

Case Report: Multiple Endocrine Insufficiency Secondary to the use of CTLA-4 Inhibitors for the Treatment of Subungual Melanoma

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ABSTRACT

The case of a 60-year-old woman diagnosed with subungual melanoma who received treatment with ipilimumab for 7 sessions and amputation of the first finger of her left hand and who presented multiple glandular damage is presented. The adverse effects associated with antineoplastic therapy induced by inhibition of the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) checkpoints occur in approximately 0.5-10.5% hypophysitis as the main affectation, adrenalitis, alterations in gonadal hormones and thyroid stimulating hormone 91%, 84% and 83%, respectively. With overall survival of 21.4 months in those who developed hypophysitis compared to 9.7 months in those who did not develop it. Some other disorders with a lower proportion are diabetes mellitus due to insulin deficiency, hyponatremia and diabetic ketoacids. In this case, diabetes mellitus occurred due to insulin deficiency with diabetic ketoacids related to thyrotoxicosis, being a rare presentation. We consider that this case is of interest and useful for the initiation of therapy, as well as for follow-up, through thyroid profile, measurement of cortisol, ACTH, insulin, ovarian profile, prolactin and vasopressin, as well as MRI, in order to rule out prevention or treatment. the adverse effects related and reducing the mortality mentioned in the literature.

KEYWORDS: Primary hyperthyroidism, secondary adrenal insufficiency, diabetic ketoacidosis ipilimumab, melanoma.

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INTRODUCTION

Melanoma is the most serious form of skin cancer (1). In the United States, it is the fifth most common cancer in men, and in women its incidence increases with age. Survival rates for people with melanoma depend on the stage of the disease (2). Subungual melanoma (SUM) is a rare form of melanoma and is often diagnosed in later stages. Approximately two-thirds of NUM present clinically as longitudinal melanonychia but longitudinal melanonychia has a wide differential diagnosis (3). NUM Represents 0.7 to 3.5% of all melanoma cases. Surgical treatment options for NUM include en bloc excision, digit amputation, and Mohs micrographic surgery. Newer treatments for advanced NUM include systemic immune and targeted therapies such as CTLA-4 immune checkpoint inhibitors (IPILIMUMAB) (4).

Immune checkpoints are small molecules expressed by immune cells that play a critical role in maintaining immune homeostasis. Targeting the immune checkpoints of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed death protein 1 (PD-1) with inhibitory

antibodies has demonstrated effective and long-lasting antitumor activity in subgroups of cancer patients. and melanoma. Endocrinopathies have emerged as one of the immune-related adverse events (irAEs). Hypophysitis, thyroid dysfunction, diabetes mellitus due to insulin deficiency, and secondary adrenal insufficiency have been reported as irAEs due to ICPis therapy. Hypophysitis is particularly associated with anti-CTLA-4 therapy, while thyroid dysfunction is particularly associated with anti-PD-1 therapy. Diabetes mellitus and secondary adrenal insufficiency are rare endocrine toxicities associated with ICPis therapy, but can be life-threatening if not recognized and treated promptly. Most ICPis-related endocrinopathies occur within 12 weeks of initiation of ICPis therapy, but several have been reported to develop months or years after initiation of ICPis. The mainstay of management of endocrinopathies related to ICPis is hormone replacement and symptom control (5).

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PRESENTATION OF THE CASE

This is a 60-year-old woman, originally and resident of Uruapan, Michoacán, Mexico. Her personal history highlights the diagnosis of breast cancer diagnosed 10 years ago, receiving treatment based on a right radical mastectomy and lymphadenectomy without a diagnosis of diabetes mellitus and hypertension. Subsequently, she was diagnosed with subungual melanoma in the left thumb, performing amputation of said finger, and began treatment with Ipilimumab, receiving 7 cycles of chemotherapy.

She was admitted to the emergency department brought by her relative because 2 days after the administration of ICPis she had an attack on her general condition, myalgias in both legs, and they noticed dyspnea. Upon examination, the patient was found awake with no neurological alteration, with dehydrated oral mucosa, rhythmic heart sounds, polypnea, without added lung sounds, soft abdomen, with moderate colicky pain (7/10 Eva scale) with no evidence of peritoneal irritation, extremities. no alterations.

Studies are carried out where hemoglobin is reported: 14.1 gr/dl hematocrit: 41.1% leukocytes: 10900 platelets: 276000 glucose: 601mg/dl creatinine: 0.96 mg/dl BUN: 11mg/dl total cholesterol: 215 mg/dl triglycerides: 532mg/dl Uric acid: 11.7 mg/dl Na: 136mmol/L Corrected Na 144mmol/L K: 5.5mmol/L Ca: 9.8mg/dL P: 4.1mg/dl Mg: 1.3mg/dL pH: 7.1 PCO₂: 18 mmHg HCO₃: 6.2 mmol/L PO₂: 98 mmHg lactate: 2.2 mmol/L glucosuria: 500 mg/dl proteinuria: 25 mg/dl ketonuria: 15 total bilirubin: 0.5 mg/dl TGO: 25U/L TGP: 28U/L FA: 137 U/ L GGT: 34U/L total proteins: 6.2gr/dl Osm cal 336mOsm/kg, albumin: 3.7g/dl globulin: 2.5 mg/dl amylase: 43 U/L and lipase 35 U/L; integrating diagnosis of Diabetic Ketoacidosis; starting treatment.

On the third day of hospitalization, tachycardia, fever and diaphoresis begin; without identifying an infectious focus; A thyroid profile was performed in which TSH was reported: 0.093 uIU/mL (0.35 - 5.1 uIU/mL) Free T₄: 3.4 ng/dL (0.50 - 1.40 ng/dL) compatible with primary hyperthyroidism for which treatment with thiamazole was added. . Its evolution towards improvement, presenting criteria for resolution of CAD and normalization of the thyroid profile; After 14 days of hospitalization, he is discharged due to improvement.

She was readmitted after a month due to a 2-day history manifested by nausea, vomiting, asthenia, adynamics and mild abdominal pain. It is worth mentioning that the patient suspended the use of thiamazole and continued only with the insulin-based treatment. The physical examination revealed hypotension (blood pressure 70/40 mmHg), hyperpigmentation of the face and hands predominantly in the ocher-colored knuckle region, the rest of the examination without relevant findings. Studies are carried out where glucose is reported: 82mg/dl creatinine: 0.58mg/dl BUN: 4.5mg/dl urea: 9.7mg/dl Na: 129mmol/L Cl: 100 mmol/L K: 4.2mmol/L hemoglobin: 12.3gr/ dl leukocytes: 5200 platelets: 215000 TSH: 0.36uIU/mL (0.35-4.9 uIU/mL) free

T₄: 0.081ng/dL prolactin: 29ng/ml cortisol: 50nmol/L (201 – 536nmol/L) insulin: 0.26 uIU/ ml (0.99-12.3 uIU/ml), ACTH: 9.5 pg/ml (0-46 pg/ml); Hypothyroidism and secondary Adrenal Insufficiency were diagnosed when the TSH was found inappropriately normal due to the level of free T₄ for the reference value as well as for the ACTH level, it was decided to start hormone replacement treatment with Levothyroxine and Glucocorticoid; as well as insulin; presenting reversal of the shock symptoms and clinical improvement; A magnetic resonance imaging study of the brain was performed, reporting data compatible with Hypophysitis. She was discharged due to improvement on the sixth day.

He is currently under outpatient follow-up and undergoing hormone replacement therapy based on insulin, levothyroxine and glucocorticoid.

DISCUSSION

Adverse effects related to immune therapy are rare; and to a lesser extent more than three different conditions; as it arose in the case presented; hypophysitis, diabetes mellitus due to insulin deficiency, secondary adrenal insufficiency (acute thyroiditis with evolution to hypothyroidism). On the other hand, the relative ease with which hypothyroidism develops diabetic ketoacidosis has been described, as well as the dramatic picture of diabetic ketoacidosis complicated by a thyrotoxic crisis, which has been fatal in a good number of cases (6). Given that the complications that have been described are rare, in many cases it is likely that they will not be suspected in time, case reports with very low incidence are mentioned. (7,8,9) and above all the risk of presenting more than one endocrine condition, so they should be kept in mind whenever treatment is started in a patient with ICPisi. request a complete hormonal profile prior to the start of treatment, as well as during subsequent follow-up in each chemotherapy session for timely detection of adverse effects and therefore treatment if necessary. In order to reduce the risk of death due to adverse effects because the overall survival rate is less than 24 months for those who develop hypophysitis, without attributing the extra risk of the multiple complications presented.

Hypophysitis is a low-morbidity disease of multiple subtypes. The description of hypophysitis related to cytotoxic antibody treatment against T cell antigen 4 is one of the first descriptions of drug-triggered hypophysitis. As the use of this novel cancer treatment increases, so must our awareness of immune-related adverse effects and their treatment.

Treatment of hypophysitis remains controversial with recommendations ranging from hormone replacement to recently described therapies such as azathioprine and radiation (10). Immune-related adverse events (IrAEs) are thought to arise from general immunologic improvement, and temporary immunosuppression with glucocorticoids, tumor necrosis factor-alpha antagonists, mycophenolate mofetil, or

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other agents may be an effective treatment in most patients. cases. Although rare, fulminant and even fatal toxicities can occur with ICPisi. Therefore, prompt recognition and management of irAEs is considerable. Despite significant clinical benefits, ICPisi are associated with a unique spectrum of side effects known as iraE (11).

CONCLUSIONS

Melanoma is the most serious form of skin cancer, with subungual presentation being a rare form; The most current treatments include targeted systemic immune therapies, such as CTLA-4 immune checkpoint inhibitors (ipilimumab); Endocrinopathies have been described with adverse effects related to these therapies. Therefore, in this clinical case the development of these rare adverse effects is presented, which will be useful for the analysis of other clinical cases that have not yet been reported.

INTEREST CONFLICT

The authors declare no conflict of interest.

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