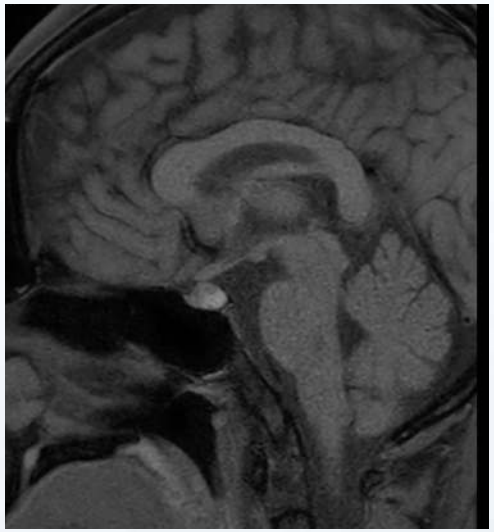
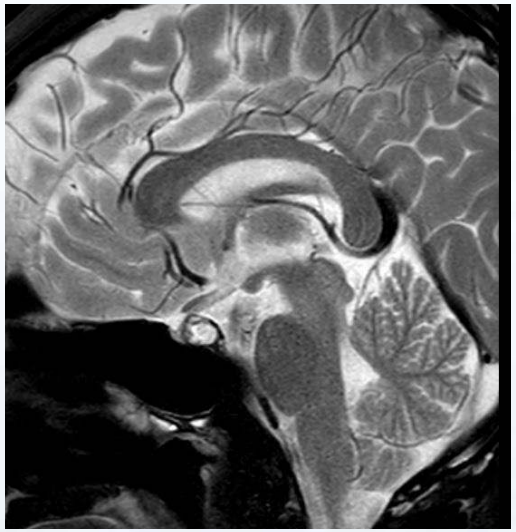
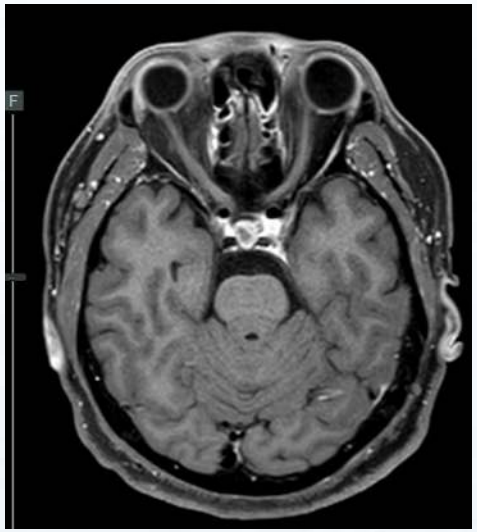
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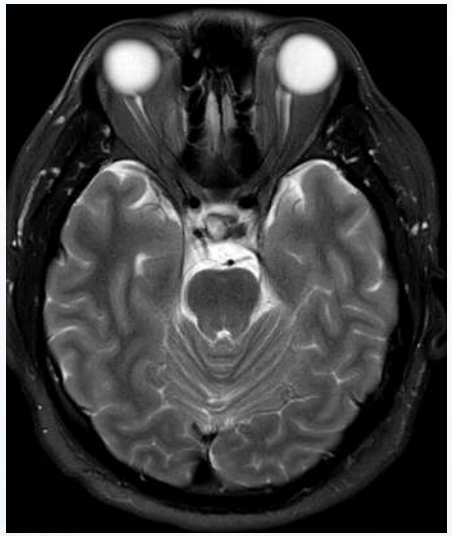
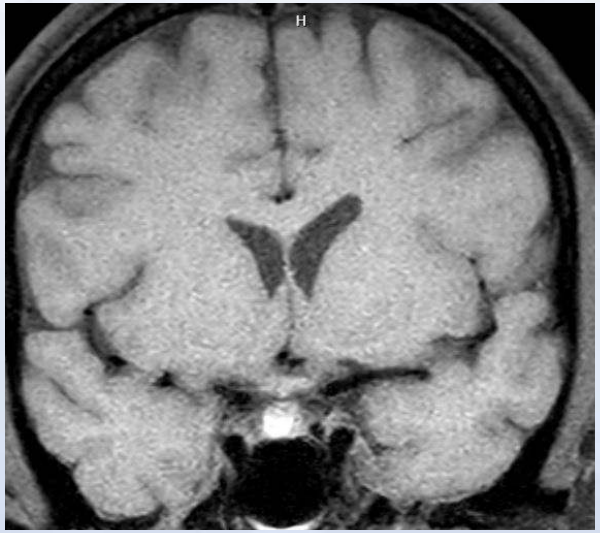
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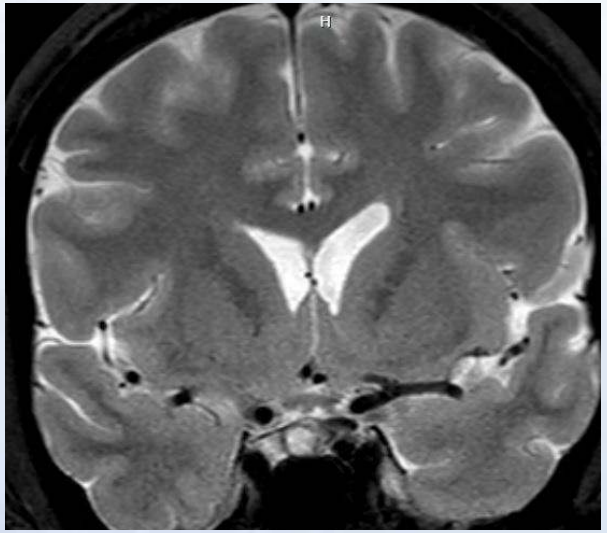
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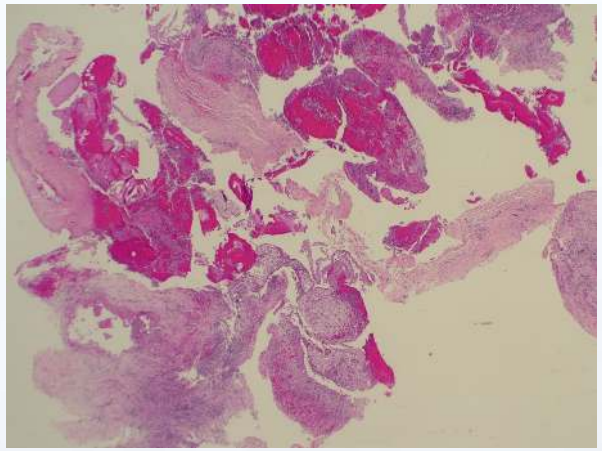
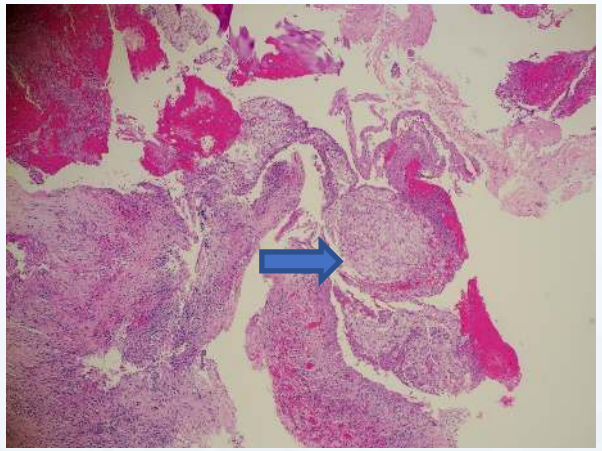
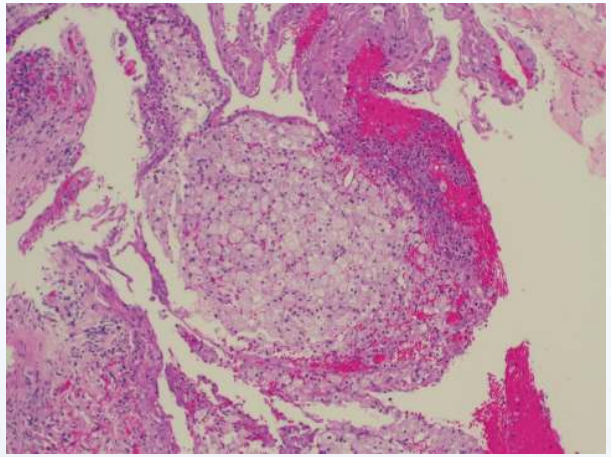
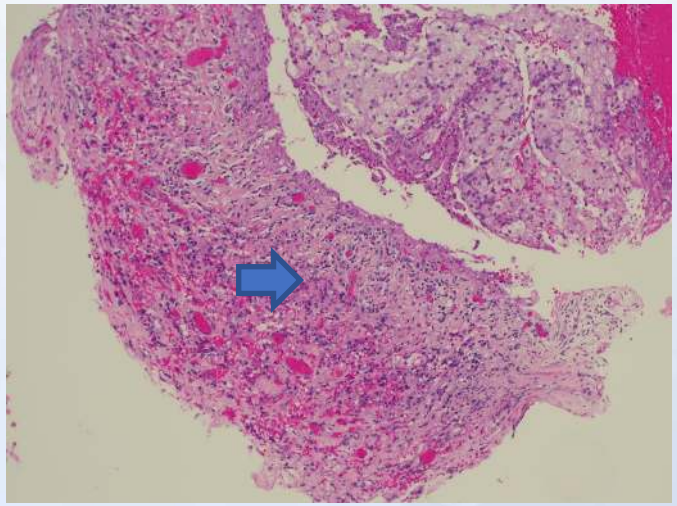


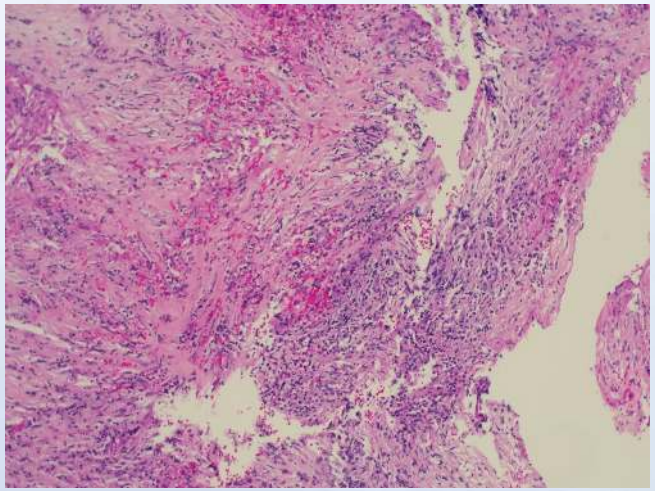


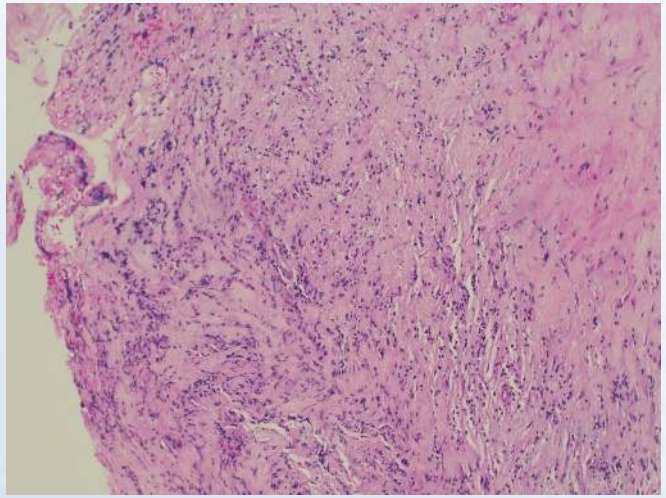


Foamy macrophages



Lymphocytes and plasma cells





fibrosis

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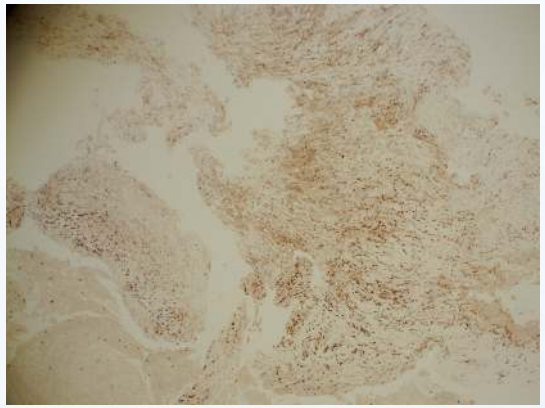
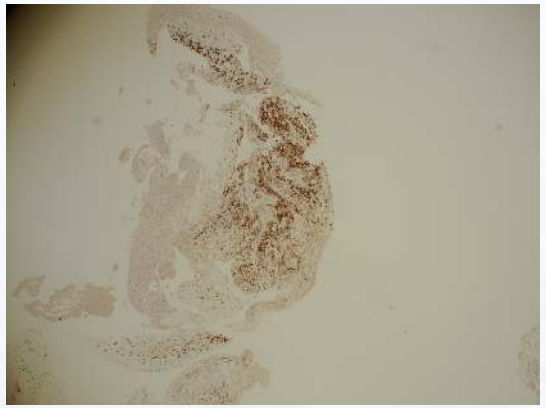
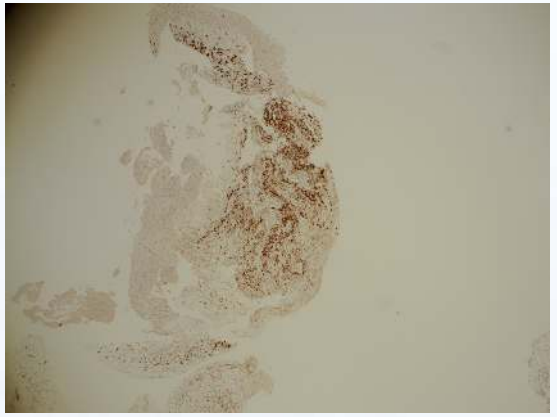
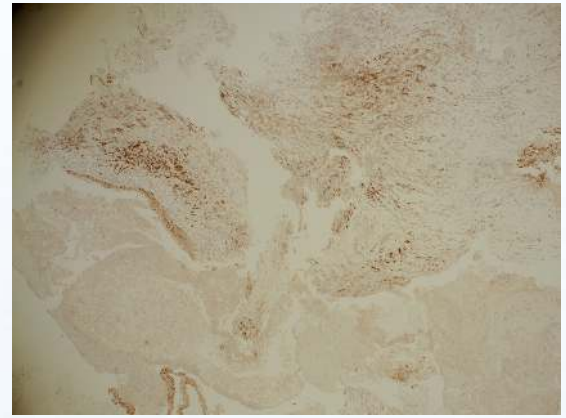



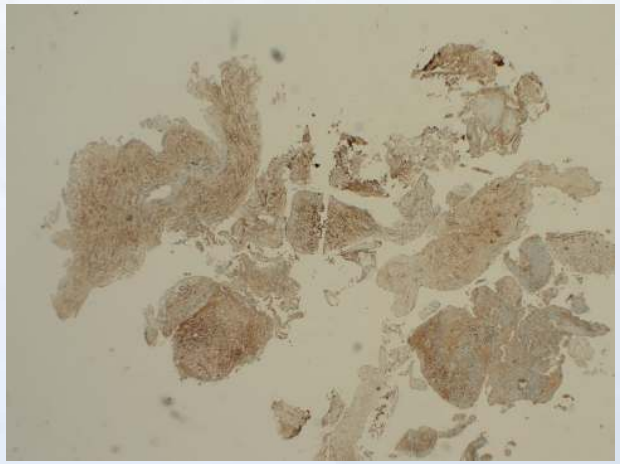
CD3



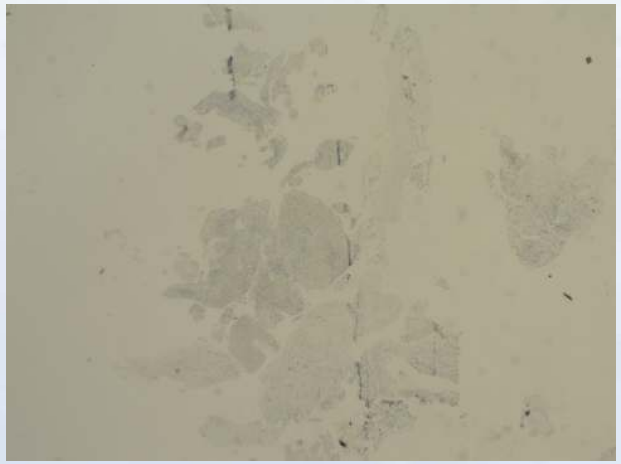
CD20



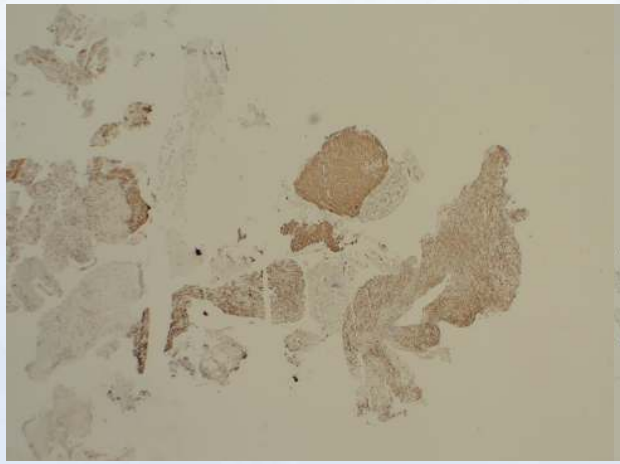
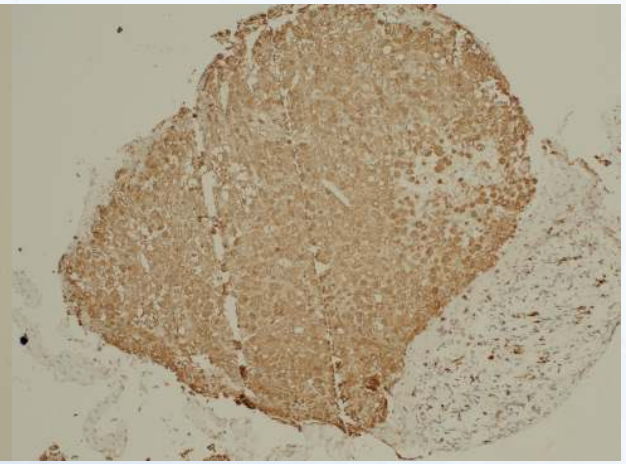
CD138



IgG



IgG4

CD68

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Pituitary tissue biopsy

- Chronic hypophysitis with clusters of foamy macrophages
- Negative for malignancy or pituitary tissue
- IHC reveals
  - CD3 : positive in small lymphocytes
  - CD20 : positive in small lymphocytes
  - CD138 : positive in few plasma cells
  - CD68 : positive in multiple or cluster of foamy macrophages
  - IgG : positive in few plasma cells
  - IgG4 : negative

From histomorphology and IHC panel,
xanthomatous hypophysitis is most likely

Diagnosis : Xanthomatous hypophysitis

Hypophysitis

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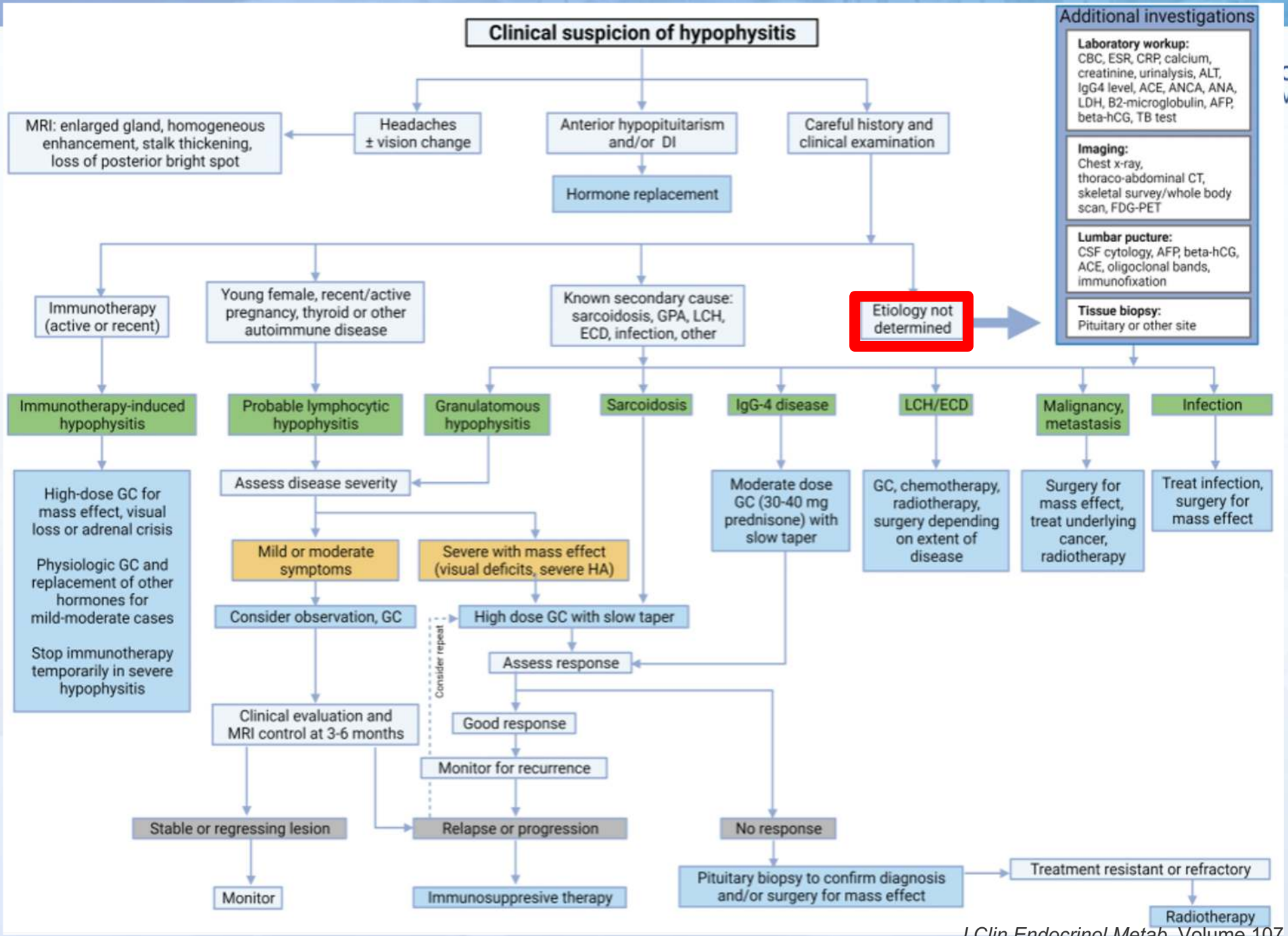
Primary (autoimmune or idiopathic)
Lymphocytic hypophysitis
Granulomatous hypophysitis
Xanthomatous hypophysitis
IgG-4 mediated (plasmacytic) hypophysitis
Necrotizing hypophysitis
Mixed forms (lymphogranulomatous; xanthogranulomatous)

Secondary	
AIH associated with other endocrinopathies	Autoimmune Polyglandular Syndrome, Autoimmune thyroid disease, Autoimmune adrenalitis, Type 1 diabetes mellitus
AIH associated with systemic diseases	Erdheim-Chester disease, Rheumatologic conditions (e.g.: sarcoidosis, Sjogren's,SLE), Vasculitides, Primary biliary cirrhosis, Atrophic gastritis, Optic neuritis, Myocarditis, IgG4-related disease, Langerhans cell histiocytosis, Rosai-Dorfman disease, Tolosa-Hunt syndrome, Cogan's syndrome, Thymoma (anti-Pit-1 antibody syndrome)
AIH secondary to Drugs	Immune checkpoint inhibitors, Interferon-α , Ribavirin, Ustekinumab
AIH secondary to sellar and/or suprasellar lesions	Germinoma, Rathke's cleft cyst, Craniopharyngioma, Pituitary adenoma, Pituitary apoplexy, Pituitary hyperplasia,Primary pituitary lymphoma, Gliomas, Meningiomas,Pituicytomas, Chordomas, Teratomas, Dermoids ,Epidermoids
AIH secondary to infections	Tuberculosis, Syphilis, Viruses, Parasites, Abscesses

Rev Endocr Metab Disord.(2018) 19:335–347



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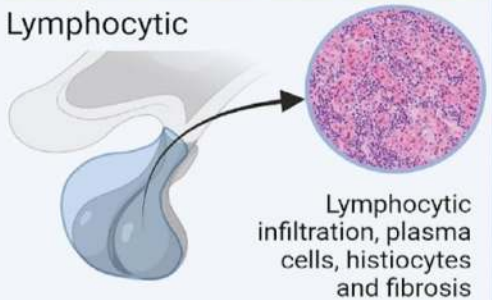
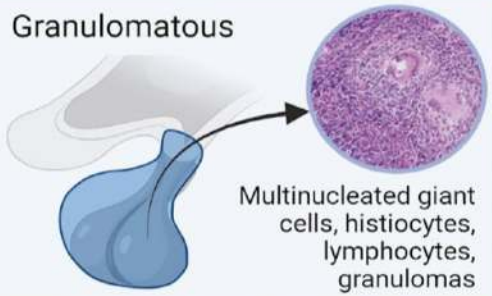
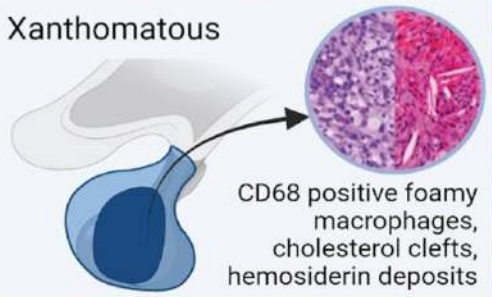
Summary of hypophysitis types, features and treatment options

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

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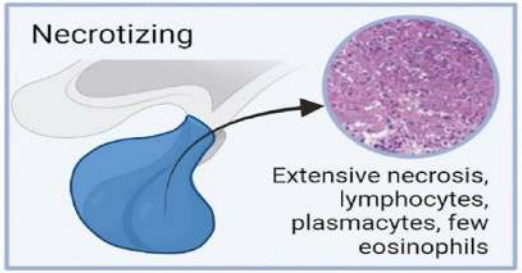
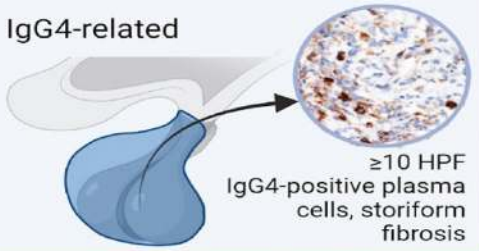
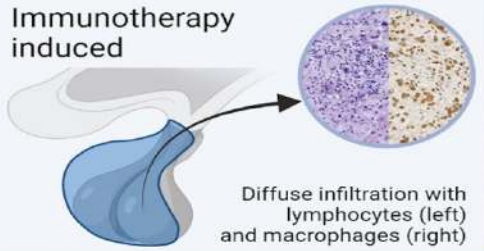
Summary of hypophysitis types, features and treatment options

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

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Xanthomatous hypophysitis

- The rarest subtype of primary hypophysitis
- Only 37 cases from 1998-2022

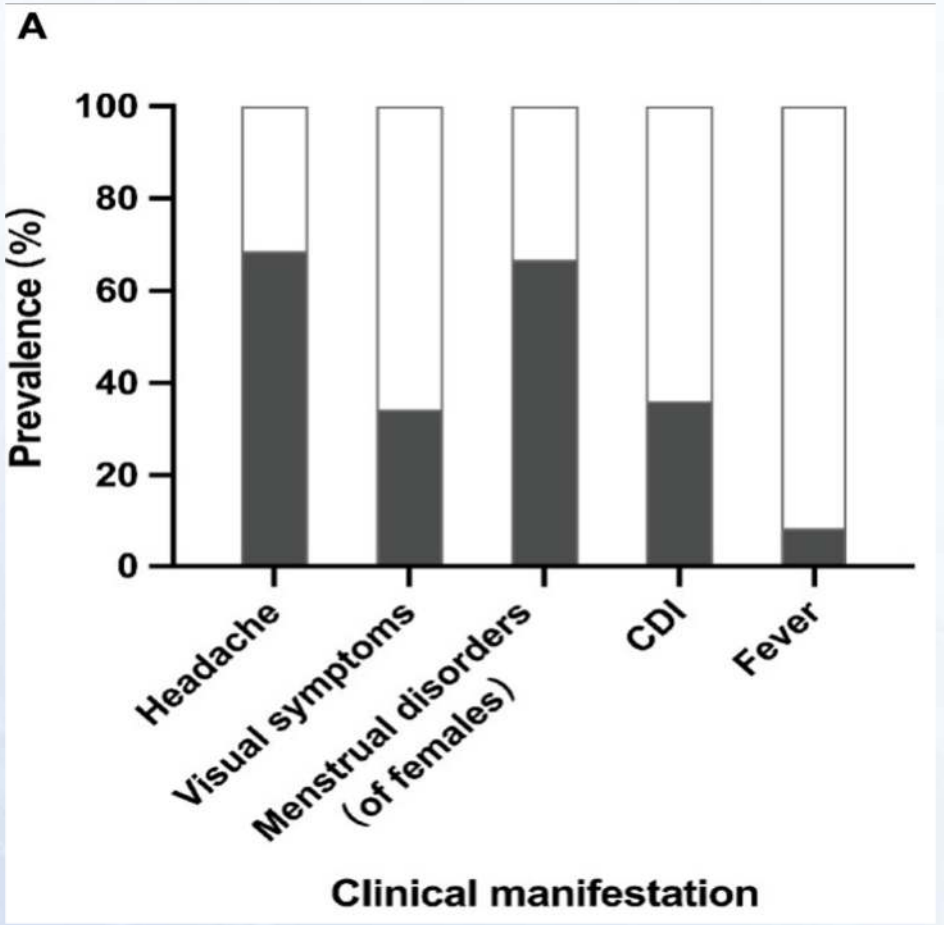
Characteristic

Age : mean 39.1 years (range 12-72 years)

Gender : 75% were female

Symptoms

- Headache 68.6%
- Visual impairment 34.3%
- DI 36.1%
- Menstrual disorder in female 66.7%
- Fever 8.3%



Front Endocrinol.(2021);12:735655

Xanthomatous hypophysitis

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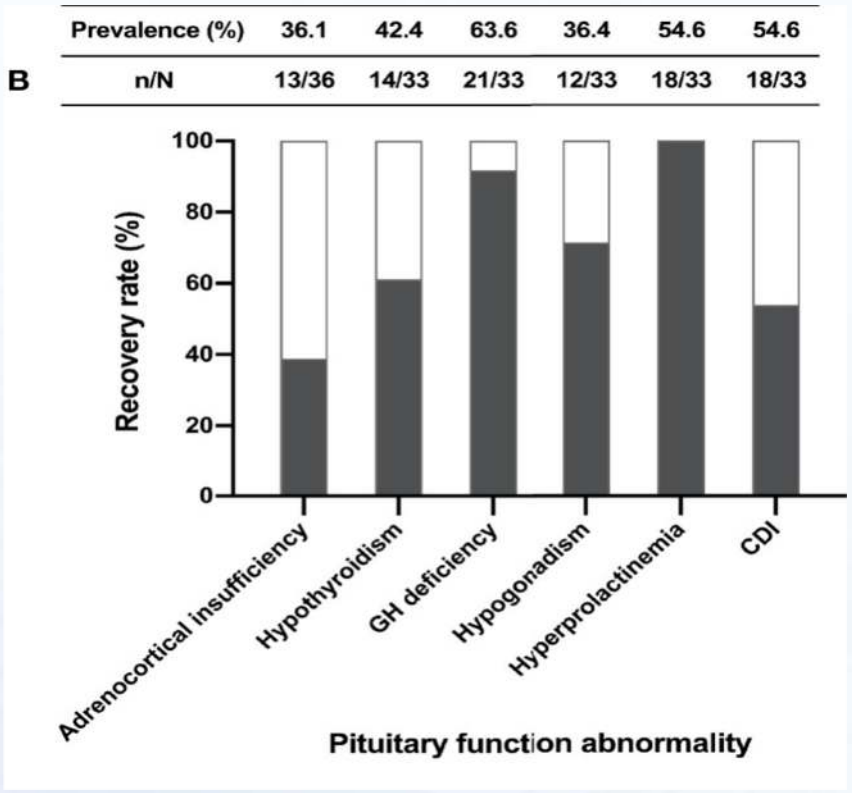
Pituitary hormone dysfunction

- Hypogonadotropic hypogonadism 63.6%
- Adrenocortical insufficiency 54.5%
- Central hypothyroidism 54.6%
- GH deficiency 63.6%
- Hyperprolactinemia 42.4%



MRI presentation

- Cystic mass with ring or peripheral enhancement
- Mean maximum diameter was 16.3 ± 4.8 mm.
- Pituitary stalk thickening : 50.0%

Gross presentation : cystic lesion with yellowish pus-like fluid
Pathological feature : foamy histiocyte infiltration, which can be marked by **CD68** glycoprotein on immunohistochemistry

Front Endocrinol.(2021);12:735655

Xanthomatous hypophysitis

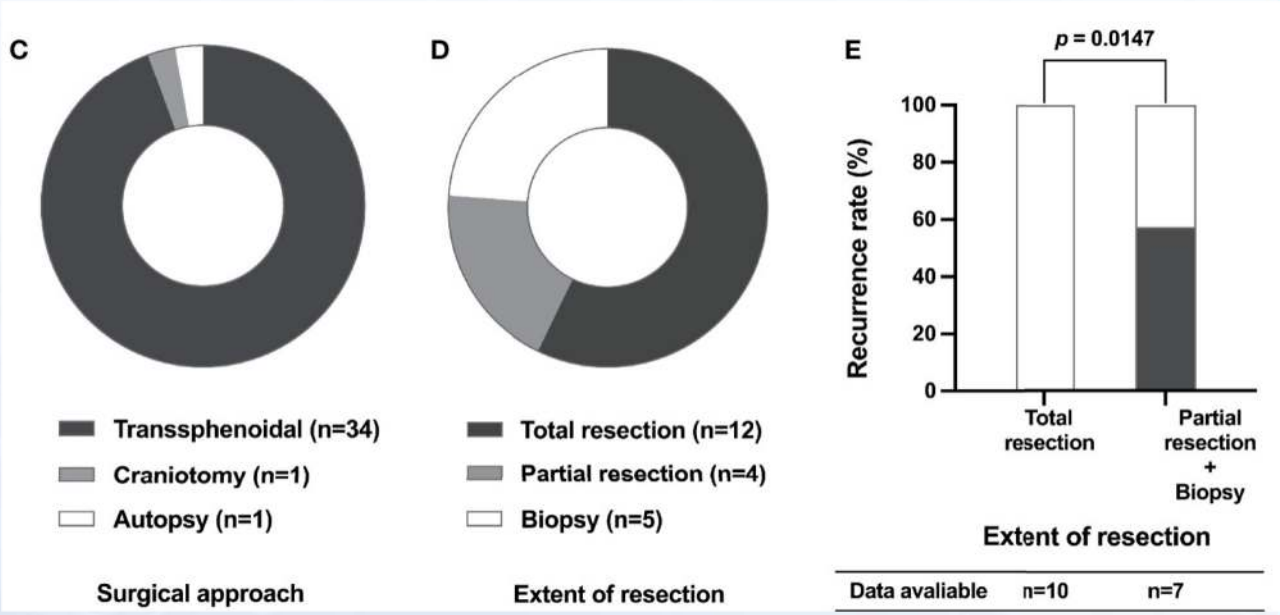
Treatment

- Lack of best evidence for treatment
  -- lack of follow up data
- Surgical resection should be considered, especially for patients suffering from mass effects and pituitary dysfunction

→ total mass resection is recommended

- Close follow-up and routine assessment of pituitary function

- Hormone replacement therapy



Front Endocrinol.(2021);12:735655

Summary

- Xanthomatous hypophysitis is a rare entity of primary hypophysitis. Less than 40 cases have been reported until now.
- Patients could present with both anterior and posterior pituitary hormone dysfunction.
- Not all hypophysitis patients have stalk thickening
- Pituitary biopsy is usually considered either when a diagnosis is unclear.
- The pathological results show a presence of foamy macrophages and positive CD68
- There is no therapeutic cure. The main management is hormone replacement.