Urgent need to define Pretreatment predictors of immune check point inhibitors related endocrinopathies: A case report and review of literature

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ABSTRACT

Immune check point inhibitors have revolutionized the treatment of metastatic malignancies. They are a promising area in oncology and more drugs are likely to be available in the coming years. Along with the promise of better response oncologically, there is an increased incidence of endocrinopathies related to autoimmunity. This case report illustrates the dramatic development of hypothyroidism in a patient with underlying subclinical hyperthyroidism. It also suggests the potential pretreatment predictors of endocrinopathies related to these immune check point inhibitors.

Key words: immune check point inhibitors, endocrinopathies, metastatic malignancy

INTRODUCTION

Immune check point inhibitors are a new class of monoclonal antibodies which have shown excellent results in the treatment of metastatic malignancies. But they are what we call as broad spectrum endocrine poisons. It is very important that these endocrinopathies are not missed and are appropriately treated. This would not only reduce the cost, but also improve the morbidity and mortality associated with the use of immune check point inhibitors.

CASE REPORT

The patient was a 65-year-old Caucasian male admitted to the hospital for suspected pneumonia related sepsis. He had been feeling weak and lethargic for days. His recent history was significant for squamous cell lung cancer. He had received 6 cycles of chemotherapy with carboplatin/paclitaxel. Two months prior to the presentation, his thyroid function tests (TFT) were consistent with the subclinical hyperthyroidism. His thyroid stimulating hormone (TSH) was < 0.015 µIU/mL and his free T4 was 1.24 ng/dL. On admission, his TSH

was $> 100 \mu IU/mL$ and his free T4 had dropped to 0.28 ng/dL. Endocrinology was consulted for the abnormal thyroid function tests (TFT) (Figures 1 and 2). The acute rise in TSH and acute fall in free T4 level was very striking. On further questioning, the patient confided that he had been getting new medicine at his oncologist's office. A call to the oncologist's office confirmed that he got the first dose of immune check point inhibitor (nivolumab 240 mg) 2 weeks back. He was then started on low dose thyroid hormone replacement therapy (THRT) with levothyroxine at 50 mcg daily. Further work in the hospital was not indicative of sepsis. His antibiotics were stopped, and he was subsequently discharged from the hospital.

DISCUSSION

Metastatic malignancies and immune modulation

The era of immune modulation in the treatment of cancer is relatively recent and trials are underway to see their effect in a range of malignancies. The European Society for Medical Oncology in Vienna highlighted the role of immunotherapy in advanced kidney and lung cancers. [1,2]

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Figure 1: Dramatic rise in thyroid stimulating hormone (TSH) 8 weeks after starting nivolumab

Immune checkpoint inhibitors are also showing promising results in urological cancers.^[3-5] Currently, they are the primary treatment modality for the treatment of metastatic melanoma and non-small cell lung cancer. They have been used solo and in combination.

The most widely used immune check point inhibitors include the inhibitors of cytotoxic- T lymphocyte associated protein-4 (CTLA-4) and programmed death 1(PD-1). These proteins allow tumors to evade the immune system. The CTLA-4 is thought to suppress the immune response early and acts principally in lymph nodes. PD-1 is a receptor seen mostly in peripheral tissues and is expressed

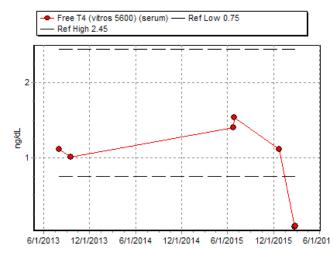


Figure 2: Dramatic fall in freeT4 8 weeks after starting nivolumab

on T and B cells, and Natural killer cells. Like CTLA-4, it is a negative regulator of the immune system. It binds to PD-1 ligand, which is expressed in many tumor cells and hematopoietic cells. The interaction of PD-1 with PD-1 ligands blocks the expression of T effector cells. The PD-1 and PD-1 ligands are upregulated by cytokines like IL-2 in the same manner it upregulates CTLA-4 expression. Monoclonal antibodies of the IgG4 class could potentially prevent the interaction of PD-1 receptors on immune cells and PD-1 ligands on tumor cells and hematopoietic cells (Figure 3). Inhibition of these 2 pathways leads to an increased activation of the immune system, which may be used against the cancer cells.^[6,7]

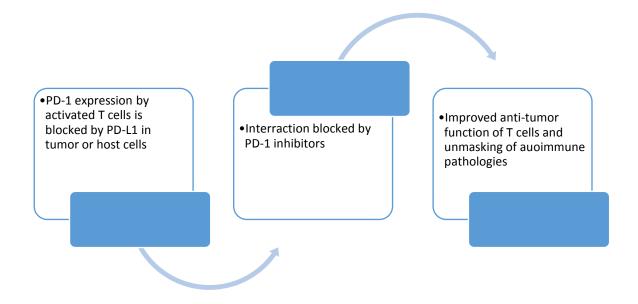


Figure 3: Mechanism of action of programmed cell death-1 (PD-1) inhibitors

A series of checkmate trials have led to the accelerated approval of these immune check point inhibitors in the treatment of metastatic melanoma, renal cell cancer, non-small cell lung cancer, small cell cancer and urothelial cancer. [8-14] Also, its use in the treatment of hepatocellular cancer is under an expedited review by FDA. [15] The first CTLA-4 inhibitor in the market was ipilimumab and one of the most widely used PD-1 inhibitor is nivolumab. Both have been used with great success in the treatment of metastatic melanoma with improved survival at 5 years. [16-20] It is also showing promise in the treatment of Hodgkin's lymphoma. [21] With their outstanding efficacy in many cancers, their use is likely to increase in clinical practice. They are effective in younger as well as older age groups. [22]

Immune mediated endocrinopathies related to the use of PD-1 inhibitors

Common terminology criteria for adverse events (CTCAE) grades the medication related side effects from grade 1-4. Grade 1 being the mildest and grade 4 the most severe. In grade 2 side effects, daily activity is affected and minimal medical intervention is necessary. With grade 3, marked limitation of activity happens and hospitalization may be required. Most of the PD-1 inhibitor related side effects are classified as grade 2. But if the care providers are complacent, these endocrinopathies could be missed and this could lead to grade 3-4 side effects per CTCAE criteria. Most of the endocrinopathies if recognized in time are reversible or easily managed.^[23-30]

In this context, it is very important that physicians of all specialties be familiar with the immune mediated adverse events (irAEs). This would help in early identification and treatment. [31] Common irAEs include skin rashes, hepatitis, nephritis, diarrhea /colitis, pneumonitis and endocrine dysfunction. [32] The most common endocrine glands affected are thyroid, adrenal and pituitary. These glands are highly vascular and that could be the reason for their propensity to be affected disproportionately. There could be a clinical bias in picking these, as the side effects related to these are potentially life threatening and could easily be quantified with lab parameters.

The thyroid gland is the most common endocrine organ affected by PD-1 inhibitors. The patient may manifest with transient or long-term hypo or hyperthyroidism, thyroid eye disease, painless thyroiditis or sometimes thyroid storm. [33] This calls for frequent monitoring and cautious use of THRT or thionamides as the case might be. [34] Hypothyroidism is more common as was seen in our case, although the patient had an underlying subclinical hyperthyroidism. The highest grade of this side effect is usually classified as grade 2 in checkmate 057 trial, in which nivolumab was assessed in the treatment of non-

squamous cell non-small cell lung cancer (NSCLC). [35] But if the endocrinopathies are not captured and treated in time, it could quickly progress to grade 3 or 4. This of course would require hospitalization and possibly increase mortality and morbidity associated with the use of PD-1 inhibitors. Also, the treatment of these immune related side effects includes the use of glucocorticoids. But steroids are not recommended when treating immune check point inhibitor related thyroid dysfunction. The thyroid disorders are treated in the usual manner and there is no need to interrupt the treatment with PD-1 inhibitors. [23,30,36,37] The long-term data on treatment of PD-1 inhibitor related endocrinopathies is not there, largely because these drugs are used in metastatic malignancies and not for long periods of time.

Fulminant type 1 diabetes (DM1) has been reported with the use of PD-1 inhibitors. [38] DM1 could present as diabetic ketoacidosis (DKA). This may lead to hospitalization and could be potentially life threating, if not picked up on time. [39]

PD-1 inhibitors are a big advancement in the armamentarium of the oncologist in their fight against metastatic malignancies. Also, timely and appropriate management of irAEs is likely to maximize the therapeutic benefit of these immune check point inhibitors. [5,40] They have been shown to be safe with respect to cardiac toxicity. The drug has been shown not to increase the QT interval.[41] But irAEs, though benign, are relatively common with PD-1 inhibitors. It could vary from new onset vitiligo to DKA related to a new onset of DM1. Due diligence needs to be exercised before ascribing the cause of presenting pathology to these immune modulators. [42] But if not recognized in time, these endocrinopathies could potentially present as life threatening acute emergencies.^[33] A team based approach that includes an endocrinologist could potentially help in maximizing the benefits associated with the use of immune modulating drugs in the treatment of metastatic malignancies. [43] In our case, the patient got the first dose of nivolumab and had profound changes in thyroid function profile. This raised the question whether some patients are more at risk for endocrinopathies related to these medications and need more intense monitoring of their hormonal levels. The hospitalization in this case could have been prevented if the dramatic rise of TSH had been picked up earlier, and the patient was started on thyroid hormone replacement therapy (THRT).

Potential pretreatment predictors of PD-1 inhibitor related endocrinopathies

Evaluation of other immune check points like LAG3, TIM-3, BLTA and B7-H3 are also under evaluation and newer immune check point modulators are likely to be available in

the years ahead.^[44] With wide spread use of immune check point inhibitors, it is becoming increasingly important to minimize the irAEs. Cancer immune therapy consortium has come out with guidelines to ensure minimal side effects and maximize benefits from these immune check point inhibitors. ^[43] The crux lies in identifying patients who are at high risk for immune therapy related endocrinopathies. Potential pretreatment predictors include duration or dose of PD-1 inhibitors, preexisting autoimmune disease, race, and combination therapy with other PD-1 inhibitors. The incidence of thyroid dysfunction associated with ipilimumab is reported to be 1-6%, but in combination with nivolumab it is 9.9-22%. ^[29,35] This reinforces the need for more diligent monitoring of TFT in patients on combination therapy.

Since unfolding of the autoimmunity is the prime mechanistic explanation for endocrinopathies related to these drugs it would be prudent to get pretreatment assessment of thyroid function. This could potentially help define the pretreatment possibility of PD-1 inhibitor related endocrinopathies. This has been reported in the past. It was true in our case too as the patient had underlying subclinical hyperthyroidism. This could also help define the group of patients who are likely to have transient versus permanent endocrinopathies in the post treatment phase.

CONCLUSION

As the use of PD-1 inhibitors becomes more widespread, there is a need to identify patients who are at an increased risk of PD-1 inhibitor related endocrinopathies. Pretreatment collaboration between oncologists and endocrinologists would be helpful. This could potentially help reduce the morbidity and mortality in patients with metastatic malignancy and at the same time help reduce cost.

Conflict of Interest

The authors declare no conflict of interest.

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