upper and lower extremities.

Magnetic resonance imaging (with gadolinium) of the neuraxis was normal. Computed tomogram scan of the chest, abdomen, and pelvis revealed complete regression of previously demonstrated metastatic disease. Muscle biopsy from the left deltoid (Figure) demonstrated features similar to those of acute polymyositis. Patchy endomysial inflammatory infiltrates were present, consisting predominantly of T lymphocytes and

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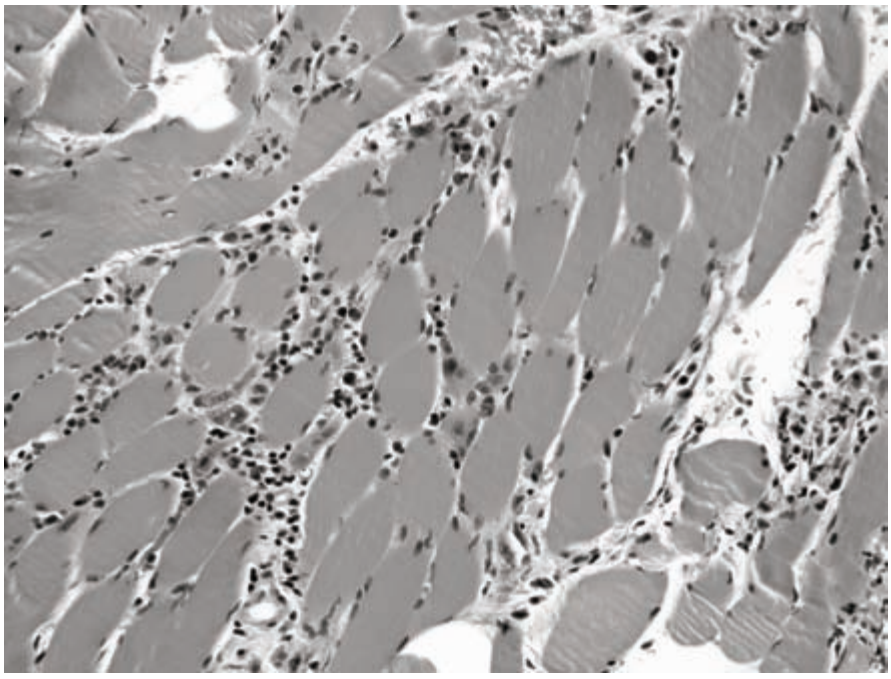

Figure: *Left deltoid muscle biopsy, hematoxylin and eosin stained permanent section, original magnification x 40. Endomysial mononuclear inflammatory infiltrates with occasional regenerating fibers.*

macrophages, along with occasional CD20 immunopositive B lymphocytes, plasma cells, eosinophils, and neutrophils. Of the T lymphocytes present, CD8 immunopositive T-cells were more numerous than those demonstrating CD4 immunopositivity. Occasional necrotic and regenerating fibers were present in areas involved by inflammation. The usual range of muscle fiber diameter was maintained, with no evidence of hypertrophic fibers, group atrophy, or perifascicular atrophy. Vacuoles, inclusions, ragged red fibers, and fiber-type grouping were not present. There was no increase in the amount of endomysial connective tissue or fibers with internal nuclei. Blood vessels appeared unremarkable. There were no nerve twigs available for examination. No definite abnormalities were seen with ubiquitin, amyloid precursor protein, or tau immunostaining, as compared to a normal control muscle. Electron microscopy revealed no additional abnormalities. Neither tubulofilamentous inclusions nor myeloid bodies were seen, and endothelial cells were free of tubuloreticular inclusions.

Treatment with intravenous gammaglobulin 400/mg/kg for ten days and high dose solumedrol (1 gm IV daily) was followed by oral prednisone (1mg/kg daily), and the patient improved to near baseline function over three weeks and was discharged home. At follow-up four months later, she was continuing to use prednisone 20 mg daily. She had mild weakness of the left finger extensors and intrinsic hand muscles. As of last follow-up she remains free of recurrent melanoma.

Discussion

Immune-modulating therapies are promising new approaches to the treatment of malignant neoplasias. The spectrum of IRAE will likely continue to expand as these treatments become more common, and their impact on outcomes will need to be thoroughly investigated. In this case report we outline a new IRAE associated with anti-CTLA-4 treatment. As in previous reports, this high-grade IRAE was associated with a favorable response to treatment, and adverse effects were manageable with immunosuppressive therapies. Whether these therapies targeted at IRAE have any impact on the mechanism or efficacy of ipilimumab remains unknown.

The diagnosis of an inflammatory myopathy was suspected due to dramatic elevation of CK, and confirmed by muscle biopsy. The presence of eosinophils is of uncertain significance, but may prove helpful in diagnosing this particular type of autoimmune mysositis. Given the known association of ipilimumab with IRAE's and timing of symptoms in this case, the presumed pathogenesis is autoimmunity induced by ipilimumab. It remains to be determined why different targets are affected in IRAE's related to ipilimumab, and this report aims to highlight the need for surveillance for other neurologic sequelae. Given the severity of the reaction in this case, neurologic consequences of this promising new therapy may prove to be dose-limiting.

The gene for CTLA-4, on chromosome 2, has also been associated with susceptibility and resistance to various

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autoimmune diseases in previous reports. For example, in the non-obese diabetic mouse model of autoimmune diabetes, CTLA-4 expression seems to be aberrant in activated T cells[9]. This same mouse strain seems to be resistant to development of experimental autoimmune encephalomyelitis, the principal animal model of multiple sclerosis[10]. CTLA-4 alleles have also been postulated as a factor in autoimmune thyroid disease[11], and in murine models of myasthenia gravis[12]. While CTLA-4 has not been associated with any neurologic illnesses in humans to date, this case and the literature from animal models suggest that the role of this antigen should be further explored in autoimmune diseases affecting the nervous system, specifically in neuromuscular illnesses.

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