Pituitary carcinoma, clinical updates and treatment strategies

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No disclosures

Question 1: Name the pituitary carcinoma, part 1

• A)
• B)
• C)
• D)
30yo, ki-67 index 22.7%
58yo, XRT 1996 El Salvador, ki-67 index 2.8%, rare cells reactive for p53
70yo, ki-67 index 0.5%, neg p53 staining
18yo, ki-67 index 8.4%, some cells p53 pos

Debulking 4/11, forced to leave US, returned to care 2017, surgery 5/17, ki-67 1.8%, radiotherapy

Cushing’s, AI a/TSS 6/12, biochem recurrence 2015 (neg MRI), TSS 8/15 w/ remission, lost to follow up 8/18 at which time UFC nl

Craniotomy 10/15, slow growth of inferior remnant, radiotherapy 9/18, stable

Question 1: Name the pituitary carcinoma, part 2

• A)
• B)
• C)
• D)

Initial visit March 2013, 18yo female

History: 100 lb weight gain over a couple years, facial/truncal acne, scalp hair thinning, insomnia, violaceous striae, facial/abdominal/back hirsutism, oligomenorrhea

Exam: 140/90, 6ft, 294 lbs, centralized obesity, facial plethora, pigmented abd striae, +facial/truncal acne, +dorsocervical prominence and supraclavicular fullness

Social hx: noncontributory

Family history: no endocrinopathies, no pituitary disease, no features of MEN1/4
• Labs: 24hr UFC **360.9mcg** (nl <50)
  LNSC  **0.16, 0.29, 0.25** (nl <0.09)
  1mg DST cortisol **16.5** (no dex level)
  ACTH 63, 89

• 8mm lesion on MRI

• 8mm lesion on MRI

• TSS 3/28/13
  • Pathology: most tumor cells reactive for ACTH, ki-67 index 8.4%, some cells are positive for p53
  • Postop MRI did not show residual tumor
  • Biochemical remission, AI
    • LNSC: <50 (nl <100), 0.3, 0.4 (nl <4.3)
    • 24hr UFC: undetectable, 6.2mcg, 4.2mcg (nl <50)
    • AM serum cortisol: 3.2, 1.2, 2.4
  • Symptom improvement in spring 2013
  • HPA axis recovery documented 6/13—7am cortisol 18.2

• Symptom recurrence 7/13
  • LNSCs 8.4, 8.9, 10.0, 5.9, 4.3, 7.3 (nl <4.3)

• MRIs in 10/13 & 12/13 showed recurrent tumor

• 2nd TSS 12/18/13
  • Pathology: ki-67 index 5.5%, 10% of tumor cells stain for p53, mitoses are present
  • Biochemical remission
    • LNSC: 0.6, 2.8, 2.2 (nl <4.3)
    • 24hr UFC: 10.5, 9.8 (nl <42.3)
    • AM cortisol: 5.3, 3.1, 5.8
  • Recurrence summer 2014
    • LNSC: 0.28, 0.05, 0.11, 0.08 (nl <0.09)
    • 24hr UFC: 195.1mcg (nl <50)
Medical therapy initiated
- Ketoconazole 500mg tid
- Metyrapone 4.25g divided qid
- CAB 0.5mg qhs
  Remained hypercortisolemic with a 24hr UFC of 151mcg on the above combined regimen

Proton SRS, 20 Gy, 9/11/14

Enrolled in study of LCI699 (osilodrostat)
- Following washout, 24hr UFC >1,000mcg
- Began study medication 12/16
  - UFC 1,600's on 2mg bid, UFC normalized on 20mg bid
  - withdrawn from study due to LFT elevation

Pro-radiation

Post-radiation

Brain tumor protocol MRI, c/t/l spinal MRI, CT c/a/p early 2017

FDG-PET CT rec’d

Hurricane Irma

Bilateral adrenalectomy Mayo Jacksonville 9/17

L4-5 hemilaminectomy and microdiscectomy 12/17

ACTH levels
- 12/17  2,572
- 6/18   7,625
- 10/26/18 11,384

FDG PET-CT 12/18
• Liver lesion biopsied 2/19, ACTH+ neoplasm with neuroendocrine differentiation c/w metastasis of known atypical pituitary adenoma

• Liver met negative on Ga68 PET-CT

• Fractionated radiation (50Gy) to liver met 4/19
  • Regressed and no longer visible on PET-CT 6/19

• ACTH levels
  • 12/17 2,572
  • 6/18 7,625
  • 10/18 11,384
  • 9/19 5,616
  • 1/20 14,879

• Sclerotic subcentimeter non-FDG avid skeletal lesions noted on 2019/2020 CTs
  • R humerus, R iliac, R proximal femur, T12

• Radiotherapy 3/20 to R humerus, R iliac, R proximal femur

• Additional small non-FDG avid skeletal mets slowly developing, asx
  • R iliac, L iliac, sacrum, vertebrae

Pituitary carcinoma, epidemiology & presentation

• Defined by the presence of metastatic disease

• Prevalence
  • 0.2% (6 / 3,000 pituitary adenomas at Mayo 1955-1994, Pernicone Cancer 1997)
  • 0.15% (2 / 1,300, Beauchesne Neurosurg 1995)
  • 0.04% (1 / 2,500, comment K Post to Scheitauer Neurosurg 2005)
  • 0.4% (4 / 1,055, 2001-2016, Alshaikh Endocr Pathol 2019)
  • 0.14% (5 / 3489, 1996-2005, German registry, Saeger EJE 2007)

• In 75% of cases metastatic disease was determined postmortem (Mountcastle Am J Med Sci 1989, Cusimano Skull Base Surg 1994)
• 207 cases in US
  • based on clinically relevant pituitary adenoma prevalence of 1:1500, US 2010 census of 308.7 million, & 0.1% pituitary carcinoma, Heaney JCEM 2011
• 0.0006% of all pituitary adenomas
  • based on 10% prevalence of pituitary adenomas & the 207 estimate

• No gender predilection
• Mean age 46.3 (9-75) (Yoo Pituitary 2018)
  • 3 cases of pediatric pituitary carcinoma (youngest actually being 8 yo in 1962 missed by Yoo 2018); 8 cases where initial tumor dx in childhood
• Subtypes  (Yoo Pituitary 2018, Ragel Neurosurg Foc 2004, McCormack EJE 2018)
  • 85-88% have positive hormonal staining (vs null cell)
  • ACTH > PRL > GH > TSH/LH/FSH
• Latency period
  • Range months-30 years (Pernicone Cancer 1997, Kemink J Endo Invest 1999)
  • Mean 9 yrs (Yoo Pituitary 2018)

• Locations of Metastases
• Yoo Pituitary 2018, n=72
  • Brain 43%, spinal cord 37%
  • Liver, LN, bone
• Kaltsas Pituitary 1998, n=98
  • CNS 45%
  • Systemic (liver, bone) 39%
  • Both 16%

• Prognosis / Mortality
• Mountcastle Am J Med 1989: 36 cases, mean survival 4 yrs
• Pernicone Cancer 1997: 15 cases, 66% mortality at 1 yr
• Sironi J Clin Path 2002: 33 pts with PRL+ carcinomas, mean survival 2.4 yrs
• Yoo Pituitary 2018: 34 deaths (avg 10 mos), 28 alive (unknown f/u), 10 NA
• Lenders Pituitary 2018: 38 nonfx carcinomas, median survival 8 mos
• Prognosis / Mortality
  • Santos-Pinheiro EJE 2019: 17 pts (1994-2017), median follow up 2 yrs (1-13)
    --2yr survival: 71%, 3yr: 59%, 5yr 35%
    --All >5yr survivals received TMZ
  • J Neurooncol Pract 2016: 23pts (2006-2014) txd w/ TMZ
    --5yr PFS 36.1% & OS 56.2%
  • Carey J Neurol Surg B Skull Base 2020: 92 cases (NCD 2004-2014)
    --1yr OS 93.3%, 5yr OS 80%
    --No tx 40%, surg along 45%; only 13% invasive primary tumors

• “I know it when I see it”
  • Supreme Court Justice Potter Stewart describing his threshold test for obscenity in Jacobellis v. Ohio, 1964
  • 2018 European Soc of Endo guidelines, Kasuki & Raverot Rev Endocr Metab Disord 2020
    • “in patients with a radiologically invasive tumor and unusually rapid tumor growth rate, or clinically relevant tumor growth despite optimal standard therapies (surgery, radiotherapy, and conventional medical treatments)”

WHO classification of pituitary tumors
• 2004
  • 3 categories: pituitary adenoma, atypical pituitary adenoma and pituitary carcinoma
  • Atypical pituitary adenomas: ki-67 index > 3%, extensive p53 immunoreactivity, elevated mitotic index, invasive growth
• 2017
  • “atypical” category gone, abandons p53 staining
  • ki-67 index/mitotic index, invasion used for consideration of aggressive tumors
  • “high-risk” pituitary adenomas: sparsely granulated GH, silent corticotroph, prolactinomas in men, Crooke’s cell adenomas, plunhormonal pit-1 positive adenomas

• Ki-67, the swan ganz catheter of neuroendocrinology?
  • p53
    • Lack of consensus criteria/methodology for positivity & variable tumor group definitions
    • Still included in 2018 Euro Soc guidelines
  • Mitotic index
    • No reliable cutoff for pituitary carcinoma/aggressive pituitary adenomas
  • Combination (Trouillas Acta Neuropathol 2013, Raverot JCEM 2017)
• McCormack EJE 2018
  • Survey, 40 pituitary carcinoma, 125 aggressive pituitary adenomas
  • Aggressive pituitary adenomas: 87% invasive growth
  70% growth a/ XRT
  69% growth a/ 2 prior surgeries
  54% resistance to medical therapy
  • TMZ utilized in 116/125 aggressive adenomas & all 40 pituitary carcinomas
  • Ki-67 index >3%: 81% aggressive,
  85% carcinomas (>10% in 1/3)
  • p53 expression (pos vs neg): 73% aggressive,
  78% carcinomas
  • Mitoses > 2/10 HPF: 63% aggressive,
  90% carcinomas

• Ultrastructural features (EM) (Scheithauer Ultrastruct Pathol 2001)
  • Tumor invasiveness
    • Microscopic, Meij J Neurosurg 2002
      35% 1-2cm, 55% 2-4cm, 70% >4cm
    • Macrosopic
  • Age ?
    • McCormack EJE 2018
      Aggressive adenomas—mean age 42.7, SD 16.2
      Pituitary carcinoma—mean age 44.7, SD 15.1

Genetics of pituitary carcinoma

• Upregulation
  • PTTG, EGFR, RAS, ERBB2 (HER2/neu), TP53, Cystedin1, PTGS2, LGA23, HIF1A,
  VEGF, MMP-9, miR-20a, 106b, 17p, 122, 493, p21, miRNAs

• Downregulation
  • MGMT, MSH6, CDKN1B, RB1, p53, BCL2, Bax, Bcl-x, Bad, p16, p27, MT3, MRNA
    (Yang Medicine 2016, DeSilvaia and McCormack 2018)
  • ATRX (Casar-Borota JCEM 2021)
    • 18 pit CA, 30 aggressive adenomas
    • 9 (5 pit CA) neg IHC (confirmed loss-of-function mutation)

• Mutational burden/landscape
  • Adenomas, low # somatic mutations w/ a dominant mutation in > 10-15% of all pituitary
    adenomas, variable degree of genomic disruption by copy number alterations (frequently
    arm-level in size), variable methylation patterns in adenoma subtypes
    Clin Can Res 2018)
  • MEN1, AIP-FIPA, CDKN1B (MEN4), PRKAR1A (Carney complex), GNAS
    (McCune-Albright), USP8

Question 3: What treatment would you choose first?

• A) Temozolomide
• B) Targeted therapy (anti-VEGF/VEGFR, EGFR, mTOR
  inhibitor, etc)
• C) Lutathera
• D) Checkpoint inhibitor immunotherapy
• E) Repeat radiation therapy
• F) Combination therapy
**Temozolomide (TMZ)**

- First use in pituitary carcinoma reported in 2004 (Fadul, Society for Neuro-Oncology Ninth Annual Meeting, Abstract)
- Oral alkylating agent, good CNS penetrance
- methylates N7 position of guanine (preferentially), N3-adenosine, & O6-guanine
  - Unrepaired O6-MeG mispairs with thymine, activating mismatch repair (MMR) in futile cycles→cell cycle arrest→apoptosis
- methylguanine-DNA methyltransferase (MGMT) repairs O6-methylation
- Responsiveness to TMZ: functional MMR & low MGMT levels

**Temozolomide, dose regimens & tolerability**

- Side effects
  - Fatigue (60%), n/v, myelosuppression
  - 29/190 (15%) pituitary pts d/c’d 2/2 SEs
- Dosing
  - Raverot EJE 2018: 77/86 150mg/m²/d 5 days every 4 weeks
  - McCormack EJE 2018: 139/150 150mg/m²/d 5 days every 4 weeks
  - Dose-dense (21/28 days) & daily (metronomic) dosing
- Duration
  - McCormack EJE 2018: 1-36mo, median 9mo (median 12mo responders vs 5.5mo PD)

**Temozolomide, response rate & survival**

- Radiographic response/tumor volume reduction
  - McCormack EJE 2018 (157 pts, 40 carcinoma): 37% (SD 33%, PD 30%)
  - Raverot EJE 2018 (106pts, 34 carcinoma): 47%
- Time to radiographic response
  - Initial response
    - Bengtsson JCEM 2015 (10 responders): median 3 mo (range 1-6)
    - Losa J Neurooncol 2016 (11 responders): 11/11 at 3 months
    - Lasolle EJE 2017: (22 responders): 19/22 at first eval a/ 3-6mos of tx
  - Max response
    - McCormack EJE 2018: (n=39) in 3 mo (23%), 6mo (59%)

**Temozolomide, survival**

- Median PFS
  - Elbelt JCEM 2020: 23mo for all (n=47)
  - 22mo for adenoma
  - 24mo for carcinoma (n=13)
- Overall survival
  - Losa J Neurooncol 2016: 47.7% at 2yrs (n=31)
- Lasolle EJE 2017: median 40mo
  - Responders (n=20), median OS 44mo (95%CI 42-NA)
  - Nonresponders (n=18), median OS 16mo (95% CI 9-26), p=0.002
**Temozolomide, relapse & repeat therapy**

- Relapse-free survival post-TMZ
  - Lasolle EJE 2017: median 30 mo, n=20
  - Losa J Neurooncol 2016: 2yr relapse-free rate 59.1%, n=25

- Repeat tx with TMZ
  - McCormack EJE 2018: 2/18 responded
  - Raverot EJE 2018 (6 studies): 1/16 responded
  - Elbell JCEM 2020: 0/5 responded

**Predictors of temozolomide efficacy**

- MGMT status
  - MGMT promoter methylation correlates with decrd protein expression (IHC) & OS in glioblastoma (Hegi NEJM 2005, Cao Neurosurg 2009)
  - IHC does have some predictive capacity

- MMR proteins
  - McCormack EJE 2018, n=65
  - Raverot EJE 2018, n=99
  = responders

**Temozolomide, combination therapy**

- Radiation
  - TMZ, a radiosensitizing agent; XRT vs XRT + TMZ (Stupp NEJM 2005)
  - Raverot EJE 2018: 17 pts, 75% response (some had no prior radiotherapy)
  - McCormack EJE 2018: 14 pts, 71% response vs 34% TMZ alone
  - Minniti J Neuroonol 2020: 21 pts, TMZ + rXRT
    - 13/21 responded

- Combination w/ other chemotherapy
  - Zachariah Neurosurg 2014: sequential capectabine + TMZ 3/4 pts respond, 1 SD
  - McCormack EJE 2018: 6 pts
    - 2/6 respond, 2 SD

**Targeted therapies**

- Anti-VEGF/VEGFR
  - 17 cases (15 bevacizumab, 1 apatinib, 1 sunitinib)
  - 5 radiographic response (3 concurrent TMZ, 1 concurrent TMZ + radiotherapy)
  - 7 SD (8 years, 26 mos, 18mos, 6mos, 5 mos, NA in 2)

- EGFR inhibitors
  - 9 cases (8 lapatinib, 1 erlotinib)
  - 1 radiographic response
  - 4 SD (6mos for all 4)

Targeted therapies

- mTOR
  - 6 cases (6 everolimus)
  - 1 radiographic response
  - 1 SD (5 mos)

- BRAF V600E in wtUSP8 corticotroph adenomas
  - Chen Nature Commun 2018: 15/91
  - Stiera Neuro Oncol 2019: 1/94

- CDK4/6
  - 1 case (palbociclib)
  - 1 radiographic response

- BRAF V600E in wtUSP8 corticotroph adenomas
  - Chen Nature Commun 2018: 15/91
  - Stiera Neuro Oncol 2019: 1/94

Targeted therapies

- 8.3% eligible for genome-targeted therapy
  - Marquart, JAMA Oncol 2018

- Genome, transcriptome, proteome studies for pituitary carcinoma are lacking

Peptide receptor radionuclide therapy (PRRT): Lutathera (\(^{177}\)Lu-Dotatate)

- Approved by FDA in 2018 for SSTR-positive gastroenteropancreatic NETs

- Lutetium\(^{177}\): half life 6.71 days (160hrs)
  - emits beta particles w/ a mean tissue range of 1mm & some gamma rays

DPTA-octreotide (pentetreotide)—Octreoscan, In\(^{111}\)
DTPA,Tyr\(^3\)-octreotate (DOTATATE)—Ga\(^{68}\) PET

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Breeman Eur J Nucl Med 2001
Octreoscan vs Ga68 PET-CT

\[ \text{In}^{111} : \text{gamma rays} \]
\[ \text{Ga}^{68} : \text{positrons} \]

Single-photon emission computerized tomography (SPECT)

Positron emission tomography

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**PRRT in aggressive pituitary tumors & pituitary carcinoma**

- Case reports, n=12 (Petersenn Rev Endocr Metab Disord 2020)
  - Stable disease/partial response in 6 (median follow up 44mo, range 1-8yrs)
  - 8/12 received lutathera (2 \( \rightarrow \) In\(^{111}\)pentetreotide, 2 \( \rightarrow \) Y\(^{90}\) DOTATATE)

- Normal pituitary gland exposure:
  - Gupta Clin Nuc Med 2013: 61pts bdx \( \geq \) 2 cycles, cumulative activity 5.5-27.7 GBq
  - (3.7-7.4/dose), total exposure 0.137-0.266 Gy/g of pituitary tissue
  - Strosberg NEJM 2017: 7.4 GBq/dose q8wks x 4 doses
  - Teunissen Eur J Nucl Med Mol Imag 2009: 76pts, 22.2-29.6GBq, 1-2yr flu, no changes observed in pituitary function

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**SSTR expression in pituitary tumors**

**mRNA**

**Protein (IHC)**

- **Checkpoint inhibitor (CPI) therapy for pituitary carcinomas/aggressive pituitary adenomas**
  - Ipi + nivo
  - ACTH 45,550\( \rightarrow \)4,764 (1wk)\( \rightarrow \)66 (5 cycles), 59 (6mos)
Mutational burden & anti-CTLA-4 response

Snyder et al, NEJM 2014
Van Allen et al, Science 2015

Mutational burden & anti-PD-1 response

Rini, Science 2015
Yarchoan et al, NEJM 2017

PD-1 blockade is effective in tumors with mismatch-repair deficiency

Le et al, NEJM 2015
Le et al, Science 2017

CPIs in pituitary carcinomas/aggressive pituitary adenomas, add'l cases

- Majd J Immunother Cancer 2020
  - Pembrolizumab:
    - 1 prolactinoma
      - PD
      - prior cisplatin/etoposide, TMZ, CAPTEM
      - neg PD-L1 IHC, “intermediate mutational burden”
      - 1 silent corticotroph tumor
        - SD x 4 months
      - prior TMZ, “low tumor mutational burden”, neg PD-L1 IHC
      - 2 Cushing’s disease
        - PR in both (12 mos & 42 mos)
      - prior TMZ + CAPTEM, MSH2 & MSH6 mutation
      - prior TMZ, PD-L1 staining neg, mutation status of tumor at TMZ unknown
CPIs in pituitary carcinomas/aggressive pituitary adenomas, add’l cases

- Lamb Front Endocrinol 2020
  - Lactotroph carcinoma: ipi + nivo x 2 cycles, nivo x 8 mos, ipi + nivo x 4 cycles
  - PR then regrowth on nivo, PD on repeat ipi + nivo
  - 6.8muta/MB (“low”), mismatch-repair deficient (unspecified), PD-L1 expression <1%

- Caccese Anticancer Drugs 2020
  - Aggressive corticotroph adenoma, mismatch-repair deficient
  - (abstract only available)

- Sol EJE 2021
  - Corticotroph tumor: ipi + nivo x 4 cycles, nivo
  - SD for 1 year
  - prior TMZ tx

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CPIs in pituitary carcinomas/aggressive pituitary adenomas

- Tumoral CTLA-4 expression a marker for efficacy
- variable pituitary CTLA-4 expression levels (qRT-PCR & IHC)
- ipi ab subtype: classical complement pathway, ADCC
- complement deposition on rodent pituitary cells a/ anti-CTLA-4 tx
- tremelimumab hypophysitis autopsy specimen
- CTLA-4 germline mutation patient data
- anti-PD-1 and anti-PDL1 ab subtypes
- different frequency, timeline, and clinical presentation for ipi vs PD-1/PD-L1 hypophysitis

- Pseudoprogression and assessment of efficacy
- Phase 2 studies

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Where does this leave us?

- Antiresorptive therapy
- TMZ
- Biopsy and mutation testing, targeted therapy
- Checkpoint inhibitor therapy

Some positive notes...

- HS valedictorian
- Master’s degree
- Engagement
Conclusions

• Existing evidence is poor
  • Limited numbers, potential overlap between study cohorts & survey data
  • Lack of controlled trials
  • 2018 ESE guidelines: 19/20 recommendations low to very low quality of evidence
  • “We recommend monitoring of haematological parameters, liver function tests and careful clinical observation for potential adverse effects during treatment” (for TMZ)

• Our ability to predict pituitary carcinoma or true aggressive tumor behavior is poor

• Survival rates have improved, new therapies are emerging