

Giant cell arteritis secondary to combined nivolumab and ipilimumab in metastatic pleural mesothelioma

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Abstract

We report a rare case of isolated giant cell arteritis caused by combined immunotherapy with nivolumab and ipilimumab in metastatic pleural mesothelioma. Whilst combination immunotherapy is thought to provide synergistic anti-tumor effects in metastatic malignancies, it has also been associated with an increased frequency of severe immune-related adverse effects. To our knowledge, giant cell arteritis has been described in only four previous cases in relation to single agent immunotherapy, and our patient is the first reported case of isolated giant cell arteritis from combination immunotherapy. This report adds to the literature a rare case of an important adverse effect that clinicians should be aware of, especially with increasing use of combination immunotherapy.

Keywords: Giant cell arteritis, immunotherapy, ipilimumab, mesothelioma, nivolumab, vasculitis

INTRODUCTION

Giant cell arteritis (GCA) is a large vessel vasculitis that causes devastating irreversible visual loss if not recognized and treated promptly. Here we report a rare case of GCA caused directly by combined immunotherapy used for metastatic malignancy.

CASE REPORT

A 69-year-old Caucasian male with a history of ischemic heart disease and radical prostatectomy for prostate cancer presented with dyspnea. Following a pleurodesis and biopsy for a malignant pleural effusion, he was diagnosed with metastatic epithelioid mesothelioma. Due to his excellent baseline functional status, he was referred for a trial and subsequently underwent randomization to combination therapy with nivolumab (two weekly) and ipilimumab (six weekly).

After three months of immunotherapy, he developed low-grade fatigue, myalgias and asymptomatic hypothyroidism (TSH 42.7mU/L) requiring replacement with thyroxine. Five months later, he began to experience intermittent blurred vision, scalp tenderness and jaw claudication, however both a CT and contrast-enhanced MRI brain performed were unremarkable. Two weeks later, he developed an episode of diplopia, followed

by a 15 minute episode of amaurosis fugax of his left eye, leading to admission to hospital. Here, a left sided temporal artery biopsy was performed, demonstrating chronic granulomatous inflammation with giant cells and focal destruction of the internal lamina, in keeping with giant cell arteritis. High dose prednisolone was commenced with rapid resolution of symptoms and reduction in erythrocyte sedimentation rate (ESR, 72mm/hr to 30mm/hr within four days). The patient's immunotherapy was ceased, and follow-up imaging revealed stable disease. Ten months later, ESR was between 5-12mm/hr on prednisolone doses of less than 7.5mg/day.

DISCUSSION

Immunological checkpoints form part of a complex system of self-regulation that acts to prevent autoimmunity and promote self-tolerance by inhibiting T cells. Immune checkpoint inhibitors block these pathways, activating T cells and therefore allowing them to attack tumor cells.¹ Current Pharmaceutical Benefits Scheme listed agents include ipilimumab, a cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) inhibitor, nivolumab and pembrolizumab, programmed cell death-1 (PD-1) inhibitors, and atezolizumab and durvalumab, programmed cell death-ligand 1 (PD-

L1) inhibitors. These monoclonal antibodies have been increasingly used in the treatment of various malignancies including metastatic non-small cell lung cancer and melanoma.² Early results from trials in metastatic mesothelioma are promising.³

Although CTLA-4, PD-1 and PD-L1 inhibitors all regulate T-cell activation, they are thought to have different mechanisms of action. It is believed that CTLA-4 acts proximally in the immune response, while PD-1 and PD-L1 act more distally, in peripheral tissues.¹ Therefore, these agents likely modulate immunity at different levels and combination therapy may provide synergistic anti-tumor effects.^{2,4}

Whilst checkpoint inhibitors have revolutionized the treatment of many malignancies, they present a unique spectrum of adverse effects distinct from traditional chemotherapy, called immune-related adverse effects (irAEs). These result from activation of the patient's immune system in an organ-specific mechanism and breakdown of self-tolerance.¹ The most common irAEs are colitis, dermatitis, endocrinopathies, and hepatitis, although any organ can be affected.¹ Furthermore, CTLA-4 and PD-1 therapy have slightly different irAEs, which may be related to their distinct mechanisms of action. For example, CTLA-4 inhibitors cause more colitis and hypophysitis, whilst PD-1 inhibitors cause more pneumonitis and thyroiditis.¹ Finally, severe irAEs are more frequent with combination therapy as opposed to single agent immunotherapy which may limit their use.⁴

Giant cell arteritis is a vasculitis that may occur either alone or in combination with polymyalgia rheumatica. If not recognized and treated promptly, it can cause devastating and irreversible loss of vision. To our knowledge, GCA has been described in only four previous cases in relation to single agent immunotherapy: two cases of polymyalgia rheumatica and GCA due to ipilimumab,⁵ one case of polymyalgia rheumatica and GCA due to nivolumab,⁶ and one case of isolated GCA due to pembrolizumab.⁷ Our patient is the first reported case of isolated GCA from combination immunotherapy. This report adds to the literature a rare case of an important adverse effect that all clinicians need to be aware of, especially with increasing use of combination immunotherapy for metastatic malignancies.

DISCLOSURE

Financial disclosures: None

Conflict of interest: None

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