It’s not a tumor!: Update on Hypophysitis

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Medical Director Pituitary Center
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‘...And there is nothing new under the sun.

Is there a thing of which it is said, “See, this is new”? It has been already in the ages before us.....’

Ecclesiastes 1
Case 1

“Rathke’s cyst or cystic adenoma”
Case 2

“pituitary macroadenoma measuring 12 mm AP by 19 mm transverse by 12 mm craniocaudal. The native pituitary gland is draped over the posterosuperior aspect of the mass, with posterior and mild rightward displacement of the infundibulum.”
Case 3

Sellar based mass, pituitary macroadenoma versus meningioma.
Case 4

“likely represents a pituitary macroadenoma but cannot rule out metastatic disease”
Case 5
– Radiologists may not know the whole story
  • “Clinical correlation is recommended”
– Endocrinologists should look at the imaging themselves
## Radiologic appearance

<table>
<thead>
<tr>
<th>Feature</th>
<th>LYH</th>
<th>Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric mass</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Pre-contrast homogeneous appearance</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Intact sellar floor without depression</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Suprasellar extension</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Stalk thickening</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Stalk displacement</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Homogenous enhancement with Gadolinium</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Loss of posterior pituitary bright spot</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Dural tail (reaction)</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Fukuoka H. Endocrine Clinics NA. 44: 143-149
Case 1

- 39 yo female referred by a colleague for a pituitary mass
- 02/2015
  - excessive thirst and urination (“4 gallons per day”)
- 10/2015
  - secondary amenorrhea
  - exhaustion (falling asleep at work)
- 01/2016
  - Headaches (sinusitis? Didn’t respond to Abx)
  - Nausea and weight loss
- 03/2016
  - Headaches escalated
  - CT head showed a pituitary mass confirmed on MRI
  - Prolactin 70, LH, FSH undetectable, estradiol <15
  - Cortisol 2, ACTH <5 (started on hydrocortisone replacement)
  - TSH 0.1, Free T4 0.7 (started on levothyroxine)
Case 1

- Is this “just a cyst?”
Case 1

• Is this “just a cyst?”

• Clinical clues.....
  – Autoimmune disease
    • Mother and sister hypothyroidism
    • Recent diagnosis of psoriatic arthritis (Umbrel/Otezla)
    • ANA homogeneous 1:512
    • TPO Ab 312 (<9 IU/ml)
  – Symptoms of polyuria and polydipsia
Case 1

- Is this just a cyst?

“...the association of DI at presentation and the strange appearing stalk broaden the differential to infiltrative lesions....this could include hypophysitis, LCH, germ cell tumor, metastatic disease or hematologic malignancy... overall, needs at minimum transsphenoidal biopsy of the mass....”
Case 1

- The majority of the adenohypophysis is infiltrated by a previous cellular inflammatory infiltrate of lymphocytes, histiocytes, numerous plasma cells, and small collections of eosinophils. Immunoperoxidase stains for CD1a are negative in histiocytic cells, but these same cells are positive for S100, consistent with activated histiocytes. Kappa and lambda immunoperoxidase stains positively labeled poly-phenotypic plasma cells, consistent with an inflammatory process. The posterior pituitary is obliterated by scar tissue which is severely sclerotic.

DIAGNOSIS

- RATHKE'S CLEFT CYST ADENOHYPOPHYSIS WITH LYMPHOCYTIC HYPOPHYSITIS
Case 1

• Clinical course
• Prednisone 60 mg x 2 weeks tapered over 10 weeks
Case 1

- Rathke’s cyst rupture as a primary event
  - Cyst wall undergoes metaplastic changes
  - Leakage of fluid contents (?mucins)
    - Granulomatous (giant cells, histiocytes, surrounded by T cells and plasma cells)
    - “stage of the same disease?”
    - “foreign body reaction”
  - Lymphocytic reaction is less expected but reported (3 cases)

Case 1- 2 weeks post-op
Case 1- post-corticosteroids
Case 1- On MTX
Lymphocytic Hypophysitis


• Anterior hypophysitis and Hashimoto's disease in a young woman.

• 22 yo F
  – 3 months post-partum
  – Weakness, goiter, amenorrhea, weakness
  – Died of adrenal insufficiency 14 months after giving birth
Lymphocytic Hypophysitis

- Autoimmune driven lymphocytic infiltration
- 1:9 million annual incidence
- 4 to 6:1 female predominance ("autoimmunity" esp. Hashimoto’s)
- “most often presents during pregnancy or post-partum as an enlarged pituitary with local signs, such as severe headache and visual disturbance”
Association with thyroid autoimmunity

Association with thyroid autoimmunity

• 102 APA-positive AITD patients

• Anterior pituitary
  – Growth hormone deficiency in 35.2% (GHRH arginine)
  – Increased prevalence with higher titers
  – MRI
    • Severe GHD (n=18)
      – 8 empty sella, 2 hyperplasia, 2 stalk thickening, 6 normal

• Posterior pituitary
  – n=2, 1 had Central diabetes insipidus

Lymphocytic hypophysitis

- Anti-pituitary antibodies
  - ~30% sensitive
  - Also found in type 1 diabetes, autoimmune thyroid disease, and pituitary adenomas
  - Not a diagnostic tool
- Alpha-enolase
- Secretogranin II
- T-box transcriptional factor T-pit
- Pit 1
- Intermediate lobe specific protein

Fukuoka H. Endocrine Clinics NA 44: 143-149
Case 2

- 43 yo female
- Background of Crohn’s also with large bowl lesions previously on Asacol and prednisone (2 years ago); Flares 1-2 times per year.
- New onset of severe headaches April 2017 accompanied by photophobia and halos
- ER CT head Aug 2017 but no follow-up until November (Harvey)
Case 2

- 43 yo female
- Background of Crohn’s also with large bowel lesions previously on Asacol and prednisone (2 years ago); Flares 1-2 times per year.
- New onset of severe headaches April 2017 accompanied by photophobia and halos
"pituitary macroadenoma measuring 12 mm AP by 19 mm transverse by 12 mm craniocaudal. The native pituitary gland is draped over the posterosuperior aspect of the mass, with posterior and mild rightward displacement of the infundibulum."
Case 2

• Referring endo did prolactin = 62
• Started on cabergoline
• Seen at the pit center....

“From imaging report, likely a pituitary adenoma, however with her autoimmune history and the "stalk" thickening I see, also need to consider hypophysitis. “
Case 2

- Outside endo did prolactin = 62
- Started on cabergoline
- Seen at the pit center....
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<thead>
<tr>
<th>Test</th>
<th>Latest Ref Range</th>
<th>Value</th>
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<tbody>
<tr>
<td>SODIUM</td>
<td>133 - 146 MEQ/L</td>
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<tr>
<td>OSMOLALITY URINE</td>
<td>50 - 800 mOsm/kg</td>
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<td>ACTH</td>
<td>6 - 58 PG/ML</td>
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<td>CORTISOL TOTAL</td>
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<tr>
<td>LUTEINIZING HORMONE</td>
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<tr>
<td>FOLLICLE STIMULATING HORMONE</td>
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<td>ESTRADIOL</td>
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<tr>
<td>TSH REFLEX</td>
<td>0.400 - 4.100 UIU/ML</td>
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<tr>
<td>FREE T4</td>
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<tr>
<td>T3 FREE</td>
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<tr>
<td>TPO Ab</td>
<td>&lt;9 IU/ML</td>
<td>&lt;1</td>
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</table>
“From imaging report, likely a pituitary adenoma, however with her autoimmune history and the "stalk" thickening I see, also need to consider hypophysitis."
A. PITUITARY GLAND, TRANSSPHENOIDAL HYPOPHYSECTOMY: GRANULOMATOUS HYPOPHYSITIS
B. PITUITARY GLAND, DESIGNATED "FIBROUS SELLA DURA, BIOPSY: INFLAMMATORY HYPOPHYSITIS FRAGMENTS OF DENSE FIBROCONNECTIVE TISSUE, CONSISTENT WITH DURA, WITH MILD CHRONIC INFLAMMATION
Granulomatous Hypophysitis

– Sellar disease
  • Rathke’s
  • Craniopharyngioma
  • Germinoma
  • Pituitary adenoma

– Systemic disease
  • Thyroiditis
  • Wegener’s
  • Langherhans cell histiocytosis
  • Giant Cell
  • Sarcoid
  • Takayasu
  • Crohn’s disease
  • TB
  • HIV
  • Interferon/Ribaviron
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<td>ANGIOTENSIN CONVERTING ENZYME</td>
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<td>NON-REACTIVE</td>
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<tr>
<td>HEP C ANTIBODY</td>
<td>Latest Ref Range: NON-REACTIVE</td>
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<td>MYELOPEROXIDASE AB</td>
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<td>NIL</td>
<td>Latest Ref Range: &lt;=8.0 IU/ML</td>
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<td>QUANTIFERON TB GOLD</td>
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<td>TB-NIL</td>
<td>Latest Ref Range: &lt;0.35 IU/ML</td>
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Case 2 Post-op MRI
Case 2- MRI post steroids
Case 3

• 51 yo AAF
• 06/2013
  – nausea and 40 lb weight loss
  – extensive GI work-up (?gastritis)
• 08/2013
  – Cholecystectomy without resolution
• 09/2013
  – Continued intractable vomiting
  – CT brain for ?increased ICP led to MRI of the brain
Case 3

Sellar based mass, pituitary macroadenoma versus meningioma.
Case 3

• Normal visual fields

• Hypopituitarism
  – Adrenal insufficiency
  – Secondary hypothyroidism
  – Low gonadotropins
  – Low IGF-1
  – No DI
Case 3

• 12/2013
  – TSR
  – “lymphocytic hypophysitis with massive lymphoplasmacytic infiltrate with admixed eosinophils and fibrosis.
  – CD3, CD5, CD20, CD43 mixed lymphoid population

• Autoimmune work-up
  – ANA, Anti-dsDNA, Celiac, mitochondrial Ab, thyroid
Case 3

• 07/2014
  – Admission for nausea and vomiting
  – visual field defects and R> L blurred vision
Case 3

- 07/2014
  - Admission for nausea and vomiting
  - visual field defects and R> L blurred vision
  - IV solumedrol
Case 3
Case 3

• Normal visual fields
• Hypopituitarism
  – Adrenal insufficiency
  – Secondary hypothyroidism
  – Low gonadotropins
  – Low GH
  – No DI
Case 3

• 12/2013
  – TSR
  – “lymphocytic hypophysitis with massive lymphoplasmacytic infiltrate with admixed eosinophils and fibrosis.
  – CD3, CD5, CD20, CD43 mixed lymphoid population
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Case 3

- 07/2014
  - Admission for nausea and vomiting
  - visual field defects and R> L blurred vision
  - IV solumedrol
Case 3

- Pathology sent to MGH

“storiform fibrosis with intense staining for IgG4”
Hypophysitis

- Circa 1900-2000
  - Lymphocytic (LYH)
  - Granulomatous hypophysitis
  - Xanthomatous hypophysitis

- Circa 2004-2007
  - Add IgG4 hypophysitis
IgG4 Hypophysitis

• First described by.....?

  – 73 yo male with a “pituitary tumor”
  – Background of pancreatitis and cholecystectomy with pathology described as having “pseudotumor” qualities
  – Strong staining for IgG4 in all tissues
IgG4 Hypophysitis

- First described by......
- 2006 by Tanabe et al. *Internal Medicine*
- 71 yo male with IgG4-related disease
- Multifocal Systemic Fibrosis Complicating Sclerosing Sialadenitis, Hypophysitis, and Retroperitoneal Fibrosis, but Lacking Pancreatic Involvement
- Pituitary showed uptake on PET scan
Criteria for IgG4 hypophysitis: Leporati’s criteria 2011

1) Pathology >10 IgG4 per hpf
2) Pituitary MRI with space occupying lesion or thickening of the stalk
3) Other biopsy proven IgG4 organ involvement
4) Elevated serum IgG4 (>140 mg/dl)
5) Glucocorticoid response with disappearance of pituitary mass lesion and improvement in symptoms.
IgG4 hypophysitis

- “more prevalent in men” 9:1
- First reports all came from Asia
- Elderly (60s)
- 84 cases
  - Men: women >2:1
  - Pituitary function
    - Panhypopit 52%
    - Isolated DI 18%
    - Normal 1%
    - DI in 70%, LH/FSH 46%, GH 40%, TSH 40%
  - 75% had other organ involvement
    - 3.0/1.8 systemic disease in men/women
    - 13/21 with isolated hypophysitis were women
  - 61 with IgG4 levels pre-corticosteroids
    - 56 elevated (median 264.5 mg/dl, range 16.9-2620)
    - 13 normal

IgG4 hypophysitis

- Glucocorticoid responsive
  - Prednisone 30-40 mg per day tapered after 2 weeks to maintenance
  - 97% responded to steroid therapy (MRI)
    - Pharmacologic doses in 46%
    - Replacement doses in 24%
  - Combination with azathioprine
  - Pulse solumedrol followed with Rituximab (only case of recovery of pituitary axes)

Gu et al. 2017. Medicine
<table>
<thead>
<tr>
<th>Other IgG4-related diseases</th>
<th>Number of cases</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroperitoneal fibrosis</td>
<td>22</td>
<td>26.2</td>
</tr>
<tr>
<td>Mikulicz’s disease, Küttner’s tumor</td>
<td>21</td>
<td>25.0</td>
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<tr>
<td>Lymph node swelling</td>
<td>20</td>
<td>23.8</td>
</tr>
<tr>
<td>Lung inflammatory pseudotumor interstitial pneumonia</td>
<td>17</td>
<td>20.2</td>
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<tr>
<td>Autoimmune pancreatitis</td>
<td>12</td>
<td>14.3</td>
</tr>
<tr>
<td>Tubulointerstitial nephritis, kidney inflammatory pseudotumor</td>
<td>10</td>
<td>11.9</td>
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<tr>
<td>Hypertrophic pachymeningitis</td>
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<td>8.3</td>
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<tr>
<td>Orbital pseudotumor iridocyclitis</td>
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<td>8.3</td>
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<tr>
<td>Liver inflammatory pseudotumor</td>
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<td>Nasal sinus inflammatory pseudotumor</td>
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<td>Gastric wall thickness</td>
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<td>Iliopsoas muscle</td>
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<tr>
<td>Prostatitis</td>
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</table>

IgG4 hypophysitis: APA antibodies

IgG4 hypophysitis: Corticotrophs

IgG4 hypophysitis: anti-POMC antibodies

Is this more common than we realize?

• (Prior IgG4 hypophysitis was only 1.3% of case reports)
• 170 consecutive patient with hypopituitarism and/or DI
• IgG4 hypophysitis in 30% of hypophysitis cases and 4% or all hypopit/DI cases
• Co-existing organ involvement in ~60%
Case 3

• IgG1 1050 (304-1319 mg/dl)
• IgG2 232 (121-489 mg/dl)
• IgG3 118 (12-70 mg/dl)
• IgG4 17 (17-153 mg/dl)
Case 3 MRI

- Recent diagnosis of anticardiolipin syndrome and Rheumatoid arthritis
Case 4

- 27 yo male
- Hodgkin’s Lymphoma Stage IIB 2009
- Refractory to multiple therapies
  - ABVD, C-MOPP, CART, Brentuximab 2012-14
  - XRT to head and neck
- Started on Nivolumab 04/2016
- Inpatient stay 12/2016
  - Hypotension/tachycardia and started on prednisone
    - Cortisol 12, ACTH 27
  - TSH elevated >100 (TSH elevated 04/2016)
    - levothyroxine increased
- Difficulty with word finding and stuttering
  - Concerns re: nivolumab encephalitis >>>> CT head >>>>>>MRI
“likely represents a pituitary macroadenoma but cannot rule out metastatic disease”
Case 4

• Assessed in Endocrinology clinic 02/2017
  – Passed an ACTH stimulation test
    • Cortisol 5.9, 22.2, 24.3
    • FSH 16.22, LH 10.80, Prolactin 11.98, IGF-1 73 (L)
  – TSH > 100, Free T4 0.21
  – TPO Ab, TSI negative
Hypophysitis

- Circa 1900-2000
  - Lymphocytic (LYH)
  - Granulomatous hypophysitis
  - Xanthomatous hypophysitis

- Circa 2004-2007
  - Add IgG4 hypophysitis

- Circa 2008-present
  - Checkpoint inhibitor hypophysitis
Checkpoint inhibitors

- Enhance antitumor activity by decreasing immune tolerance
  - Cytotoxic T-lymphocyte antigen-4 receptor (CTLA4)
    - T cells in lymphoid organs
  - Programmed cell death protein 1 (PD1)
    - T cells in tissues

Checkpoint inhibitors

• Anti CTLA4  Ipilimumab
  – Melanoma
  – Dose dependent
  – 6-12 weeks after initiation of therapy (earlier if at higher doses)
  – Hypophysitis 0-17% (lymphocytic)
  – Hypothyroidism 2-13% (silent, autoimmune)

• Anti-PD1 Nivolumab
  – NSCLC, RCC, melanoma, colorectal
  – Rare hypophysitis <1%
  – Hypothyroidism ~2-3%

• Pembrolizumab

Corsello et al. 2013. JCEM 98: 1361-1375
Checkpoint inhibitors: Hypophysitis

- Not a new entity per se.... Just LYH except more often in males
- Diabetes insipidus is rare
- Glucocorticoid responsive
- ACTH targeted

Corsello et al. 2013. JCEM 98: 1361-1375
Checkpoint inhibitor hypophysitis

Shintaro Iwama et al., Sci Transl Med 2014;6:230ra45
<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Cancer type</th>
<th>Clinical hypophysis</th>
<th>Overall pituitary antibodies</th>
<th>Cell-specific pituitary antibodies</th>
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<tr>
<td></td>
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<td>Before Ipi</td>
<td>After Ipi</td>
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Shintaro Iwama et al., Sci Transl Med 2014;6:230ra45
Case 4

- Broad differential diagnosis
  - Pituitary adenoma
    - MRI appearance
    - no hormonal deficits
  - Metastatic lymphoma
    - PET negative
    - no DI
  - Novilumab induced hypophysitis
    - Rarely seen
    - No pituitary hormonal deficits including ACTH
  - Hyperplasia
    - long standing hypothyroidism caused by neck radiation
Hypophysitis

• Circa 1900-2000
  – Lymphocytic (LYH)
  – Granulomatous hypophysitis
  – Xanthomatous hypophysitis

• Circa 2004-2007
  – Add IgG4 hypophysitis

• Circa 2008-present
  – Checkpoint inhibitor hypophysitis
Checkpoint inhibitors

• Anti CTLA4 Ipilimumab
  – Melanoma
  – Dose dependent
  – 6-12 weeks after initiation of therapy (earlier if at higher doses)
  – Hypophysitis 0-17% (lymphocytic)
  – Hypothyroidism 2-13% (silent, autoimmune)

• Anti-PD1 Nivolumab
  – NSCLC, RCC, melanoma, colorectal
  – Rare hypophysitis <1%
  – Hypothyroidism ~2-3%

Corsello et al. 2013. JCEM 98: 1361-1375
Checkpoint inhibitors: Hypophysitis

- Not a new entity per se…. Just LYH except more often in males
- Diabetes insipidus is rare
- Glucocorticoid responsive
- ACTH targeted

Corsello et al. 2013. JCEM 98: 1361-1375
Checkpoint inhibitor hypophysitis

Shintaro Iwama et al., Sci Transl Med 2014;6:230ra45
<table>
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Shintaro Iwama et al., Sci Transl Med 2014;6:230ra45
• Type II hypersensitivity reaction
  – CTLA-4 antibody binding to pituitary cells
  – initiates tissue destruction
• Lack of expression of CTLA4 antigen in posterior pituitary cells may explain lack of DI
• Some potential for recovery
  – Thyroid in 37%–50%
  – Gonadal in 57% of men
  – Rarely adrenal
    • ? Axis suppression by steroids vs. destruction corticotrophs
Case 4

• Broad differential diagnosis
  – Pituitary adenoma
    • MRI appearance
    • no hormonal deficits
  – Metastatic lymphoma
    • PET negative
    • no DI
  – Novilumab induced hypophysitis
    • Rarely seen
    • No pituitary hormonal deficits including ACTH
  – Hyperplasia
    • long standing hypothyroidism caused by neck radiation
Case 5

• 48 yo female, otherwise healthy
• On OCPs for years for endometriosis
  – Gyne found elevated FSH and LH and discontinued estrogen therapy as was post-menopausal
  – No cycles but started “bioidentical hormones” and nature thyroid for a mildly elevated TSH
• Intractable headaches
• Described vision problems at work (jewelry maker) and saw Ophthalmology
What could this be?
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49 y.o. female who presented with headaches, visual changes and an enlarged pituitary with a convex border on MRI. My differential diagnosis includes:

**Pituitary hyperplasia.** The FSH is very very high which I have seen before in women with premature ovarian failure or early surgical menopause. Previously on OCPs and symptoms were exacerbated when went on to menopausal level HRT (lower).

Pathology: PITUITARY GLAND, TRANSSPHENOIDAL HYPOPHYSECTOMY: ADENOHYPOPHYSIS WITH INCREASED GONADOTROPH CELLS, SUGGESTIVE OF GONADOTROPH CELL HYPERPLASIA
Hypophysitis

• An important consideration even when imaging reportedly shows a mass

• Clinical context is key
  – Diabetes insipidus
  – Autoimmune milieu for lymhocytic hypophysitis
  – Primary disease that could cause granulomatous changes
  – Check point inhibitors
‘...And there is nothing new under the sun.

Is there a thing of which it is said, “See, this is new”? It has been already in the ages before us.....’

Ecclesiastes 1
Our team

All appointments in one day in a shared clinic space