CASE REPORT

Nivolumab causing painless thyroiditis in a patient with adenocarcinoma of the lung

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SUMMARY

Thyroiditis is characterised by transient hyperthyroidism, followed sometimes by hypothyroidism, and then recovery. We report a case of painless drug-induced thyroiditis—in a patient with no history of any thyroid disorder—treated with Nivolumab (an IgG4 monoclonal antibody against Programmed Death Receptor 1). The purpose of this case report is to increase awareness among clinicians regarding this possible adverse effect from Nivolumab, and discuss the possible pathophysiology and management strategies in such patients.

BACKGROUND

Nivolumab is an IgG4 monoclonal antibody against Programmed Death Receptor 1. It is an immunotherapeutic drug that was initially used in the treatment of melanoma, and is now approved as a second-line drug of choice for non-small cell lung cancer. It works by activation of host T cells against the malignant cells. One of the adverse effects of this drug is painless thyroiditis (PTS), which occurs secondary to the activation of T cells against the host cells.

CASE PRESENTATION

A 55-year-old woman presented to the emergency room, with progressive worsening dyspnoea on exertion and palpitations. This was associated with two-pillow orthopnoea. She also reported fatigue, nausea, abdominal pain, loose bowel movements and anxiety. One year prior to this presentation, the patient had been diagnosed with adenocarcinoma of the lung, for which she completed a course of carboplatin and pemetrexed over the following 6 months. Three months later she was diagnosed with metastasis to the brain and spine, and received whole brain radiation therapy. The patient was subsequently started on Nivolumab. Three weeks after the second cycle of chemotherapy, the patient started noticing the aforementioned symptoms. Her other medical history included migraine headaches, hypertension, hyperlipidaemia and diabetes mellitus type II. Her home medications were aspirin, atorvastatin, amlodipine, metformin, metoprolol and lisinopril. None of these home medications had been changed recently.

On examination, the patient was alert, awake and oriented to time, place and person. Her blood pressure in the emergency room was 113/82 mm Hg, heart rate 120 bpm and respiratory rate 20/min; she had a temperature of 98°F (36.6°C) and was saturating at 95% on room air. Cardiopulmonary examination revealed tachycardia and bilateral crackles at the lung bases. Palpation of the thyroid gland revealed neither thyromegaly nor nodules. No thyroid bruit was auscultated. Neither lid lag nor exophthalmos was appreciated. No peripheral oedema was appreciated on examination of the extremities. The rest of the physical examination was unremarkable.

INVESTIGATIONS

Chest X-ray showed cardiomegaly and pulmonary congestion. ECG showed sinus tachycardia at 120 bpm with no acute ST-T wave changes. Laboratory chemistries showed white cell count of 10.3 k/mm^3 (normal 4.5–11 k/mm^3), haemoglobin of 12.4 g/dL (normal 12–16 g/dL) and platelets of 498 k/mm^3 (normal 140–450 k/mm^3). Serum electrolytes, renal function tests and liver function tests were normal. Troponin was negative. D-dimer was elevated at 1.328FEU, therefore CT angiography (CTA) of the chest was carried out, which was negative. US Doppler of the legs was negative for venous thromboembolism. Thyroid-stimulating hormone (TSH) levels were checked and found to be <0.01 μIU/mL (normal 0.3–5 μIU/mL). Free T4 was elevated at 2.06 ng/dL (normal 0.7–1.6 ng/dL) and free T3 was 554.2 pg/dL (normal 230–420 pg/dL). The TSH level 1 month prior was normal at 2.76 μIU/mL. Thyroid peroxidase (TPO) antibody was found to be low (<28 U/mL) and thyroid-stimulating immunoglobulin (TSI) was also low at 26%. Thyroglobulin antibody was elevated at 17 IU/mL(normal <1). As the patient had received whole brain radiation therapy, pituitary work up was pursued. The 8:00 am cortisol level was 17 μg/dL. Serum adrenocorticotropic hormone (ACTH), insulin-like growth factor 1 (IGF-1), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin levels were normal. Thyroid ultrasound revealed a normal thyroid gland with no nodules and with normal vascularity. Cardiac echocardiogram showed preserved systolic function with an ejection fraction of 69.4% with grade 1 diastolic dysfunction.

TREATMENT

The patient was diagnosed with thyrotoxicosis likely due to thyroiditis and was given supportive management. She was treated with furosemide for fluid overload and her home dose of metoprolol was increased from 50 to 200 mg a day. Her shortness of breath improved with diuresis and tachycardia resolved. Further chemotherapy with Nivolumab was discontinued.

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OUTCOME AND FOLLOW-UP

Three months later, repeat free T4 was 1.08 ng/dL and free T3 was 244.4 pg/dL. The patient's TSH normalised to 2.97 μIU/mL. Metoprolol was eventually tapered down to her baseline dose. She had a stable outpatient course with no further events.

DISCUSSION

Thyroiditis is the inflammation of the thyroid gland and can be painful or painless.[1] Painful thyroiditis is caused by an infection, radiation or trauma. On the contrary, PTS can be caused by an autoimmune condition, medications or a fibrotic process.[2–4] Medications reported to cause PTS include lithium, amiodarone, interferon α and interleukin-2.[5] Anticytotoxic T lymphocyte antigen 4 (CTLA-4) monoclonal antibody (mAb) and IgG4 mAb against programmed death receptor-1 (eg, Nivolumab) have also been reported to cause PTS.[6–9] These are both novel immunotherapeutic drugs used in the treatment of several metastatic malignancies. They work by activating host T cells against malignant antigens. While the target of these T cells are malignant antigens, the inhibition of checkpoint blockage for T-cell function by these drugs can theoretically lead to an attack on other normal tissue, including that of the thyroid gland.[6–8]

We report a case of PTS leading to thyrotoxicosis in our patient who was treated with Nivolumab for adenocarcinoma of the lung. Nivolumab has been used in the past for treatment of melanoma.[10] The US Food and Drug Administration, in March 2015, approved Nivolumab as a second-line drug in the treatment of non-small cell lung cancer. Common adverse effects of this novel drug include fatigue, fever, rash and diarrhoea, among others. The adverse effects are due to the autoimmune activation of the T cells against the normal tissue.[11] Hepatitis, colitis, thyroiditis and hypophysitis have been reported secondary to the use of this drug.[12] Hypothyroidism and hyperthyroidism have both been reported in study trials.[13 14]

Graves' disease was excluded by a low TSI level and normal vascularity on thyroid ultrasound. Normal ultrasound findings also excluded toxic nodule as the cause of thyrotoxicosis. Radioactive iodine uptake scan was not performed because the patient received iodine contrast load with CTA of the chest, performed to exclude pulmonary embolism. It is important to note that the patient's symptoms and the laboratory findings of elevated free T3 and T4 preceded the CTA. The patient did not take any other drugs associated with thyroiditis. We used the Naranjo Adverse Drug Reaction scale to assess the association of our patient's symptoms and the precipitating cause—Nivolumab. The score was 7, indicating Nivolumab as the probable cause of our patient's presenting symptoms.[15]

Patients with drug-induced thyroiditis require discontinuation of the medications and initiation of supportive therapy. Management of the thyrotoxic phase includes achieving a temporary β-blockade.[6] This provides relief from the adrenergic symptoms. While propranolol has the theoretical advantage of inhibiting coversion of T4 to T3, β-1 selective agents (metoprolol or atenolol) are more conveniently dosed and better tolerated.[16] The transient thyrotoxic phase can often be followed by the hypothyroid phase thus potentially requiring thyroid replacement therapy. It is thus essential to monitor thyroid function tests in these patients. Our patient presented with signs and symptoms of thyrotoxicosis, which responded well to β-blockade, and the thyroid function tests normalised on withdrawal of the drug.

In conclusion, Nivolumab can lead to PTS causing thyrotoxicosis. It is essential to keep this possible adverse effect among the differential diagnosis when patients on Nivolumab therapy present to the emergency room, with similar signs and symptoms.

Learning points

- We should maintain a high index of suspicion for signs of thyrotoxicosis in patients on Nivolumab therapy.
- Discontinuation of the drug usually results in resolution of symptoms.
- Treatment is supportive and hinges on achieving adequate β-blockade along with symptomatic management.
- The thyrotoxic phase of thyroiditis can be followed by a hypothyroid phase requiring hormone replacement and thus adequate follow-up of the patient is essential.

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Contributors IV participated in the care of the patient, and contributed to writing the case and discussion. AM contributed to writing the case and discussion, and provided expert opinion regarding the endocrinological pathophysiology. HT contributed to writing the discussion. AA contributed to writing the case and discussion, and provided the review of the literature.

Competing interests None declared.

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Unexpected outcome (positive or negative) including adverse drug reactions