

FIGURE 5
Management of Immune-Related Hypophysitis^{2,4,10,13,14,17,23,24,25}

Background: The incidence of hypophysitis is highest in anti-CTLA4 therapy (1%) and in combination therapy (8%). It occurs more frequently in males and usually occurs after 2-6 months of treatment. Hypophysitis can remain undetected since the symptoms might be vague⁵ Laboratory testing of morning cortisol, adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle stimulating hormone (FSH) and growth hormone (GH) define the diagnosis. Hypophysitis presents with low TSH and low free T4. Radiographic imaging (MRI) of the brain and pituitary gland may be warranted to identify lesions such as pituitary adenomas that may require intervention. Hormone replacement should be initiated according to hormone dysfunction and is usually long-term. An endocrinologist should be involved and consulted as soon as hypophysitis is suspected.

		MANAGEMENT				
		Description	Referral	Corticosteroids	Supportive Therapy	Immune Therapy
HYPO-PHYSITIS	GRADE 1	Asymptomatic or mild symptoms (fatigue, weakness); clinical or diagnostic observations only.	If symptomatic, monitor TSH, T4, ACTH, LH, FSH and morning cortisol. Consider radiographic pituitary imaging.	No steroid needed for immune suppression. See supportive therapy for hydrocortisone hormone replacement.	If morning cortisol <250 or random cortisol <150 nmol/L: hydrocortisone PO TID (20 mg QAM/10 mg QPM/10 mg QHS).	Monitor closely and continue immune therapy.
	GRADE 2	Moderate (headaches, hypotension); limiting age appropriate instrumental ADL.	Consult with endocrinologist.	Prednisone 1 mg/kg orally or Methylprednisolone, 1–2 mg/kg/day i.v. (if hypotensive) for 3–5 days, followed by prednisone, 1–2 mg/kg/day gradually tapered over 4 weeks [‡]	If falling TSH +/- low FT4, consider need for thyroxine replacement (0.5-1.5 mcg/kg). Always replace cortisol for 1 week prior to thyroxine initiation.	Withhold therapy until resolution to grade 0-1. Upon improvement, treatment may be resumed after corticosteroid taper, if needed. Treatment should be continued in the presence of hormone replacement as long as no symptoms are present.
	GRADE 3	Severe or medically significant but not immediately life threatening. Disabling; limiting self care ADL.	Hospitalization indicated. Rule out sepsis. MRI pituitary, consult radiologist and endocrinologist.	Slow tapering is imperative as early reduction of glucocorticoids may induce relapse or trigger an adrenal crisis.	Most patients who experience ≥ Grade 2 hypophysitis fail to recover pituitary function and require lifelong hormone replacement therapy.	Therapy should be permanently discontinued for severe or life-threatening grade 3 or 4 toxicity. If residual toxicity ≤ grade 2 and < 10 mg prednisone/day or equivalent: restart of anti-cancer treatment can be considered if benefit outweighs risk.
	GRADE 4	Life-threatening consequences or any visual disturbances; urgent intervention indicated.				

[§] nonspecific symptoms such as headache, visual impairment, fatigue, weakness, confusion, memory loss, erectile dysfunction and loss of libido, anorexia, labile moods, insomnia, temperature intolerance, subjective sensation of fever, and chills.

[‡] Alternatively dexamethasone, 4 mg every 6 hours for 1 week, gradually tapered to 0.5 mg/d, with substitution to replacement doses of hydrocortisone.