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Combination immune checkpoint inhibitor-induced hypophysitis:

A case report and review of the clinical and imaging findings

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Goals and Objectives

1. Describe a case of immune-checkpoint inhibitor-induced hypophysitis in a patient on combination immune checkpoint inhibitor therapy for metastatic melanoma.
2. Discuss the imaging findings of autoimmune hypophysitis associated with immune checkpoint inhibitors.
3. Familiarize the audience with the occurrence of this rare complication of a novel therapy, so that it may be more readily recognized.

Introduction

Immune checkpoint inhibitors have emerged as a promising new class of anti-cancer drugs. Unfortunately, while potentiating the immune system's response to cancer cells, these drugs also place the patient at risk for the development of immune-related adverse events (irAEs). Most often, the gastrointestinal tract and skin are involved. However, involvement of the endocrine system also occurs. While thyroid dysfunction is the most common endocrinological irAE, hypophysitis is also frequently seen - and is especially associated with ipilimumab (1).

Case Presentation

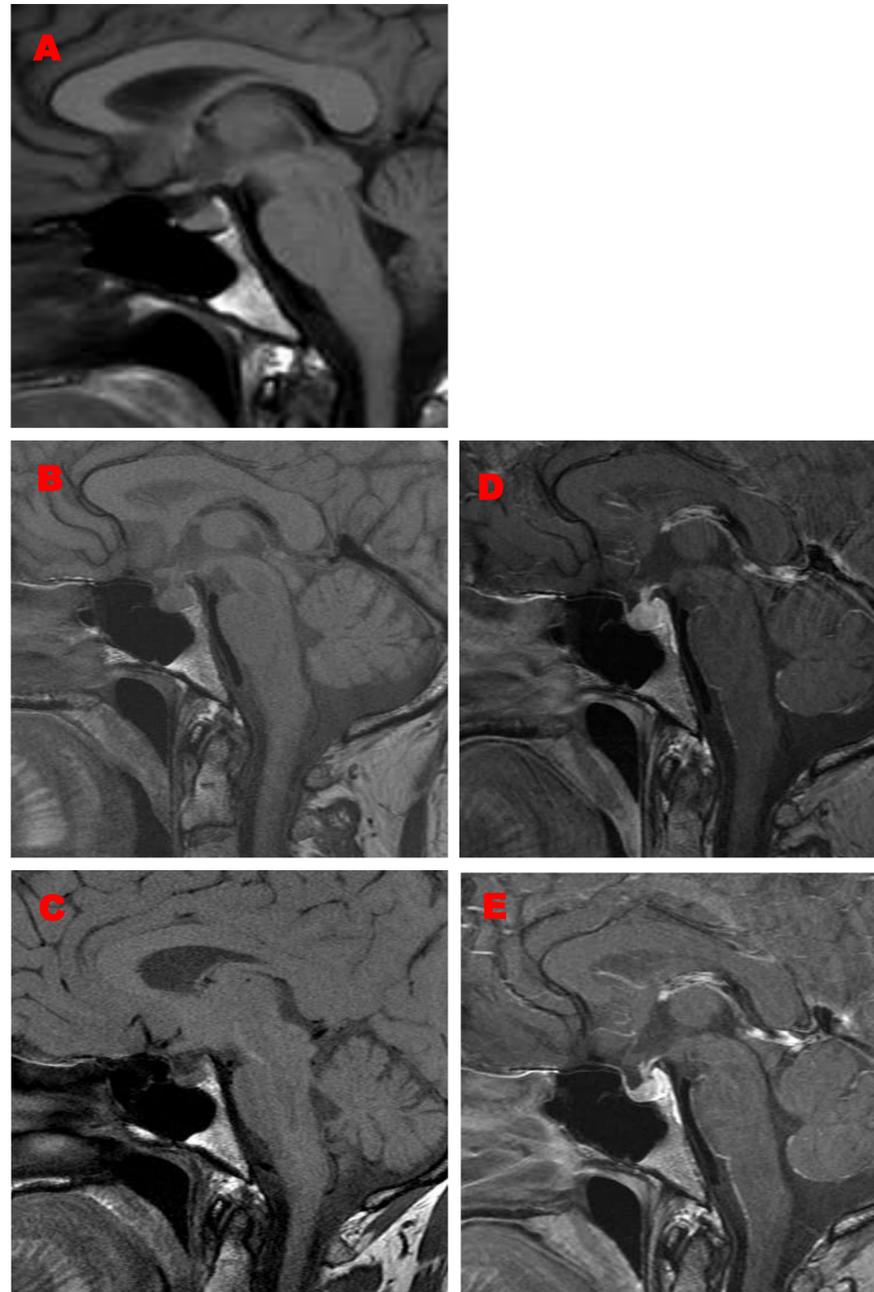
A 60-year-old male undergoing combination immune checkpoint therapy with nivolumab (an anti-PD-1 antibody) and ipilimumab (an anti-CTLA-4 antibody) for metastatic melanoma developed headaches. An MRI of the brain was obtained and demonstrated new enlargement of the pituitary.

Initial differential considerations included a metastatic lesion to the pituitary stalk, however the patient was also found to be hypothyroid. Further endocrinological evaluation revealed low testosterone, low random cortisol level, and low TSH, consistent with pituitary insufficiency.

For management, checkpoint inhibitor therapy was held and the patient was treated with prednisone 1mg/kg for 2 weeks, with excellent clinical response, including resolved headaches and improved energy. Follow-up MRI demonstrated resolution of the pituitary enlargement.

Following resolution of initial symptoms, this patient was initially resumed on single agent nivolumab, however due to progression of disease was changed to trametinib (MEK inhibitor antibody) and dabrafenib (BRAF inhibitor antibody) for targeted BRAF mutated melanoma. At the time of this report, the patient has had recurrence hypothyroidism and is undergoing repeat endocrinological evaluation for recurrent hypopituitarism.

Figures



Sagittal pre-contrast MR images demonstrate a normal appearance of the pituitary prior to initiation of the combination checkpoint inhibitor therapy (A) and interval enlargement of the pituitary approximately three months later near the end of the combination therapy (B) with predominantly homogeneous enhancement (D). A sagittal post-contrast T1 MR image following checkpoint inhibitor therapy discontinuation and steroid treatment demonstrates near resolution of the pituitary enlargement (C) and symmetric enhancement (E).

This pattern of symmetric enhancement of the pituitary stalk with resolution is characteristic of ipilimumab associated autoimmune hypophysitis, but it is not specific (2,3).

Discussion

CTLA-4 and PD1 are immune-checkpoint proteins involved in the regulation of T-cell proliferation. Inhibition of these proteins results in increased T-cell activation, which has shown positive effects on the treatment of melanoma, although the mechanism is not known (4). However, decreased regulation of T-cell activation leads to less specific immune activity, which results in immune-related adverse events (1).

Of these, panhypopituitarism can be one of the most profound. Symptoms of combination immune checkpoint inhibitor therapy induced autoimmune hypophysitis are variable and can include headache, fatigue, hypopituitarism, and/or hyponatremia, as were seen in this patient. Vision changes and other endocrinopathies, such as type 1 diabetes and diabetes insipidus, can also be seen, although was not present in this case (2,5).

While hypophysitis can occur with ipilimumab alone (up to 17% incidence), frequency and severity is greater when combined with nivolumab (5). Treatment consists of discontinuation, corticosteroids, and hormone replacement. Recovery of hormone function, particularly of corticotrophins, is variable (1).

Conclusion

As new cancer therapies emerge, physicians must remain aware of the potential for unique adverse effects – such as those occurring with immune checkpoint inhibitor therapies, including hypophysitis. As the imaging appearance of hypophysitis is not specific, understanding the clinical context in which it occurs can aid radiologists in recognizing it as a possible diagnosis and help guide appropriate clinical management.

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