HYPOPHYSITIS

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AGENDA

- Definition
- Epidemiology
- Classification
- Clinical presentation
- Diagnosis
- Management
- Take home message

DEFINITION

- Rare inflammatory disorder of pituitary gland & infundibulum as a result of an autoimmune (majority form), infiltrative, infectious, neoplastic, or sometimes unknown pathogenic processes (Highly heterogenous).
  - Primary: Autoimmune
  - Secondary: several forms of systemic diseases and medications
- Clinical spectrum:
  - Asymptomatic cases
  - Rapidly progressive disease → may be fatal

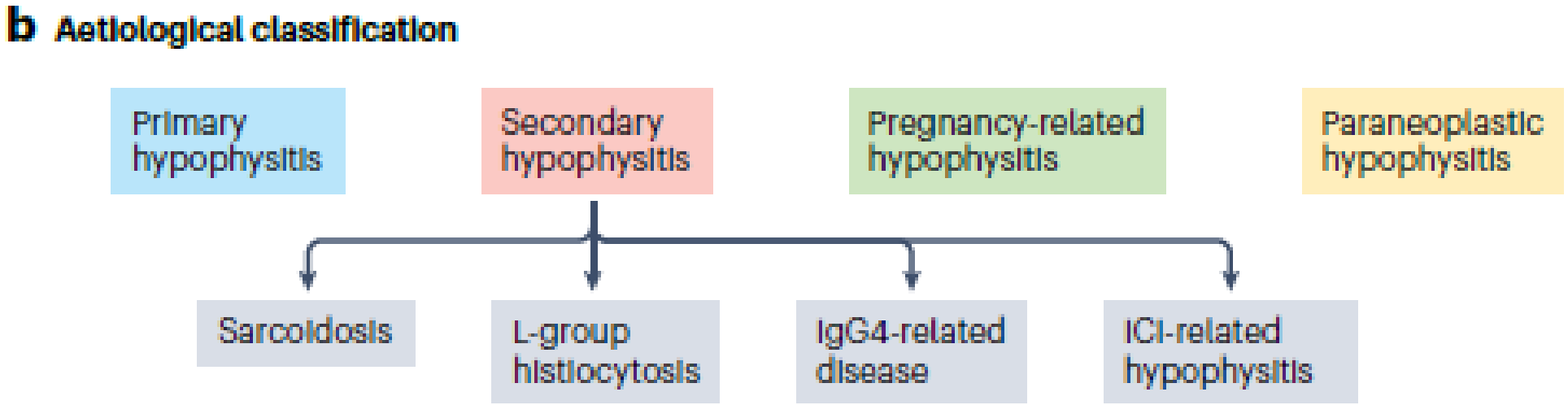
EPIDEMIOLOGY

- Reported AHy Cases Over Time
  - 1962–1981: 16 cases
  - 1982–2001: 290 cases
  - 2002–2004: 73 cases
- Several subtle cases may have gone undiagnosed
- 📈 Rising Hypophysitis Cases
  - Greater physician awareness & knowledge
  - Increase in pituitary imaging & surgeries
  - Growth of specific forms like ICIHy
  - Newly identified types:
    - Paraneoplastic hypophysitis
      - Anti-PIT1Hy
      - Isolated ACTH deficiency

1. ETIOLOGICAL CLASSIFICATION

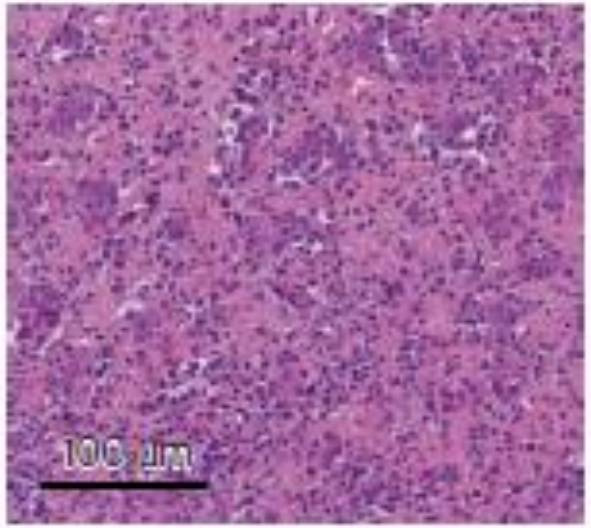
- Primary Hypophysitis (PHy):
  - Autoimmune forms → distinct immunological & histopathological features
  - Idiopathic forms → cause/pathogenesis unknown
- Secondary Hypophysitis (SHy):
  - Triggered by autoimmune, inflammatory, infectious, vascular, neoplastic conditions
  - Can occur as adverse effect of medications
- Autoimmune Hypophysitis (AHy):
  - Encompasses most PHy cases
  - Also includes SHy linked to systemic autoimmune diseases & polyendocrinopathies

2. AETIOLOGICAL CLASSIFICATION

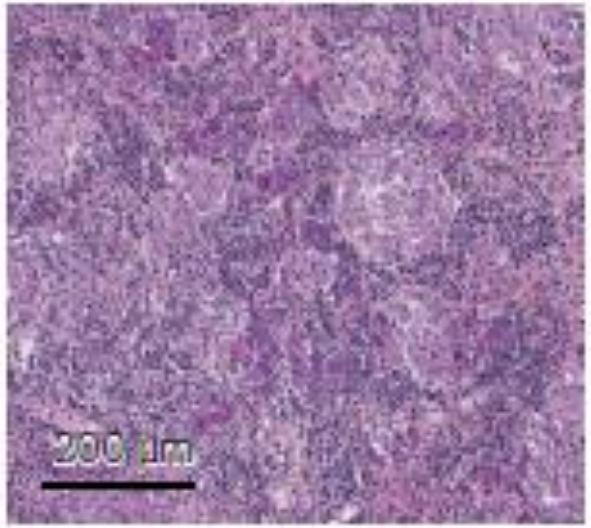


Nature Reviews Endocrinology 2025

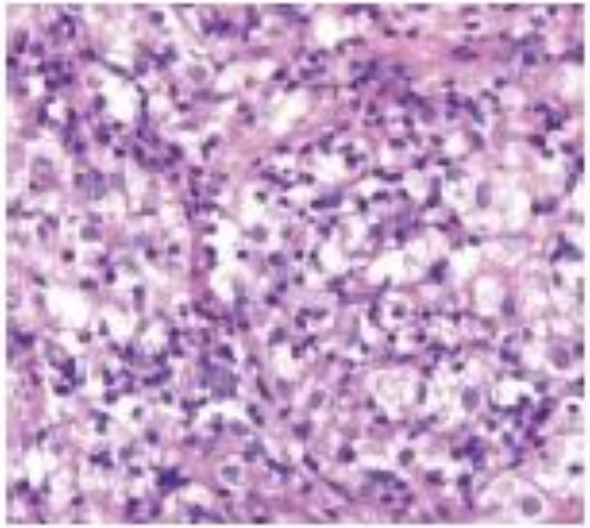
2. HISTOLOGICAL CLASSIFICATION



Lymphocytic hypophysitis



Granulomatous (and lymphogranulomatous) hypophysitis

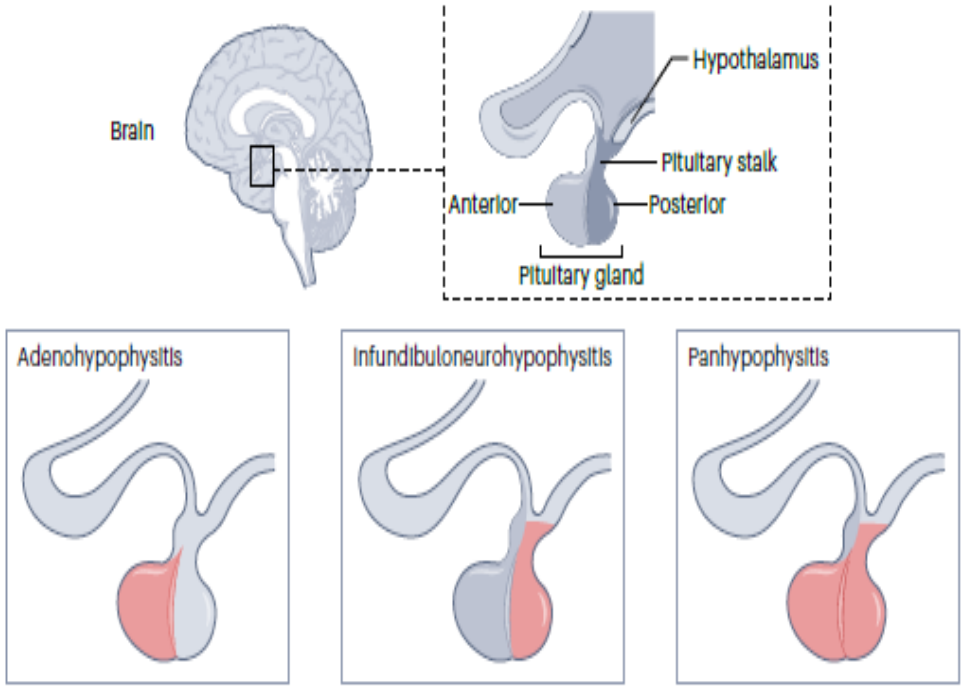


Xanthomatous (and xanthogranulomatous) hypophysitis

3. ANATOMICAL CLASSIFICATION

- Hypophysitis can also be classified based on the anatomical site of pituitary gland involvement.

1. Only the anterior pituitary (Adenohypophysitis)
2. Posterior pituitary (Infundibuloneurohypophysitis)
3. The entire pituitary gland (panhypophysitis)



PRIMARY HYPOPHYSITIS

LYMPHOCYTIC HYPOPHYSITIS—LHY

- The most common form of hypophysitis**: ~71.8%** of all cases.
- Autoimmune association: Up to 50% of cases linked with other autoimmune endocrinopathies or systemic autoimmune diseases.
- Terminology: LHy and autoimmune hypophysitis (AHy) have been used interchangeably in literature.

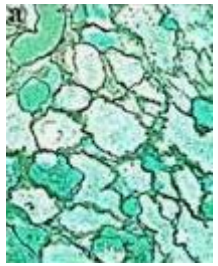
- LHy has been classically described to occur during pregnancy and the post-partum period

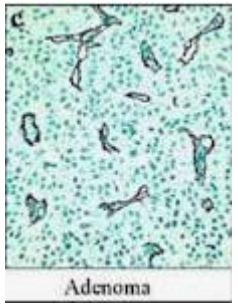
PREGNANCY-RELATED HYPOPHYSITIS

- Occur during or within 1 year of the start of pregnancy
- more frequently presented with chiasmal syndrome (50% of patients)
- ACTH (71%) → TSH, Gonad (60%)→ AVP def.(Rare-12%)
- MRI findings:
  - slightly thickened pituitary stalk
  - predominant intrasellar involvement, (pseudo-adenoma-like appearance)
  - history of autoimmune disease (22%)

CLINICAL PARADOX, MECHANISTIC INSIGHTS

- □ Paradox in Pregnancy
- Unlike many autoimmune conditions that improve during pregnancy, LHy paradoxically manifests during pregnancy.
- Possible mechanism: Molecular mimicry due to shared antigens (e.g., enolase isoforms) between pituitary and placenta → targeted by pituitary antibodies → may explain increased frequency during pregnancy.
- 🔬 Pathological Features
  - Lymphocytic infiltration → pituitary fibrosis.
  - Reticulin network:
    - Preserved in hypophysitis.
    - Disrupted in pituitary adenomas (helpful distinguishing feature).





PATHOLOGICAL HALLMARKS, AND GENETIC PREDISPOSITION

Pituitary Antibodies

- Pathogenic role not well-established.
- Clinical utility limited due to:
  - Low sensitivity and specificity.
  - Lack of independent confirmation.

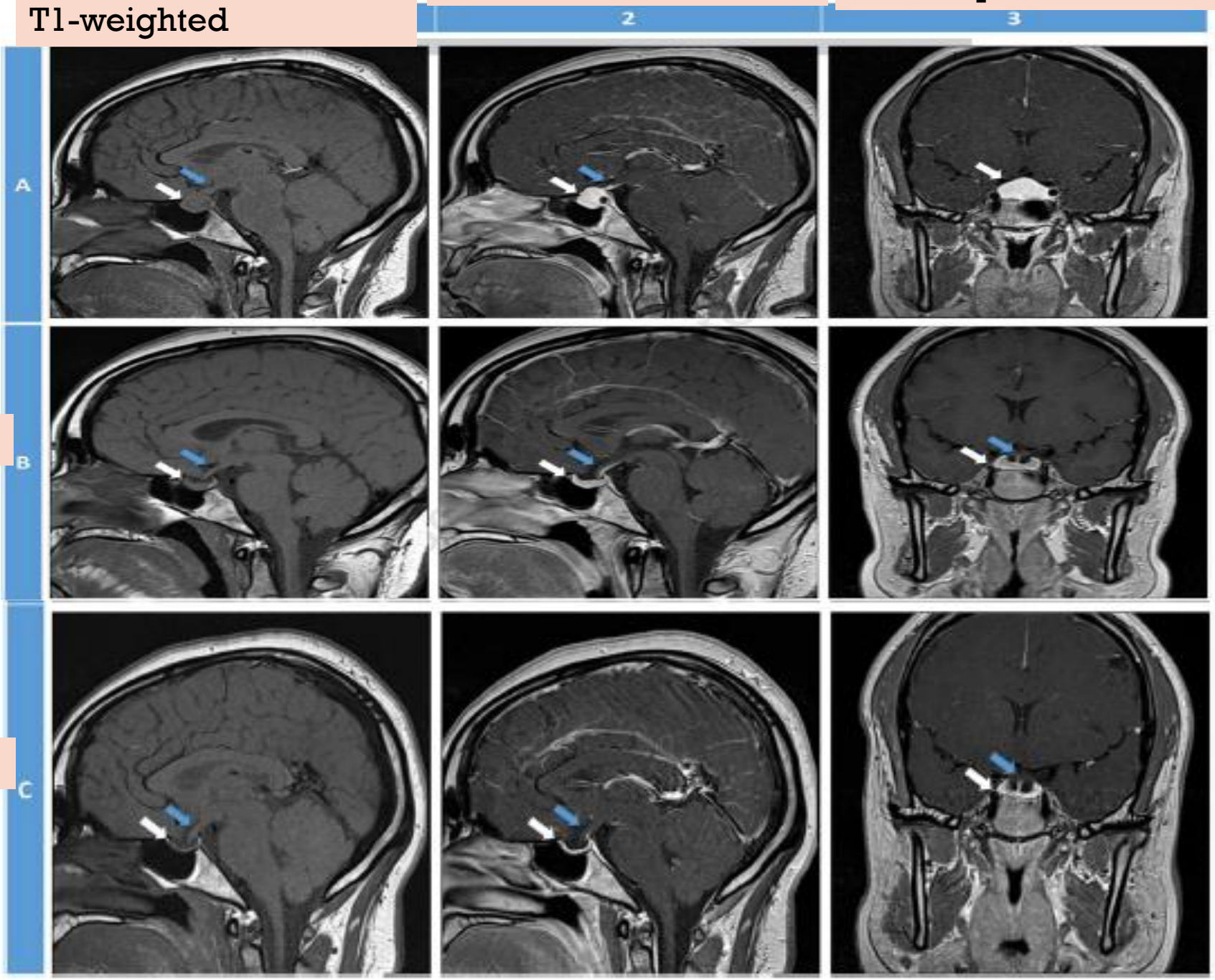
Genetic Associations

- Several HLA alleles linked with LHy:
  - HLA-DQ8
  - HLA-DR4
  - HLA-DR5
  - HLA-DR53

sagittal non-contrast T1-weighted

sagittal post-contrast

coronal post-contrast



2 Months later

17 Months later

22 A 30-year-old woman develops progressive, severe headaches, nausea, vomiting, and fatigue during her 33rd week of pregnancy. She has no notable medical history and was able to become pregnant within 2 months of trying. Her pregnancy course has been smooth until now.

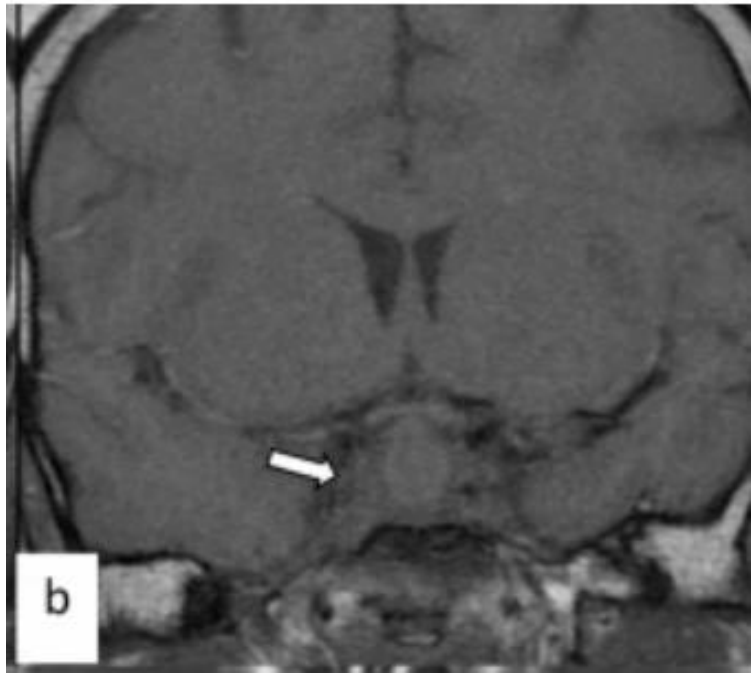
Physical examination findings are normal for 33 weeks' gestation. Her obstetrician persuades the radiologist to perform a noncontrast MRI of her head, and she is found to have a diffusely enlarged pituitary gland with suprasellar extension to the optic chiasm, but without compression of the chiasm.

Laboratory test results:

Total T_4 = 13.0 μg/dL (5.5-12.5 μg/dL)
(SI: 167.3 nmol/L [70.8-160.9 nmol/L])
TSH = 1.3 mIU/L (0.5-5.0 mIU/L)
Cortisol (8 AM) = 9.0 μg/dL (5-25 μg/dL)
(SI: 248.3 nmol/L [137.9-689.7 nmol/L])
Prolactin = 137 ng/mL (4-30 ng/mL)
(SI: 6.0 nmol/L [0.17-1.30 nmol/L])

Which of the following is the most likely diagnosis of the mass?

A. Pituitary adenoma
B. Histiocytosis
C. Lymphocytic hypophysitis
D. Rathke cyst
E. Metastasis



22 ANSWER: C) Lymphocytic hypophysitis

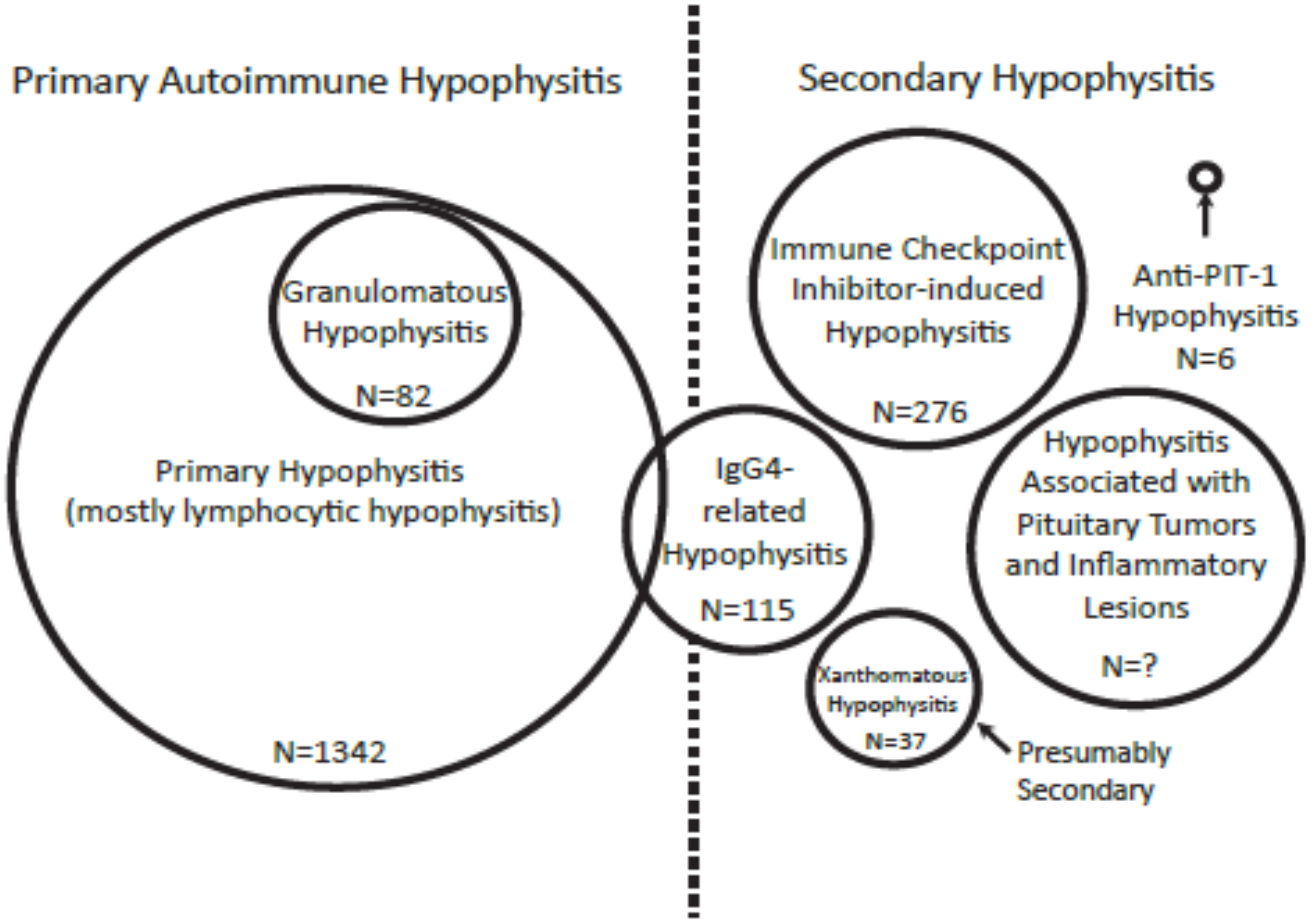
This pregnant woman has pituitary enlargement presenting near term, and it is most likely to be lymphocytic hypophysitis (Answer C). MRI shows diffuse pituitary enlargement, which is more compatible with hypophysitis than pituitary adenoma (Answer A). Had gadolinium been given, there would have been diffuse enhancement rather than focal enhancement. No data show adverse effects of performing MRI or giving gadolinium during pregnancy, although it is recommended to withhold gadolinium during pregnancy. One of the striking features of hypophysitis occurring during pregnancy is the high risk of ACTH deficiency, and this should be evaluated.

GRANULOMATOUS HYPOPHYSITIS

- 📊 Prevalence: Accounts for ~20% of primary hypophysitis cases.
- 🧍‍♀️ Demographics: Female predominance (ratio ~2.5:1); typical onset in the 4th decade of life (mean age ~44 ± 15 years).
- 🔗 Associations: Can occur alongside autoimmune disorders.
- ⚠️ Severity:
  - More frequent headaches
  - Higher rates of anterior hypopituitarism
  - Diabetes insipidus (up to 75%)
  - Greater radiographic abnormalities
- 💊 Treatment Response: Usually less responsive to glucocorticoids compared to lymphocytic hypophysitis.
- 🌐 Systemic Link: Granulomatous forms related to systemic disorders may not always show multisystem involvement.

MIXED FORMS OF HYPOPHYSITIS

- Lymphogranulomatous hypophysitis
- Xanthogranulomatous hypophysitis (XGHy)



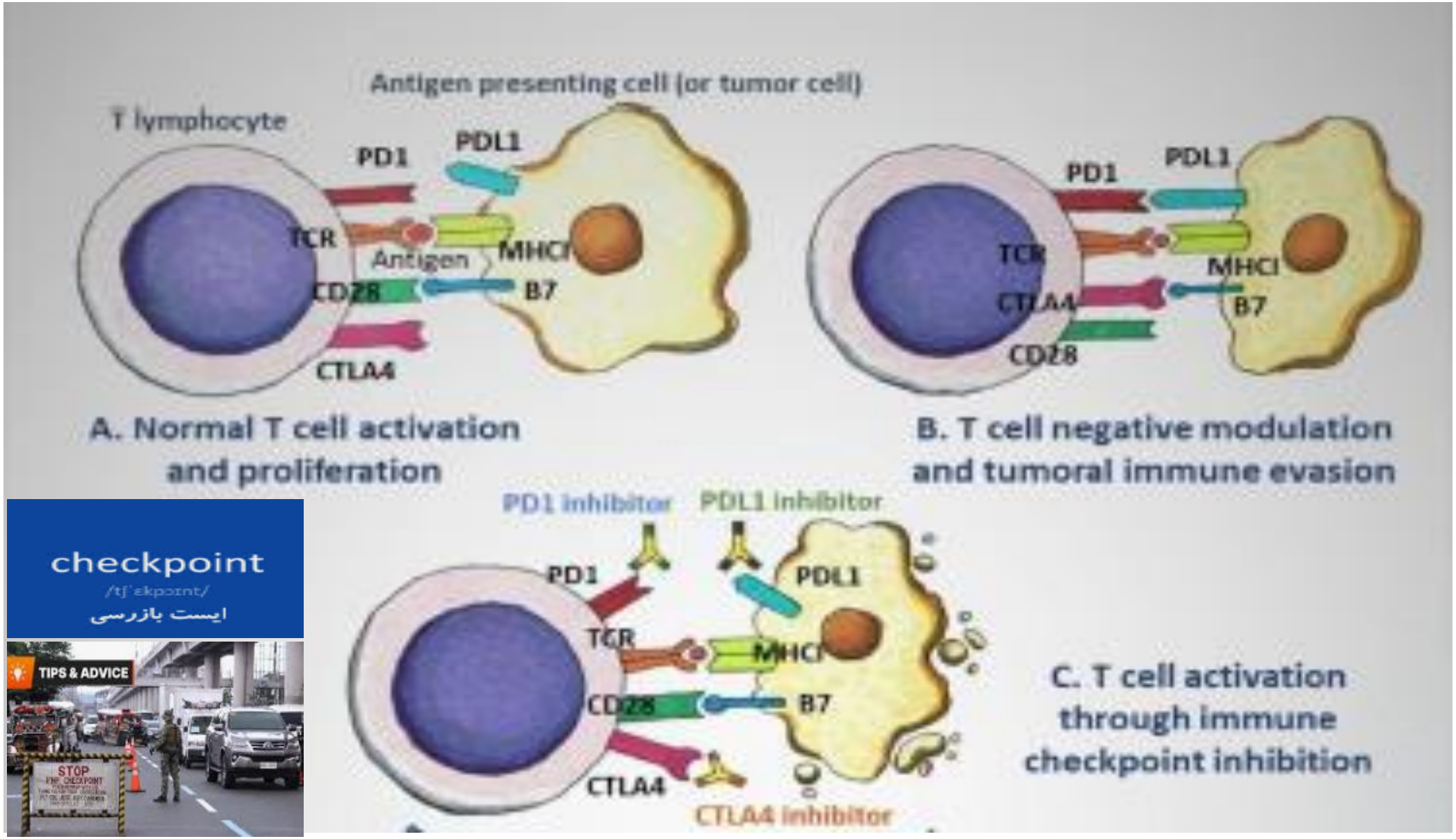
subtypes of hypophysitis

(primary hypophysitis, granulomatous hypophysitis, IgG4-related hypophysitis, immune checkpoint inhibitor induced hypophysitis, xanthomatous hypophysitis)

SECONDARY HYPOPHYSITIS

ICI-INDUCED HYPOPHYSITIS

- 🌐 Immune Checkpoint Inhibitors (ICIs) in Oncology
- Impact: Revolutionized cancer treatment by enhancing host immune response against tumor cells.
- FDA-approved ICIs: 7 agents — ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, cemiplimab, avelumab.
- In trials: Tremelimumab and others.
- Mechanism: Monoclonal antibodies targeting:
  - CTLA-4 (on T cells)
  - PD-1 (on T cells)
  - PD-L1 (on antigen-presenting and tumor cells)
- Effect: Block immune tolerance and tumor immune escape → activate T cells.



checkpoint

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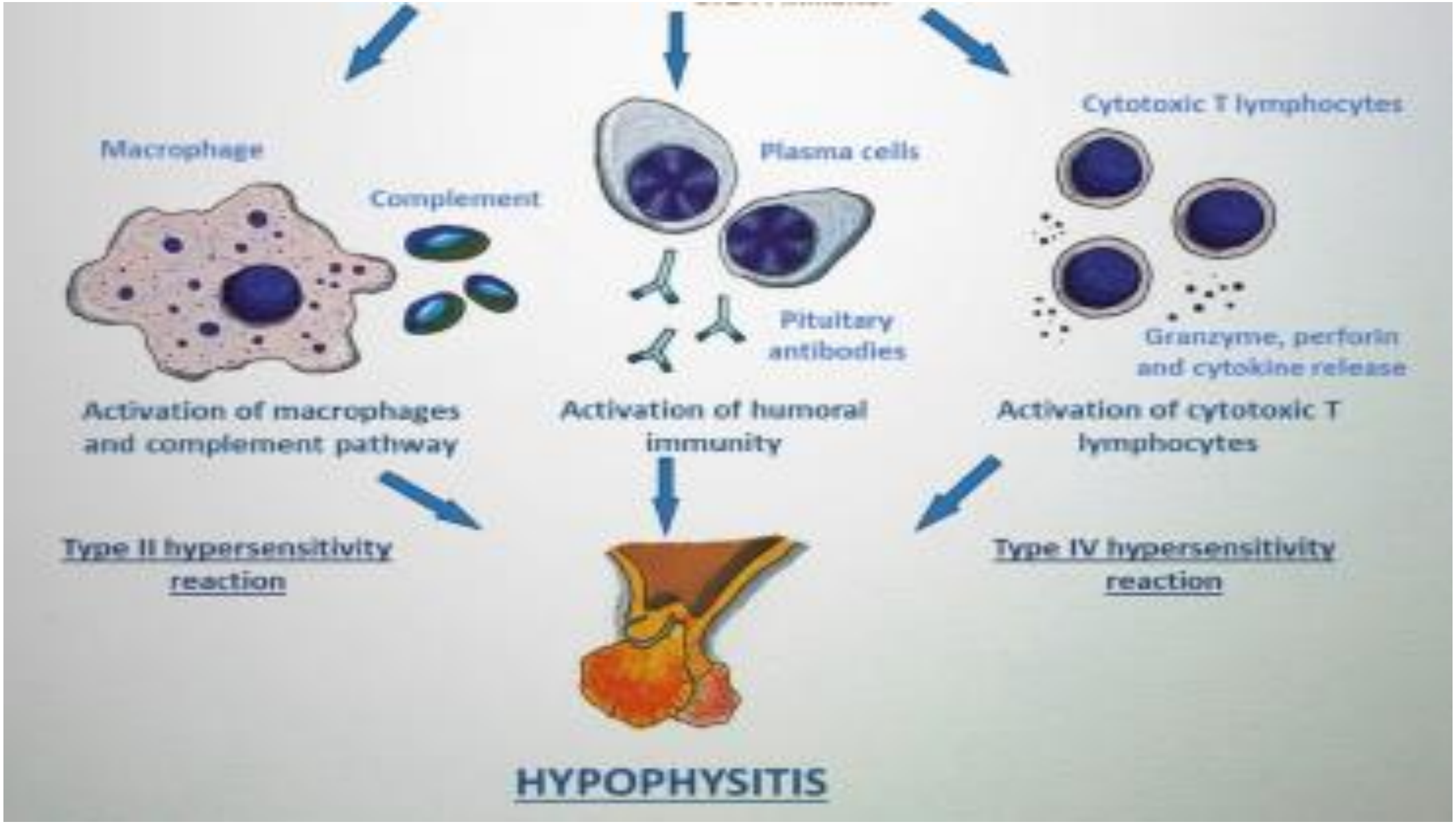

Macrophage
Complement
Plasma cells
Cytotoxic T lymphocytes
Pituitary antibodies
Granzyme, perforin and cytokine release
Activation of macrophages and complement pathway
Activation of humoral immunity
Activation of cytotoxic T lymphocytes
Type II hypersensitivity reaction
Type IV hypersensitivity reaction
HYPOPHYSITIS

ICI-Induced Hypophysitis (ICIHy)

- Epidemiology:
  - Male predominance (F:M = 1:4).
  - Older age of onset (~59 ± 13 years).
- Prevalence:
  - CTLA-4 inhibitors: 11–13.6%.
  - PD-1/PD-L1 inhibitors: 1–2%.
- Clinical profile differences:
  - CTLA-4i: higher incidence, earlier onset (~9.3 weeks).
  - PD-1/PD-L1i: milder course, later onset (~25.8 weeks), isolated adrenal insufficiency, fewer headaches, rare MRI changes.
  - ➢ Hormonal deficit: ACTH deficiency is most frequent across all ICIs.

Pathogenesis & Antibodies

- Autoantibodies associated:
  - Against integral membrane protein 2B (linked to ACTH release).
  - Against G(olf) subunit alpha (linked to hormone synthesis, esp. TSH).
- Antibody class differences:
  - CTLA-4 inhibitors: IgG1/IgG2 → activate cytotoxicity/complement.
  - PD-1/PD-L1 inhibitors: IgG4 → less cytotoxic/complement activation.

RISK FACTORS, AND MANAGEMENT STRATEGIES

- ⚠ Risk Factors
  - Male sex.
  - Older age.
  - Higher drug doses.
- □ Diagnosis & Management
  - Imaging: Limited role; mainly to exclude other causes of hypopituitarism.
  - Monitoring: Monthly adrenal and thyroid function checks for first 6 months, extend as needed.
- Treatment considerations:
  - Delay immunotherapy in acute setting until stabilization.
  - Discontinuation does not improve pituitary outcome and risks cancer progression.
  - High-dose glucocorticoids reserved for severe cases (mass effect, visual loss, adrenal crisis).

ICIHY MANAGEMENT

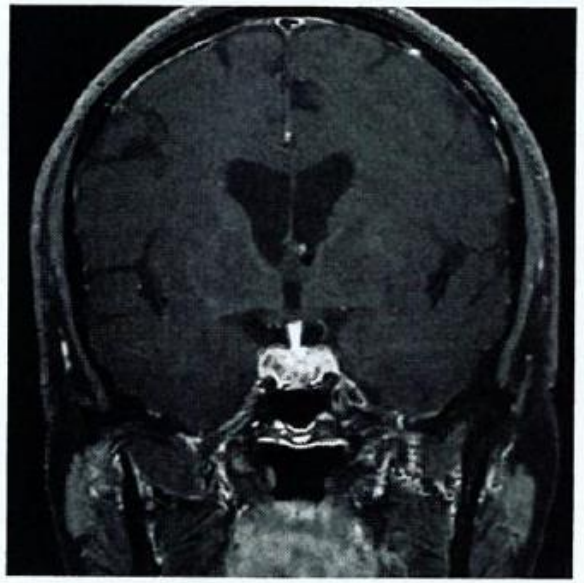
- ICI-Induced Hypophysitis (ICIHy)
  - Generally more refractory to glucocorticoid therapy.
- Management depends on severity grade:
  - **Grade 1** (asymptomatic) / **Grade 2** (mildly symptomatic)
    - Hormone replacement only.
    - ICI therapy can continue (no discontinuation needed).
  - **Grade 3** (moderately symptomatic)
    - Delay ICI therapy.
    - Consider re-initiation based on clinical response to hormone replacement ± glucocorticoids.
  - **Grade 4** (severe or life-threatening)
    - Discontinue ICI therapy.
    - Administer high-dose glucocorticoids.
  - ➢ Special Note
    - High-dose glucocorticoids are not recommended in ICIHy except for acute presentations (e.g., symptomatic mass effects).

89 You are asked to evaluate a 39-year-old woman who is in the emergency department. She describes a 3-day history of frontal headache, vomiting, and fatigue. She has a history of stage IV melanoma and type 2 diabetes mellitus. She is currently treated with ipilimumab immunotherapy (for the past 3 months), premixed insulin twice daily, ramipril, simvastatin, and pancrelipase. She reports noticing more hypoglycemia recently.

On physical examination, she is drowsy but arousable. She appears dehydrated. Her temperature is 99.5°F (37.5°C), blood pressure is 105/68 mm Hg, and pulse rate is 110 beats/min. There are no focal neurologic findings, and visual fields are normal.

Laboratory test results:

White blood cell count = 13,500/μL (4500-11,000/μL)
(SI: 13.5 × 10^9/L [4.5-11.0 × 10^9/L])
C-reactive protein = 5.0 mg/L (0.8-3.1 mg/L) (SI: 48 nmol/L [7.62-29.52 nmol/L])
Sodium = 129 mEq/L (136-142 mEq/L) (SI: 129 mmol/L [136-142 mmol/L])
Potassium = 4.5 mEq/L (3.5-5.0 mEq/L) (SI: 4.5 mmol/L [3.5-5.0 mmol/L])
Serum urea nitrogen = 28 mg/dL (8-23 mg/dL) (SI: 10.0 mmol/L [2.9-8.2 mmol/L])
Creatinine = 1.8 mg/dL (0.6-1.1 mg/dL) (SI: 159.1 μmol/L [53.0-97.2 μmol/L])
Cortisol = 4.8 μg/dL (5-25 μg/dL) (SI: 132.4 nmol/L [137.9-689.7 nmol/L])
TSH = 0.8 mIU/L (0.5-5.0 mIU/L)
Free T_4 = 0.65 ng/dL (0.8-1.8 ng/dL) (SI: 8.4 pmol/L [10.30-23.17 pmol/L])



Contrast-enhanced pituitary MRI is shown (*see image*).

Which of the following is the most likely cause of this patient's pituitary abnormality?

A. Hypophysitis
B. Hemorrhage
C. Abscess
D. Metastasis
E. Adenoma

OTHER FORMS OF SECONDARY HYPOPHYSITIS

- 1. Autoimmune conditions
  - Autoimmune polyglandular syndromes (APS)
  - Other autoimmune diseases:
    - Systemic lupus erythematosus (SLE)
    - Sjögren's syndrome
    - Behçet's syndrome
    - Coeliac disease–associated haplotypes (esp. DQ8, DQ2 in Caucasian patients)
- 2. Vasculitic processes
  - Granulomatosis with polyangiitis (GPA)
  - Microscopic polyangiitis
- 3. Drug-induced
  - Immune checkpoint inhibitors (ICI)
  - Interferon alpha

OTHER FORMS OF SECONDARY HYPOPHYSITIS (SHY)

- 4. Inflammatory Conditions
  - Sarcoidosis
  - IgG4-related disease
- 5. Infectious Diseases
  - Tuberculosis
  - Syphilis
  - Fungal infections
- 6. Proliferative Disorders
  - Langerhans cell histiocytosis
  - Erdheim–Chester disease
- 8. Neoplastic Conditions
  - Germinoma
  - Craniopharyngioma
  - Lymphoma

NOVEL CAUSES OF SECONDARY HYPOPHYSITIS

- Paraneoplastic Hypophysitis (Anti-PIT1Hy)
- Novel autoimmune hypophysitis (AHy) subtype.
- Also called "anti-PIT1 antibody syndrome."
- Hormonal Profile
  - Selective deficiencies:
    - Growth hormone (GH)
    - Thyroid-stimulating hormone (TSH)
    - Prolactin
- Other pituitary axes remain intact.

ANTI-PIT1 HYPOPHYSITIS (ANTI-PIT1HY)

- Molecular & Immune Basis
  - PIT1 is a POU-domain transcription factor essential for differentiation of somatotrophs, thyrotrophs, and lactotrophs.
  - Mutations cause congenital GH, TSH, and prolactin deficiencies.
- Immune markers:
  - Circulating anti-PIT1 antibodies (diagnostic biomarker).
  - Cytotoxic T lymphocytes (CTLs) are the true mediators of pituitary cell destruction.
  - Additional immune findings:
    - Circulating anti-proopiomelanocortin (POMC) antibodies.
    - Peripheral blood lymphocytes reactive to POMC protein, confirming CTL-mediated reaction.

ANTI-PIT1 ANTIBODY SYNDROME

- Clinical Features
  - Age of onset: Typically after the 7th decade of life.
  - Paraneoplastic association:
    - Most cases linked to thymoma.
    - Can also occur with other malignant neoplasms.
  - Concomitant autoimmune endocrinopathies: May co-occur with type 1 diabetes mellitus.
- Diagnostic Triad

1. Acquired selective GH, TSH, and prolactin deficiencies.

2. Presence of circulating anti-PIT1 antibodies or PIT1-reactive CTLs.

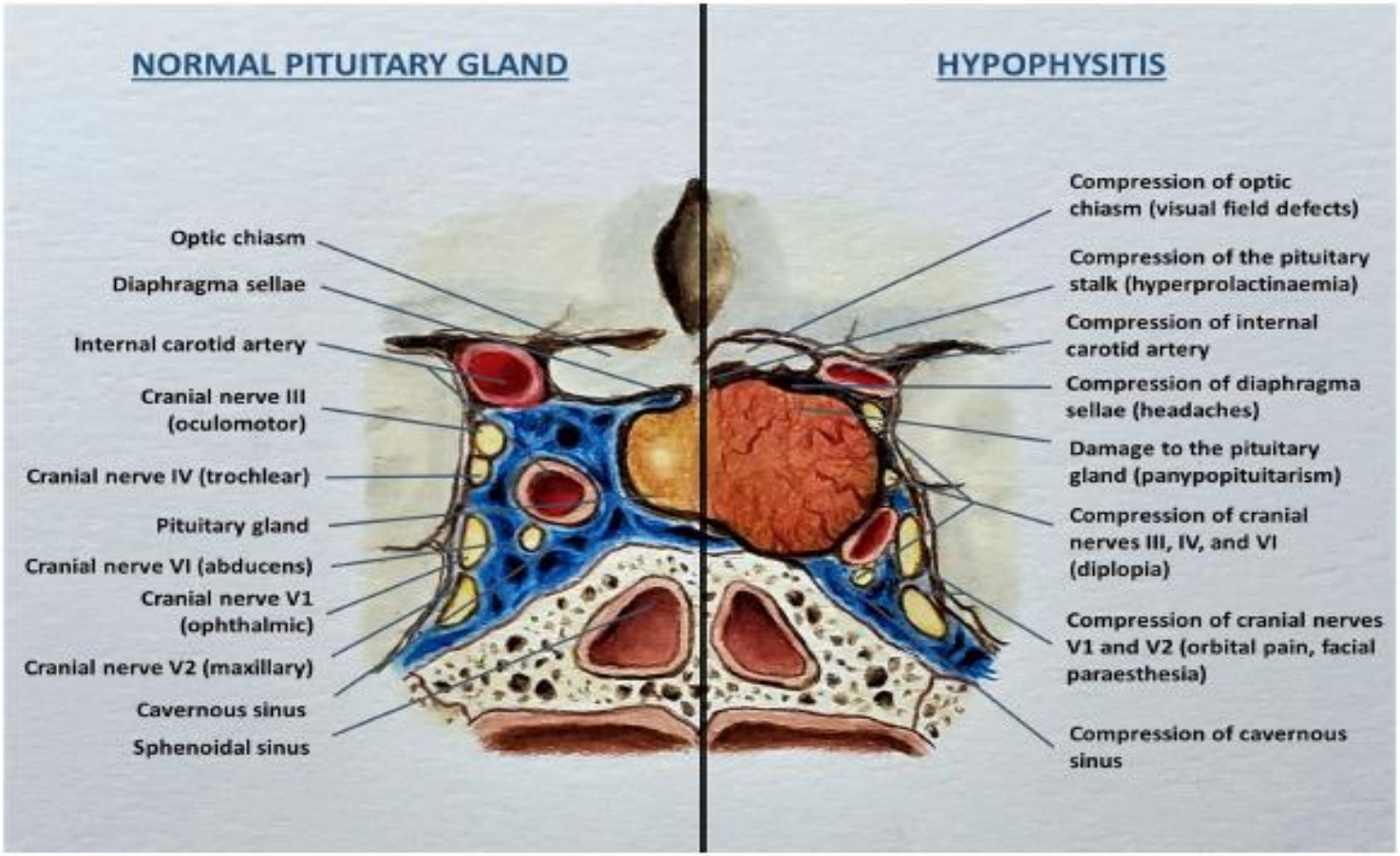
3. Underlying thymoma or other malignant neoplasm.

ACQUIRED, ISOLATED ACTH-DEFICIENCY

- Also is a paraneoplastic syndrome
- Circulating anti-proopiomelanocortin (POMC) antibodies were detected and the peripheral blood lymphocytes were reactive to POMC protein, indicative of a CTL-mediated reaction

Clinical Features of Hypophysitis

- Spectrum of Presentation
  - Can range from asymptomatic cases
  - To hypopituitarism with hormonal deficiencies
  - To acute mass effects (e.g., pituitary apoplexy)
  - In severe cases, may lead to circulatory collapse and adrenal crisis, even death.
- Core Clinical Manifestations
- **1.** Mass effects
  - Headaches
  - Visual disturbances (due to compression of optic chiasm)
- **2.**Anterior pituitary hormone deficiencies
- **3.** Central diabetes insipidus (DI)
- **4.** Hyperprolactinaemia
- **5.** Hypothalamitis: disturbances in satiety or body temperature



Normal anatomy of the sellar region and the adjacent neurovascular structures (left panel) and the mass effects of hypophysitis (right panel).

CLINICAL FEATURES OF HYPOPHYSITIS (PHY VS SHY)

- Primary Hypophysitis (PHy, 1917–2016 cohort):
  - Headaches: 47%
  - Low cortisol: 35%
  - Polyuria & polydipsia: 35%
  - Visual disturbance: 31%
  - Low sex steroids: 20%
  - Low thyroxine: 16%
- Secondary Hypophysitis (SHy, CTLA-4 blockade):
  - Headaches: 60%
  - Low cortisol: 72%
  - Polyuria & polydipsia: 0.9%
  - Visual disturbance: 3%
  - Low sex steroids: 15%
  - Low thyroxine: 20%

MOST COMMON PRESENTING FEATURES

- Mass effects: Headaches and visual disturbances, especially in acute or subacute phases.
- Headache characteristics:
  - Usually generalized
  - Often severe
- Caused by upward expansion of the inflamed pituitary impinging on the dura mater and optic chiasm, or lateral extension compressing the cavernous sinus.

OTHER PRESENTING FEATURES

- Visual Symptoms
  - Extremely rare in ICI-induced hypophysitis (ICIHy) (~3%).
  - Also rare in xanthomatous hypophysitis (XGHy).
- Asthenia (Fatigue/Weakness)
  - Very common:
  - 86% of patients with primary hypophysitis (PHy).
  - 58% of patients with ICIHy.
- Hormonal Deficiencies: Hypopituitarism due to anterior pituitary hormone loss is a major feature.
  - Typical sequence in panhypopituitarism (other causes):
    - GH → LH/FSH → TSH → ACTH
    - Mnemonic: "Go Look For The Adenoma"
  - Sequence in hypophysitis (distinct pattern):
    - ACTH → LH/FSH , TSH →GH and prolactin deficiencies

DIAGNOSTIC CHALLENGE IN ICIHY

- Hypocortisolism symptoms (fatigue, tiredness, weight loss) in ICIHy can overlap with malignancy-related symptoms, potentially leading to missed diagnosis of adrenal insufficiency (AI).

SECONDARY HYPOPHYSITIS (SHY) ASSOCIATIONS

- Autoimmune endocrine disorders:
  - Graves' disease
  - Hashimoto thyroiditis
  - Type 1 diabetes mellitus
  - Autoimmune polyglandular syndromes (APS)
- Non-endocrine autoimmune conditions:
  - Systemic lupus erythematosus (SLE)
  - Rheumatoid arthritis
  - Sjögren's syndrome
  - Vasculitis
  - Coeliac disease
- Inflammatory conditions:
  - Sarcoidosis
  - IgG4-related disease

DIAGNOSIS OF HYPOPHYSITIS

- Challenges
  - Rare condition → low clinical suspicion in general population.
  - Non-specific symptoms → may be misattributed to other causes.
  - Silent progression → fibrosis and late presentation with panhypopituitarism.

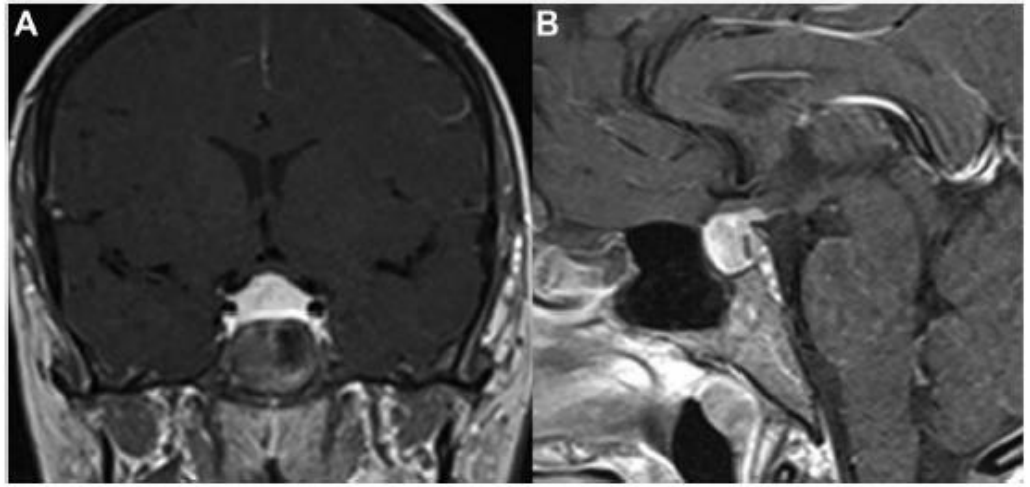
➢ These factors contribute to delayed or missed diagnosis.

DIAGNOSTIC APPROACH

- 1.Biochemical Evaluation
  - Measure pituitary hormones.
  - Assess hormones of target endocrine glands (to confirm functional impact).
- 2. Imaging Evaluation
  - MRI or other imaging to detect pituitary enlargement, inflammation, or structural changes.
- 3. Evaluation of Secondary Causes of Autoimmune Hypophysitis (AHy)
  - Rule out associated autoimmune, inflammatory, infectious, or neoplastic conditions.

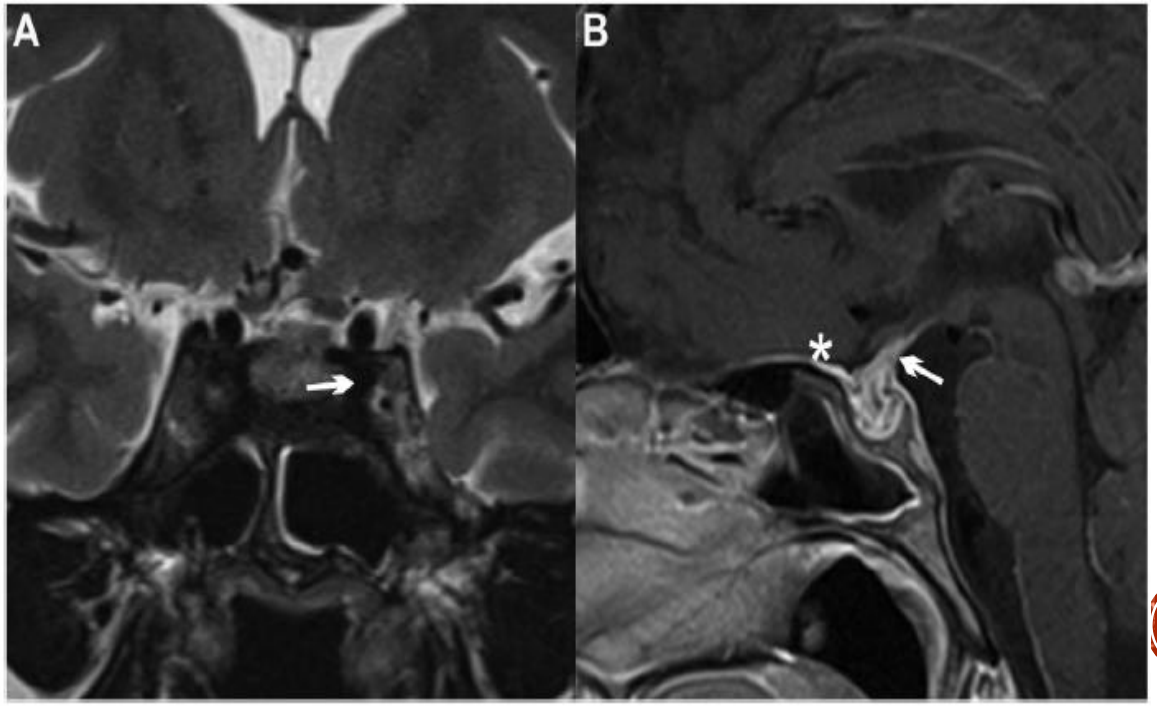
IMAGING IN HYPOPHYSITIS

- MRI is the best imaging modality for diagnosing hypophysitis.
- Abnormalities detected in:
  - Up to 98% of primary hypophysitis (PHy).
  - 77% of ICI-induced hypophysitis (ICIHy).
- Common MRI Findings (with frequency ranges)
  - Pituitary enlargement: 23–93%
  - Homogeneous pituitary contrast enhancement: 23–92%- Adenoma-like pattern
  - Pituitary stalk thickening (>4 mm AP diameter): 34–96%
  - Loss of posterior pituitary bright spot (T1-weighted): 18–71%
  - Other Frequent Signs



OTHER FREQUENT SIGNS IN MRI

- Intrasellar + suprasellar extension:
  - 50–92% in lymphocytic/primary hypophysitis (LHy/PHy).
  - Up to 100% in granulomatous hypophysitis (GHy).
- Parasellar T2 dark sign: up to 50% of PHy cases.
- <u>Rare Radiographic Findings</u>
  - Parasellar extension
  - Cystic changes
  - Central necrosis/apoplexy
  - "Figure of 8" appearance
  - Dural/meningeal tail
    (contrast-enhanced inflamed dura)
  - Empty sella (late-stage disease)

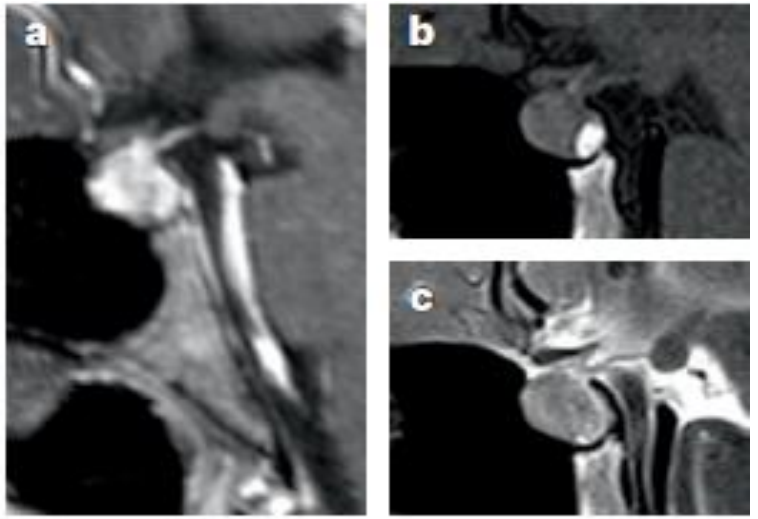


DIFFERENTIAL DIAGNOSIS

- The main challenge in diagnosing hypophysitis on MRI lies in differentiating hypophysitis from a pituitary adenoma
- <u>Features Favoring Hypophysitis</u>
  - 1. Onset: Late pregnancy or early postpartum period.
  - 2. Contrast enhancement: Relatively homogeneous gadolinium uptake with higher post-contrast enhancement.
  - 3. Posterior pituitary: Absence of the normal "bright spot" on MRI.
  - 4. Pituitary stalk: Thickening (>4 mm).
- <u>Features Favoring Pituitary Adenoma</u>
  - Asymmetric pituitary expansion.
  - weak and heterogeneous enhancement,
  - cavernous extension,
  - erosion of the sellar floor
  - deviation of the stalk
  - and identification of a healthy portion of the pituitary gland

DIFFERENTIAL DIAGNOSIS: MIMICS OF HYPOPHYSITIS ON IMAGING

- Physiologic Pituitary Changes/ Pituitary hypertrophy can resemble hypophysitis in:
  - Children
  - Puberty
  - Pregnancy



- Pathological Conditions
  - Sheehan's syndrome

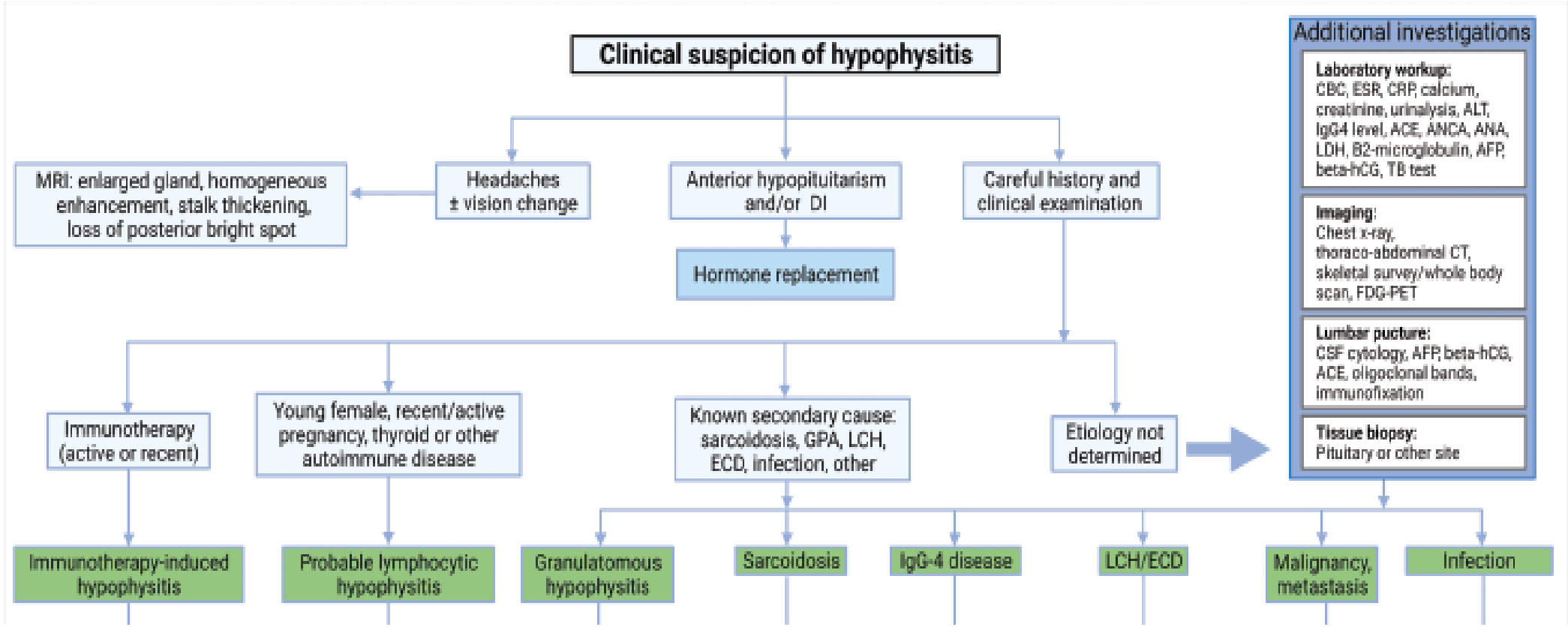
    (postpartum pituitary necrosis)
  - Isolated thyrotroph hyperplasia from severe, long-standing primary hypothyroidism.

DIFFERENTIAL DIAGNOSIS OF HYPOPHYSITIS

- Categories of Secondary Causes
  - Inflammatory
  - Infectious
  - Neoplastic
- Recommended Evaluations
  - Granulomatous hypophysitis (GHy) suspicion:
    - Quantiferon testing → rule out tuberculosis
    - Serum angiotensin-converting enzyme (ACE) levels → assess for sarcoidosis
    - ANCA antibodies → evaluate for vasculitis
  - Proliferative disorders:
    - Erdheim–Chester disease or Langerhans cell histiocytosis
      - Work-up: whole body bone scan, skeletal survey, biopsy
  - Neoplastic causes (sellar/suprasellar germinomas):
    - Serum alpha-fetoprotein (AFP)
    - Beta-HCG

ADDITIONAL DIAGNOSTIC TOOLS IN HYPOPHYSITIS

- HLA Testing & Pituitary Antibodies
  - Current role: Uncertain clinical value.
  - Not reliable as standalone diagnostic markers.
- Immunoglobulin Levels
  - ✓ Indication: Must be measured if IgG4-related hypophysitis (IgG4Hy) is suspected.
  - ✓ Helps differentiate from other inflammatory pituitary conditions.
- Pituitary Biopsy
  - Gold standard for establishing the diagnosis of autoimmune hypophysitis (AHy).
  - Reserved for cases where:
    - Diagnosis remains uncertain Biopsy
    - results are expected to alter management decisions


Clinical suspicion of hypophysitis
MRI: enlarged gland, homogeneous enhancement, stalk thickening, loss of posterior bright spot
Headaches ± vision change
Anterior hypopituitarism and/or DI
Careful history and clinical examination
Hormone replacement
Immunotherapy (active or recent)
Young female, recent/active pregnancy, thyroid or other autoimmune disease
Known secondary cause: sarcoidosis, GPA, LCH, ECD, infection, other
Etiology not determined
Additional investigations
Laboratory workup: CBC, ESR, CRP, calcium, creatinine, urinalysis, ALT, IgG4 level, ACE, ANCA, ANA, LDH, B2-microglobulin, AFP, beta-hCG, TB test
Imaging: Chest x-ray, thoraco-abdominal CT, skeletal survey/whole body scan, FDG-PET
Lumbar puncture: CSF cytology, AFP, beta-hCG, ACE, oligoclonal bands, immunofixation
Tissue biopsy: Pituitary or other site
Immunotherapy-induced hypophysitis
Probable lymphocytic hypophysitis
Granulomatous hypophysitis
Sarcoidosis
IgG-4 disease
LCH/ECD
Malignancy, metastasis
Infection

TREATMENT OF HYPOPHYSITIS

- Challenges
  - No clear consensus on optimal strategy.
    - Rarity of the disease.
    - Heterogeneity in clinical presentation and natural history.
    - Lack of clinical trials comparing treatment modalities.
- Therapeutic Focus
  - 1. Correction of hormonal abnormalities
    - Hormone replacement therapy to address pituitary deficiencies
  - 2. Alleviation of neurological and mass effects

MANAGEMENT

1. Conservative management
2. Substitutive treatments
3. Disease controlling therapies
   - Glucocorticoids
   - Immunosuppressive treatment
   - Surgery
   - Radiotherapy

DISEASE CONTROLLING THERAPIES

- Indications
  - Rapid onset of neurological symptoms
  - Mass effects due to pituitary enlargement

- Efficacy:
  - Reduce pituitary swelling
  - Restore pituitary function

GLUCOCORTICOIDS

- Glucocorticoids are the cornerstone of therapy for autoimmune hypophysitis (AHy). Common formulations:
  - Prednisone
  - Methylprednisone
  - Dexamethasone
- Subtype-Specific Effectiveness
  - IgG4-related hypophysitis (IgG4Hy): Glucocorticoid therapy is the mainstay of treatment.
  - Granulomatous hypophysitis (GHy) and Xanthomatous hypophysitis (XHy): Glucocorticoid therapy is less effective.

GLUCOCORTICOID & IMMUNOSUPPRESSIVE THERAPY

- Glucocorticoids: Initial high-dose therapy:
  - Hypophysitis + chiasmal compression or oculomotor nerve palsy
    - IV 1gr/d-3-5 d → Oral GC 1 mg/Kg with gradual tapering over 1 year
  - Hypophysitis + Mass effect (no visual involvement)
    - Oral GC 1 mg/Kg with gradual tapering over 1 year
  - Hypophysitis + Substantial endocrine involvement
    - Oral GC 0.5-1 mg/Kg with gradual tapering over 1 year
  - Tapering: Gradual taper over weeks to months (one year).
  - Duration guided by clinical response.

ALTERNATIVE IMMUNOSUPPRESSIVE AGENTS

- Used in relapse or glucocorticoid non-response:
  - Mycophenolate mofetil
  - Azathioprine
  - Methotrexate
  - Cyclosporine
- Rituximab Potential benefit in:
  - IgG4-related hypophysitis (IgG4Hy).
  - Biopsy-proven B-lymphocyte predominant, steroid-refractory hypophysitis.

SURGICAL MANAGEMENT OF HYPOPHYSITIS

- Indications
  - Uncertain diagnosis requiring tissue confirmation. (Non-resection biopsy)
  - Rapid progression of neurological symptoms (e.g., visual impairment, headaches).
  - Large space-occupying lesions accessible via transsphenoidal approach.
- Advantages
  - Provides conclusive histopathological diagnosis.
  - Definitively reduces mass effects from autoimmune hypophysitis (AHy).
  - Particularly beneficial in certain forms of primary hypophysitis (PHy), such as granulomatous hypophysitis (GHy).

STEREOTACTIC RADIOTHERAPY IN HYPOPHYSITIS

- Indication: Considered in cases refractory to both medical and surgical treatments.
- Role: Serves as a last-line therapeutic option when conventional approaches fail.
- Longtime efficacy and consequences unknown

PROGNOSIS OF HYPOPHYSITIS

- Natural Course
  - Can be self-limiting with spontaneous remissions.
    - Spontaneous recovery of anterior pituitary function: up to 33%.
  - Long-term inflammation may cause fibrosis and pituitary shrinkage, leading to empty sella.
- Response to Therapy
  - Glucocorticoid therapy:
    - Improves mass effects and radiologic features in >75% of patients.
    - Similar improvement rates in anterior pituitary function.

- Hormonal axis recovery:
  - Cortisol and gonadotroph axes → more likely to improve.
  - Diabetes insipidus (DI) → rarely recovers, often refractory.

PROGNOSIS

- Outcomes
  - Relapse/recurrence: 38–46% of patients.
  - Disease progression: ~3%.
  - Mortality: 6–7%, mainly due to adrenal crisis.

TAKE HOME MESSAGES

- Diagnosis: Gold standard: histopathology.
- Often sufficient: MRI findings, pituitary hormone deficiencies (anterior pituitary, hyperprolactinemia, vasopressin deficiency), and clinical signs (headache, visual impairment).
- MRI Characteristics:
  - Moderate pituitary enlargement.
  - Homogeneous enhancement.
  - Suprasellar extension.
  - Thickened pituitary stalk.
  - Loss of posterior pituitary T1-weighted bright spot.
- Systemic Associations:
  - Can be the first sign of systemic diseases such as sarcoidosis, L-group histiocytosis, or IgG4-related disease.
  - Screening for systemic disease is essential at diagnosis and should be repeated over time.

TAKE HOME MESSAGES

- Anti-CTLA4 and anti-PD1–PDL1 therapies are immune checkpoint inhibitors that can cause hypophysitis. In patients receiving these treatments, pituitary function needs to be monitored regularly.
- Glucocorticoids are the therapy that has shown the most evidence of efficacy in hypophysitis.
  - Benefits: help prevent endocrine deterioration and relieve headaches.
  - Limitation: their impact on visual pathway compression remains uncertain.

THANK YOU FOR YOUR ATTENTION

TREATMENT

- In cases of severe headache and significant mass effect, high-dose GCs are first-line treatment.

- Sarcoidosis: Pituitary involvement occurs in <1 %
- hypophysitis may be its only presenting feature. In a series of hypothalamo-pituitary sarcoidosis, only 11/24 (46%) patients had a previous diagnosis of sarcoidosis
- Only one third of patients had an elevated serum ACE vs 71% controls without pituitary involvement
- Elevated enzyme in CSF is found in approximately 50% of cases
- Hypogonadism was the most frequent axis affected, and DI was present in half of cases.
- uitary MRI changes include a hypothalamic-pituitary or stalk thickening in almost all cases, which regress upon GC treatment.

- Granulomatosis with polyangiitis hypophysitis is rare (< 1%) and is usually found in association with multisystem disease (ear, nose, and throat disease and lung, as well as kidney, skin, eyes, and arthralgias)
- young females, and DI is almost universally present
- Pituitary tuberculoma,
- Usually in patients originating from endemic regions
- n afebrile patient with headaches, visual impairment, and hypopituitarism with DI
- PCR for mycobacterium on CSF can confirm diagnosis
- treated with a combination of antituberculous medications

HISTIOCYTOSIS

- Histiocytosis is a spectrum of disease originating from abnormal Langerhans cells (dendritic or antigen-presenting cells) and includes LCH and Erdheim-Chester disease (ECD)
- n both conditions, infiltration preferentially affects neurohypophysis, with DI the most common presenting feature,
- most often encountered in children
- Systemic manifestations in LCH and ECD mainly affect dermatological and skeletal systems. In LCH adults, 50% of patients will show lytic bony lesions (with skull, pelvis, and femur most affected), but most are asymptomatic (60,79-82). In ECD, bone involvement usually presents as osteosclerotic painful lesions affecting the lower limbs

- DI and growth hormone abnormalities are the most common (15%-50%) followed by hypogonadism (34%)
- Treatment modalities include surgery, GCs, immunosuppressive agents, chemotherapy, radiotherapy and targeted agents (BRAF inhibitors, MEK inhibitors)

IGG4-RELATED HYPOPHYSITIS (IGG4HY)

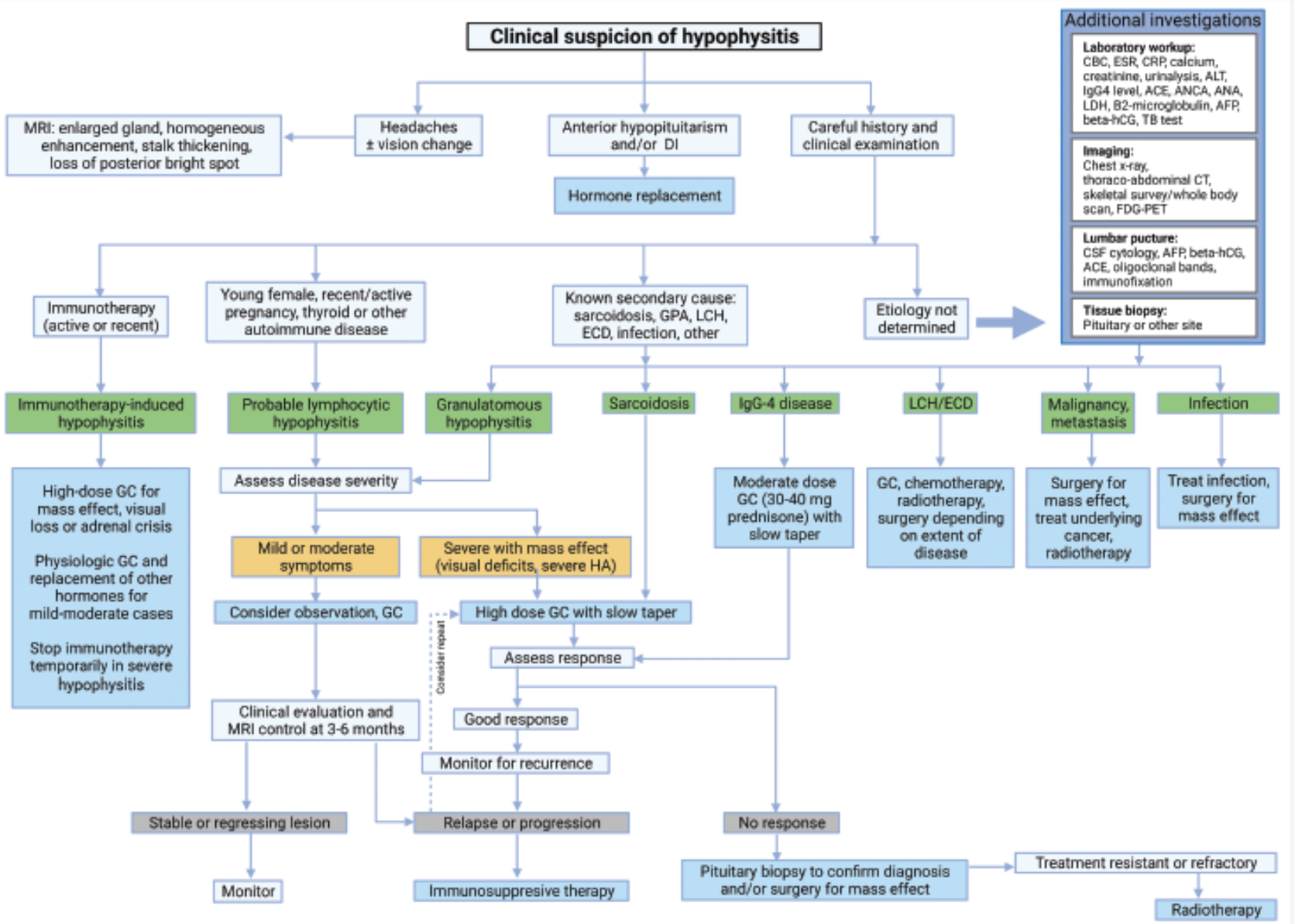
- isolated pituitary lesion (sometimes classified as primary hypophysitis) or a multisystemic disease
- female: male = 1:3- Unlike other forms of Phy
- Isolated form: female: male = 2:1
- the most frequent being retroperitoneal fibrosis, sclerosing sialadenitis, adenopathy, and pancreatitis but may also include lung interstitial infiltration, pericardial and vascular fibrosis, nephritis, or Riedel thyroiditis
- Mean age at diagnosis is 55 to 65 years old
- FDG-PET scanning may reveal multisystemic hyperfunctional lesions
- Diagnosis is established based on the previously described histologic criteria or on compatible MRI findings combined with
  - (1) other tissue biopsy proven disease or
  - (2) elevated IgG4 levels >140 mg/dL and a good response to GC treatment

- In more than half of patients both pituitary and stalk are enlarged on imaging. Notably, 15% to 25% of patients will have normal IgG4 serum levels, mostly women. Also isolated form is more prevalent in female.
- Response to supraphysiological GC doses is universal and prevents fibrosis
- Relapses are infrequent, and rituximab might be a good alternative

PARANEOPLASTIC PITUITARY AUTOIMMUNITY

- Tumors that express Pit-1 or proopiomelanocortin/ACTH may lead to production of anti-Pit-1 and anti-ACTH antibodies
- Pit-1 is a transcription factor implicated in the differentiation of anterior pituitary cells, namely somatotrophs, lactotrophs, and thyrotrophs.
- Interestingly, Pit-1 hypophysitis has been observed mostly in patients with thymomas and other malignancies such as lymphoma and isolated ACTH deficiency in gastric cancer, lymphoma, and ACTH-expressing large cell neuroendocrine carcinoma
- Hypopituitarism is irreversible, and treatment relies on management of the underlying cancer and hormonal replacement

- Interestingly, Pit-1 hypophysitis has been observed mostly in patients with thymomas and other malignancies such as lymphoma and isolated ACTH deficiency in gastric cancer, lymphoma, and ACTH-expressing large cell neuroendocrine carcinoma.
- Clinical presentation is a hormonal deficiency, without headache, and may precede a diagnosis of underlying cancer for a few years
- Imaging is often unremarkable or reveals mild pituitary atrophy or heterogeneous gland enhancement


Clinical suspicion of hypophysitis
Additional investigations
Laboratory workup: CBC, ESR, CRP, calcium, creatinine, urinalysis, ALT, IgG4 level, ACE, ANCA, ANA, LDH, B2-microglobulin, AFP, beta-hCG, TB test
Imaging: Chest x-ray, thoraco-abdominal CT, skeletal survey/whole body scan, FDG-PET
Lumbar pucture: CSF cytology, AFP, beta-hCG, ACE, oligoclonal bands, immunofixation
Tissue biopsy: Pituitary or other site
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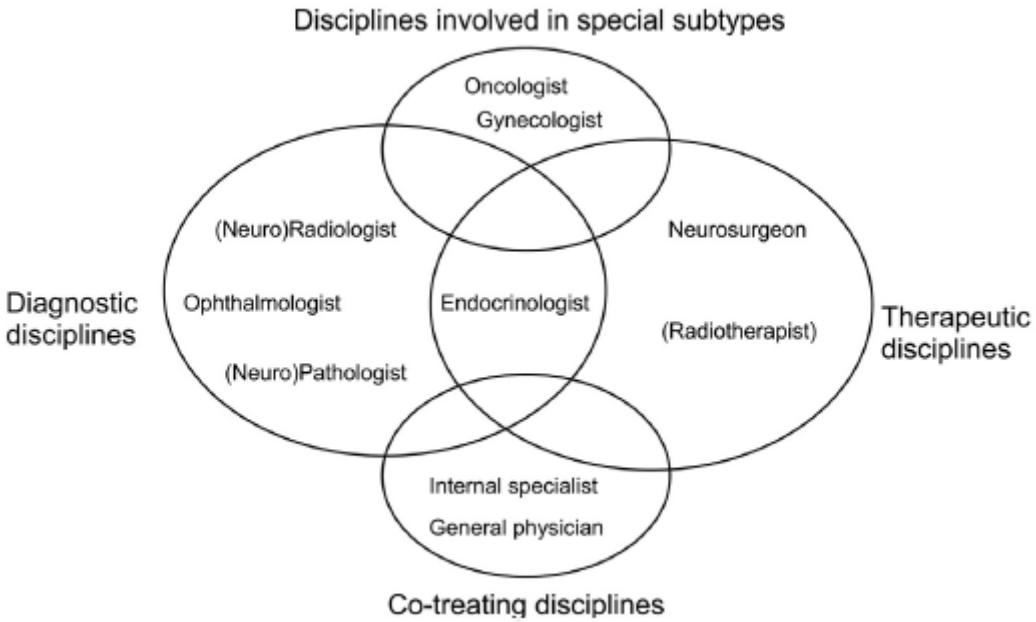
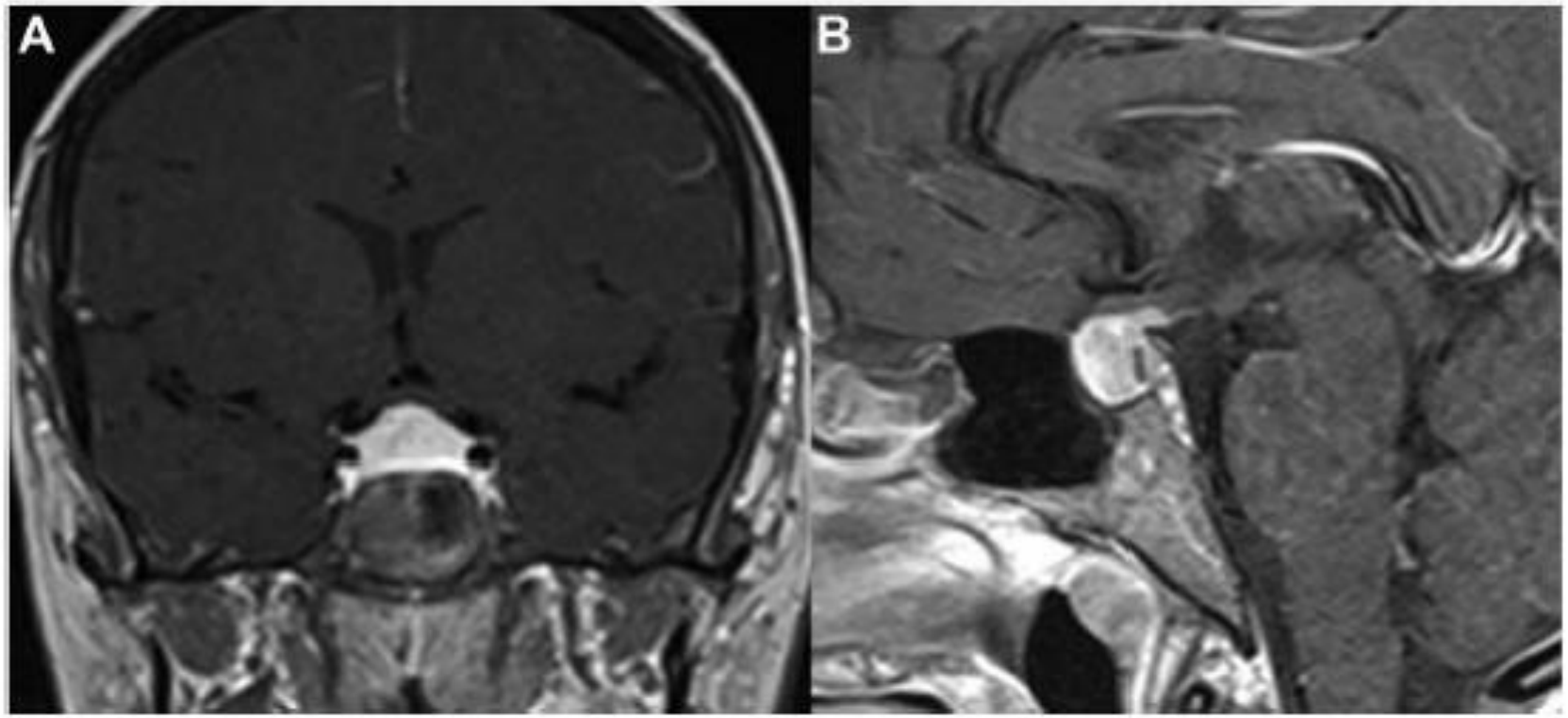
Etiology not determined
Immunotherapy-induced hypophysitis
Probable lymphocytic hypophysitis
Granulatomous hypophysitis
Sarcoidosis
IgG-4 disease
LCH/ECD
Malignancy, metastasis
Infection
High-dose GC for mass effect, visual loss or adrenal crisis
Physiologic GC and replacement of other hormones for mild-moderate cases
Stop immunotherapy temporarily in severe hypophysitis
Assess disease severity
Moderate dose GC (30-40 mg prednisone) with slow taper
GC, chemotherapy, radiotherapy, surgery depending on extent of disease
Surgery for mass effect, treat underlying cancer, radiotherapy
Treat infection, surgery for mass effect
Mild or moderate symptoms
Severe with mass effect (visual deficits, severe HA)
Consider observation, GC
High dose GC with slow taper
Consider repeat
Assess response
Clinical evaluation and MRI control at 3-6 months
Good response
Monitor for recurrence
Stable or regressing lesion
Relapse or progression
No response
Monitor
Immunosuppresive therapy
Pituitary biopsy to confirm diagnosis and/or surgery for mass effect
Treatment resistant or refractory
Radiotherapy

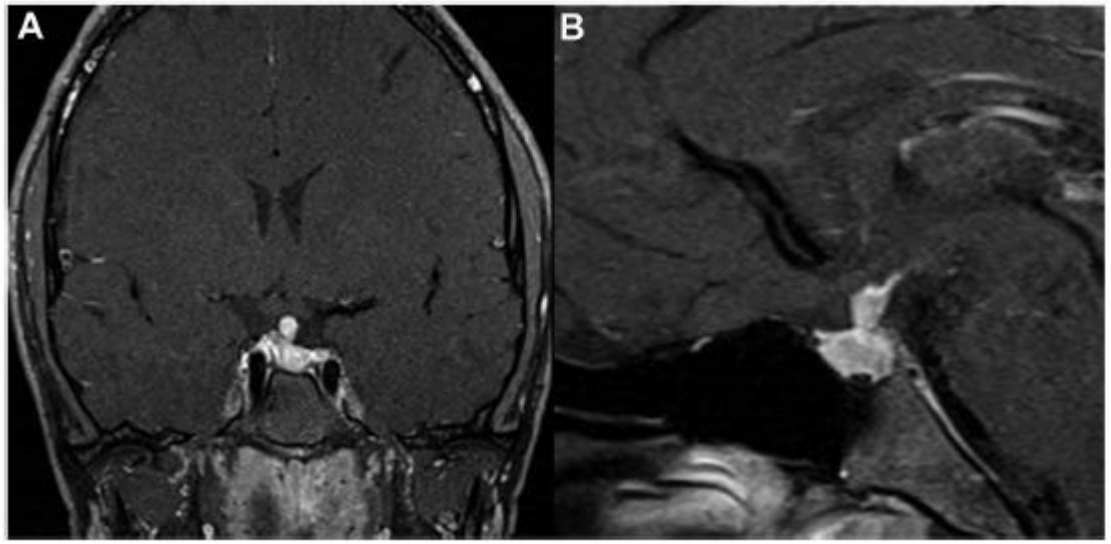
MULTIDISCIPLINARY TEAM CONCEPT: INVOLVED SPECIALTIES IN THE MANAGEMENT OF PATIENTS WITH HYPOPHYSITIS



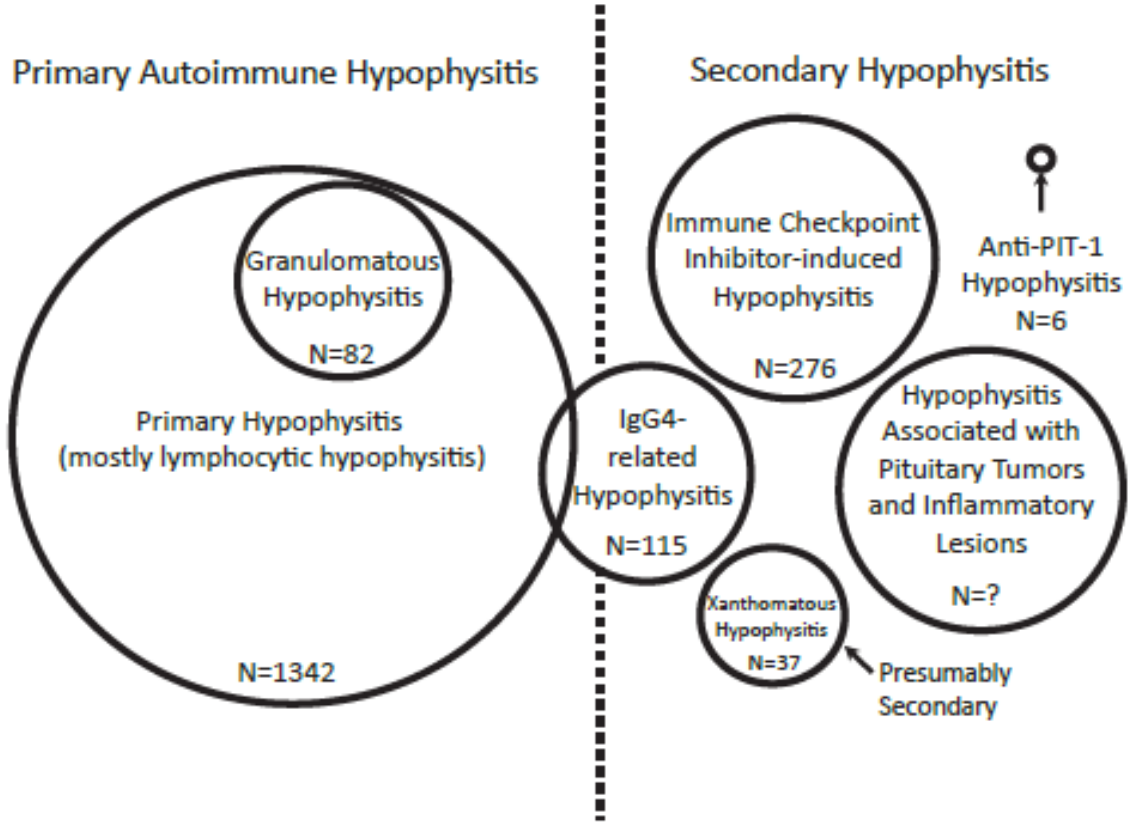


Typical appearance of adenohypophysitis on magnetic resonance imaging in a postpartum 34-year-old woman who presented with headache, malaise, and failure to lactate. T1-weighted magnetic resonance imaging with contrast. A, Coronal view. B, Sagittal view.

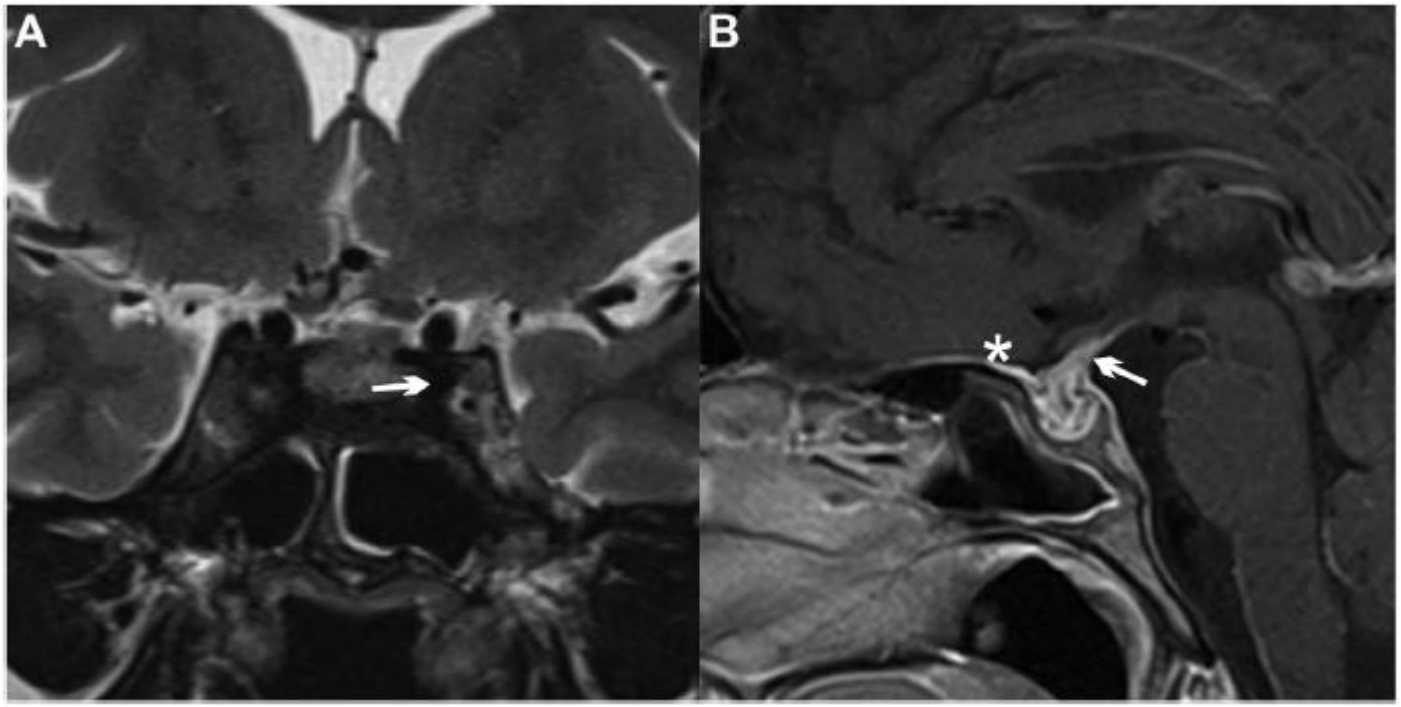
TYPICAL MAGNETIC RESONANCE IMAGING APPEARANCE OF INFUNDIBULONEUROHYPOPHYSITIS IN A 20-YEAR-OLD MAN WITH POLYURIA AND POLYDIPSIA CAUSED BY DIABETES INSIPIDUS. T1-WEIGHTED MAGNETIC RESONANCE IMAGING WITH CONTRAST. A, CORONAL VIEW. B, SAGITTAL VIEW.



SUBTYPES OF HYPOPHYSITIS (PRIMARY HYPOPHYSITIS, GRANULOMATOUS HYPOPHYSITIS, IGG4-RELATED HYPOPHYSITIS, IMMUNE CHECKPOINT INHIBITOREINDUCED HYPOPHYSITIS, XANTHOMATOUS HYPOPHYSITIS



MAGNETIC RESONANCE IMAGING OF A 28-YEAR-OLD WOMAN WHO PRESENTED WITH VISUAL IMPAIRMENT AND ANTERIOR PITUITARY HORMONE DEFICITS. A, THE T2-WEIGHTED CORONAL VIEW SHOWS THE DARK SIGN (ARROW) THAT SURROUNDS THE PITUITARY GLAND. IT INDICATES HYPOPHYSITIS WITH INVOLVEMENT OF THE CAVERNOUS SINUS. B, THE POSTCONTRAST T1-WEIGHTED SAGITTAL VIEW SHOWS THE THICKENED PITUITARY STALK (ARROW) AND DURAL ENHANCEMENT AT THE ADJACENT SKULL BASE (ASTERISK).



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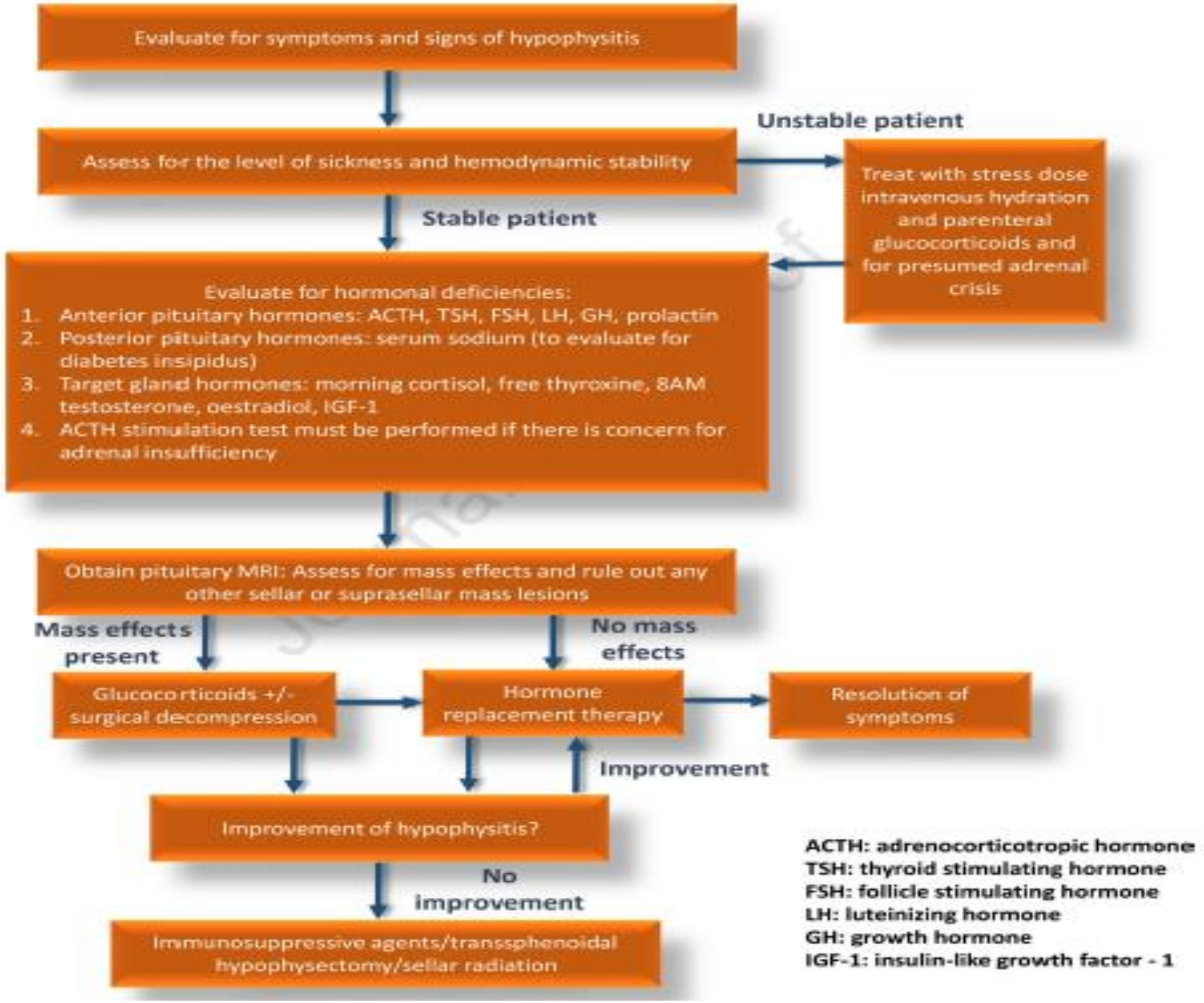
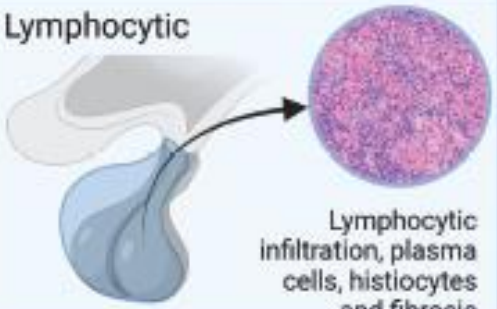
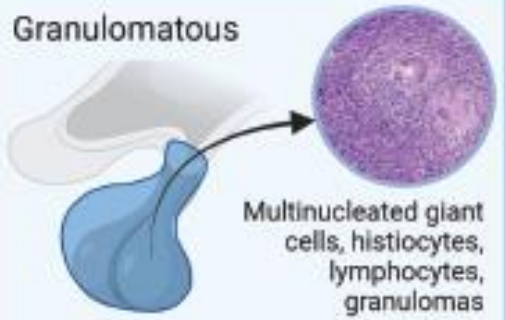
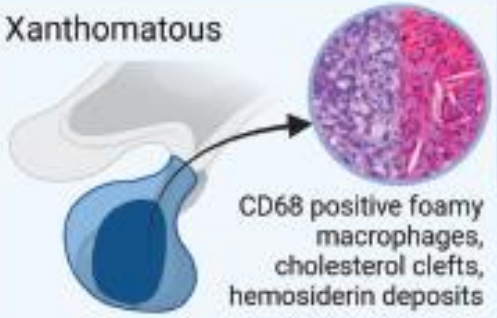
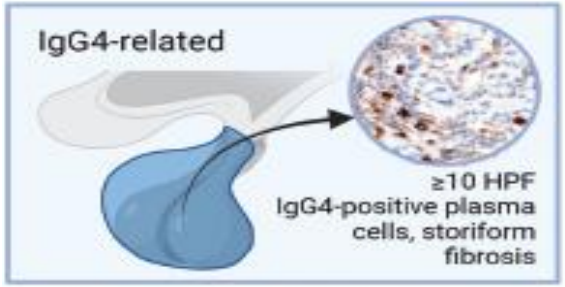
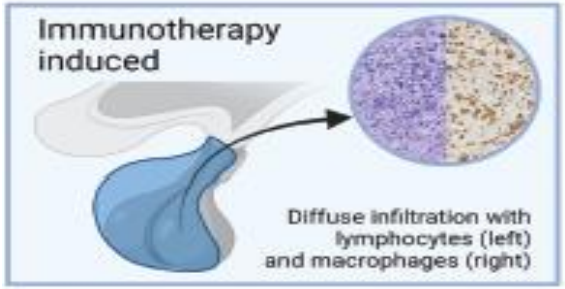


Hypophysitis type	Etiology, demographics	Clinical presentation	Treatment, outcome
Lymphocytic  Lymphocytic infiltration, plasma cells, histiocytes and fibrosis	Primary: F > M; F: 3rd decade, pregnancy and peripartum; M: 4th decade; co-existing autoimmunity Secondary: Found in sellar and suprasellar lesions (adenoma, craniopharyngioma, cyst, germinoma, lymphoma, *etc.*)	Deficiencies: Anterior hypopitutarism; DI is less frequent MRI: Enlarged homogeneously enhancing gland; stalk thickening. Empty sella in later stages Autoimmunity: thyroid disease, type 1 DM, celiac disease, connective tissue disorders, autoimmune GI disorders	Observation in mild-moderate cases GC in moderate-severe cases Immunosuppressants, surgery, radiation in GC-resistant cases Outcome is usually favorable
Granulomatous  Multinucleated giant cells, histiocytes, lymphocytes, granulomas	Primary: Idiopathic F > M, 5th decade Secondary: Isolated or part of systemic disease, *e.g.* sarcoidosis, GPA, tuberculosis, LCH/ECD	Deficiencies: Anterior hypopituitarism, frequent DI. More severe than lymphocytic type, frequent headache MRI: Enlarged gland; stalk thickening	GC less effective for idiopathic granulomatous hypophysitis Immunosuppressants, surgery, radiation for GC-resistant, LCH Chemotherapy (LCH, ECD) Outcome variable
Xanthomatous  CD68 positive foamy macrophages, cholesterol clefts, hemosiderin deposits	F > M, 4th decade Secondary to local processes; hemorrhage/rupture of Rathke cleft cyst, craniopharyngioma; also seen in systemic autoimmune disorders	Deficiencies: Anterior hypopituitarism, DI Frequent headache MRI: Cystic mass	Surgery is usually necessary Limited reponse to GC Outcome variable; complete recovery has been described

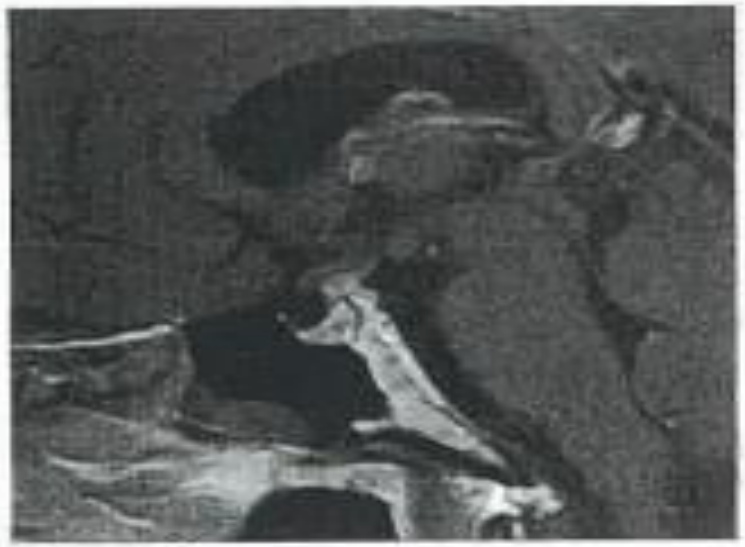
Necrotizing  Extensive necrosis, lymphocytes, plasmacytes, few eosinophils	Very rare, few cases described F > M, 2nd–4th decade Etiology unknown; possibly autoimmune	Deficiencies: Anterior hypopituitarism, DI MRI: Enlarged gland; stalk thickening; poor contrast enhancement; apoplexy-like appearance	Surgery for mass effect Role of GC and immunosuppressants unknown Pituitary deficiencies usually persist
IgG4-related  ≥10 HPF IgG4-positive plasma cells, storiform fibrosis	M > F, 5th–7th decade Secondary to IgG4 related disease but can be isolated	Deficiencies: Anterior hypopituitarism; DI very common MRI: Enlarged gland; stalk thickening Systemic IgG4 disease: retroperitonal fibrosis, pancreatitis, sialadenitis, polyadenopathy, Riedel thyroiditis; IgG4 levels variable	GC – usually excellent radiographic response to supraphysiologic doses Hypopituitarism may be permanent
Immunotherapy induced  Diffuse infiltration with lymphocytes (left) and macrophages (right)	M > F, 6th decade Ipilimumab: 8–10% (up to 17%) Tremelimumab: 0–2.6% Nivolumab: 0–3% Pembrolizumab: 0–5% Nivolumab + Ipilimumab: 8–13%	Deficiencies: Anterior hypopituitarism with predominant AI; rarely DI MRI: Enlarged gland (usually mild/moderate); stalk thickening	Replacement dose GC in mild-moderate cases High-dose GC and withdraw immunotherapy temporarily in severe cases Radiographic outcome favorable; pituitary deficiencies usually persistent
Other autoimmune  Pathiology not well described; lymphocytic infiltration	Anti-PIT-1 hypophysitis – associated with thymoma Anti-POMC or anti-ACTH – associated with APS, ectopic POMC and ACTH expressing NETs Antibodies against pituitary cells have been implicated	Deficiencies: Anti-PIT-1 hypophysitis – GH, PRL, and TSH deficiency Anti-POMC or Anti-ACTH: Isolated ACTH deficiency Other isolated deficiencies MRI: usually normal or atrophic gland	Role of GC is unkown Treat underlying condition Pituitary deficiencies persist

89 A 36-year-old man seeks evaluation for a 2-month history of increasing tiredness, excessive thirst, and polyuria. He has also noticed intermittent back pain and some shortness of breath when exercising. He has no relevant medical history. He drinks 10 units of alcohol per week and has a 20 pack-year cigarette smoking history.

On physical examination, his height is 74 in (188 cm) and weight is 190 lb (86.4 kg) (BMI = 24 kg/m^2). His resting pulse rate is 68 beats/min and regular, and blood pressure is 125/80 mm Hg. He has no clinical stigmata of endocrine dysfunction. There is mild tenderness over the midthoracic vertebrae, but the rest of the physical examination findings are normal.

Laboratory test results:

Fasting plasma glucose = 75 mg/dL (70-99 mg/dL) (SI: 4.2 mmol/L [3.9-5.5 mmol/L])
Serum calcium = 8.8 mg/dL (8.2-10.2 mg/dL) (SI: 2.2 mmol/L [2.1-2.6 mmol/L])
Serum sodium = 142 mEq/L (136-142 mEq/L) (SI: 142 mmol/L [136-142 mmol/L])
Serum potassium = 3.9 mEq/L (3.5-5.0 mEq/L) (SI: 3.9 mmol/L [3.5-5.0 mmol/L])
Serum creatinine = 1.2 mg/dL (0.7-1.3 mg/dL) (SI: 106.1 µmol/L [61.9-114.9 µmol/L])
TSH = 0.9 mIU/L (0.5-5.0 mIU/L)
Free T_4 = 1.2 ng/dL (0.8-1.8 ng/dL) (SI: 15.44 pmol/L [10.30-23.17 pmol/L])
Cortisol (8 AM) = 13.5 µg/dL (5-25 µg/dL) (SI: 372.4 nmol/L [137.9-689.7 nmol/L])
Prolactin = 34 ng/mL (4-30 ng/mL) (SI: 1.48 nmol/L [0.17-1.30 nmol/L])
FSH = 2.7 mIU/mL (1.0-13.0 mIU/mL) (SI: 2.7 IU/L [1.0-13.0 IU/L])
LH = 2.5 mIU/mL (1.0-9.0 mIU/mL) (SI: 2.5 IU/L [1.0-9.0 IU/L])
Total testosterone = 330 ng/dL (300-900 ng/dL) (SI: 11.5 nmol/L [10.4-31.2 nmol/L])



Water-deprivation test:

Time	Urine osmolality
0 h	123 mOsm/kg
8 h	147 mOsm/kg
After desmopressin (2 mcg intramuscular)	685 mOsm/kg

MRI of the sella (sagittal T1 contrast) is shown (*see image*).

CT of the chest shows bilateral upper and middle zone micronodular and cystic infiltrates. Radionuclide bone scan shows increased focal tracer uptake in several vertebrae.

Which of the following is the most likely unifying diagnosis?

A. Hodgkin lymphoma
B. Langerhans cell histiocytosis
C. Lymphangitis carcinomatosis
D. Sarcoidosis
E. Tuberculosis

69 A 66-year-old man is referred for evaluation of secondary hypogonadism. Over the past few months, he has experienced headaches, tiredness, and 10-lb (4.5-kg) weight loss. He has noticed reduced libido, erectile dysfunction, and reduced appetite. He has no history of polyuria or polydipsia, tingling, or paresthesia. His primary care physician has documented a low serum testosterone concentration and inappropriately normal gonadotropin levels:

Total testosterone = 50 ng/dL (300-900 ng/dL) (SI: 1.7 nmol/L [10.4-31.2 nmol/L])
LH = 2.5 mIU/L (1.0-9.0 mIU/mL) (SI: 2.5 IU/L [1.0-9.0 IU/L])
FSH = 3.2 mIU/mL (1.0-13.0 mIU/mL) (SI: 3.2 IU/L [1.0-13.0 IU/L])

His medical history is remarkable for autoimmune pancreatitis, retroperitoneal fibrosis, and primary hypothyroidism. Findings on recent cardiac evaluation are normal, including those from echocardiography. Chest x-ray is normal. Current medications are levothyroxine, 125 mcg daily; atorvastatin, 10 mg daily; and pancreatic enzymes with meals.

On physical examination, he is a thin man in no acute distress. His blood pressure is 120/65 mm Hg, and pulse rate is 85 beats/min. His height is 64 in (162.6 cm), and weight is 148.5 lb (67.5 kg) (BMI = 26 kg/m^2). He has no jaundice or skin hyperpigmentation. His thyroid is diffusely enlarged and firm. Testes are soft and testicular volume is approximately 10 mL bilaterally.

Laboratory test results:

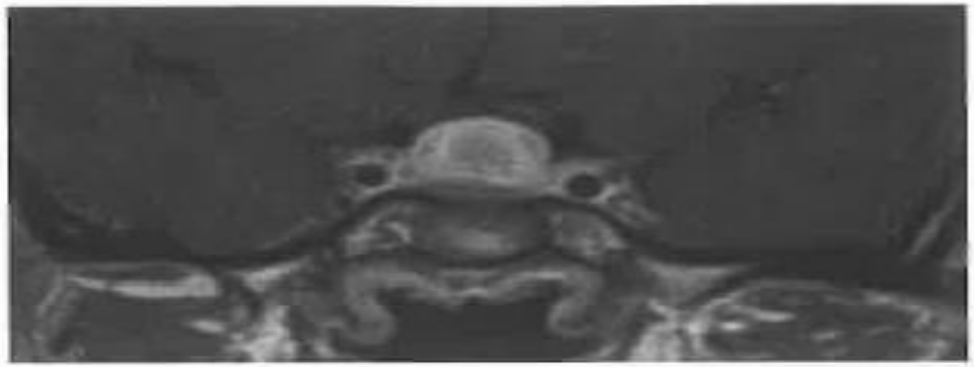
TSH = 0.3 mIU/L (0.5-5.0 mIU/L)

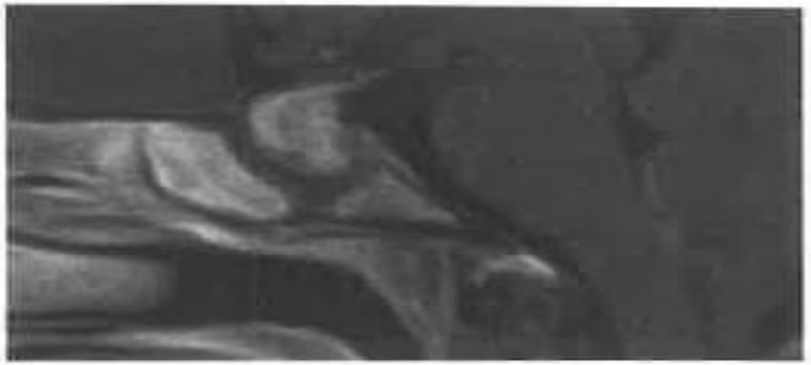
Free T_4 = 1.2 ng/dL (0.8-1.8 ng/dL) (SI: 15.4 pmol/L [10.30-23.17 pmol/L])

Cortisol (8 AM) = 5.2 µg/dL (5-25 µg/dL) (SI: 143.5 nmol/L [137.9-689.7 nmol/L])

ACTH (8 AM) = 9 pg/mL (10-60 pg/mL) (SI: 2.0 pmol/L [2.2-13.2 pmol/L])

A gadolinium-enhanced pituitary MRI is shown (see images).





Which of the following is this patient's most likely diagnosis?

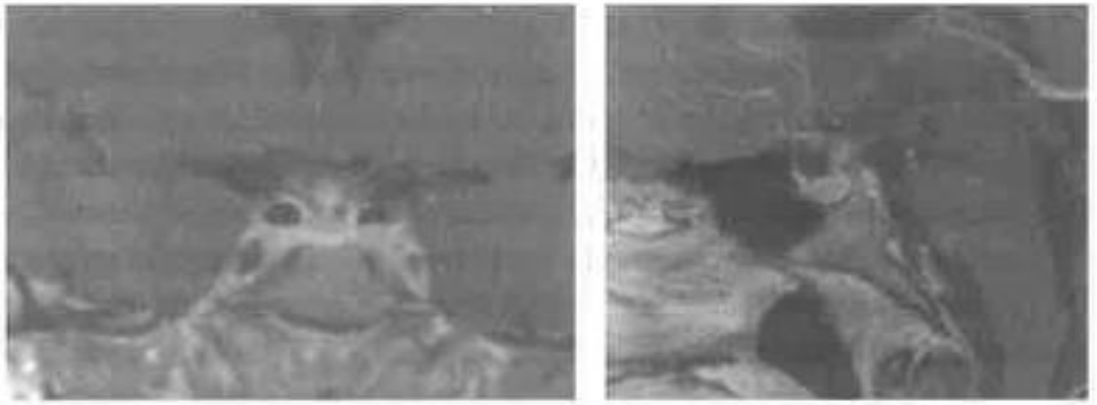
A. Pituitary amyloidosis
B. Pituitary sarcoidosis
C. IgG4-related hypophysitis
D. Granulomatous hypophysitis
E. Lymphocytic hypophysitis

116 A 22-year-old man is referred for evaluation of recently diagnosed diabetes insipidus. He first noticed polyuria and polydipsia about 3 months ago. His primary care physician ruled out diabetes mellitus and hypercalcemia and measured a 24-hour urine output of 13 L (urine was dilute). The patient responded well to desmopressin therapy (0.2 mg orally twice daily), with normalization of urination. His anterior pituitary function is normal, with the exception of central hypogonadism as demonstrated by the following laboratory test results:

Total testosterone = 137 ng/dL (300-900 ng/dL) (SI: 4.8 nmol/L [10.4-31.2 nmol/L])
LH = 2.5 mIU/mL (1.0-9.0 mIU/mL) (SI: 2.5 IU/L [1.0-9.0 IU/L])
FSH = 3.2 mIU/mL (1.0-13.0 mIU/mL) (SI: 3.2 IU/L [1.0-13.0 IU/L])

On physical examination, he is normally androgenized. He has a full beard. His blood pressure is 115/78 mm Hg, and pulse rate is 72 beats/min. His height is 67.5 in (171.5 cm), and weight is 195 lb (88.5 kg) (BMI = 30 kg/m^2). Examination findings are normal, with the exception of small, soft testes, about 8 mL in volume bilaterally.

A gadolinium-enhanced pituitary MRI is shown (*see images*).



Which of the following is the best next step in this patient's evaluation?

A. Pituitary stalk biopsy
B. PET-CT of the brain
C. Lumbar puncture
D. Skeletal survey
E. ^{68}Ga DOTATATE scan

ESAP 2022

38 A 58-year-old woman with a history of non–small cell lung cancer is undergoing treatment with the anti-PD-1 antibody nivolumab. The treatment course has been complicated by rash and colitis, but she has been able to continue therapy despite these adverse effects. After 1 year of therapy, she now describes tiredness, loss of appetite, and weight loss. Her free T_4 and TSH concentrations are normal, but she has a low morning cortisol concentration of 1.9 μg/dL (52.4 nmol/L) and an ACTH concentration less than 5 pg/mL (<1.1 pmol/L). Her oncologist has prescribed hydrocortisone, 15 mg in the morning and 5 mg in the afternoon, with almost immediate improvement of her symptoms and no negative effects. She feels well and has no headaches, tremors, insomnia, neck pain, polyuria, polydipsia, shortness of breath, or chest pain. Her physical examination findings are normal.

Which of the following is the most likely finding on pituitary-directed MRI?

A. Diffuse pituitary enlargement
B. Empty sella
C. Large pituitary mass suspicious for pituitary metastasis
D. Normal pituitary gland
E. Thickening of the pituitary stalk

103 A 23-year-old man with no notable medical history has been experiencing polydipsia and polyuria for the last 10 months. He reports waking every 1 to 2 hours at night to urinate and drink water. He

recently developed a feeling of fullness and ringing in the right ear. Review of systems is notable for fatigue and decreased libido.

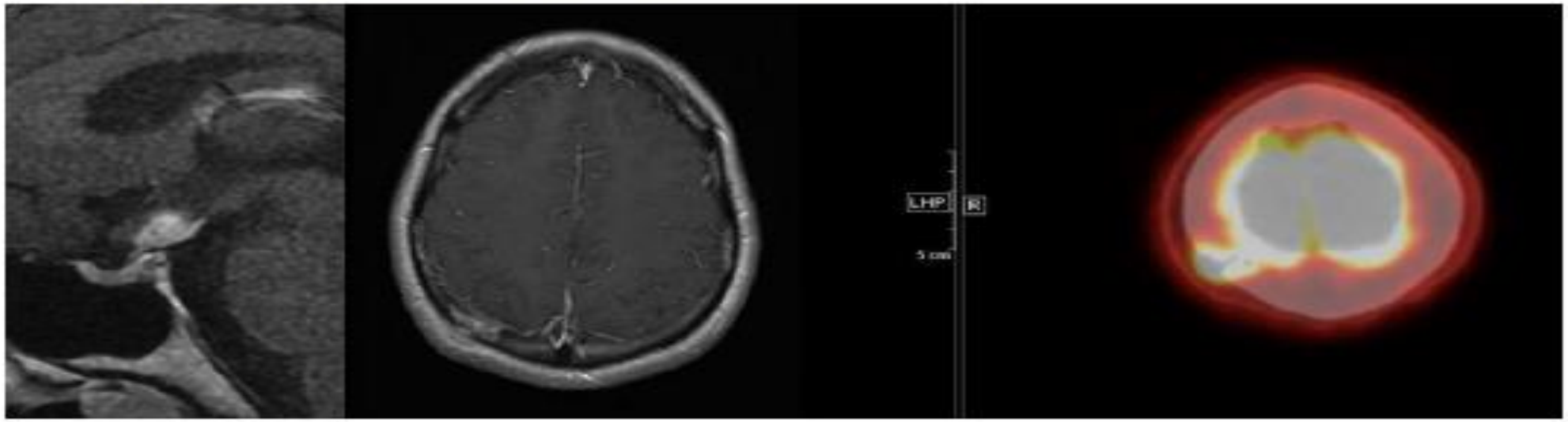
On physical examination, there is dullness of the eardrum to external light (absent light reflex), bulging of the right ear canal, and few small lymph nodes in the inguinal region. His temperature is 98.2°F (36.8°C), blood pressure is 126/82 mm Hg, and pulse rate is 71 beats/min. His height is 72 in (182.9 cm), and weight is 220.5 lb (100 kg) (BMI = 29.9 kg/m^2). He has noncentripetal fat distribution. Evaluation by an otolaryngologist identifies an ear canal lesion.

Laboratory test results:

Serum sodium = 141 mEq/L (136-142 mEq/L) (SI: 141 mmol/L [136-142 mmol/L])
Calcium = 10.2 mg/dL (8.2-10.2 mg/dL) (SI: 2.6 mmol/L [2.1-2.6 mmol/L])
Albumin = 4.2 g/dL (3.5-5.0 g/dL) (SI: 42 g/L [35-50 g/L])
Creatinine = 1.2 mg/dL (0.7-1.3 mg/dL) (SI: 106.1 µmol/L [61.9-114.9 µmol/L])
TSH = 1.17 mIU/L (0.5-0.5 mIU/L)
Free T_4 = 0.7 ng/dL (0.8-1.8 ng/dL) (SI: 9.0 pmol/L [10.30-23.17 pmol/L])
Testosterone = <10 ng/dL (300-900 ng/dL) (SI: <0.3 nmol/L [10.4-31.2 nmol/L])
LH = 1.0 mIU/mL (1.0-9.0 mIU/mL) (SI: 1.0 IU/L [1.0-9.0 IU/L])
FSH = 1.6 mIU/mL (1.0-13.0 mIU/mL) (SI: 1.6 IU/L [1.0-13.0 IU/L])
Prolactin = 17 ng/mL (4-23 ng/mL) (SI: 0.74 nmol/L [0.17-1.00 nmol/L])
Cortisol (8 AM) = 19 µg/dL (5-25 µg/dL) (SI: 524.2 nmol/L [137.9-689.7 nmol/L])
ACTH = 12 pg/mL (10-60 pg/mL) (SI: 2.6 pmol/L [2.2-13.2 pmol/L])
Serum osmolality = 287 mOsm/kg (275-295 mOsm/kg) (SI: 287 mmol/kg [275-295 mmol/kg])
Urine osmolality = 87 mOsm/kg (150-1150 mOsm/kg) (SI: 87 mmol/kg [150-1150 mmol/kg])
Complete blood cell count, normal

C-reactive protein, normal
ACE, normal
hCG, normal
α-Fetoprotein, normal
Urinalysis, low specific gravity

MRI of the pituitary gland and PET-CT are shown (*see images*).



Which of the following is the best next step in this patient's management?

A. Biopsy of the ear canal lesion
B. Cerebral spinal fluid analysis (cytology, flow cytometry, immunohistochemistry for ACE, human chorionic hCG, α-fetoprotein, and lactate dehydrogenase)
C. Prednisone, 60 mg daily, and MRI imaging in 3 months
D. Reduction of fluid intake and repeated urine osmolality measurement
E. Transsphenoidal biopsy of the hypothalamic lesion