Nivolumab Associated Thyroiditis in a Patient with Squamous Non-Small Cell Lung Cancer

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Background

Nivolumab is a fully human, IgG4 monoclonal antibody that binds to the programmed death-1 (PD-1) receptor. This receptor is expressed on activated T cells. The ligands for this receptor are PD-L1 and PD-L2 which are upregulated in many tumors, including non-small cell lung cancer (NSCLC) and melanoma. PD1, PD-L1/PD-L2 binding inhibits T cell activation. Nivolumab block this interaction and contribute to the maintenance of anti-tumor effects of T cells. Nivolumab is approved for the treatment of advanced melanoma and NSCLC. Studies have reported several adverse events with the use of immune check point inhibitors like nivolumab that called immune related adverse events (irAEs). Most common irAEs are skin toxicities, diarrhea, colitis, hepatitis, pneumonitis, renal insufficiency and endocrinopathies. Endocrine related adverse events are hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis and adrenal insufficiency. Here, we present a case of thyroiditis after nivolumab therapy.

Case

A 61-year-old female patient with metastatic NSCLC was consulted to endocrinology department for abnormal thyroid function test results. Results are consistent with hyperthyroidism. TSH: 0.01 µIU/mL (0.34-5.6), fT_4: 45.4 pmol/L (7.86-14.41), fT_3: 10.8 pmol/L (3.2-6.3). Physical examination was normal other than minimally enlarged thyroid. She did not have a history of prior thyroid dysfunction. In 2006, she was diagnosed with stage III ovarian carcinoma and after surgery she received six courses of paclitaxel-carboplatin therapy. Relapse occurred after seven years in remission and she was given six courses of paclitaxel-carboplatin and four courses of ipilimumab therapy. In march 2015, she was diagnosed with metastatic NSCLC and received thirteen weeks of paclitaxel-carboplatin therapy. Six courses of nivolumab (3 mg/kg) therapy was given fortnightly and thyroid function test were normal before nivolumab therapy. Hyperthyroidism was developed after two course of nivolumab and TSH receptor antibody, anti thyroglobulin antibody, anti TPO antibody levels were all negative. Thyroglobulin levels were >500 ng/ml (0-85), thyroid ultrasonography showed paranchymal heterogenity and small multiple nodules. Thyroid scintigraphy result was consistent with thyroiditis too but the patient did not give consent to iodine uptake test. These results indicated nivolumab associated thyroiditis. Propranolol treatment was given to the patient. Two weeks later she had severe diarrhea and serum aminotransferase levels were elevated. Gastroenterology and oncology departments related these symptoms to nivolumab therapy and they were regressed by the time. She was followed by two week intervals. Propranolol treatment was discontinued after thyroid function test results returned to normal six weeks later. Hypothyroidism was developed (TSH: 81 µIU/mL) fourteen weeks later and levothyroxine therapy was initiated after that. Patients test results and treatments are shown at the table below (Table 1).

Table 1. Thyroid function test result and treatments after nivolumab therapy.

	Weeks after first nivolumab course					
	4 weeks	8 weeks	10 weeks	14 weeks	20 weeks	22 weeks
TSH µIU/mL (0.34-5.6)	0.01	0.01	1.1	81	1.9	8.3
sT_4 pmol/L (7.86-14.41)	45.4	23.5	13.2	3.7		19.6
sT_3 pmol/L (3.2-6.3)	10.8	4.5	2.8	1.1	3.9	2.9
Treatment	Propronalol 4x20 mg	Propronalol 3x20 mg	None	Levothyroxine 25 → 100 mcg	Levothyroxine 75 mcg	Levothyroxine 87.5 mcg

Discussion

Nivolumab and other immune check point inhibitors are newly developing agents but with the expanding indications, more patients will use nivolumab and come up with adverse events. The most common endocrinopathies reported with immune checkpoint inhibitor therapy are hypophysitis and hypothyroidism. Hypothyroidism occurs in 4-10% of the patients who receive nivolumab therapy and is rarely severe. It is commonly seen after subclinical hyperthyroidism. Nivolumab therapy may be continued without interruption with appropriate levothyroxine replacement. The incidence of hyperthyroidism is lower than hypothyroidism (1-7%). Hyperthyroidism may be commonly transient due to thyroiditis and if symptoms are not severe, there is no need to discontinue nivolumab therapy. We also continue nivolumab therapy in our patient with close monitoring. Most patients become hypothyroid and need long term thyroid hormone replacement as our patient. It is recommended that baseline and before each nivolumab dose thyroid function tests should performed and consultation with an endocrinologist is necessary when abnormal thyroid hormone levels are detected.