

55 yo Man with Urinary Frequency

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, 2018

Dr. Upala does not have any relevant financial
relationships with any commercial interests



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Learning Objectives

- Review manifestation of acromegaly
- Review comorbidities in acromegaly



HPI

- 55 Yrs male with a history of T2DM without known complications, heart transplant (2007, following NICM), HTN, primary hypothyroidism who presents with urinary frequency in the past year
- He has been having increase urination and nocturia without any sign of infection
- From health screening, PSA has been increasing since 2016
- He also reports erectile dysfunction (normal sexual desire but no erection or ejaculation)



HPI

- In Feb 2018, he had facial palsy and was diagnosed with Bell's palsy
 - During evaluation, he was found to have 1 cm pituitary mass on a brain MRI
 - He was treated with pulse steroids with significant improvement
 - Prior to MRI brain, His wife also notices that his hands are getting bigger and enlarged/coarsened face
 - His family thinks that he has been gaining weight and ignore the change in appearance
 - Denies any change in belt or clothes size, excessive sweating, body odor, hoarseness, headache, impaired vision
 - Sometimes he feels fatigue and weakness with SOB and chest discomfort in the past year
-



HPI

- He was diagnosed with non-ischemic cardiomyopathy in 2007 and underwent cardiac transplantation in the same year
- He also follows up with his cardiologist and was recently diagnosed with cardiac allograft vasculopathy
- During cardiac evaluation, he was found to have left atrial dilatation and trace tricuspid regurgitation but the rest of echocardiogram was normal
- He takes oral prednisone 2 mg qd, mycophenolate and tacrolimus (same dose for few years)



HPI

- His DM was uncontrolled as he stopped the medications at some point during the last year because he did not want to take medications and weight loss 11 lbs
 - Even he has been losing weight but his snoring has been getting worse in the past year
 - Fasting reported to be in mid high 200s
 - A1c >14 in June 2018 after being 7.5 in July 2017
 - He was diagnosed with T2 diabetes in 2006 with A1c 6.7 then he received high dose steroids during transplant process.
 - Previous DM meds - metformin 1000 Bid, Januvia 100 qd and Lantus 10u qd
-



Other History

- Past Medical History
 - HTN
 - T2DM
 - Heart transplant
 - Primary hypothyroidism
- Past Surgical history
 - s/p heart transplant
- Family History
 - Father and sister: T2DM
 - Mother: HTN
- Allergy
 - No Known Allergies
- Social History
 - Former smoker
 - No alcohol intake
 - No recreational drugs
- Medication
 - levothyroxine 112 mcg qd
 - prednisone 2 mg qd
 - mycophenolate
 - tacrolimus



Review of Systems

- Constitutional: No fevers, night sweats, appetite change, + **weight loss, malaise, fatigue, snore**
- HEENT: No photophobia, blurred vision, no pain, hearing loss, difficulty swallowing, thirst, hoarseness
- Resp: No cough, dyspnea, +**increased WOB**
- CV: +**CP, diaphoretic**, palpitation, LE edema, no DOE, orthopnea, PND, palpitations,
- GI: No abdominal pain, nausea, vomiting, diarrhea, constipation
- GU: No dysuria, +**urgency**, no polyuria, hematuria
- MSK: No myalgias, joint pain, back pain
- Neuro: No syncope, No numbness, paresthesias, seizures, tremors, headaches
- Heme: No adenopathy or easy bruising/bleeding
- Endo: No heat or cold intolerance, dry skin, dry hair, hair loss
- Derm: No rashes, ulcers, abdominal striae, hirsutism, acne
- Psych: No anxiety or depression



Physical Exam

BP: 108/74

Pulse: 71

Resp: 18

Weight: 70.3 kg (155 lb) Height: 170.2 cm (5' 7") Body mass index is 24.28 kg/(m²)

General: Appears well-nourished. Appears stated age. No distress. No anxiety.

Eyes: Conjunctiva normal. Pupils are equal, round, and reactive to light.

Mouth/Throat: Mucous membranes are moist. **no frontal bossing, no prognathism, poor dentition (cannot assess teeth spacing)**

Neck: Supple. No adenopathy. No thyromegaly. No thyroid nodules appreciated.

Cardiovascular: Regular rate and regular rhythm. No murmur appreciated. Radial pulse is 2+.

Pulmonary: Clear to auscultation bilaterally. No crackles or wheezes.

Abdomen: Soft, non-tender, non-distended.

Musculoskeletal: Normal range of motion.

Neurological: Alert & oriented. Normal proximal muscle tone. No tremor on outstretched hands.

Skin: Warm. +minimal acanthosis nigricans. No violaceous striae on the abdomen. + skin tags

Psychiatric: normal mood.



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Lab

Lab Component	
Component	Value
Sodium	141
Potassium, Ser/Plasma	5.5 (H)
Chloride	108
Carbon Dioxide	23
BUN	35 (H)
Creatinine	1.1
Glucose, Ser/Plasma	179 (H)
Calcium	10.1
GFR Estimate (Calc)	70

Lab Component	
Component	Value
Total Protein	7.9
Albumin	4.2
Bilirubin, Total	0.3
Bilirubin, Conjugated	0.1
Bilirubin, Unconjugated	0.1
Alk Phos, Serum	86
AST (SGOT)	14
ALT (SGPT)	11

Lab Component	
Component	Value
Thyrotropin	0.43
Thyroxine	9.0
Thyroxine, Free	1.80 (H)
Triiodothyronine	98

Lab Component	
Component	Value
Hb A1C	12.3 (H)
HbA1c (POC)	9.0 (H)

Lab Component	
Component	Value
25-Hydroxy Vitamin D	33

Lab Component	
Component	Value
Urine Albumin/Creatinine	340.6 (H)

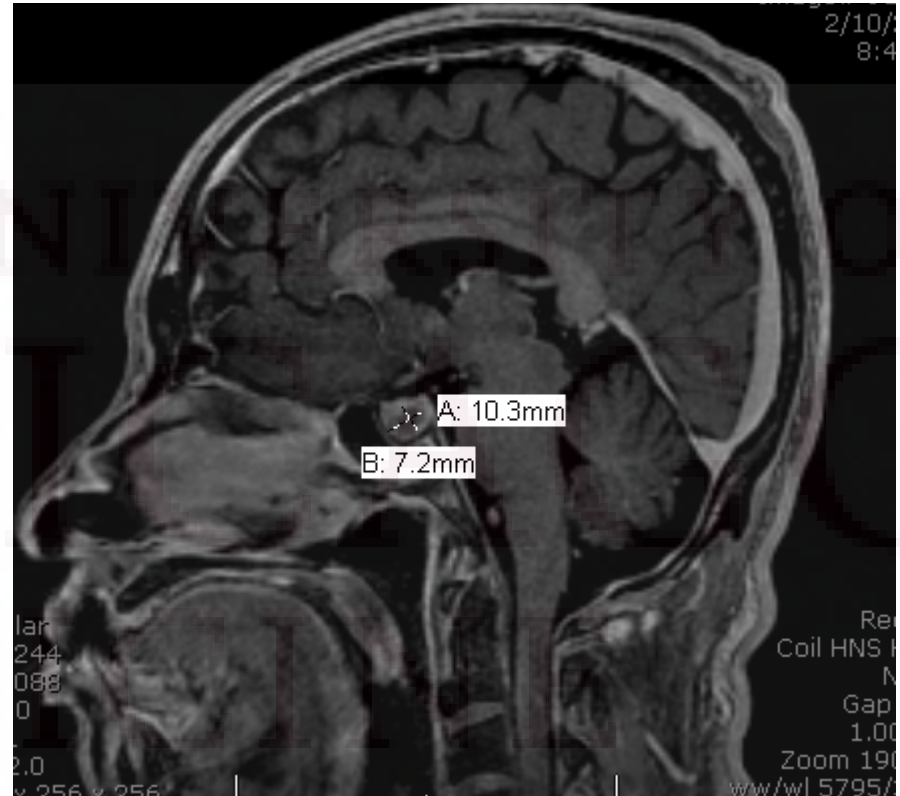
Lab Component	
Component	Value
Cholesterol	151
HDL Cholesterol	41
Triglycerides	157 (H)
LDL	79
Cholesterol, Calc	

Lab Component	
Component	Value
WBC	7.2
RBC	3.72 (L)
Hemoglobin	11.7 (L)
Hematocrit	32.7 (L)
MCV	87.9
MCH	31.5
MCHC	35.8 (H)
RBC Dist Width	13.7
Platelet Count	195
Mean Platelet Volume	9.4
Differential Method	
No RBC or WBC abnormalities det	
Granulocytes	59
Lymphocytes	27
Monocytes	9
Eosinophils	1
Basophils	0
Abs Grans	3.68
Abs Lymphocytes	1.54
Abs Monocytes	0.51
Abs Eosinophils	0.07
Abs Basophils	0.02
Neutrophils	63
Bands	1



Imaging (MRI Brain 2/2018)

- Incidental noted is an enlarged pituitary gland with associated an hypoenhancing left paramedian lesion measures 10 x 7 x 7 mm (AP x CC x TR).
- The infundibulum is slightly deviated to the left



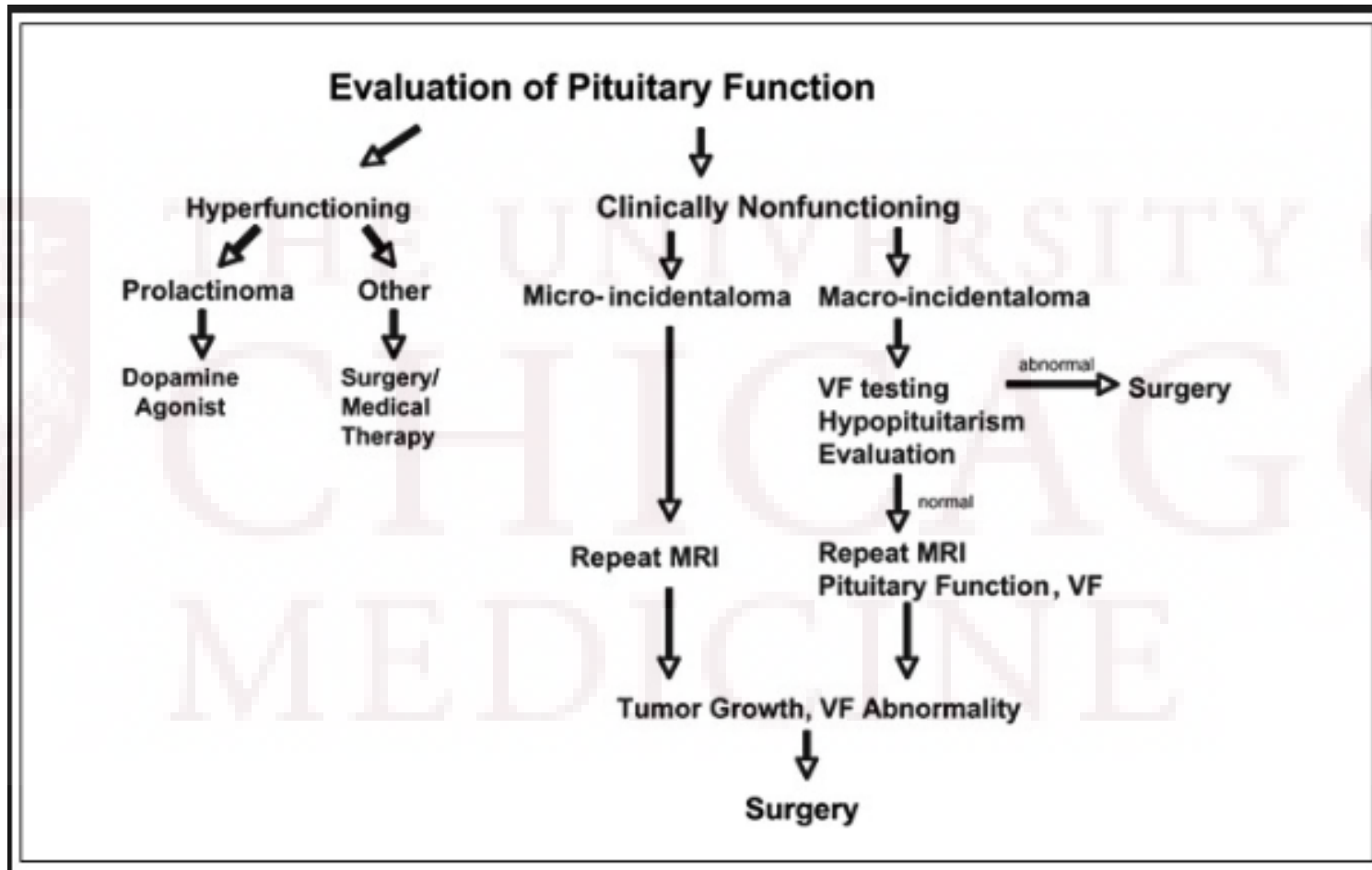
DDX Sellar Mass

1. Cases of sellar/parasellar masses: Differential diagnosis based on MRI / CT

Langerhans cell histiocytosis (LCH)	pituitary adenomas	hypothalamus and optical tract gliomas
Rathke cleft cysts	xanthogranuloma	thrombosis arachnoid cysts
epidermoid tumors	germinomas	inflammatory variations
germ cell tumors	aneurysmata	colloidal cysts of the third ventricle



Evaluation



Labs

- Work up?





Evaluation of Pituitary Axis

• Prolactin	: 6.85 (4-15.2)
• FT4	: 1.59 (0.9-1.7)
• TSH	: 0.47 (0.3-4)
• TT3	: 98 (80-195)
• Cortisol	: 10.8
• ACTH	: 9.9 (<52)
• Total testosterone	: 251 (<240-950)
• Free testosterone	: 67 (90-300)
• Te Binding Globulin	: 42 (10-80)
• LH	: 7.5 (2-6.8)
• FSH	: 24.7 (1.2-8)





Evaluation of Pituitary Axis

- GH : 2 (0-10.8)
- IGF-1 : 454 (37-275)



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Work Up

- Next step?

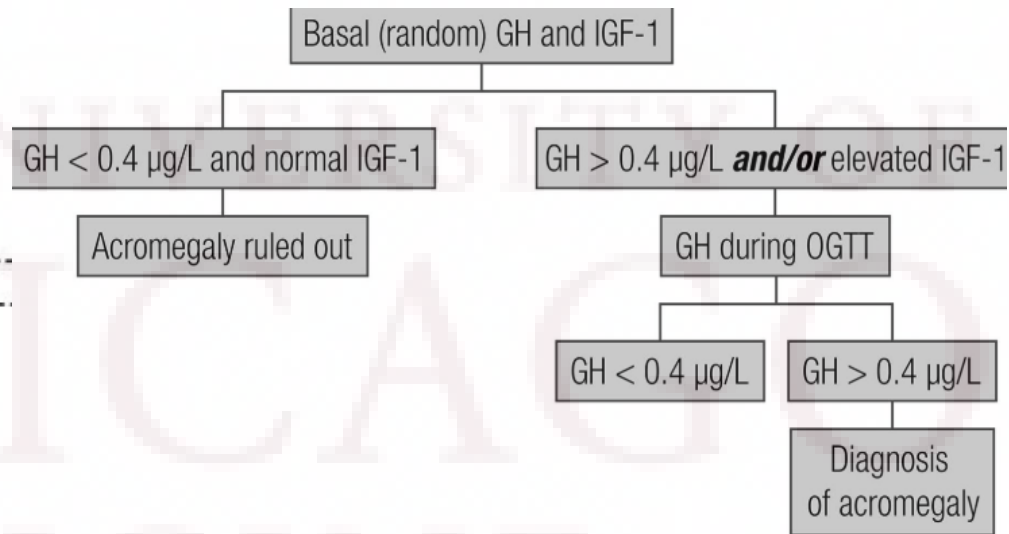
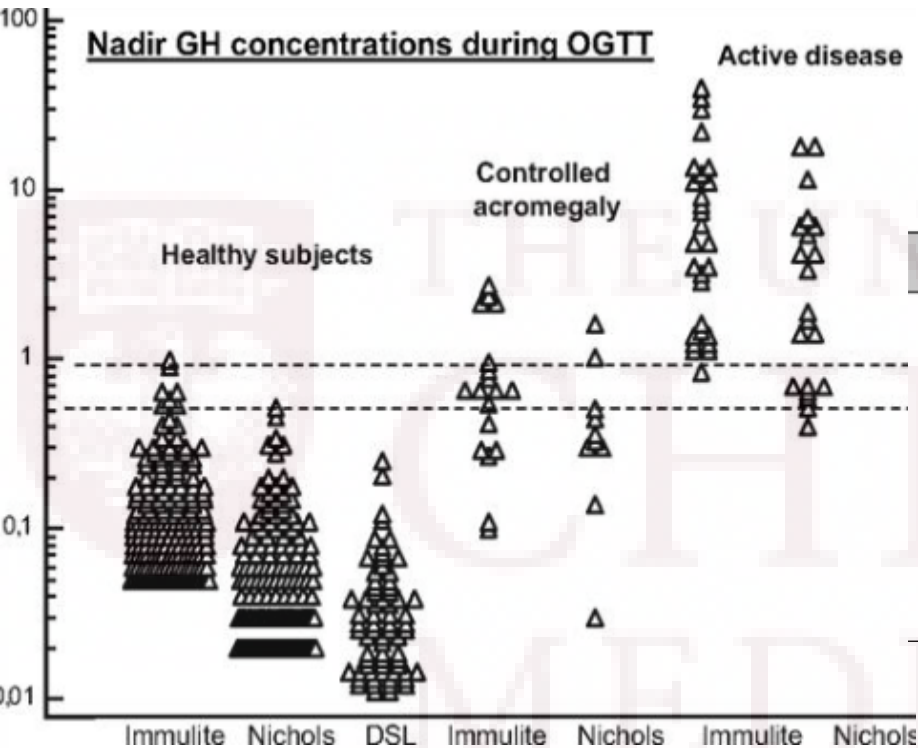


OGTT

	Ref. Range	7/11/2018 08:45	7/11/2018 09:00	7/11/2018 09:30	7/11/2018 10:00	7/11/2018 11:00
Elapsed Time (Endo Lab):	Latest Units: minute		0	30	60	120
Growth Hormone, Stimulated (Endo Lab)	Latest Units: ng/mL		3.22	3.01	2.79	2.55
POC Glucose	Latest Ref Range: 76 - 120 mg/dL	131 (H)				
Glucose Tol.	Latest Units: mg/dL		130	162	169	223
Time	Latest Units: minute		0	30	60	120

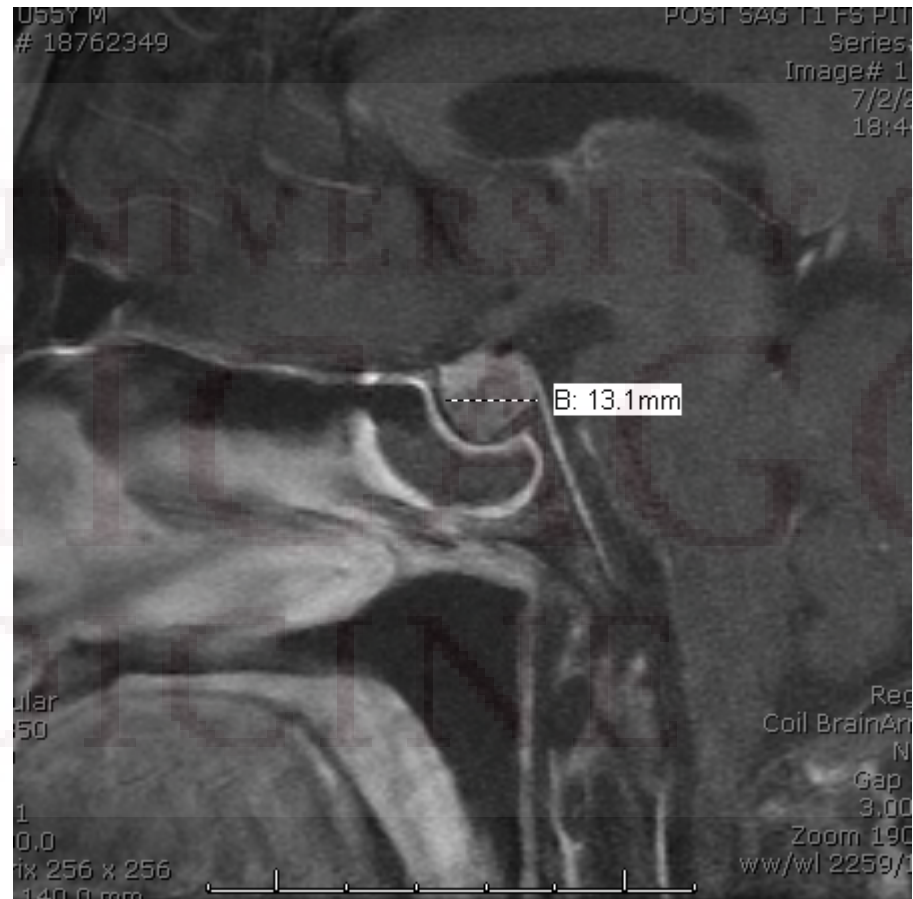


Evaluation of Pituitary Axis

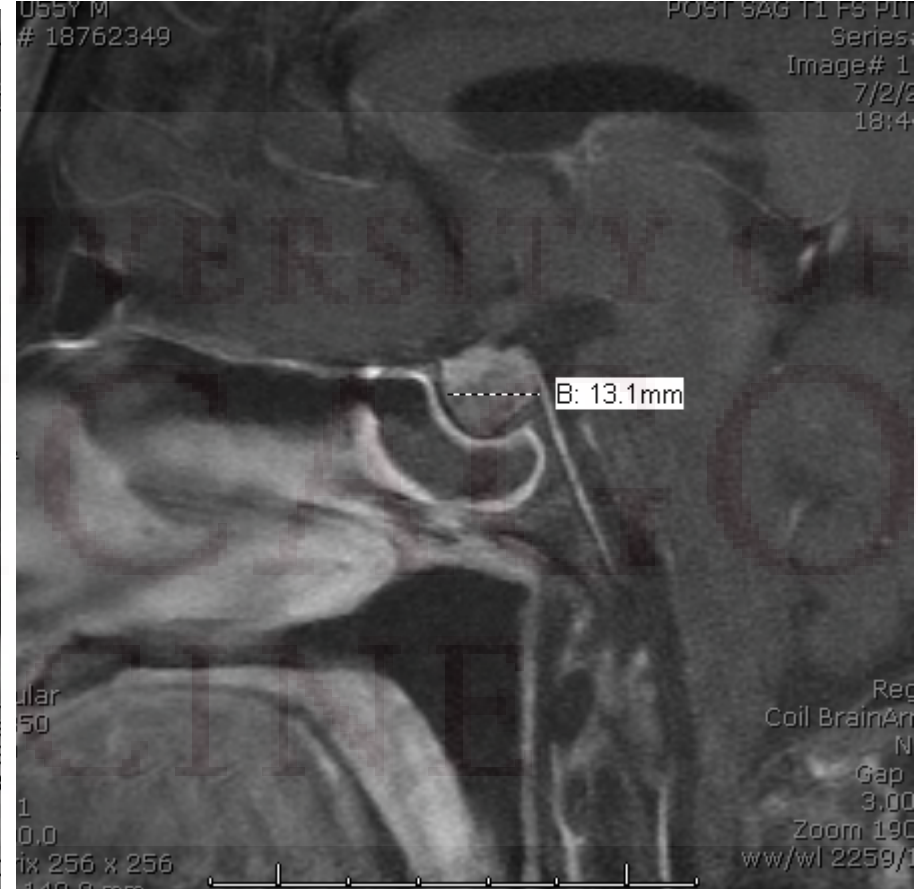
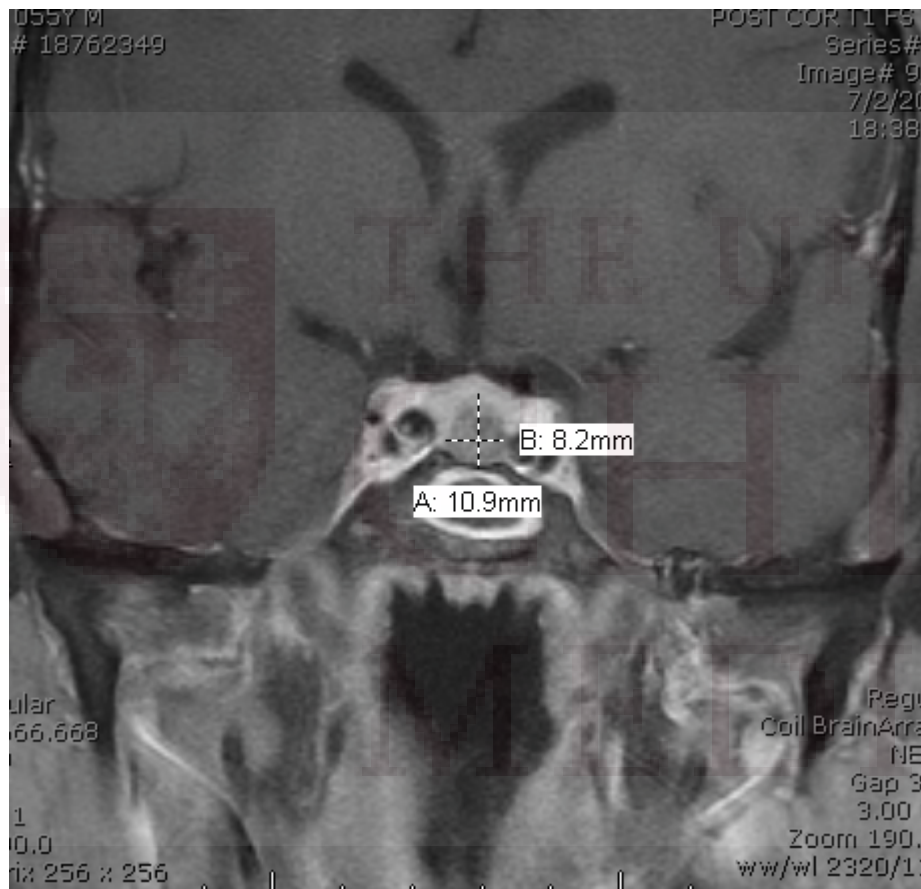


Imaging (MRI pituitary 7/2018)

- A hypoenhancing lesion is present within the sella measuring up to 13 mm in diameter, over which drapes the native pituitary parenchyma. The differential diagnosis would include macroadenoma.
- The lesion does not appear to be cystic and as such a cystic etiology is considered less likely.
- Sequelae of prior inflammation may also be considered.



Imaging (MRI pituitary 7/2018)



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Pituitary Work Up

- GH axis
 - Elevated IGF1 2x the UNL
 - Of note at the time of the tests BG was 390, and GH added on was 2, thus unsuppressed confirming acromegaly
 - OGTT confirms for acromegaly
 - Adrenal axis - on prednisone 2mg
 - The current dose if not enough to replace adrenal function
 - Was change to Hydrocortisone 15mg in AM and 10mg in early afternoon
 - Thyroid axis - on L-T4 112mcg
 - Gonadal axis - with evidence of primary hypogonadism - low testosterone and elevated LH and FSH - patient was referred to Urology with US
 - Normal prolactin - also confirmed by 1:10 dilution
-



Management

- Stress dose steroids during surgery and post operative exogenous glucocorticoid therapy
- Surgery (transphenoidal hypophysectomy)

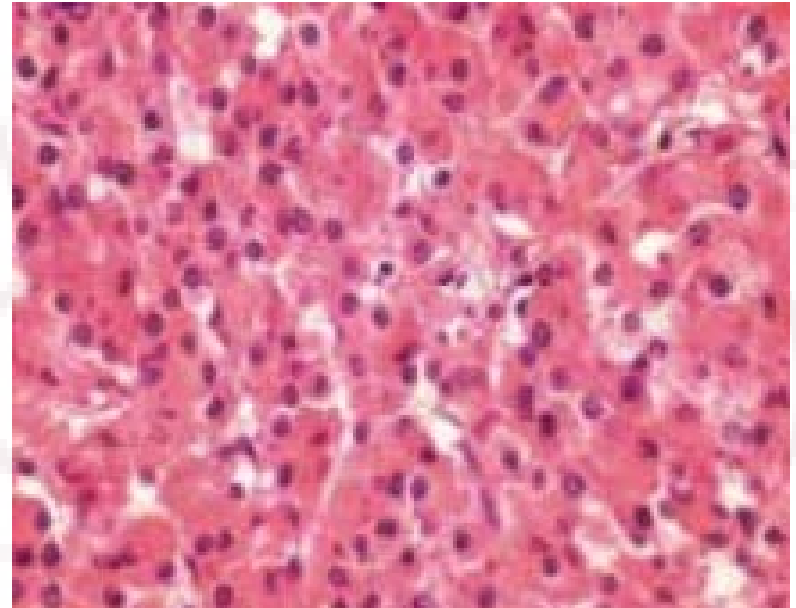
Pathology Report

- PITUITARY ADENOMA,
NECROINFLAMMATORY DEBRIS AND
MUCOUS WITH FOCAL BACTERIAL COLONIES.
- A sheet like growth of monomorphic anterior
pituitary type

cells that express some growth hormone based
on the performed
immunohistochemical studies

- negative for ACTH, TSH, LH, FSH, and
prolactin.
- Synaptophysin is diffusely positive and
cytokeratin Cam5.2 shows

staining with distinct perinuclear globular
accentuation



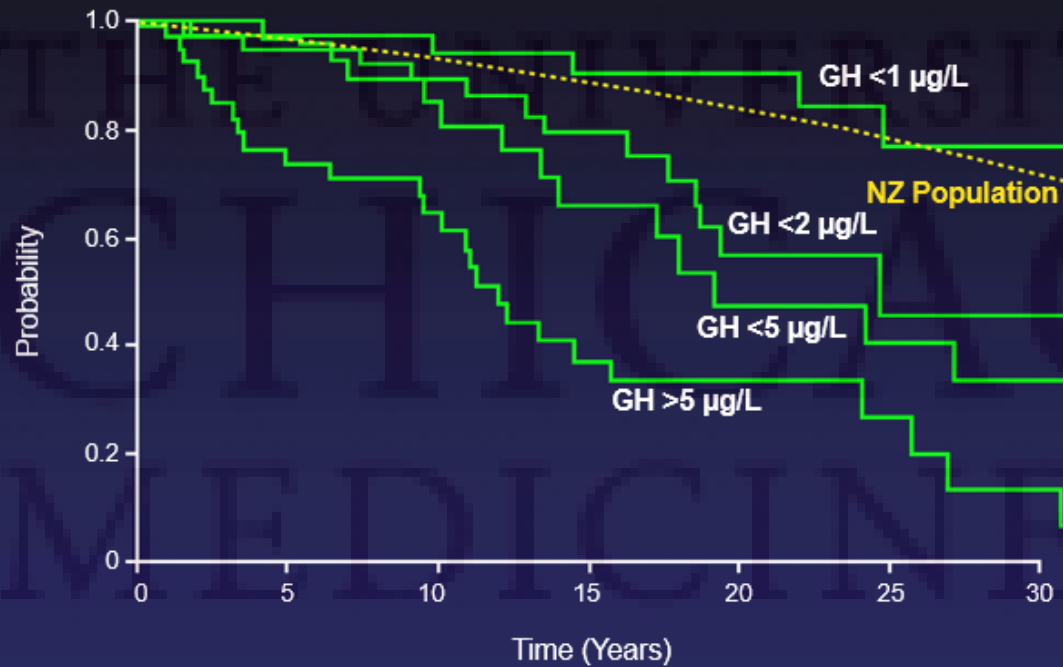
Epidemiology

- Estimated incidence of 8-13 cases per 100,000 patients per year
- Men and women –equally affected
- Mean age at diagnosis- early to mid 40s
- Two times increase in mortality and a 10 years reduction in life expectancy



Epidemiology

Mortality in Acromegaly



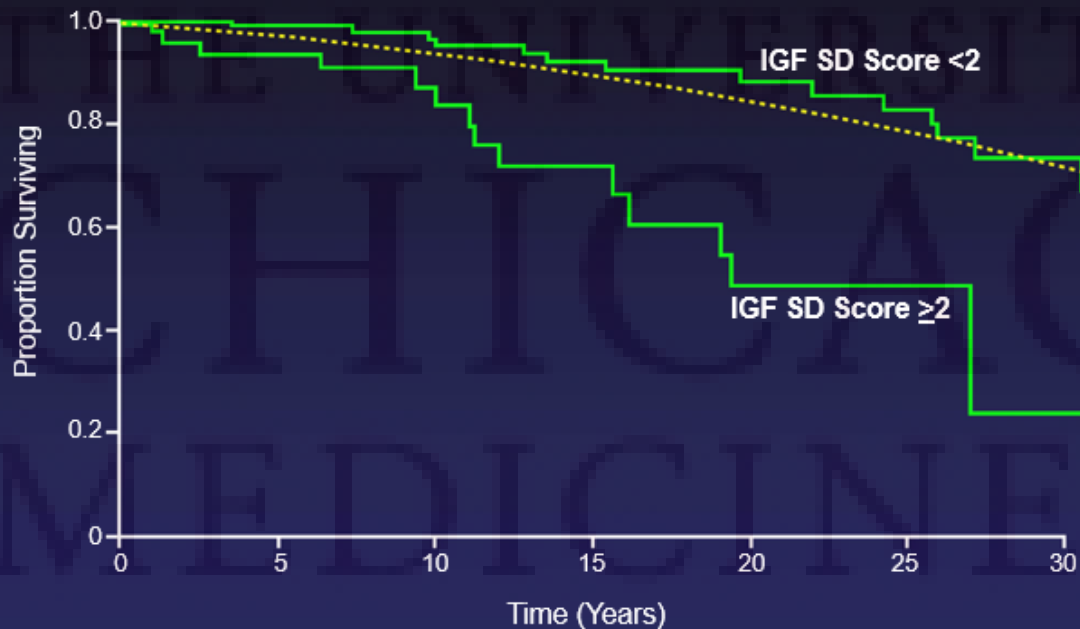
Holdaway IM, JCEM; 2004, 89:667



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Epidemiology

Factors Influencing Mortality in Acromegaly



Holdaway IM, JCEM; 2004, 89:667



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Clinical Presentation

Table 3
Presenting Clinical Features
of Acromegaly

Feature	Percent
Acral enlargement	86
Maxillofacial changes	74
Excessive sweating	48
Arthralgias	46
Headache	40
Hypogonadal symptoms	38
Visual deficit	26
Fatigue	26
Weight gain	18
Galactorrhea	9

Adapted from Drange MR, Fram NR, Herman-Bonert V, Melmed S. Pituitary tumor registry: a novel clinical resource. *J Clin Endocrinol Metab.* 2000;85:168-174.



Table 4
Summary of Diagnostic Features of Acromegaly

Category	Major diagnostic features	Additional diagnostic features
Symptoms	Headache Heat intolerance Ring and shoe sizes Facial bony changes	Hypogonadism (amenorrhea, impotence) Visual changes Sleep apnea
Signs	Prominent forehead Broad nose Prominent lower jaw Visual field loss	Large hands and feet Skin tags Bite abnormalities Carpal tunnel Oily skin
Magnetic resonance imaging findings	Dedicated pituitary magnetic resonance imaging Commonly, macroadenoma	Microadenoma (rarely) Extension lateral to carotid predicts incomplete resection
Biochemical results	Elevated level of insulinlike growth factor-I Growth hormone nadir >1.0 ng/mL after oral glucose dose Panel suggests lower growth hormone nadir (>0.4 ng/mL) after oral glucose dose	Elevated prolactin level Random growth hormone <0.4 ng/mL and normal insulinlike growth factor-I make the diagnosis highly unlikely
Pathologic findings	Growth hormone-staining pituitary adenoma	Somatostatin resection subtype characterization to predict response to somatostatin analogue therapy

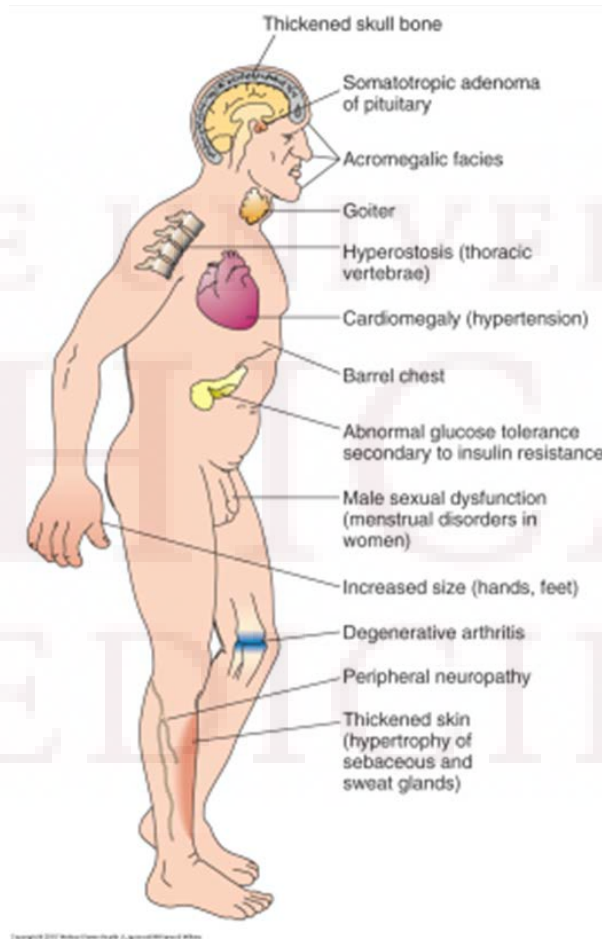


Clinical Question

- Cardiomyopathy and acromegaly



Active acromegaly: multi-systemic disease



Acromegaly and Heart

Major components:

- cardiac hypertrophy
- impaired diastolic filling
- decreased ejection fraction

Worsened by:

Diabetes mellitus

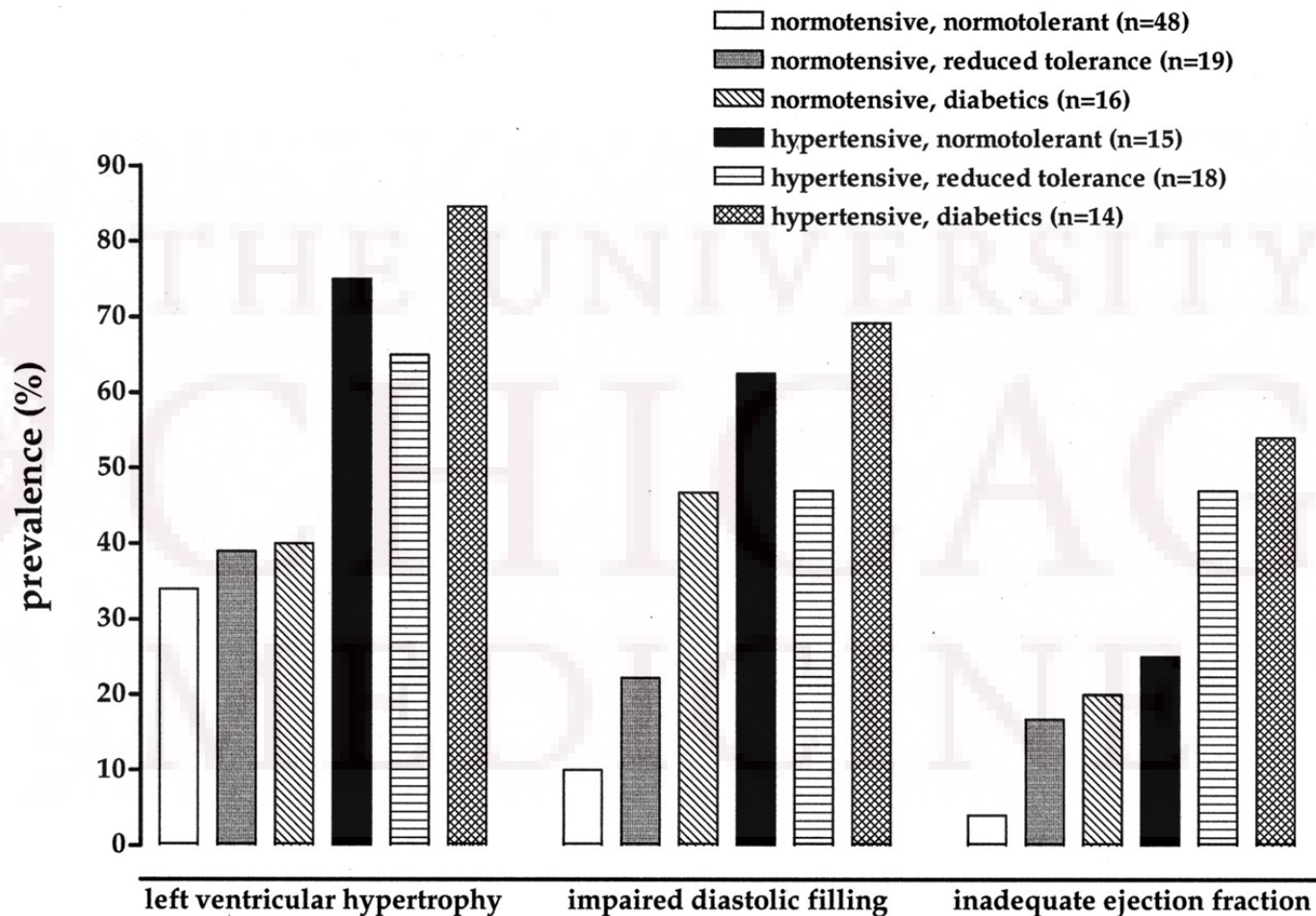
Hypertension

Increasing age

- The risk for coronary artery disease is not increased, and remains stable after successful treatment



Acromegalic cardiomyopathy



Acromegaly

- Biochemical control (36 mths): not all changes are reversed

	Active acromegaly	After biochemical control	
No. of subjects	76	76	
Severe hypertension	57	8 %	< 0.0001
Left ventricular hypertrophy	79	53 %	0.001
Diastolic dysfunction	59	29 %	< 0.0001
Systolic dysfunction	21	4 %	0.003

Colao et al. Clin Endocrinol. 2008;69:613-20



Acromegaly

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Acromegaly

Aortic valve regurgitation

Acromegaly

20 %

controls

4 %

$p=0.002$

Mitral regurgitation

Acromegaly

5 %

controls

0 %

$p=0.001$



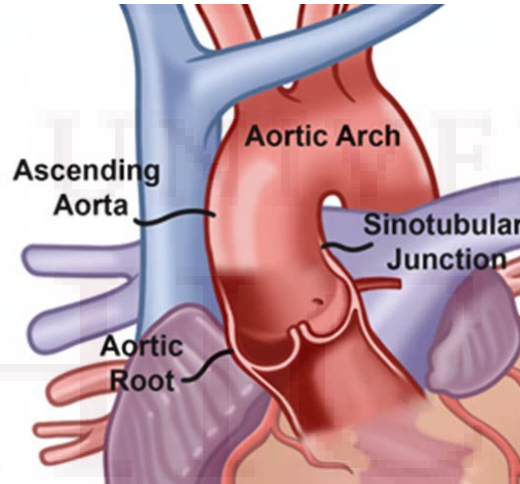
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Pereira et al. JCEM 2004;89:71-5

Acromegaly

Increased aortic root diameters

Acromegaly controls
 30 ± 4 vs 26 ± 3 mm



Acromegaly controls
 33 ± 5 vs 30 ± 4 mm

No change during follow up of controled acromegaly (1.9 year)



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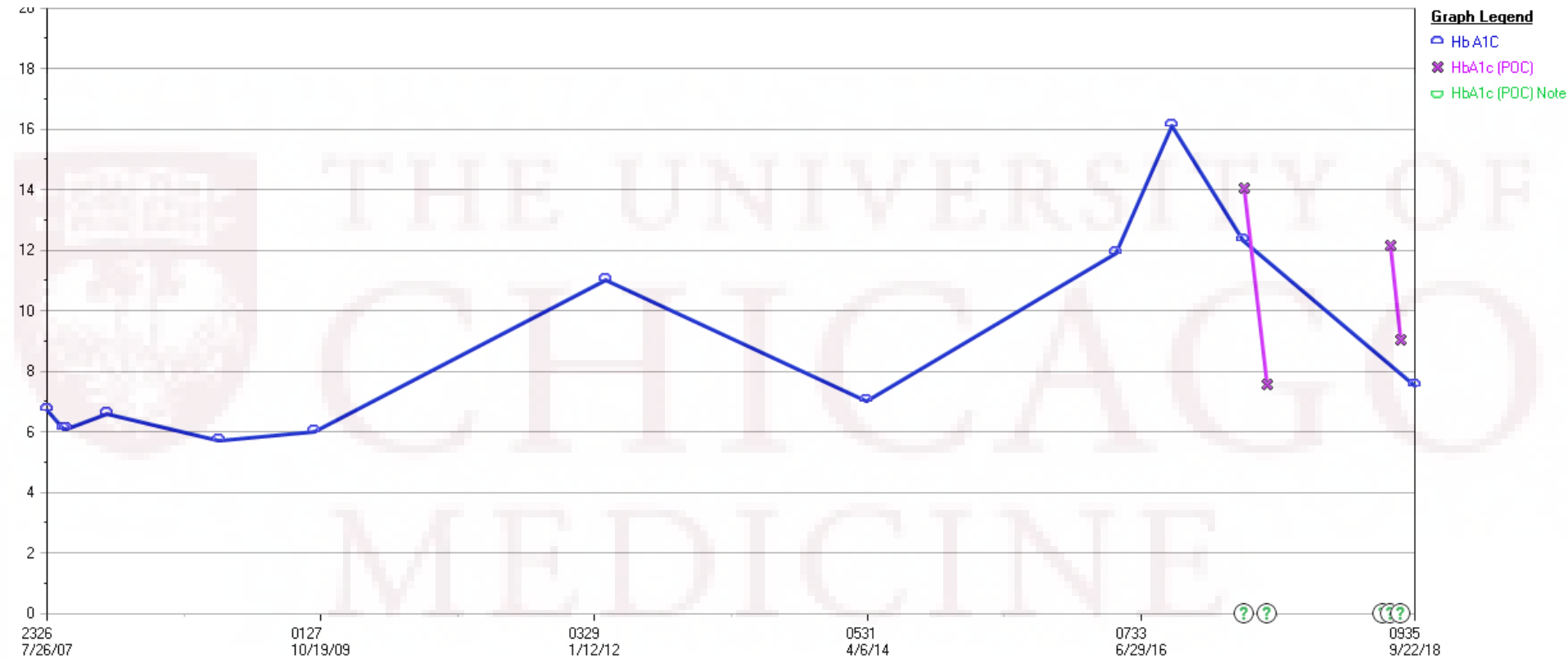
Van der Klaauw et al. Eur J Endocrinol 2008;159:97-103

Our Patient

- Echocardiogram (2017)
 - Normal left ventricular thickness, mild tricuspid regurgitation
- Pathology (2007)
 - Right ventricular endomyocardium biopsy: cardiac tissue with myocyte hypertrophy and focal minimal fibrosis
 - Heart; resection for transplantation: multifocal, predominantly lymphocytic infiltrate in the myocardium associated with myocardial damage and areas of fibrosis. Residual myocytes are hypertrophied



Diabetes



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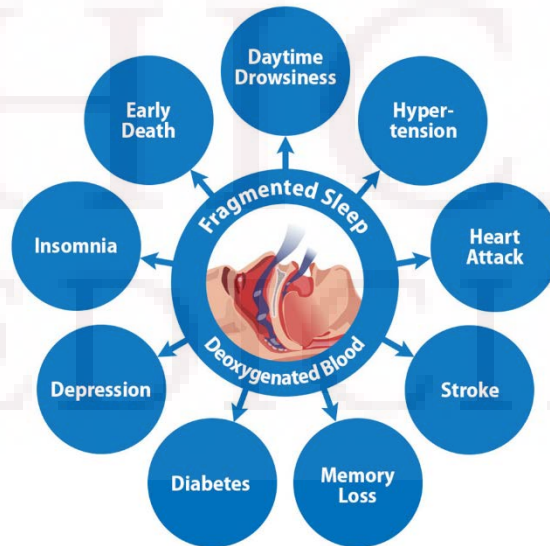
Clinical Question

- OSA and acromegaly



Prevalence of OSA

- Active acromegaly 69% (range 27-87 %)
- Controlled acromegaly 41 %





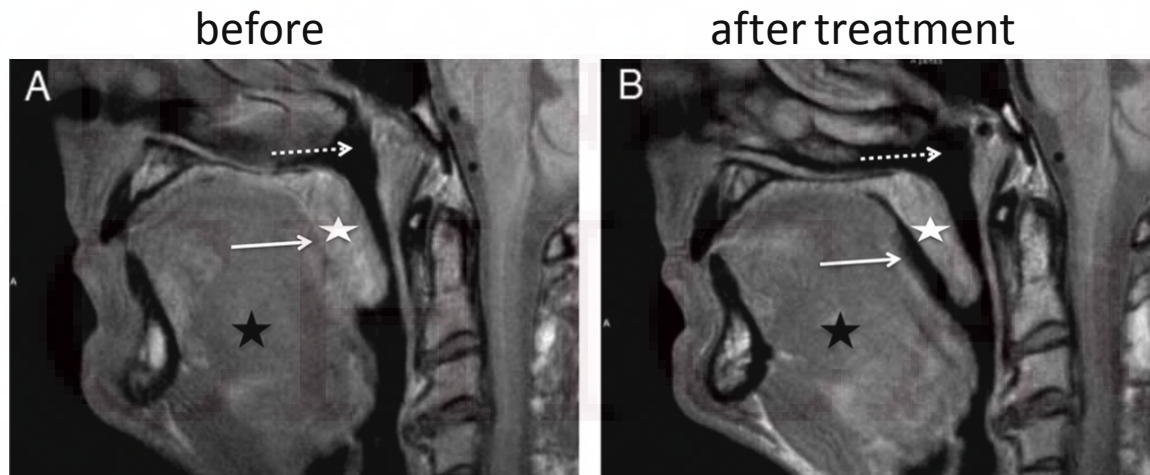
OSA and Acromegaly

- Factors contributing to obstructive sleep apnea in acromegaly
 - Macroglossy
 - Swelling of the pharyngeal walls
 - Altered anatomy
- Management
 - 1) Assess for obstructive sleep apnea
 - 2) Determine whether treatment, e.g. with CPAP, is necessary



OSA and Acromegaly

- Effect of treatment of acromegaly

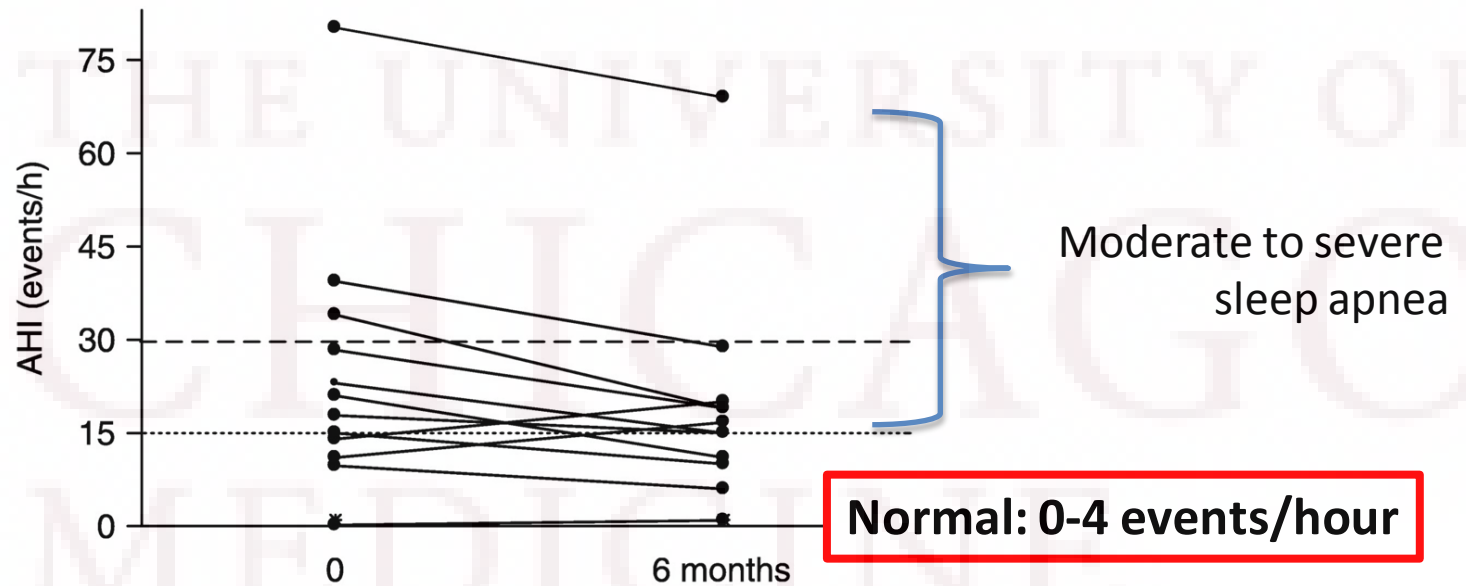


Decreased thickness of - nasopharynx
- soft palate
- tongue



OSA and Acromegaly

Apnea–Hypopnea Index



- Pegvisomant improves sleep apnea in acromegaly



Our Patient

- Polysomnography: pending

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Clinical Question

- Clinical outcome in acromegaly

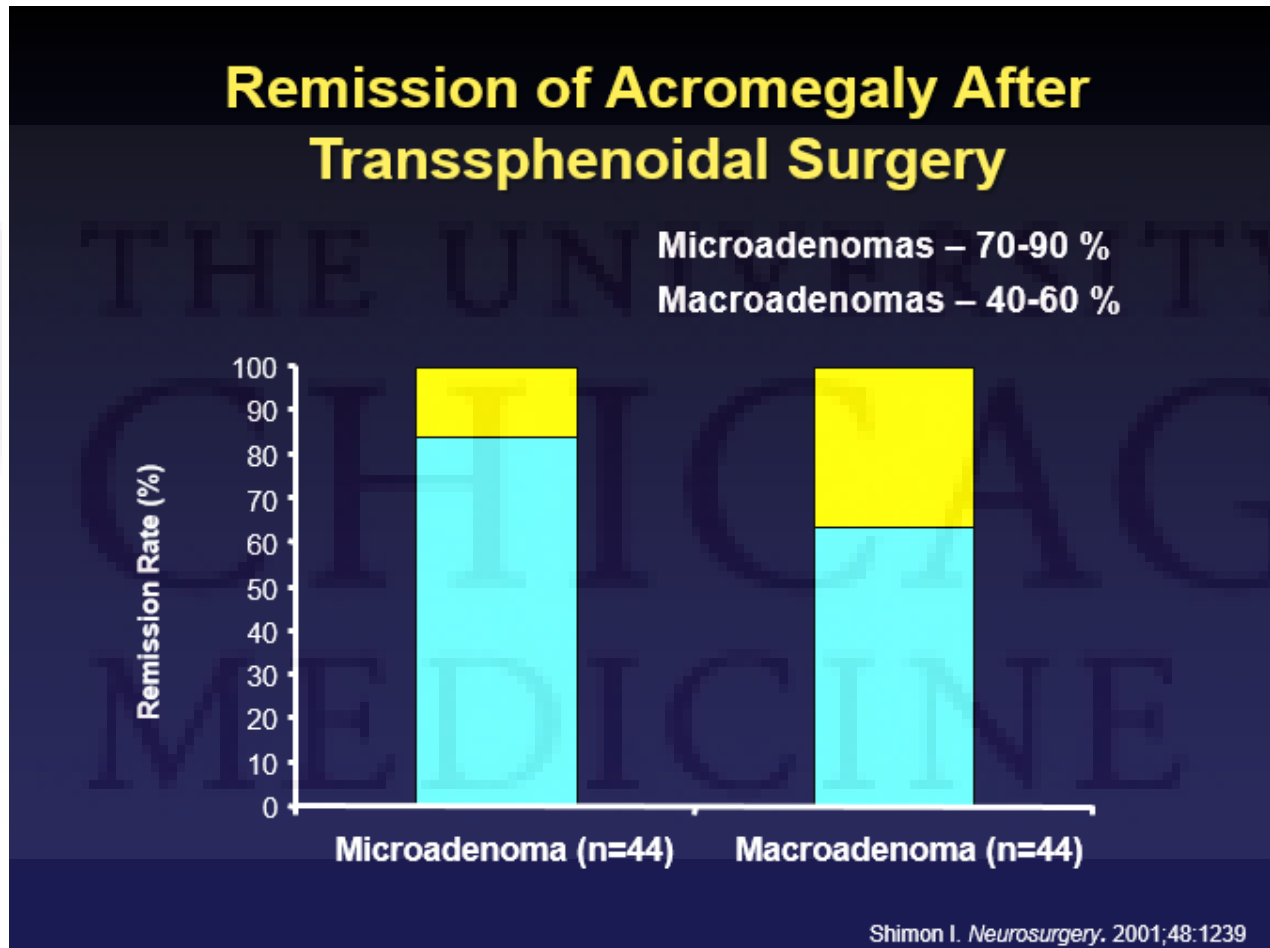


Surgical Outcome in Acromegaly

- Experience of the neurosurgeon
- Adenoma size
- Invasiveness into adjacent structures
- Pre-operative GH level

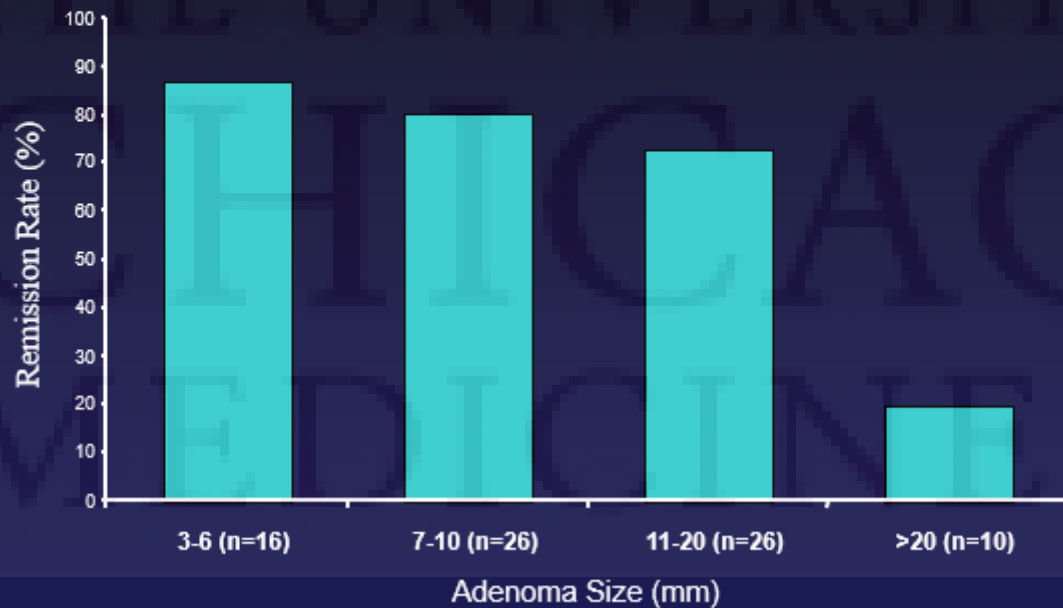


Surgical Outcome in Acromegaly



Surgical Outcome in Acromegaly

Remission of Acromegaly After Transsphenoidal Surgery According to Adenoma Size



Shimon I. *Neurosurg.* 2001;48:1239



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Clinical Question

- Prostate and acromegaly



Prostate and Acromegaly

- Case control study
- Tertiary referral center university hospital in Northern India
- 53 men with acromegaly and 50 healthy men matched for age and BMI
- Outcome: International Prostate Symptom Score (IPSS), prostate-specific antigen (PSA) levels, dimensions of the prostate on trans-rectal ultrasonography, parameters on uroflowmetry, and immunopositivity with anti-IGF1 antibody in prostatic tissue biopsies



Prostate and Acromegaly

Table 3 Comparison of various parameters between acromegaly patients with active and inactive disease compared with healthy controls. Data are presented as mean $\pm$ s.d. (range).

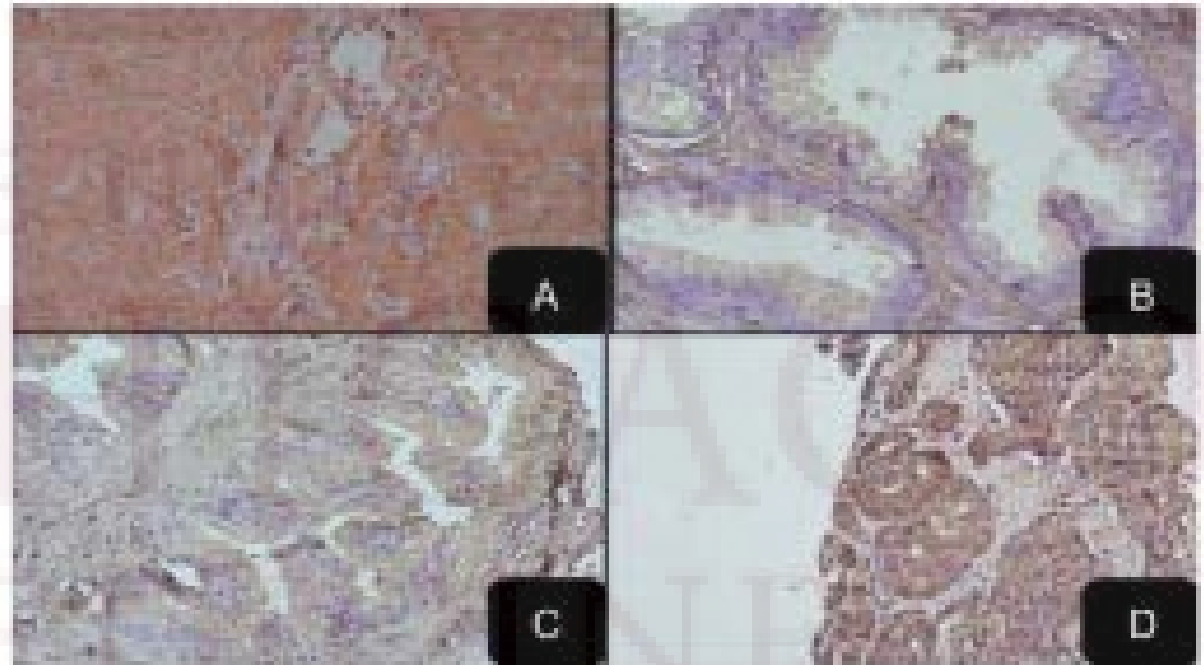
Parameters	Inactive disease	Active disease	P value	Controls	P value (inactive vs control)
n	15 (28.3%)	38 (71.69%)	0.20	50	
Age (years)	35.20 $\pm$ 9.04	39.03 $\pm$ 9.95	0.202	41.0 $\pm$ 11.0 (20–60)	0.062
GH (ng/ml) nadir after OGTT	0.38 $\pm$ 0.33 (0.03–0.97)	18.44 $\pm$ 16.87 (1.05–76)	0.001	0.4 $\pm$ 0.4 (0.02–1.70)	0.72
IGF1 (ng/ml)	203.30 $\pm$ 152.64 (23.15–545)	575.59 $\pm$ 372.52 (96–1515)	0.001	171.7 $\pm$ 38.6 (111–267)	0.94
Testosterone (nmol/l)	10.38 $\pm$ 13.15 (0.08–49.97)	7.54 $\pm$ 6.57 (0.16–32)	0.937	14.3 $\pm$ 3.8 (10.1–23)	0.003
IPSS (0–35)	3.27 $\pm$ 2.63 (0–9)	3.58 $\pm$ 4.37 (0–21)	0.810	0.5 $\pm$ 0.2 (0–2)	0.001
USG – prostatic hyperplasia (PV $\geq$ 30 ml)	0	7 (18.42%)	0.172	0	0.99
PSA (ng/ml)	1.18 $\pm$ 0.83 (0.20–2.60)	0.80 $\pm$ 0.57 (0.2–2.5)	0.022	0.5 $\pm$ 0.4 (0.08–2)	0.001
DRE – prostatomegaly	3 (20%)	14 (36.8%)	0.333	5 (10%)	0.37
TRUS (prostate)					
TR (cm)	4.28 $\pm$ 0.78 (2.34–5.72)	4.57 $\pm$ 0.68 (2.80–6.15)	0.277	3.6 $\pm$ 0.4 (2.3–4.2)	0.001
AP (cm)	2.46 $\pm$ 0.51 (1.77–3.64)	2.75 $\pm$ 0.62 (1.49–4.04)	0.088	2.9 $\pm$ 0.6 (1.4–3.7)	0.005
CC (cm)	3.30 $\pm$ 0.60 (2–4.20)	3.43 $\pm$ 0.83 (1.23–4.77)	0.034	2.3 $\pm$ 0.6 (1.4–4.8)	0.001
TV (ml)	17.98 $\pm$ 5.86 (11.70–26.50)	23.16 $\pm$ 9.20 (6.70–49.68)	0.04	12.5 $\pm$ 3.7 (6.3–19.7)	0.001
Median lobe (ml)	4.84 $\pm$ 2.14 (1.76–9.72)	6.44 $\pm$ 4.35 (1.50–20)	0.28	2.8 $\pm$ 1.1 (2.1–3.6)	0.001
Cysts	1 (6.66%)	5 (13.5%)	0.66	4 (8%)	0.99
Nodules	2 (13.33%)	1 (2.63%)	1.00	1 (2%)	0.41
Calcifications	2 (13.33%)	14 (36.84%)	0.11	8 (16%)	0.99
Uroflowmetry					
Volume (ml)	341 $\pm$ 184.33 (194–724)	408 $\pm$ 240 (129–1184)	0.33	261.0 $\pm$ 102.6 (129–688)	0.17
Maximum flow rate (ml/s)	19.89 $\pm$ 7.18 (5–32)	23.42 $\pm$ 12.38 (6.20–63)	0.63	25.3 $\pm$ 5.6 (6.20–63)	0.003
Average flow rate (ml/s)	11.38 $\pm$ 4.14 (3–20)	12.63 $\pm$ 5.94 (4.5–28)	0.74	17.4 $\pm$ 3.2 (4.5–23)	0.001
PVR (ml)	14.07 $\pm$ 19.06 (0–70)	23.39 $\pm$ 40.58 (0–150)	0.79	5.3 $\pm$ 7.5 (0–22)	0.048



Prostate and Acromegaly

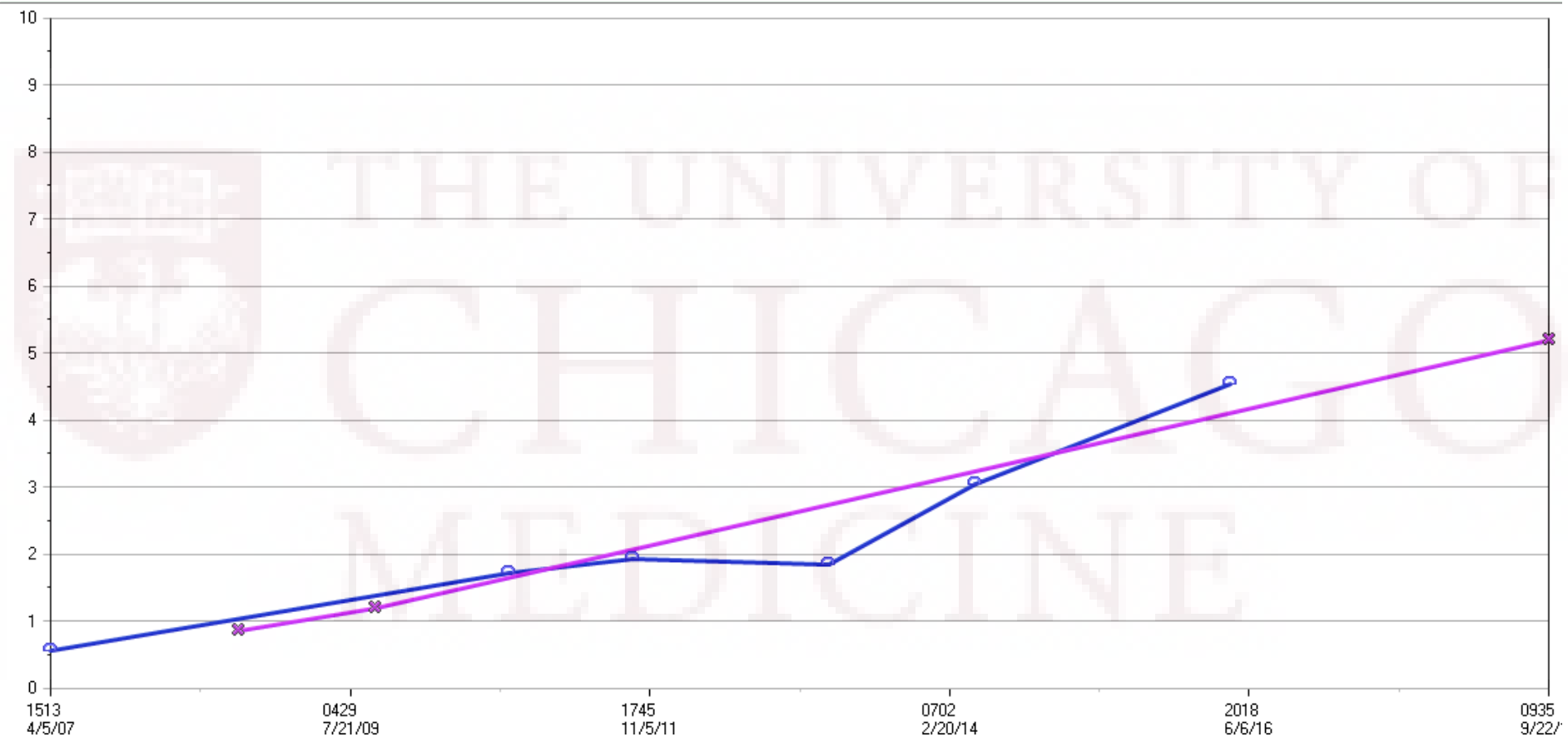
Prostate

- B: Control
- C: Acromegaly
- D: Prostate cancer





Our Patient: PSA



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Summary

- Severe comorbidities make acromegaly a life threatening disease heavily impairing quality of life of affected patients
- Early diagnosis with atypical manifestation should be recognized
- Aggressive treatment is mandatory to avoid the onset, stop the progression, or reverse comorbidities



References

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