Pakistan Endocrine Society

Pakistan Endocrine Cases Collection (PECC) 2022

3rd Edition

PAKISTAN ENDOCRINE SOCIETY

A SEQUENCE OF CLINICAL ENDOCRINE CASES

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PECC-2022

Pakistan Endocrine Case Collection

Questions, Answers & Discussions

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The Society earned national reputation for excellence in the quality of holding meeting and CME programs and tried to improve public health through practice and science of endocrinology.

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PRESIDENT'S MESSAGE

It is a matter of great pride that we are moving forward with a good pace towards the process of continuing medical education. By the grace of almighty Allah, we have been able to bring forth the third edition of Clinical Cases which will prove an important milestone towards achieving the cause of imparting knowledge to health care professionals by Pakistan Endocrine Society.

Medical education is not just a program for improving the knowledge and skill in its recipients, it is also an experience which creates better attitude and expectations.

These clinical cases will prove to be a source of knowledge for health care professionals in general and endocrine fellows in particular. It will be helpful in imparting evidence based knowledge to the health care professionals.

I am very much optimistic that these cases will be very helpful in the brain storming of professionals and a continuous source of stimulation to gain further knowledge in future.

I really acknowledge the valuable input of Dr. Suleman Elahi Malik, Dr. Sumerah Batool, Dr. Musarrat Riaz and Dr. Zareen Khan for this accomplishment.

Dr. Ibrar Ahmed
FCPS (Med), FCPS (Endocrine), FRCP (London)
Consultant Endocrinologist/Assistant Professor
Lady Reading Hospital Peshawar.
President
Pakistan Endocrine Society

FOREWORD

The third edition of Pakistan Endocrine Cases Collection (PECC) is in your hands, and I can recall the historic quotation of Sir William Osler which hung in our Medical Unit-1 at Holy Family Hospital, Rawalpindi when I was doing my residency in Internal Medicine. Sir William Osler famously said; “He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all.” The PECC 2022 fulfills both, you have the patient and the theoretical details in there, making it a perfect voyage in a charted sea. So, get ready to sail!

PECC 2022 is a carefully selected collection on interesting endocrine cases which are either rare or have presented with diagnostic or therapeutic challenges. Our Endocrine fellows-in-training from all across Pakistan have contributed with their cases and elaborated on the history, physical examination findings, differential diagnosis, diagnostic work-up, management and prognosis which is backed by latest scientific evidence and expert input from their teachers and supervisors.

In our health care set-ups, we have to tweak the international management algorithms minutely due to non-availability or non-affordability of certain tests or treatments but we are still able to help and improve our patient care; the PECC 2022 only further assists in this regard. The PECC 2022 promises to improve Endocrine training and practices on one hand and to be helpful for our trainees' post-graduate exams on the other.

I must congratulate President PES, Dr Ibrar Ahmed for the publication of the third edition of PECC. Kudos to him and his entire team for every effort that they have put in to make this happen. It requires lot of commitment and hard work for continuing such an outstanding piece of work every year.

With lots of best wishes,

Dr. Aisha Sheikh

President-elect, Pakistan Endocrine Society

CASES

Pakistan Endocrine Case Collection 2022

Question

Answers

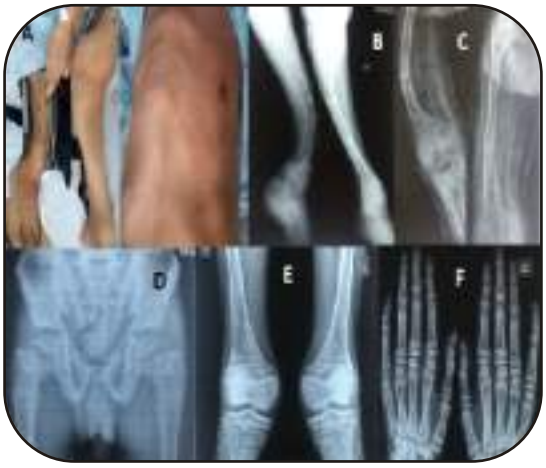
Discussion

Case 1

Dr. Erum Sohail, Dr. Tasnim Ahsan, Drd. Rukhshanda Jabeen,
Dr. Urooj Lal Rehman, Dr. Saima Ghaus
Jinnah Postgraduate Medical Centre, Karachi

Case Scenario

A 14 year male presented in Endocrine clinic in December 2019 with bone pains, bowing of legs, multiple bone deformities and fractures since childhood. He also had loose stools off and on. Patient underwent osteotomy thrice for correction of bone deformities. He received calcium and vitamin D supplements on and off. On examination he had bowing of legs; Chvostek's and Trousseau's signs were positive, there was no alopecia. There was a fracture of right femur. Investigations showed calcium (Ca): 5.3 mg/dl (8.1-10.4), phosphate (PO4): 3.6 mg/dl (4.0-7.0), alkaline phosphatase: 1120 IU/L (upto 600), vitamin D: 23.5 ng/dl (sufficiency > 30) and parathyroid hormone (PTH): 225 pg/ml (15-65). His urinary calcium and phosphate were normal. Skeletal survey showed generalized decrease bone density with coarse trabecular pattern, with multiple osteolytic lesions. 1, 25(OH) Vit D was 150 pg/ml (19.9 79.3).



A; Bowing of legs, prominent chest and multiple bone deformities
B & C; X-ray of legs showing multiple fractures, generalized osteopenia, loser zones
D, E & F; Radiological features of metabolic bone disease

What is the diagnosis?

A. Vitamin D resistant rickets type 1
B. Vitamin D resistant rickets type 2
C. X-linked hypophosphatemic rickets (XLH)
D. Vitamin D deficient rickets
E. Autosomal dominant hypophosphatemic rickets

Answer: B

Discussion:

Rickets is classified as calciopenic or phosphopenic according to the predominant mineral deficiency. Calciopenic rickets commonly results from calcium deficiency, but can also be caused by decreased activity of vitamin D, such as lack of conversion of 25(OH) D to the active metabolite 1, 25(OH) 2D leading to vitamin D-dependent rickets type 1 (VDDR-I); or resistance to the active metabolite, known as vitamin D-dependent rickets type II (VDDR-II), due to mutations leading to dysfunction of the vitamin D receptor[1]. Phosphopenic rickets is mainly due to renal phosphate wasting, which is usually hereditary. X-linked dominant hypophosphatemic rickets accounts for more than 80% and the remaining 20% are due to autosomal dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, and hereditary hypophosphatemic rickets with hypercalciuria[2].

VDDR-II is a rare autosomal recessive disorder caused by mutation in the vitamin D receptor gene, leading to end-organ resistance to $1,25(OH)_2$Vitamin D. Affected children usually appear normal at birth, but develop rickets within the first 2 years of life. A unique feature of the syndrome is alopecia, which is seen in approximately two-thirds of cases and is a marker of disease severity[3].

The laboratory findings include low serum calcium and phosphate and increased serum alkaline phosphatase activity with secondary hyperparathyroidism and markedly increased PTH levels. Serum 25(OH)D values are usually normal and 1,25(OH)2D levels are substantially increased. This clinical finding distinguish VDDR II from 1a-hydroxylase deficiency in which serum 1,25(OH)2D values are low or absent[4].

Patients with HVDRR improve clinically and radiologically when treated with pharmacologic doses of vitamin D ranging from 5000 to 40,000 IU/d, 20 to 200 mg/d of 25(OH)D3, and 17 to 20 mg/d of 1,25(OH)2D3[5]. When patients fail to respond to vitamin D or 1,25(OH)2D3, intensive calcium therapy is also used[6]. Our patient responded very well to high doses of Calcium, Vitamin D and alphacalcidiol. Clinical and biochemical improvement was evident within 3 months of initiation of treatment.

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Case 2

Dr. Hina Shahabuddin, Dr. Zareen Kiran, Dr. Akhtar Ali Baloch, Dr. Nazish, Dr. Rajesh
National Institute of Diabetes and Endocrinology, Dow University of Health Sciences, Ojha Campus

Case Scenario:

35 year old gentleman diagnosed with ESRD 3 years back on hemodialysis was referred by nephrologist in October 2021 to us in the National Institute of Diabetes and Endocrinology OPD with presenting complaint of bilateral toes pain and fore feet pain for 5 months.His past medical history revealed TB for which he took ATT for 9 months and ESRD.Family history was unremarkable. On examination he was vitally stable, pale and no neck mass was palpable. Rest of the systemic examination was unremarkable.

His lab workup of September 2021 showed:
Urea 119.84mg/dl
Cr 9.82mg/dl
Na 139mEq/L
K 4.6mEq/L
Chloride 106mEq/L
HCO3 15.9mWq/L
Calcium 9.1mg/dl
Phosphorus 6.9mg/dl
Vit D 11 ng/ml
PTH >2500pg/ml
Magnesium 2.55mg/dl
Alkaline Phosphatase >1000 pg/ml
TSH 1.85 uIU/ml

Ultrasound neck showed a fairly defined lobulated hypoechoic lesion measuring 1.6 X 1.3cm visualised outer to the left lobe of thyroid and in between left lobe and carotid vessels. No vascularity seen in colour doppler imaging, possibility of enlarged parathyroid gland.

Sestamibi MIBI Parathyroid scintigraphy findings were in favour of functioning parathyroid adenoma over the left lobe of thyroid gland.

He underwent parathyroidectomy of left parathyroid gland. Biopsy showed low grade tumour measuring 2 x 1cm showing capsular and vascular invasion and focal invasion into the adipose tissue and attached small amount of thyroid tissue. There was no perineural invasion.

What is the diagnosis?

A. Primary Hyperparathyroidism
B. Secondary hyperparathyroidism
C. Tertiary Hyperparathyroidism
D. Parathyroid carcinoma
E. Vitamin D deficiency

Answer: D

Discussion:
Presence of underlying ESRD makes primary hyperparathyroidism unlikely. Secondary hyperparathyroidism could be the possibility however, high normal calcium despite low vitamin D levels goes against the diagnosis. Vitamin D deficiency with underlying ESRD could result in raised PTH but high normal calcium goes against the diagnosis. Tertiary hyperparathyroidism could be the possibility due to the presence of high normal calcium despite vitamin D deficiency. However PTH levels greater than 1000pg/ml makes parathyroid carcinoma the most likely diagnosis. Parathyroid carcinoma is a rare endocrine tumour.

The clinical and biochemical presentation of benign parathyroid disease and parathyroid carcinoma overlaps. However, some features increase the likelihood of parathyroid cancer such as the incidence of parathyroid cancer is equal between the two sexes whereas hyperparathyroidism of benign etiology affects more females (3:1). Contrary to parathyroid adenomas, patients with parathyroid carcinomas are more likely to have symptoms, large tumour size, bone and kidney disease, marked hypercalcemia, and very high serum PTH concentrations (5- to 10-fold higher than the upper limit of normal) [1-4]. The classic pathologic features of a trabecular pattern, mitotic figures, thick fibrous bands, and capsular and vascular invasion, when present, are highly suggestive of parathyroid carcinoma [5,6]. The two criteria upon which a more definitive diagnosis of parathyroid cancer can be made are local invasion of contiguous structures or lymph node or distant metastases. Gross invasion beyond the capsule and including extracapsular vascular invasion appear to correlate best with cancer diagnosis [7]. The use of an immunohistochemical panel that includes parafibromin, galactin-3, PGP9.5, and Ki67 has been suggested to assist in diagnosing parathyroid carcinoma, with a sensitivity of 80 percent and specificity of 100

percent [8]. Preoperative localization studies do not reliably distinguish parathyroid carcinoma from adenoma.Surgery is the cornerstone of therapy for parathyroid carcinoma and in case of its local recurrence or metastatic disease. Radiotherapy and chemotherapy has been disappointing. The initial treatment of hypercalcemia in patients with parathyroid carcinoma includes hydration with intravenous fluids to replenish fluid volume and intravenous bisphosphonates. With disease progression, hypercalcemia typically becomes refractory to initial medical therapy. The addition or substitution of cinacalcet has been reported to successfully control hypercalcemia in some patients. Denosumab is an option for patients who have hypercalcemia refractory to both bisphosphonates and cinacalcet.

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Case 3

Dr. Muhammad Ubaid, Dr. Ibrar Ahmed
Lady Reading Hospital, Peshawar

A 54-year-old lady with history of mildly impaired left ventricular systolic function and was under treatment from cardiologist, referred for assessment of thyroid swelling. On initial evaluation she was complaining of palpitation, shortness of breath, lower back pain and thyroid swelling. On examination pulse 96 /min BP 140/80 mm hg .no thyroid eye sign and bilateral multinodular enlarge thyroid. rest examination was not remarkable. Base line investigations were in normal range. Serum calcium and vitamin D were also normal. ECHO show ejection fraction of 48 percent. Thyroid function test shows free T4 1.04 ng/dl, T3 1.5 nmol /l, TSH 0.002 iu /ml. Thyroid scan was suggestive of multinodular goiter. DEXA scan of lumbar spine show T score of -3.1 and hip joint T score of 2.7. which one of the following is correct answer?

A: Observe the patient

B: start patient on antithyroid drugs

C: Start patient on antithyroid and bisphosphonate

D: Start patient on calcium and vitamin d only

E: Start patient on beta blockers only.

Answer: C

Discussion

Our patient thyroid function test shows normal t 3, t 4 and suppressed TSh suggestive of subclinical hyperthyroidism leading left ventricular systolic dysfunction and osteoporosis. Patient was started on antithyroid drugs and bisphosphonates and show significant improvement of back pain and palpitations. Patient will be followed in OPD with repeat thyroid function test.

Osteoporosis (OP) is a skeletal disease characterized by reduced bone strength which predisposes to an increased risk of fracture. Bone strength is primarily a function of bone density and quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and the amount of bone loss. Bone quality refers to macro-and micro-architecture, bone turnover, size, accumulated damage (e.g. micro fractures) and mineralization[1].The definition of osteoporosis (OP) by the World Health Organization (WHO) is densitometric and non-clinical and is based on the measurement of bone mass with the DEXA method in the spine or hip. It establishes four categories: normal, osteopenia, osteoporosis and established osteoporosis. The presence of pathological low bone mass, osteopenia or osteoporosis, is the best indicator of fracture risk for the region where the bone mass is measured, hence its interest, since bone loss is asymptomatic until it produces its natural consequence: the osteoporotic fracture[2].

Some of the most important aspects of preventing osteoporosis include eating a healthy diet, getting regular exercise, and avoiding smoking regular calcium and vitamin D intake[3].certian medications like steroids increase risk of osteoporosis and should not be used for prolonged time[4]. Experts suggest screening for osteoporosis for women 65 years and older and for women under 65 who have gone through menopause and have risk factors (such as past fracture, certain medical conditions or medications, or cigarette or alcohol use). Screening involves physical examination, discussion of the person's history, and measurement of bone density through imaging test[5]. Depending on your situation, your health care provider may also recommend medication or hormonal therapy. Most people at high risk for fracture are treated with drugs that slow the breakdown and removal of bone (anti-resorptive drugs). For people with severe osteoporosis at very high risk for fracture, a drug that stimulates new bone formation (anabolic drug) [6]. Bisphosphonates are medications that slow the breakdown and removal of bone (ie, resorption). They are widely used for the prevention and treatment of osteoporosis in postmenopausal women's sometimes prescribed. Commonly prescribed bisphosphonates are alendronate, residronat, ibandronat etc[7].other drugs used include selective estrogen receptor modulators, PTH related peptide, denosomab, harmone replacement therapy etc[8].

Subclinical hyperthyroidism is characterized by a low or undetectable concentration of serum thyrotropin (TSH) with free tri-iodothyronine (FT3) and free thyroxine (FT4) levels within laboratory reference ranges. Although there is evidence that subclinical hyperthyroidism may have adverse tissue effects, the level of TSH suppression that determines these negative effects, and the management and treatment of this condition remain controversial issues[9].The definition of subclinical hyperthyroidism is based only on laboratory, not clinical, criteria and the term probably represents a misnomer[10.] Subclinical hyperthyroidism may be caused by exogenous or endogenous factors, and may be transient or persistent [11]. Adverse tissue effects are similar, whatever the cause of subclinical hyperthyroidism and mainly depend on the duration of the disease. The exogenous form of

subclinical hyperthyroidism is usually related to TSH-suppressive therapy with L-thyroxine (L-T4) for a single thyroid nodule, multinodular goitre, or differentiated thyroid carcinoma. In addition, TSH may be unintentionally suppressed during hormone replacement therapy in about 20% of hypothyroid

patients [12]. The endogenous form is usually related to the same causes as overt thyrotoxicosis, namely Graves' disease, autonomously functioning thyroid adenoma, and multinodular goitre. The two latter causes are particularly frequent in the elderly, especially in areas of iodine deficiency[13].

'subclinical' hyperthyroidism reduces the quality of life, affecting both the psycho and somatic components of well-being, and produces relevant signs and symptoms of excessive thyroid hormone action, often mimicking adrenergic overdrive. 'Subclinical' hyperthyroidism exerts many relevant effects on the cardiovascular system. It is usually associated with a higher heart rate and a higher risk of supraventricular arrhythmias[14]. In addition, 'subclinical' hyperthyroidism may accelerate the development of osteoporosis, and hence increase bone vulnerability to trauma, particularly in postmenopausal women with a pre-existing predisposition. subclinical' hyperthyroidism and its related clinical manifestations are reversible or may be prevented by timely treatment[15]. In patients treated for benign thyroid nodular disease, the dose of L-T4 should be carefully customized, keeping serum TSH near, but not below the lower limit of the normal reference range. In patients on hormone replacement therapy for hypothyroidism, periodic evaluations of serum TSH levels should ensure that replacement therapy is not under- or over-prescribed. In patients with differentiated thyroid cancer with a high risk of recurrences or with known metastatic disease, in whom long-term sustained TSH suppression is warranted, â-blockade and bone-sparing drugs may be considered, in particular in patients above the age of 45 years. treatment of endogenous subclinical hyperthyroidism should be considered in the presence of TSH <0.1 mU/l especially for patients who are older than 60 years and for those with an increased risk for heart disease, osteopenia or osteoporosis, or for those with clinical symptoms suggestive of hyperthyroidism[16].

Subclinical hyperthyroidism is an important cause of cardiovascular and musculoskeletal complications.by timely diagnosis and intervention these complications can be prevented and treated

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Case 4

Dr. Mohammad Salman Aamir, Dr. Tahir Ghaffar
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Case Description

A 29 years old man was referred to Endocrine unit for the review of his persistently raised TSH despite optimal dosing of Thyroxine for 2 years. He was initially diagnosed and treated for Hyperthyroidism with Neomercazole and then Radioactive Iodine (RAI). POST RAI he developed Hypothyroidism and was subsequently treated with optimal doses of Thyroxine. Despite optimal doses of Thyroxine TSH remains elevated. Previous Thyroid Function Tests (TFTs) also showed persistently raised T3T4 and Raised TSH. Pt was clinically Thyrotoxic.

Laboratory test Results:

Date	TSH (0.3-4.2)	T4 (5.2-14.1)	Free T4(0.9-1.7)	T3(0.8-2.0)
Dec 2015	5.9		48.9	
Oct 2016	2.6		22.4	6.2
Oct 2017	4		23.3	2.5
Aug 2020	22.73		7.7	6.51
Sep 2020	28.68	24.86		5.9

What are investigations required? differential diagnosis, management?

A. TSH Secreting Pitutary Adenoma (TSHoma)
B. Partial Thyroid Hormone Resistance
C. Generalized Hormone Resistance
D. Factitious Hyperthyroidism

Answer: A

TSH-secreting pituitary adenomas (TSHoma) are rare pituitary tumors that secrete an abnormal Thyroid Stimulating Hormone (TSH) which constitutes up to 1%2% of all pituitary adenomas. It is present with signs and symptoms of hyperthyroidism and they are characterized by elevated serum levels of free thyroid hormones with measurable TSH levels. Patients often remain misdiagnosed for years. This case report is to emphasize the importance of diagnosing it early and accurately to ensure timely management and relief of symptoms before perpetual damage is done.

TSHoma is highly under diagnosed. It is important to consider the pitfalls in diagnosis where normal or low alpha sub unit levels could lead to dubious differentials. The use of advance technology i.e functional MRI scans to confirm diagnosis should be carried out early on leading to timely treatment options including radiotherapy and surgery.

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Beck-Peccoz, P., Giavoli, C. and Lania, A., 2019. A 2019 update on TSH-secreting pituitary adenomas. *Journal of endocrinological investigation*, *42*(12), pp.1401-1406.

Case 5

Dr. Nauman Wazir, Dr. Alamin Alkundi
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Case Scenario:

A 47 years old lady who was had been under review of our Endocrine department since 2008. She first presented with symptomatic fatigue, and body aches. Her Lab parameters are shown in chronological order in the table given. Nuclear medicine imaging (I 123 MIBI scan done in April 20009 showing an ill-defined focal uptake in relation to lower pole of right thyroid gland) was consistent with primary hyperparathyroidism secondary to right lower parathyroid adenoma. Parathyroidectomy was performed in September 2009 as per the then published guidelines. Histology then demonstrated proliferation of parathyroid chief cells surrounded by thin fibrous capsule. The cells were arranged in solid nests and sheets without adipose tissue component. In one small focus there was significant mitotic activity and cells showed mild nuclear atypia but significant mitotic activity was not evident. There was no evidence of desmoplastic fibrous band formation. After the initial parathyroidectomy, she had a recurrence of primary hyperparathyroidism as evident by high serum calcium and PTH levels alongside subtraction imaging of I 123 scan showing focal uptake in relation to lower pole of left thyroid gland reporting it as "suspicious for parathyroid adenoma". Yet another parathyroidectomy was performed in June 2011. In the histology performed on the specimen after the procedure three parathyroid glands were identified, two of which appeared to be unusually large. The histological features along with the biochemical history of hypercalcemia and hyperparathyroidism and her previous procedure led the histologist to believe this was parathyroid hyperplasia and not multiple adenomas. Even after two surgeries her serum calcium levels remained elevated or at the minimum came to upper limit normal throughout the entire period. Her PTH either remained high or normal. She remained symptomatic after the two surgeries. A dual isotope parathyroid study (20 MBq I-123 and 933 MBq technetium with digital subtraction) done in June 2021 was suggestive of right lower parathyroid adenoma. In her last clinic consultation she was still symptomatic of hpercalcemic symptoms including lethargy and body aches. She was 5 feet 8 inches tall and weighed 72 kgs. Her Blood Pressure was 134/87. There were neck scars well healed from previous surgeries. Abdomen was soft and non-tender.

Table 1. Labaratory Parameters Of The Patient

Date	S Calcium (mmol/L)	PTH (pmol/L)	Vit D (nmol/L)	24 hour Ur Cal (mmol/24 hours)
29/12/2008	3.0	96		
02/01/2009				2.8
02/03/2009	3.0	117		
22/06/2009	3.1			
04/01/2010	2.9	46		
16/08/2010	2.8			
08/12/2010	2.6			
31/01/2011	2.8			
06/05/2011	2.7			
10/06/2011	2.7	8.6		
04/07/2011	2.7	7.3		
05/09/2011	2.7	5.6		
30/11/2011				2.4
01/12/2011	2.6	11.0		
05/03/2012	2.7	5.1		
10/08/2012	2.7	6.2		
13/09/2012	2.7	5.0		
05/03/2013	2.9	3.8		
06/02/2013		4.5		
15/03/2013		3.1		
02/05/2013	2.7	4.7		
28/08/2013	2.8	6.1		
12/05/2014	2.6	4.8		
25/11/2015	2.7	10.2		
04/04/2016	2.6			
09/06/2016				4.3
21/07/2017	2.6			
24/08/2018			49	
27/06/2018	2.6	8.3		
11/04/2019	2.8	6.7	<18	
27/02/2020	2.7	11.0		
04/08/2020	2.7	10.2	78	
19/01/2021	2.5	7.3		
11/11/2021	2.7	9.3	31	1.9
14/06/2022	2.6		49	

What is the diagnosis?

A. Familial Isolated hyperparathyroidism.
B. Familial Hypercalciuric Hpercalcemia
C. Multiple Endocrine Neoplasia Type 1
D. Multiple Endocrine Neoplasia Type 2A
E. Multiple Endocrine Neoplasia Type 4

Answer: B

Discussion

Familial isolated hyperparathyroidism (FIHP) is a genetically heterogeneous, non-syndromic, clinically defined diagnosis of exclusion in kindreds with two or more cases of HPT but lacking the specific features of MEN1, MEN2A, HPT-JT (Familial hyperparathyroidism Jaw Tumor Syndrome) or FHH.[1] Typically only one of the four parathyroid glands is affected It does not usually present with recurrent hyperparathyroidism. MEN 1 is also associated with pituitary or pancreatic tumors but this patient had no hint in either history or examination to extra parathyroid tumors. MEN2 is associated with Pheochromocytoma and Medullary Thyroid Cancer. She previously underwent two neck surgeries without any findings of a thyroid nodule. Her Metanephrines done were in normal range and she was normotensive. Multiple Endocrine Neoplasia Type 4 (MEN4, sometimes called MENX) is a syndrome originally described by Pellegata et al in a multi-generational family with MEN1-like features, including a proband with acromegaly and HPT but lacking MEN1 mutation.[2]

Her Urinary Calcium was normal or low throughout. Given her age of onset of her primary hyperparathyroidism, we decided to conduct a complete genetic test panel to rule out Multiple Endocrine Neoplasia (MEN) 1, 2, and other familial hyperparathyroidism syndromes by doing analysis of all the coding regions and exon/intron boundaries of the AP2S1, CASR, CDC73, CDKN1B, GNA11* and MEN1 genes and exons 5, 7, 8, 10, 11, 13, 14, 15, 16 of the RET gene by targeted next generation sequencing. The genetic test revealed heterozygous nonsense mutation on CASR gene responsible consistent with a genetic diagnosis of CASR-related Familial Hypocalciuric Hypercalcemia. (Fig. 1). Familial Hypocalciuric Hypercalcemia is a autosomal dominant genetic condition causing reduced activity of Calcium sensing Receptor (CaSR). This leads to mild hypercalcemia with normal or mildly elevated parathyroid hormone (PTH) levels[1]. In most of the cases, familial hypocalciuric hypercalcemia (FHH1) results from loss-of-function mutations in the calcium-sensing receptor (CaSR) gene on the long arm of chromosome 3 in over 85% of cases 2,3 .The patient presents with the milder disorder and incidentally has a mild elevation

in calcium and normal or mildly elevated PTH. Familial hypocalciuric hypercalcemia remains an important differential diagnosis of Primary hyperparathyroidism (PHPT). In both the conditions serum calcium and PTH levels are high. In usual clinical practice calcium creatinine clearance ratio (CCCR) is usually used to differentiate between the two conditions. Around 80% of FHH patients demonstrate urinary calcium excretion < 2.5 mmol/day and CCCR < 0.01, while ~ 20% show CCCR 0.010.02 8. In contrast, PHPT patients usually have CCCR > 0.02, while ~ 20%, who have concomitant vitamin D deficiency show CCCR < 0.01 [10]. Patients with a homozygous mutation can have severe hypercalcemia with marked hyperparathyroidism, fractures, and failure to thrive. Other two rare forms of familial hypocalciuric hypercalcemia, FHH2 and FHH3 are caused by a mutation on chromosome 19 [6,8] . The loss of function mutations in the (CaSR) gene in the parathyroid gland increases the set point for calcium sensing. It makes the parathyroid glands less sensitive to calcium, and a higher than normal serum calcium level is required to reduce PTH release. In the kidney, this defect leads to an increase in tubular calcium and magnesium reabsorption resulting in hypercalcemia, hypocalciuria, and frequently high normal levels of serum magnesium [3,8-10]. FHH is a very rare benign inherited condition that typically does not require parathyroidectomy in normal circumstances. Patients with FHH usually have no symptoms and are often diagnosed by chance during routine blood examination. Weakness, fatigue, issues with concentration, constipation, polyuria, headache, and polydipsia have been reported by some people with FHH. The calcimimetic drugs are sometimes effective to improve hypercalcemic symptoms such as muscle aches, anorexia, polydipsia and constipation [11]. Rarely, people with this disorder experience pancreatitis or a chondrocalcinosis [12]. Primary hyperparathyroidism, on the other hand, requires intervention as per the published guidelines [13]. Our patient who was treated for primary hyperparathyroidism turned out to have concomitant FHH in the last clinic consultation. FHH is a very rare genetic disease. Co-existing FHH and hyperparathyroidism is even a rarer occurrence, and limited research into the association of these two clinical entities has been done. Our team reported a case like this before [14]. The biochemical picture in the evaluation of these two clinical entities occurring together is elevated serum calcium levels, hypophosphatemia, elevated parathormone levels and low urinary calcium levels. Interestingly, throughout the entire period her 24 hour Urinary Calcium was never higher than normal range, and low only on one occasion, when she was in Vitamin D insufficient state. Lesley S.E et al. [15] in 2012 described two similar cases with FHH (one of whom had a genetically confirmed CASR mutation) and primary hyperparathyroidism. Their report suggested that surgical intervention helps to reduce calcium levels, improve symptoms, and prevent complications from hypercalcemia but may not completely normalize serum calcium levels[15].

GENOMIC LABORATORY REPORT

Report to:
Dr N Wazir
William Harvey Hospital
Ashford
(copy to Viapath Genetics Laboratory)

Patient Name:
Date of Birth:
Sex:
NHS No.:

Reason for testing
Diagnostic: To investigate the cause hyperparathyroidism.

Result summary
Consistent with a genetic diagnosis of CASR-Related Familial Hypocalciuric Hypercalcaemia

Result
is heterozygous for a likely pathogenic CASR nonsense variant (details below, see Appendix 1). Monoallelic pathogenic CASR variants cause Familial Hypocalciuric Hypercalcaemia type 1 (MIM145980).

Implications of result
Each of offspring would be at 50% risk of inheriting this variant and developing Familial Hypocalciuric Hypercalcaemia. Testing for family members is available by referral to Clinical Genetics.

Date issued: **28/07/2022** Authoriser: **Chris Bowles**

TECHNICAL INFORMATION

Variant details

Gene	Zygosity	HGVS Description	Location: GRCh37 (hg19)	Classification
CASR	Heterozygous	NM_00388.4:C.2157G>A p.Trp719Ter	Chr3:g.122002958G>A	Likely pathogenic

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Case 6

Dr Nazish Fatima, Dr Zareen Kiran, Dr Hina Shah, Dr. Rajesh Godhwani
National Institute of Diabetes and Endocrinology, DUHS, Karachi

Case Scenario:

A 28 years old, female, single, resident of Karachi presented on 11th March 2022, in outpatient department (OPD), at the National Institute of Diabetes and Endocrinology (NIDE), Dow University of Health Sciences, with chief complaints of irregular menstrual cycle since menarche, also complaining of expressive galactorrhea. There was no history of headache, blurring of vision, visual loss/ field defect, weight gain, hair loss/cold intolerance. She was not on any regular medications at the time of presentation. She had h/o primary amenorrhea at 15 years of age, was given oral contaceptive pills (OCPs) for 3-4 moths and attained menarche. At 20 years of age she received bromocriptine for 3-4 months for secondary amenorrhea and galactorrhea, as her prolactin level was high. Her cycles remained irregular and in April 2020, she consulted us, her prolactin level was high. She was initiated on cabergoline, after 5-6 months of therapy as her symptoms resolved, prolactin levels improved she stopped cabergoline and lost to follow up.

On physical examination: Weight: 62 kg, Height: 157cm, BMI: 25.2 kg/m^2. Her resting pulse: 82bpm regular, B.P.: 121/70 mmHg with no orthostatic hypotension. Secondary sexual characteristics were normal with Tanner's stage 5. There was no hirsutism/virilization. Systemic examination was unremarkable with normal visual field examination.
Laboratory test results in March 2022:

Serum Prolactin >200 ng/ml (3.8-23 ng/ml),

FSH: 3.43 mIU/ml (1.4-9.9 mIU/ml)

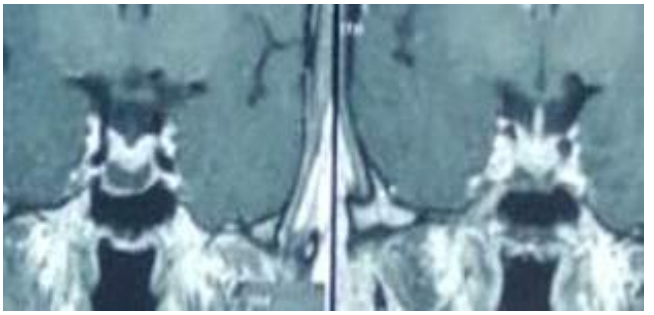
LH: 0.84 mIU/ml (1.7-15 mIU/ml)

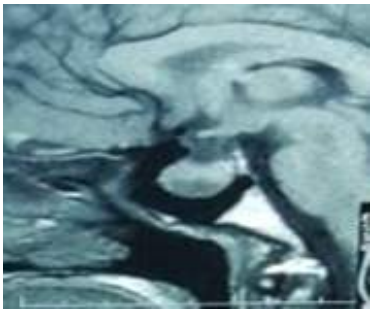
TSH: 1.57 uIU/ml (0.4-4.2 uIU/ml)

Free T4: 0.73 ng/dl (0.8-2.7 ng/dl),

8 AM Cortisol 9.06 ug/dl (5-25 ug/dl)

MRI Pituitary showing an abnormal signal intensity area in the region of the sella causing focal bulge of sellar floor. It approximately measures 1.4x1.1x0.6cm. This could represent rathke cleft cyst. There are two areas of differential enhancement seen in left side of pituitary gland, one of them adjacent to cavernous sinus measures 0.3x0.2cm. Another one along the inferior aspect measures 0.3x0.25cm, likely representing pituitary microadenomas. Pituitary stalk appears central with normal optic chiasm





She was restarted on cabergoline 0.5mg twice/week. Her cycles are still irregular but her galactorrhea resolved. Her hormonal profile is:
Serum prolactin: >200 ng/ml (3.8-23 ng/ml)
FSH 7.03 mIU/ml (1.4-9.9 mIU/ml),
LH 14.49 mIU/ml (1.7-15 mIU/ml),
Free T4 0.89 ng/dl (0.8-2.7 ng/dl),
8AM Serum Cortisol 12.03 ug/dl (5-25 ug/dl)

Now which of the following is the most appropriate management plan?

A. Refer for transsphenoidal surgery
B. Change cabergoline to bromocritine
C. Continue cabergoline at the same dosage
D. Increase the cabergoline dosage
E. Refer for stereotactic radiosurgery

Answer: D

Discussion:

Rathke's cleft cysts (RCC) are benign lesions developed from epithelial remnants of Rathke's pouch. The Rathke's pouch has an anterior and posterior wall in addition to a central embryonic cleft. The anterior pituitary and the pars tuberalis arise from the anterior wall, while the posterior portion develops into the pars intermedia. The central lumen becomes the Rathke cleft, and normally regresses. However, this structure may persist and enlarge, resulting in the formation of a cyst. The age of presentation for RCCs is typically between the third and fifth decades of life. (1) Although RCCs found in 13% to 33% of the general population at autopsy. (2) Most tend to be asymptomatic or clinically silent with surgical intervention only indicated when they become symptomatic or show documented growth. (3)The most common presenting symptoms are headaches, visual disturbances, and endocrinopathies. Rarely, they bleed, causing apoplexy, or rupture, causing aseptic meningitis. (4) As the anterior pituitary lobe may at times clonally expand to form a pituitary adenoma, RCCs and these tumors have a common embryologic ancestry. Very rarely, pituitary adenomas may occur concurrently with an RCC. (5) There is yet no direct explanation for the cause of concurrent findings of RCC and pituitary adenoma beyond case reports and case series descriptions in the literature. (6) Next to growth hormone, Prolactin was the most commonly hypersecreted pituitary hormone.(7) In this scenario, she was having incidental finding of RCCs with a microadenomas and was not complaining of any pressure symptoms, like headache, visual loss or visual field defect because of RCC, but was symptomatic for hyperprolactinemia.

Treatment for pituitary masses typically includes normalization of the hormonal abnormalities and alleviation of mass effect that was not present in our case. Medical therapy for hormone secreting tumors and surgical therapy is recommended for hormone-secreting tumors resistant to medical therapy, acute hemorrhage and masses impinging on the surrounding structures. In patients with prolactinoma, dopamine agonists, especially cabergoline, are quite efficient. Dopamine agonists decrease plasma prolactin levels and induce shrinkage in most patients and can be ceased in some of them. (8) Operative management of pituitary adenomas and suspected RCCs involves transsphenoidal resection. This approach is minimally invasive and has been proven to safely excise these masses completely, allowing for the restoration of pituitary function. (9) Recurrence of RCCs is a well-known complication after surgery with reported recurrence rates as high as 30% in large case series. Other surgical complications are endocrinopathy, visual symptoms, headache, CSF leak or hematoma (3) However, the recurrence rates for pituitary tumors such as GH-secreting adenomas are significant, ranging from 5.4% to 10%. (10) Therefore,

adjuvant therapy such as medical or radiosurgery may be indicated. (8) On the other hand, if the risk of recurrence of RCCs is low, further treatment rarely necessary, although suprasellar extension, large cyst size and packing of the sella are risk factors for recurrent cyst formation. In this vignette, her repeat MRI after 5 months of cabergoline was not showing any abnormally enhancing lesion in pituitary gland to suggest adenoma which was present in previous MRI and there was no interval change in her RCCs without any evidence of hemorrhage or mass effect. She clinically became partially asymptomatic with resolution of her galactorrhea but her cycles were still irregular, so after discussing her case in pituitary multidisciplinary team (MDT) meeting, decision was taken to up-titrate her cabergoline dose according to her symptoms and prolactin level with conservative management and monitoring of her RCC through annual imaging and/or early if she develops pressure effects or visual abnormality/field defects. Although the interval of follow-up should always be individualized to account for changes in the patient's clinical presentation, a rapid increase in the size of these cysts appears to be rare. Therefore, we suggest that an initial MRI follow-up interval of 1 year is reasonable with the option of increasing this interval if the RCC remains stable in size. For now, we propose that in the absence of clear compressive effects on structures such as the optic chiasm and given the potential for adverse outcomes with surgery, the optimal management of most RCCs consists of surveillance by imaging at regular intervals.(11)

We increased her cabergoline dose to 0.5mg three times per week after and after 1 month her prolactin level reduced to 75 ng/ml and her cycles became regular. She is in follow up with monitoring of prolactin 2-3monthly and plan to repeat MRI annually/ or if symptomaic.

In the absence of pressure symptoms, it is reasonable to manage patients with RCCs conservatively. However, surgical cyst removal appears to be indicated and safe for patients with larger, symptomatic RCCs. TSS is the safest and most effective route. Simple cyst drainage has a high rate of improvement in pituitary gland function, visual function and headache resolution with low complication rates and symptomatic recurrence risk. These findings stress the importance of careful case selection and potential utility of volumetric assessment for patients with RCCs.

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Case 7

Dr. Zareen Kiran, Dr. Nazish Fatima, Dr. Hina Shah, Dr Khalil Sheikh
National Institute of Diabetes and Endocrinology, DUHS, Karachi

Case Scenario:

21 years old female, single, resident of Karachi presented on 2nd Sept 2021, in outpatient department, at the National Institute of Diabetes and Endocrinology, Dow University of Health Sciences, with chief complaints of irregular periods and weight gain for 2 years. She was alright then she gradually developed scanty menstrual flow, with around 2-2.5 month's interval in between each cycle.There is no history of dysmenorrhea, she had weight gain of 10kg in 9-10 months along with acne and hirsutism.

She had attained menarche at the age of 15 years and had regular menstrual cycles thereafter until 2 years back. Her past history was unremarkable. Prior to her presentation, she had been diagnosed with Polycystic ovary syndrome (PCOS)-spectrum disease for which she took Tab. Diane-35 for 1.5 years, and left 4 months back. She was on topical creams, regular waxing and also took laser therapy for hirsuitism. Her mother is hypertensive and paternal aunt is diabetic.

There is no history of similar disorders in the family, she has 3 brothers and 2 sisters all are healthy and alive. At the time of presentation she was not on any regular medications, and there was no history of addiction.

On examination: she was overweight with B.P. of 150/96 mmHg, Pulse: 76bpm, Weight: 62kg, Height: 154cm, BMI: 26.1 kg/m^2. She had evidence of acanthosis nigricans and acne on chin, forehead, back and chest . Her Ferriman-Gallway hirsutism score was 17, with terminal hair on upper lips, chin, side burns, chest, back, lower abdomen. Secondary sexual characteristics were normal with Tanner's stage 5. There were no signs of virilization. She did not have any evidence of central adiposity or striae, moon face, easy bruising, skin thinning or proximal myopathy. Systemic examination was unremarkable. She had some investigations done prior to her prestation and are shown below:

Her CBC and Serum electrolytes were normal.

Laboratory Test	Results	Reference Range
TSH	4.1	0.4-4.2 uIU /ml
FSH	2.7	1.4-9.9 mIU /ml
LH	0.76	1.7-15mIU /ml
Serum Prolactin	19.1	3.8-23 ng/ml
Estradiol	<12	19.5-144.2 pg/ml
Serum Testosterone	75.8	8.4-48.1 ng/dl
Free Androgen Index (FAI)	1.36	0.5-6.5%
Sex hormone binding globulin (SHBG)	192.1	26-110nmol/L
DHEA-sulphate	875	35-430 ug/dl
Serum 17-OHP	1.202	<1.9 ng/ml
After ACTH 17-OHP	3.86	<9.9 ng/ml

Note: She was on OCP at the time of above of investigations (Investigations done on 12th June 2021)
Ultrasound Pelvis: Polycystic ovaries bilaterally.
CT-scan Abdomen with contrast: (17th July 2021)

Bulky left adrenal gland also showing hypodense area of HU of 22 on plain study with minimal post contrast enhancement up to 0.5x 0.6cm in size. Right adrenal gland is unremarkable.

Further testing illustrated the following results: (on 27th Sept 2021)

Laboratory Test	Results	Reference Range
Serum Testosterone	144.8	8.4-48.1 ng/dl
SHBG	17.9	26-110nmol/L
FAI	28.0	0.5-6.53%
Plasma ACTH	17.1 pg/ml	
Serum DHEA-SO4	>1000	35-430 ug/dl
Serum Androstenedione	8.52	0.3-3.3 ng/ml

Overnight Dexamethasone Suppression Test Serum Cortisol: 1.0 (<1.8 ug/dl)

After low dose Dexamethasone suppression:

Serum Testosterone: 36.73 ng/dl, Serum Cortisol: 0.5 ug/dl, DHEA-SO4: 153 ug/dl, serum Androstenedione: 0.982

MRI Pelvis With contrast: (24th Sept 2021)

Right ovary is about 4.9x2.3x3.2cm. Multiple small follicles seen at periphery, largest one about 0.8cm. Left ovary is about 2.9x3x2.9cm. MRI Suggestive of bilateral PCOS.

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

A. Left adrenalectomy
B. MRI pituitary protocol
C. Adrenal venous sampling
D. Right oophorectomy
E. Restart Oral contraceptive pills

Answer: C

Discussion:

"Hyperandrogenism" is a term used to describe the most common clinical signs in women with hyperandrogenemia: hirsutism, acne, and alopecia. The most commonly diagnosed conditions associated with hyperandrogenism in reproductive-age women are ovulatory disorders and polycystic ovary syndrome (PCOS). (1) Other causes can be predominantly glucocorticoid-suppressible hyperandrogenism (probably adrenocortical in origin) (2), combined ovarian and adrenal hyperandrogenism are rare forms of hyperandrogenism like non-classic congenital adrenal hyperplasia, adrenal tumors, ovarian tumors and hyperthecosis. Non-classical congenital adrenal hyperplasia (NCCAH) can be excluded as in our patient with normal basal and ACTH stimulated serum 17OH-progesterone (17-OHP) levels. Cushing's disease (ACTH producing pituitary adenoma) is a rare cause of hyperandrogenaemia in women with recent onset of hyperandrogenism.(3) However, it must always be taken into the consideration in a patient with accompanying signs of hypercortisolism which were absent in our case and overnight as well as low dose dexamethasone suppression test both had excluded the Cushing's syndrome in this vignette. In case of severe signs of hyperandrogenism, androgen secreting tumors of ovarian or adrenal origin should always take into the account in a patient with recent onset of severe signs of androgen excess and very high serum androgen levels. These tumors are identified in less than 2% of patients and associated with simultaneous elevation of several androgens, mainly androstenedione, DHEAS, and testosterone. (3)

The hypersecretion of androgens can be attributed to the ovaries, the adrenal glands, or the peripheral conversion of androgen precursors.(1) Our patient has raised androstenedione, DHEAS, and testosterone, therefore before diagnosing PCOS one must exclude other causes of hyperandrogenism. (4) In this case, the patient had an utmost presentation of common condition, her hyperandrogenism raised the concern for non-PCOS pathology requiring sequential evaluation, with pharmacological hormone suppression testing and imaging for accurate diagnosis as mentioned in case description, followed by invasive testing. From the standpoint of therapeutic strategy, determining the degree of contribution of the androgens originating from each site is critical and can be done through low dose dexamethasone

suppression test. (1) If the high level of testosterone is suppressed more than 40% and DHEAS is suppressed more than 60% after administration of dexamethasone, the source of the increased androgen is most likely the adrenal glands. (1) In our patient there was more than 80% suppression in DHEA-S, and more than 75% suppression in S. Testosterone level after dexamethasone suppression. It further supported our provisional diagnosis of left adrenal androgen secreting adenoma.

Adrenal imaging is indicated to look for an adrenal mass if the woman has a markedly elevated serum testosterone (if pelvic ultrasound is negative) or serum DHEAS concentration >700 mcg/dL [18.9 micromol/L]). Adrenal CT is the imaging test of choice and should readily identify androgen-secreting adrenal lesions. (5, 6) There was a lesion on adrenal CT, at left adrenal gland. After above work up mentioned in the case, next diagnostic modality will be combined ovarian and adrenal vein sampling (OAVS) which is usually performed for further evaluation in women with high serum testosterone concentrations (testosterone >150 ng/dL [5.2 nmol/L]) or DHEA- S level >700 mcg/dL [18.9 micromol/L]) (7) to rule out ovarian or adrenal source for high androgens. She underwent combine ovarian and adrenal venous sampling after discussion in Pakistan Endocrine Society meeting. The results were in table 1:

Table: 1 Case results of bilateral ovarian and adrenal veins sampling:

Location	Testosterone level	Reference Range
high suprarenal (IVC)	135.6	8.4-48.1 ng/dl
Left adrenal	992.8	
Right adrenal	106.1	
Left ovarian	283.4	
Right ovarian	176.8	
Peripheral	124.2	
Left Renal vein	539.2	
Right renal vein	127.1	
Low infra renal (IVC)	135.7	

With the interpretation of her central to peripheral gradient in OAVS mentioned in table 2:

Table: 2 Interpretation of results from ovarian and adrenal veins sampling:

	Central to Peripheral Gradient
Right adrenal C/P gradient	0.8
Left Adrenal C/P	8
Right Ovarian C/P	1.4
Left Ovarian C/P	2.2
Left Renal C/P	4

A >19 gradient from peripheral vein steroid concentration to concentration in a vein immediately draining either an adrenal gland or an ovary is highly indicative of the source of androgen excess. (8, 9) The peripheral-to-central testosterone concentration was 1:8 in left adrenal vein.

After re-discussing in PES meeting, she underwent left adrenalectomy with the impression of source of excess androgen from left adrenal adenoma on 7th Jan 2022. On follow up after 4 weeks of surgery, she was still complaining of hirsutism.
Histopathology of left adrenal gland:

Grossly specimen measuring 6x2.5x0.5cm in size, average weight of 7.6gm, with no distinct nodule or mass, no necrosis and hemorrhage.
On microscopic examination: showing nodularity of adrenocortical cells with slight increased thickness of zona fasciculata exhibiting rounded to oval nuclei with abundant eosinophilic cytoplasm. A few very tiny nodules of adrenocortical cells are seen around central vein. No evidence of malignancy is seen.

Features are of adrenal cortical hyperplasia. (Figure. 1)

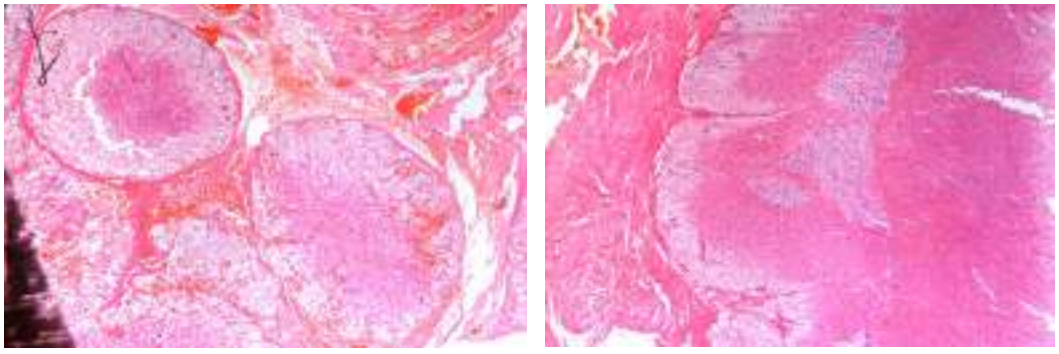

Figure. 1: Illustrating the features of adrenal cortical hyperplasia

Post-opt Investigations done 1 month after surgery shown in table 3:

Table 3: Hormonal profile after 1 month

Laboratory	Result	Reference Range
Serum Testosterone	74.51	8.4-48.1 ng/dl
Serum Androstenedione	3.85	0.3-3.3 ng/ml
Serum DHEA-SO4	548.00	35-430 ug/dl
8am Serum Cortisol	22.8	5.27-22.45 ug/dl

After 3 months of surgery, she was still having similar intensity hirsutism with no improvement, but her menstrual cycle became regular, repeat hormonal profile is shown below in table 4:

Table: 4 Hormonal profile after 3 months:

Laboratory	Result	Reference Range
Serum Testosterone	107	8.4-48.1 ng/dl
Serum SHBG	31.94	26-110nmol/L
FAI	11.62	0.5-6.53%
Serum Cortisol	20.1	5.27-22.45 ug/dl
Serum Androstenedione	5.98	0.3-3.3 ng/ml
Serum DHEA-S	575	35-430 ug/dl

In accordance with PES meeting decision and considering her dramatic response to dexamethasone with profound suppression of her androgens concentration, one possible differential was predominantly glucocorticoid-suppressible hyperandrogenism (probably adrenocortical in origin), hence, she was started on low dose steroids (5mg of prednisone). If the androgen levels are normalized after 2 to 3 months, the dose can be halved or totally discontinued. The androgen levels should then be assessed every 3 to 4 months for 1 year for recurrence of hyperandrogenemia. Of note, the possibility of recurrence of high testosterone levels is greater than recurrence of high DHEAS levels. In most instances, DHEAS levels remain suppressed indefinitely after treatment Suppression of androgens usually results in sustained amelioration of acne and has a minor effect on hirsutism (slowing of growth rate and softening of hair). Improvement in ovulatory activity, return of fertility, and increased sensitivity to the effect of clomiphene citrate on induction of ovulation often occur with glucocorticoid therapy (1) She is responding well after that therapy and is on regular follow up at endocrine OPD.

The case was also discussed with Prof Ashley Grossman, Professor of Endocrinology at University of Oxford, because of discordance between AVS and histopathlogy report, according to him the biochemistry well excluded the Cushing's syndrome and CAH, while the high DHEA-S is highly indicative of a predominantly adrenal source. Autonomous ovarian source is unlikely; and this would be very rare at this age, and she did show good suppression after dexamethasone, her examination finding of acanthosis nigricans also strongly suggests insulin resistance and PCOS. We have added metformin in her treatment regime for insulin resistence, along with that life style modification and weight reduction has been advised.

Management of non-tumor-related hyperandrogenemia and polycystic ovaries necessitates careful long-term monitoring by an endocrinologist for proper maintenance of a euandrogenemic state. Vigilance must be exercised to detect any signs of development of the metabolic consequences of hyperandrogenism, including diabetes mellitus, hypertension, dyslipidemias, or atherosclerosis.

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Case 8

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Case Scenario:

A 30 years old male visited endocrine clinic with the complaint of Bilateral enlargement of Breast tissue for the last one year associated with mild discomfort, patient denies any nipple discharge on further questioning he admitted that he had decreased libido and problems with Erection for the last 6 months, he denied any history of drugs or anabolic steroids, or any chronic illness.

General physical examination was unremarkable. On local examination of breast overlying skin was normal with bilateral gynecomastia, no discharge or nipple retraction. On Testicular examination there was slight bulge over right testicle there were no signs of chronic liver disease or chronic kidney disease rest of the systemic examination was unremarkable.

Laboratory Investigations

Serum Testosterone(t):542(300-900ng/dl.
Serum LH:4.3(1.3-9.3mIU/liter).
Serum FSH:0.5(1.3-19.3mIU/liter).
Serum Prolactin:14(4-23ng/ml.
TSH:2.9(0.5-5mIU/L.
Serum Estradiol:100l(47pg/ml).
LDH:143(100-200U/L).
Beta HCG:1.1(upto 2mIU/ml).
Alpha fetoprotein:13(10-20ng/ml).
Ultrasound Breast: Bilateral retro-mammary gynecomastia.
Ultrasound Testes:1.4×1.2cm hypo-echogenic mass with no vascularity at right apical testicle.
MRI pituitary fossa: Normal pituitary gland.
CT imaging for distant metastasis: Negative for any distant memetastasis.
Biopsy followed by surgical excision showed Leydig cell tumor.

Which of the following statement is correct regarding Gynecomastia?

A. Gynecomastia is an uncommon endocrine problem?
B. Gynecomastia is one of the earliest manifestations of Testicular tumors.
C. Gynecomastia due to the testicular tumor is not reversible?
D. Tumor markers like LDH, beta HCG, alpha-fetoprotein usually elevated in Leydig cell tumors?
E. Low levels of FSH in this patient indicate Pituitary failure?

Answer: B

Discussion

This patient has Gynecomastia due to Testicular malignancy (biopsy proven Leydig cell tumor). It may precede the onset of primary symptoms of malignancy in these types of cancers.

Gynecomastia is an enlargement of breast tissue, usually attributed to estrogen-androgen imbalance(estrogen excess or androgen deficiency) [1], It is caused by a variety of clinical conditions either Physiological or pathological like Endocrine (Hyperprolactinemia, Hyperthyroidism, Androgen resistance syndrome), certain nonendocrine illnesses(Chronic Kidney Disease, Chronic Liver disease, Obesity), Tumors (Adrenal, Lungs, Breast, Liver, and Testes).The drugs definitely associated with the onset of gynecomastia are spironolactone, cimetidine, ketoconazole, hGH, estrogens, hCG, anti-androgens, GnRH analogs and 5-α reductase inhibitors. Medications probably associated with gynecomastia include risperidone, verapamil, nifedipine, omeprazole, alkylating agents, HIV medications (efavirenz), anabolic steroids, alcohol and opioids[2].

It is common condition with estimated prevalence of 32-65%,deppending upon age and criteria used for definition[3]. About 2% of patients who have Gynecomastia are diagnosed with testicular malignancies. Gynecomastia may be the presenting symptom of patients with testicular tumors [4]. During the early stages of a testicular tumor with a nonpalpable testicular mass, it may be the first sign of clinically occult cancer due to endocrine manifestations so testicular examination should be done in all persons having Gynecomastia.

Leydig cell tumors (LCTs) are comparably rare amongst urological tumor entities accounting for approximately 3% of testicular neoplasms. They can present with typical symptoms of testicular masses and endocrine alterations or stay completely asymptomatic . They produce androgens, mainly testosterone, but can also produce estrogen[5] therefore serum testosterone levels are usually elevated which may or may not suppress FSH or LH; however, serum estradiol levels may also be increased, especially when feminization is evident.

Gynecomastia due to non-endocrine illnesses like liver failure and chronic kidney disease requires treatment of the underlying disorder, drug-induced gynecomastia requires cessation of the offending drug.

When caused by testicular malignancy, it usually regresses after few months after surgery, Results of the following laboratory studies are normal in patients with pure Leydig cell tumors:

Serum alpha-fetoprotein.
Beta human chorionic gonadotropin.
Lactate dehydrogenase.
Urine ketosteroids.
Plasma cortisol.
Adrenocorticotropic hormone stimulation test.
Dexamethasone suppression test.

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Case 9

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Case Scenario:

A 25yrs old unmarried female, university student, known case of Type1 DM from last 10yrs, and hypothyroidism from last 8yrs on thyroxine 100ug daily landed up in emergency room with the GCS of 10/15. Her vitals were BP 80/40mmhg, pulse 110bpm regular low volume, temperature 98.9F and R/R 22 breaths/min.On glucometer her blood glucose was 40mg/dl. She was resuscitated and managed accordingly.

On relevant examination patient was looking pale, lean with increased pigmentation on whole body and especially mucous membranes.

On inquiring further her mother said that she has complained of repeated hypoglycemic attacks despite of no change in routine activity and meal pattern. Her hypoglycemic attacks were used to get settled on taking some sweet. She has reduced her insulin dose up to 50% but hypoglycemic attacks remain.

Her Relevant Investigations were done:

Date	Tests Name	Results	Reference Range
4/8/22	Complete blood count: Hb: MCV: WBC: PLT:	 11.3 g/dl 87fl 6.4*1000/ul 274*1000/ul	 11.1-13.8 g/dl 76-96 fl 4.0-11.0*1000/ul 150-400*1000/ul
4/8/22	Serum Electrolytes Sodium: Potassium: Chloride: Bicarbonate:	 133 mEq/L 5.1 mEq/L 95 mEq/L 26 mEq/L	 136-145 mEq/L 3.8-5.2 mEq/L 96-107 mEq/L 22-29 mEq/L
4/8/22	Serum Creatinine:	0.73mg/dl	0.6-1.1mg/dl
4/8/22	HBA1C:	7.0%	
4/8/22	TSH:	9.1mIU/ml	0.4-4.2mIU/ml
4/8/22	FT4:	1.41	0.7-1.9ng/dl
4/8/22	Urine Detailed Report	Normal with no ketones/proteins/pus cells	
6/8/22	Short Synacthen Test Cortisol (baseline) Cortisol (30min) post cosyntropin 250mcg I/M injection Cortisol (60min)	 2.90ug/dl 4.50ug/dl 5.10ug/dl	 >6.16ug/dl Stimulated cortisol >18.0ug/dl Incremental Rise>6.88

Which of the following statement is correct Regarding Autoimmune Polyglandular syndrome (APS)?

A. APS-1is the most prevalent form of autoimmune endocrinopathy.
B. APS-2 is characterized by chronic muco-cutaneous candidiasis, hypoparathyroidism and autoimmune adrenal insufficiency.
C. The mode of inheritance of APS-3 is monogenic.
D. APS-2 is characterized by the triad of Addison disease, T1DM, and thyroid autoimmunity.
E. The all 3 cardinal features develop simultaneously in APS-2.

Answer: D

Discussion:

Autoimmune Polyglandular Syndrome:
The autoimmune polyglandular syndrome (APS) also known as Polyglandular autoimmune (PGA) syndrome is a cluster of endocrine abnormalities that occur in discreet patterns in people with immune dysregulation and that permits treatment and anticipation of associated systemic or other hormonal deficiencies. Three major entities are recognized as APS1, APS2, and APS3.

APS1 also called as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) or as Whitaker syndromeis is characterized by 3 cardinal features; chronic muco-cutaneous candidiasis, hypoparathyroidism and autoimmune adrenal insufficiency.

Two of the 3 classical features are required to make a diagnosis of APS. Additional manifestations, may includes T1DM, primary hypogonadism, malabsorption, pernicious anemia, and autoimmune hepatitis among others. The first manifestation typically Candidiasis occurs in early childhood then hypoparathyroidism in people <10 years of age. Lastly, Addison disease develops in people younger than 15 years and the complete evolution of the 3 main diseases classically take place within the first 20 years of life. However accompanying diseases continue to appear until the fifth decade of life.

APS2, the most common type of the immunoendocrinopathy syndrome is characterized by the triad of Addison disease, T1DM, and thyroid autoimmunity. Celiac disease, vitiligo, alopecia, myasthenia gravis, pernicious anemia, IgA deficiency, hepatitis, and hypogonadism are also commonly associated. Peak prevalence is in the range of 20-40 years of age. The syndrome is more prevalent in females because of autoimmune nature and associated with specific HLA DR3 and DR4 haplotypes. Autoantibodies to islet cell components, thyroid, adrenal, and celiac disease are commonly present and should be periodically sought in those with one or more autoimmune endocrinopathies such as Addison disease and T1DM. Currently, there are no unique tests to detect patients with APS-2, but testing for autoantibodies may be helpful in assessing disease risk. According to the current guidelines treatment of APS-2 should be focused on missing hormones replacement for treating the main components of APS-2.

The comparative clinical features of APS-1, APS-2 and APS-3 are shown below.

Clinical Characteristics	APS-1	APS-2	APS-3 (APS2b)
Age of manifestation	Childhood	Adulthood	Same features as APS-2 but usually without Adrenal insufficiency
Incidence [1/a]	<1:100,000	12:100,000	
Gender ratio [M:F]	3.4	1:3	
Inheritance	Monogenic	Polygenic	
Serology	Interferon α/ω-Ab	Organ-specific Ab	
Autoimmune endocrinopathies	Hypoparathyroidism (8085%) Addison's disease (6070%) Type 1 diabetes (233%) Hypogonadism (12%) Autoimmune thyropathy (10%)	Hypoparathyroidism Autoimmune thyropathy (7075%) Type 1 diabetes (4060%) Addison's disease (4050%) Hypoparathyroidism (=5%) Hypogonadism (=3%) Hypopituitarism (=2%)	
Additional non-glandular autoimmune diseases	Mucocutaneous candidiasis (7080%); autoimmune hepatitis; atrophic gastritis; alopecia areata; vitiligo, keratoconjunctivitis	Atrophic gastritis; pernicious anemia; atopic eczema; alopecia areata; myasthenia gravis; systemic lupus erythematosus; rheumatoid arthritis; autoimmune hepatitis	

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Case 10

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Case Scenario:

A 20-year-old male presented to endocrine OPD leady reading hospital Peshawar with 1-year history of palpitations, tremor and increase appetite. He has history of multiple visits to physician for the same complaint and was diagnosed as hyperthyroid (free t4 52.13 pmol/l, total t3 2.23 nmol/l Tsh 1.74iu/ml) for which anti thyroid (neomercazole 30mg) medications were started. patient used anti thyroid medications for 6 months but show no response and that's why patient left antithyroid medication. patient has family history of enlarge thyroid and similar symptoms in two cousins. On examination pulse 90/min BP 110/70 mmhg, Wight 52 kg, Height 164.5 cm, BMI 19.5. patient has no thyroid eye signs or enlarge thyroid. Rest of examinations were unremarkable. All the base line labs were with in normal range. thyroid function test repeated in hospital shows Free T4 3.11 ng/dl, free T3 10.11 ng/dl, TSH 2.48 iu/ml. thyroid function test was repeated from IRNUM to exclude any interference with antiheterophil antibodies and the results were, Free T4 4.13 ng/dl, Free T3 10.25 ng/dl, TSH 2.95 iu/ml. MRI pituitary done and was unremarkable. what is your most likely diagnosis?

A. Grave disease
B. TSH secreting pituitary adenoma
C. interference by anti heterophil antibodies
D. thyroid resistance
C. poor compliance with medications

Answer: D

Discussion:
Our patient has history history of hyperthyroidism with raised t3 and t4 and persistently non suppressed TSH and there is no response to antithyroid drugs. Patient did not show any worsening of symptoms since he left medications. His cousin was called in OPD and was investigated and shows almost similar thyroid profile. patient was labelled as having thyroid resistance syndrome. All antithyroid medications were stopped. patient reassured and started on symptomatic treatment.

Thyroid hormones are produced in the response of the thyroid gland to thyroid-stimulating hormone (TSH) secreted from the anterior pituitary gland. Circulating thyroid hormones in the forms of T4 and T3 enter cells by diffusion, and in some tissues, such as the thyroid and brain, by active transport [1]. T3 is the active form of thyroid hormones which will also be available to cells from the local conversion of T4 into T3 inside cells them self. This locally produced T3 can leave the cell and binds to T3 receptors in other tissues. In humans, approximately 80% of extra thyroidal T3 produced from T4 is produced intracellularly[2]. Intracellular T3 binds to a nuclear receptor called the thyroid receptor (TR). T3-TR complexes then bind to regulatory regions contained in the genes that are responsive to thyroid hormone and exert action [3].

There are two thyroid hormone receptors (THR), alpha (THRa) and beta (THRb) [4]. THRa is mainly found in bones, the intestine, the nervous system, and the heart. While THRb is found mainly in the retina, ear, heart, and nervous system. THRb is the main regulator of the negative feedback on the pituitary thyroid axis [5]. Most patients diagnosed with resistance to thyroid hormone (RTH) are found to have mutations in THRb with multiple variant mutations. However, recently some patients are found to have mutations in THRa. Clinical manifestations depend on the receptor affected and the magnitude of the resistance[6].

Resistance to thyroid hormone was first described as a clinical entity in 1967 [7]. Subsequent studies about the molecular pathogenesis of this syndrome identified mutations in the region of the gene that encodes the ligand-binding domain of THRb. Interestingly, patients with mutations in THRa were not identified until 2012 [8]. Patients with RTHb may have some symptoms or signs of hypothyroidism or hyperthyroidism, but these are variable and, when present, often inconsistent. They frequently have elevated thyroid hormone levels, high or normal TSH, and goiter which suggests the importance of THRb in the feedback of the hypothalamic-pituitary axis [9]. In contrast, patients with RTHa present with musculoskeletal and gastrointestinal abnormalities. They usually have near-normal thyroid function due to a lack of THRa contribution in feedback on the hypothalamic-pituitary axis [10]

On the basis of clinical features, patients with RTH syndrome and *TRB* mutations may be classified in generalized resistance to TH (GRTH) and pituitary resistance to TH (PRTH). Patients with GRTH are usually euthyroid, while patients with PRTH have mild thyrotoxic manifestations in the peripheral tissues mainly expressing the THRA isoform (heart, bone and skeletal muscles). Nevertheless, this clinical distinction may be loose and more theoretical than actual. Indeed, TRâ variants found in both GRTH and PRTH may be the same and patients of the same family may present with either form[11].

Heterogeneous clinical presentation of the syndrome may cause diagnostic difficulties thyroid resistance can be suspected in patients with elevated TH and TSH as well as symptoms of hyperthyroidism. Such clinical presentation needs differentiating with TSH-secreting adenoma, which can be excluded by performing TRH test (resulting in increased thyrotropic reaction of the pituitary) and neuroimaging. In TSH-secreting tumours, the TSH response elicited by TRH is blunted. On the contrary, TSH usually rises in response to TRH in thyroid hormone insensitivity and in healthy subjects[12].

Concomitant measurement of á-subunit at each point during the TRH test is helpful because the molar ratio of á-subunit to TRH is high (>1) in almost 85% of patients with TSH-secreting tumours[13]. Because of the laboratory results along with symptoms of hyperthyroidism the disease is often misdiagnosed as primary or secondary hyperthyroidism, causing the patients to be unnecessarily treated with antithyroid medication. When treating these patients, one should concentrate on the patient's symptoms and clinical picture instead of aiming to normalize thyroid hormone levels [14]. Most patients, if left alone, adequately overcome the resistance by increased thyroid hormone secretion and therefore do not require treatment [15]. Treating patients who present with normal TSH is more challenging; in these patients, administration of supraphysiological doses of thyroid hormone might be required and, if so, should be closely monitored. Patients who present with symptoms of hyperthyroidism should be treated symptomatically with beta-blockers or antianxiety medications, among others, depending on their predominant symptoms [16]

Several situations may be encountered in pregnant women with RTH. In a first scenario, both the mother and the fetus harbor the same mutation. In this case, the fetus is resistant to TH and tolerates the high maternal TH levels. No treatment is recommended during pregnancy. In a second scenario, a normal mother is carrying an affected fetus. Surprisingly, in this situation no increased rates of miscarriage or birth complications have been observed. Such neonates, born to normal mothers and affected fathers, do not show symptoms of TH deprivation or elevations of TSH. In a third scenario, the RTH mother has undergone previous ablative therapy (radioiodine, surgery) or is affected by Hashimoto's thyroiditis. In this situation, the outcomes (birth weight, TSH at birth) are normal, whether the fetus harbours the mutation or not. In this case, it is suggested to maintain FT4 levels within a maximum of 20% above the upper limit of normal (ULN)[17]. in fourth scenario a normal fetus is carried by a woman with RTH. Consequently, the fetus is exposed to incongruent high maternal TH levels, while the mother remains clinically euthyroid. the affected pregnant women carrying unaffected fetuses had a threefold to fourfold higher miscarriage rate [17]. In addition, the unaffected infants born to RTH mothers had significantly lower birth weight compared to infants with RTH. Their postnatal TSH level was suppressed in all cases.

According to the standard clinical practice, prenatal identification of the fetal genotype by amniocentesis and judicious treatment of RTH mothers carrying unaffected fetuses to reduce TH levels should be used to maintain FT4 levels under 20% above the ULN. This treatment can prevent the predictable low birth weight and TSH neonatal suppression. Moreover, prenatal determination of the fetal genotype can prevent unnecessary treatment of RTH mothers carrying foetuses harbouring the mutation[17].

Our patient was labelled as thyroid resistance syndrome. Patient has family history of thyroid resistance as well. Further genetic studies are advised to know the type of mutation in thyroid receptor gene.

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Case 11

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Case Scenario:

A 61 years old lady presented with the complaints of progressive hirsutism, deepening of voice and alopecia.Hirsutism started about five years ago, initially involving the face only and then spread to the rest of the body including chest abdomen and inner thighs. During her reproductive age she had no history of hirsutism or irregular cycles. She had nine children with two first trimester miscarriages she was postmenopausal for the last 20 years with no history of postmenopausal bleeding.She denied use of estrogen, progesterone or relevant health care products (oral, injectable, creams or lotions). Family history regarding hirsutism was also insignificant.

Her weight was 73kg and height was 163cm with a BMI of 27.5kg/m.^{2} She had hirsutism involving face, upper lip, chin, chest, abdomen, upper and lower limbs with a Ferriman-Gallwey score of 16/36. She had signs of virilization in the form of deepening of voice and complete scalp baldness. She had increased muscle mass which was comparatively more obvious in the upper limbs. Abdominal examination revealed no palpable mass. There were no clinical features suggestive of acromegaly or Cushing syndrome.

Her hormonal profile was as follows;

Hormones	Values (Normal Range)	Remarks
FSH	3.5mIU/ml (1.5-12.5)	Normal
LH	2.5mIU/ml (1.7-8.6)	Normal
TESTOSTERONE LEVELS	8.62ng/ml (0.04-0.4)	Raised
TSH	0.5mIU/ml (0.3-4.2)	Normal
PROLACTIN	16.7ng/ml(4.49-19.5)	Normal
17OH Progesterone levels	0.20ng/ml	Normal
DHEA So4	102mcg/dl (<15 157mcg/dl)	Normal

CT scan with contrast showed enlarged right ovary about 3.4cm into 3.3 cm(16 ml) with dense stroma along with atrophic left ovary and uterus, with no ascites or peritoneal deposits.Histopathological examination of the lesion showed pseudo lobular appearance with hypo and hyper cellular area comprising of epitheloid cells with round nuclei and clear to vacuolated cytoplasm with occasional mitosis and nuclear atypia.(Figure1).Postoperatively her serum testosterone levels were dramatically dropped from the pre operative value of 8.62 ng/ml to 0.155 ng/ml (0.04-0.4).

Which of the following most likely explains this patient's presentation?

A. Menopausal transition
B. Polycystic ovarian syndrome (PCOS)
C. Hyperthecosis
D. Sclerosal stromal tumor
E. Congenital Adrenal Hyperplasia (CAH)

Answer : D

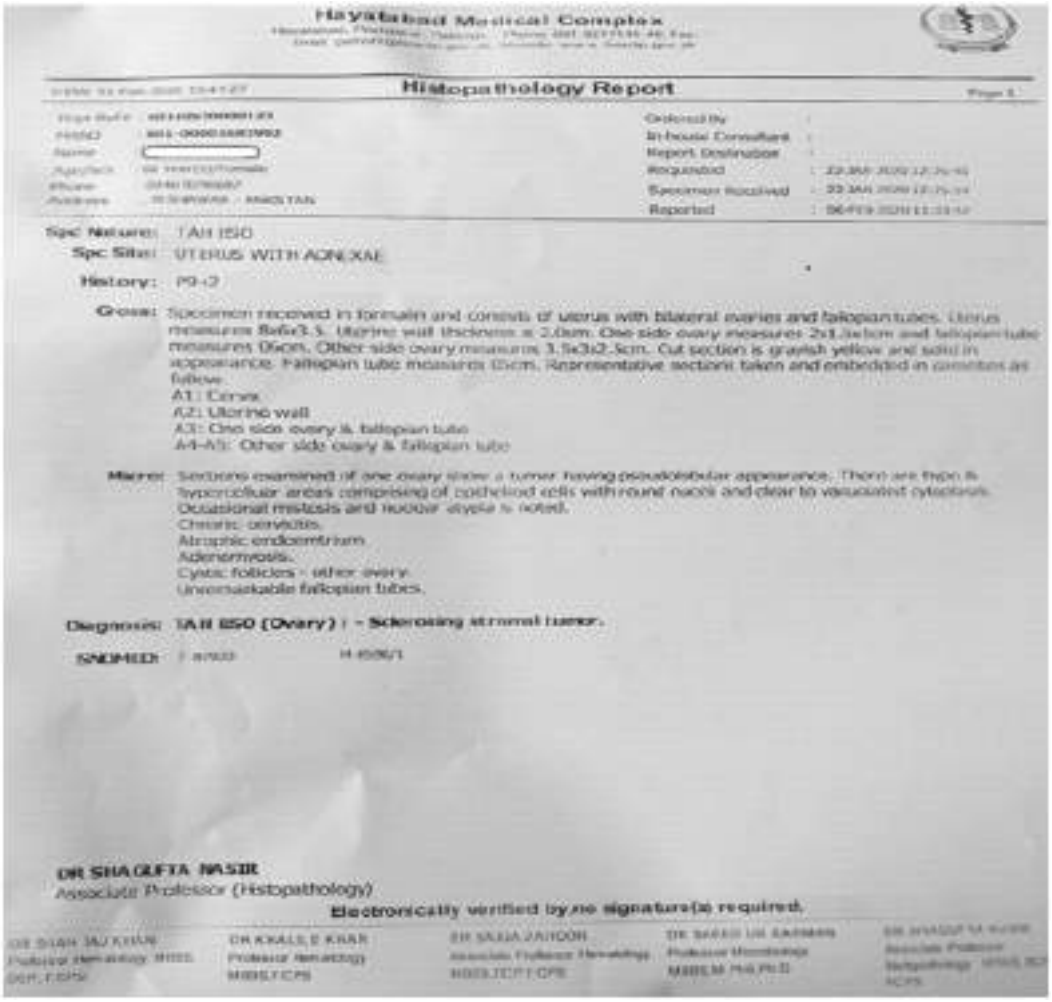
Hyperandrogenism in postmenopausal women may present with hirsutism and signs of virilization including balding, deepening of the voice, acne, increased muscle mass and clitoromegaly. In postmenopausal females, estrogen drops abruptly while androgen falls gradually over years depending upon serum Luteinizing hormone (LH) levels which increase significantly in postmenopausal women. This imbalance is further exacerbated by decrease in sex hormone binding globulin levels (SHBG) resulting in increased free androgen levels and this may manifest with few terminally hair growth but usually not able to cause significant hirsutism and specifically virilization[5].

The main androgens in women are testosterone, dihydrotestosterone, DHEA, DHEAS and androstenedione. Testosterone is the final active hormone which if high requires further evaluation to see its origin, which can be either ovaries or adrenals. One fourth of testosterone is synthesized in the adrenal gland, one fourth in the ovaries and the remaining from the peripheral conversion of their precursors (androstenedione, DHEAS, DHEA) The major androgens secreted by adrenal cortex are DHEA and its sulfate (DHEAS) while only a small amount of testosterone is directly synthesized by adrenal cortex.[6] DHEA and DHEASO4 generally regarded as adrenal origin and if normal, the testosterone is then regarded to be originating from ovary.

Raised testosterone levels can be due to tumoral or non-tumoral pathologies. The tumoral causes include androgen-secreting ovarian or adrenal tumors and non-tumoral causes include polycystic ovarian syndrome, Cushing's syndrome and congenital adrenal hyperplasia. In postmenopausal woman with significantly elevated testosterone levels along with signs of virilization, one should suspect androgen-producing tumors[7]. In patients with hyperandrogenism, tumor is also suspected when serum testosterone levels are strikingly high (2ng/ml) alongwith rapid progression of features of virilization or detection of pelvic mass on examination/imaging[8].In postmenopausal woman, ovarian causes of hirsutism and virilization are more common than adrenal origin.

The Ovarian sex cord-stromal tumors are relatively infrequent neoplasms that account for approximately 8% of all primary ovarian neoplasms It include granulosa cell tumors, fibrothecomas, Sertoli-Leydig cell tumors, steroid cell tumors, and sclerosal stromal tumors(SSTs). Our patient presented with new-onset hirsutism after menopause. The hirsutism was accompanied by virilization (voice deepening, male-pattern balding and clitoromegaly) along with significantly elevated testosterone levels. Normal levels of DHEA and 17 OH progesterone levels were favoring ovarian cause. The ultrasound being operator dependent showed normal result and CT scan was requested as the age of presentation, clinical and biochemical workup was favoring sinister cause and CT scan reported an ovarian mass which was then confirmed as sclerosal cell tumor by histopathology. Prompt surgical removal of the mass lead to normalization of serum testosterone and improvement in the hirsutism and signs of virilization.

In Conclusion hirsutism and virilization in prepubertal and postmenopausal females must be assessed for rare but sinister causes like androgen producing adrenal and/or ovarian tumors. SSTs are rare tumors accounting for only 6% of sex cord-stromal tumors .They usually present in the 2nd and 3rd decades of life but in this case it occur in the postmeopausal age. They are usually hormonally inactive but sometimes can secret androgens as in this case.[1]



Hayatabad Medical Complex

Histopathology Report

Spc Nature: TAH BSO
Spc Site: UTERUS WITH ADNEXAE
History: P9+2
Gross: Specimen received in formalin and consists of uterus with bilateral ovaries and fallopian tubes. Uterus measures 8x6x3.5. Uterine wall thickness is 2.0cm. One side ovary measures 2x1.5x1cm and fallopian tube measures 06cm. Other side ovary measures 3.5x3x2.5cm. Cut section is grayish yellow and solid in appearance. Fallopian tube measures 6cm. Representative sections taken and embedded in cassettes as follow:
A1: Cervix
A2: Uterine wall
A3: One side ovary & fallopian tube
A4-A5: Other side ovary & fallopian tube
Microscopic: Sections examined of one ovary show a tumor having pseudolobular appearance. There are tiers of hypercellular areas comprising of cuboidal cells with round nuclei and clear to vacuolated cytoplasm. Occasional mitosis and nuclear atypia is noted.
Chronic cervicitis.
Atrophic endometrium.
Adenomyosis.
Cysts follicles - other ovary.
Unremarkable fallopian tubes.
Diagnosis: TAH BSO (Ovary) : - Sclerosing stromal tumor.
SNOMED:

DR SHAGUFTA NASIR
Associate Professor (Histopathology)
Electronically verified by no signature(s) required.

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Case 12

Dr. Muhammad Usman, Dr. Gohar Khan, Dr. Ahmad Wassan
Polyclinic Hospital Islamabad

Q: 19yr boy with no previous co-morbids, student of FSC, resident of Kashmir, presented with c/o.

Generalized weakness and Headache for 2 months.

Patient was alright 2 months ago when he started having complaints of progressively increasing generalized weakness along with this he has complaints of increasing thirst and polyurea and weight gain. He also had history of progressively increasing headache and some blurring of vision.

There is no history of vomiting, abdominal pain or any ER visits or admissions in hospital. No hx of drowsiness, fits , signs of meningeal irritation.

He has hx of headache, temporal region, with hx of blurring vision. There is also hx of weight gain, acne and difficulty in standing from sitting position. He doesn't have any history of use of hakeemi or homeopathic medicine.

Rest of systemic inquiry was unremarkable

Past medical and surgical history was unremarkable.

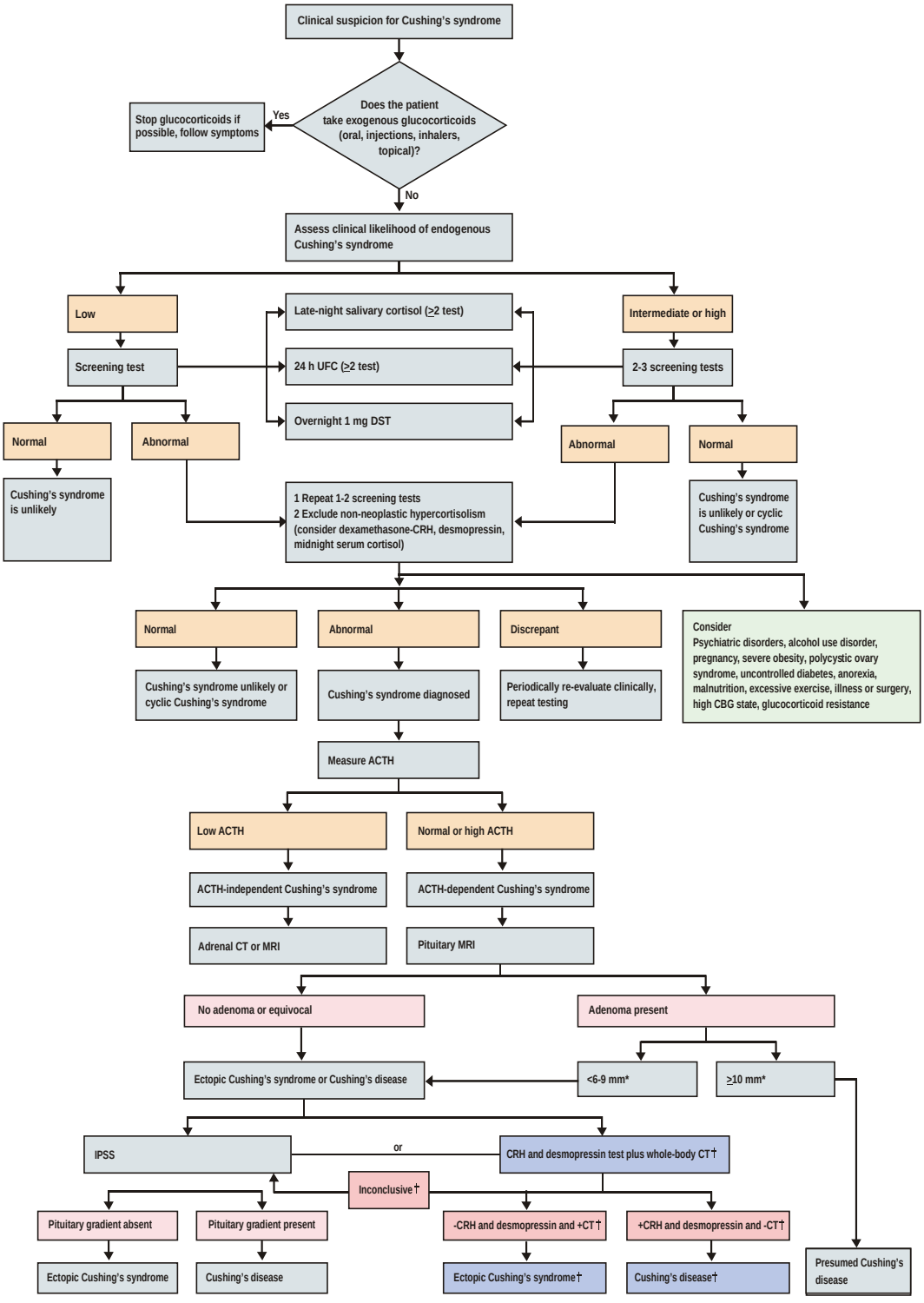
On examination

- A young boy lying on bed conscious cooperative during examination with vitals of.
- Pulse:84/min
- BP:160/110mmhg with no postural drop
- Temp: A/F
- SPO2:98% @RA

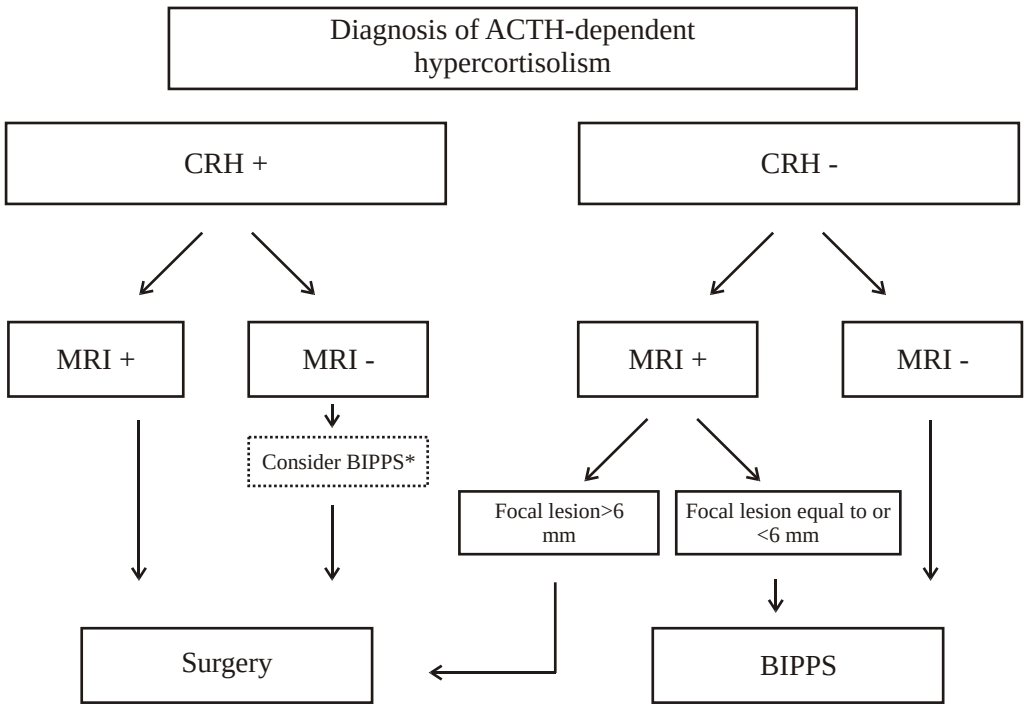
- On GPE:
- He has plethora and acne over face with hypertrichosis. He also has thin skin with bruises at cannulation site. Acanthosis nigricans at nape of neck and some supraclavicular fat pads
- Abdominal examination revealed Protuberant abdomen with vertical pinkish stretch marks over abdomen, was Soft, non tender, no ascites or visceromgaly, Bowel sounds+
- CNS examination:
- Concious with GCS 15/15 . No focal neurological deficit.
- Visual acuity 6/6 .Nomal visual field on assessment by confrontation method
- His gait was normal but he has Proximal muscle weakness of legs with difficulty standing from squatting position
- Labs: TLC:12.8, HB:13.3, PLT:190
- UREA: 23/CREAT: 0.6
- NA:141, K+:4.4
- S.ca: 9.7, S.albumin:4.4 , s.phosphorous:2.3
- Bil:0.9, ALT:67, ALP:189
- BSR:325mg/dl
- TSH:0.39 HbA1c:12.5% Anti GAD-65 antibodies: NEGATIVE
- On the basis of history, examination and lab results
- He was started on oral antidiabetic drugs but his sugars remained uncontrolled , insulin was added in regimen for sugar control .His blood pressure was also high for which anthypertensive drugs was started .His further labs was advised:
- morning serum cortisol:> 1750mmol/L (171-536)
- ONDST with 1mg of dexa
- Result serum cortisol 1605mmol/L
- 24Hr urinary cortisol: 564ug/24hr (21.5 150)
- ACTH: 101.5 (7.2- 63.3)

Question 1: What is your diagnosis?
Question 2: What are the investigations required to confirm the diagnosis?
Question 3: When to go for IPSS?
Question 4: What are the management options?
Question 5: What are post operative investigations and management?
Question 6: What are options left after failed surgery?

Answers: Cushings Disease


Clinical suspicion for Cushing's syndrome
Does the patient take exogenous glucocorticoids (oral, injections, inhalers, topical)?
Yes
Stop glucocorticoids if possible, follow symptoms
No
Assess clinical likelihood of endogenous Cushing's syndrome
Low
Intermediate or high
Late-night salivary cortisol (≥2 test)
24 h UFC (≥2 test)
Overnight 1 mg DST
Screening test
2-3 screening tests
Normal
Abnormal
Abnormal
Normal
Cushing's syndrome is unlikely
1 Repeat 1-2 screening tests
2 Exclude non-neoplastic hypercortisolism (consider dexamethasone-CRH, desmopressin, midnight serum cortisol)
Cushing's syndrome is unlikely or cyclic Cushing's syndrome
Normal
Abnormal
Discrepant
Consider
Psychiatric disorders, alcohol use disorder, pregnancy, severe obesity, polycystic ovary syndrome, uncontrolled diabetes, anorexia, malnutrition, excessive exercise, illness or surgery, high CBG state, glucocorticoid resistance
Cushing's syndrome diagnosed
Periodically re-evaluate clinically, repeat testing
Measure ACTH
Low ACTH
Normal or high ACTH
ACTH-independent Cushing's syndrome
ACTH-dependent Cushing's syndrome
Adrenal CT or MRI
Pituitary MRI
No adenoma or equivocal
Adenoma present
Ectopic Cushing's syndrome or Cushing's disease
<6-9 mm*
≥10 mm*
IPSS
or
CRH and desmopressin test plus whole-body CT†
Inconclusive†
Pituitary gradient absent
Pituitary gradient present
-CRH and desmopressin and +CT†
+CRH and desmopressin and -CT†
Presumed Cushing's disease
Ectopic Cushing's syndrome
Cushing's disease
Ectopic Cushing's syndrome†
Cushing's disease†

Simultaneous bilateral inferior petrosal sinus sampling (BIPSS) plays a crucial role in the diagnostic work-up of Cushing's syndrome. It is the most accurate procedure in the differential diagnosis of hypercortisolism of pituitary or ectopic origin, as compared with clinical, biochemical and imaging analyses, with a sensitivity and specificity of 88100% and 67100%, respectively. In the setting of hypercortisolemia, the procedure is performed to differentiate a pituitary from an ectopic source of ACTH. As ACTH secretion is intermittent and blood sampling during a nadir of ACTH between two secretory episodes might result in a false-negative ratio between central and peripheral ACTH concentration (IPS/P ratio), the procedure is undertaken under CRH stimulation in order to increase the diagnostic sensitivity. some suggest that BIPSS should be reserved to patients with clinical and biochemical evidence of CD and negative or equivocal MRI findings , whereas others recommend BIPSS for patients with equivocal responses to hormone test or in cases of discrepancies between biochemistry and imaging findings . Still others recommend BIPSS as a routine investigation in any patient with proven ACTH-dependent Cushing's syndrome. An additional reason to perform BIPSS is persistence of Cushing's syndrome after previous unsuccessful pituitary surgery, to ensure that the diagnosis of CD is correct. Previous data and the authors' experience have shown that an increase >50% in ACTH and >30% in cortisol has a very high specificity (90100%) to potentially rule out the presence of EAS.



According to the criteria established in the seminal paper by Oldfield , a central-to-peripheral ACTH maximal ratio =2 in basal conditions and =3 at any time point after CRH stimulation is strongly suggestive of pituitary secretion, i.e. CD (conventionally: positive test). If these thresholds are not met, a peripheral (ectopic) source of ACTH is presumed (conventionally: negative test)

Within 2 weeks after surgery, morning serum cortisol concentrations were obtained (n = 78) and corticotropin-releasing hormone (CRH) (n = 53) and metyrapone tests (n = 72) were performed. Three groups of outcome were identified: sustained remission, early failure (persistent CD), and late relapse. A cortisol threshold value of 200 nmol/l has a positive predictive value of 79% for immediate surgical failure (negative predictive failure [NPV] 97%). CRH test: CRH-stimulated peak cortisol > or =600 nmol/l predicted early failure in 78% (NPV 100%).

Only three were predictive of persistence of Cushing's disease after surgery: the non identification of the adenoma in histology (an adenoma was found in 87% of the patients in remission, and in 20% of treatment failures, p = 0.01), the early post-operative plasma ACTH (patients in remission: 2 pmol/L (1.1-10.8 pmol/L), treatment failures: 8.2 pmol/L (1.1-12 pmol/L), p = 0.019), and the early post-operative serum cortisol (patients in remission: 128.4 nmol/L (27.6-4644 nmol/L), treatment failures: 797 nmol/L (606-1037 nmol/L), p = 0.003). ROC curves indicated that plasma ACTH < or = 7.55 pmol/L distinguished patients in remission from treatment failures with 80% sensitivity and 97.4% specificity, and serum cortisol < or = 585 nmol/L with 100% sensitivity and 90% specificity.

Twenty-four hours after transsesphenoidal surgery for Cushing's disease, and without glucocorticoids replacement, patients with serum cortisol concentrations higher than 585 nmol/L, and/or plasma ACTH higher than 7.55 pmol/L, and/or those in which an adenoma is not identified in the histological study, have a high risk of treatment failure.

Secondary interventions for persistent or recurrent disease include repeat transsphenoidal resection, pituitary radiation, medical therapy, and bilateral adrenalectomy

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Case 13

Dr. Zaina Jabeen, Dr Khadija Irfan Khwaja, Dr Amena Moazam
Services Hospital Lahore

Case Scenario:

20 years old woman presented with progressively worsening aches and pains for 2 years. Her skeletal survey showed multiple cystic lesions in bones of lower limbs (as shown below). Initial lab evaluation revealed raised calcium levels and has been referred to endocrine clinic for endocrine assesment. She does not take calcium or vitamin D supplements, is not on any regular medications except paracetamol for aches and pains. There is no H/O fever, cough, weight loss, any urinary complaints, and any previous fractures. There is no family H/o renal stones or any endocrine tumor.

On physical examination, she has height 159cm, weight 61kg (BMI 24.2 kg/m^2). BP 125/85. There are no palpable neck masses. There is no flank tenderness.

Lab evaluation showed:

Corrected calcium 12.7 mg/dL (8.5-10.5)

Serum phosphate 2.3 mg/dL (3.5-4.5)

25-hydroxy vitamin D 22.21 ng/mL

iPTH levels 722 pg/mL (15-64ng/dL)

Serum creatinine 0.35 mg/dL (0.5-0.9)

eGFR 212.62 (>60)

TSH 1.62 mcIU/mL (0.3-5.5)

Free T4 0.89ng/dL (0.89-1.76)

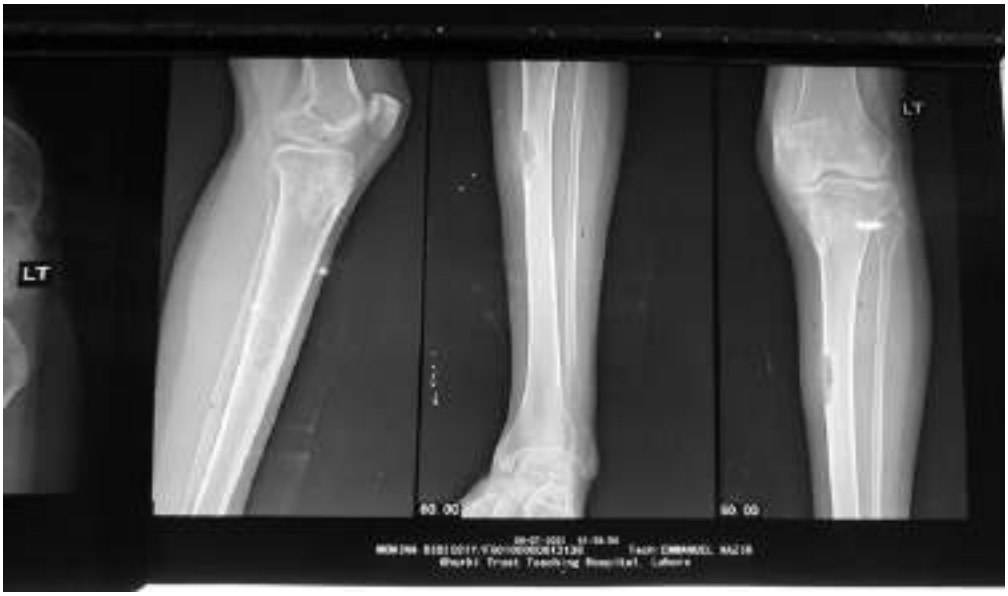
Serum metanephrines 54.71 pg/mL (less than 90)

Serum normetanephrines 165.5 (less than 190)

Cervical Ultrasonography: An extra thyroidal hypoechoic nodule 10.8 x 7 x 7 mm with absent vascularity, likely of parathyroid origin.

Du^{99m}Tc- MIBI parathyroid scan: showed no evidence of parathyroid adenoma or hyperplasia.

MRI lower limbs: multifocal expansile cystic lesions with fluid filled levels, 3.6 x 2.0cm at tibial tuberosity, another one 3.2 x 2.1 cm in distal fibula.



What should be next step in management of this patient?

A. CT scan neck
B. Ultrasound guided biopsy
C. Minimally invasive parathyroidectomy with intraoperative PTH monitoring
D. Selective arteriography
E. Bilateral neck exploration

Answer: C

In a patient with biochemically confirmed primary hyperparathyroidism with preoperatively negative sestamibi scan and discordant imaging studies, 2nd line imaging modalities may be considered including 4D CT scan, [^{18}F] fluorocholine PET/CT or patient may undergo focused or minimally invasive parathyroidectomy with intraoperative PTH monitoring.

Discussion:

Primary Hyperparathyroidism (pHPT) refers to inappropriate or uncontrolled secretion of parathyroid hormone by parathyroid glands. It is the most common cause of hypercalcemia, though ocassionally may also be associated with normal calcium levels (normocalcemic primary hyperparathyroidism). In upto 85% of cases, pHPT results from a solitary parathyroid adenoma, and 10-15% of cases may be caused by multigland disease (MGD), either due to multiple adenomas or hyperplasia. Parathyroid carcinoma is extremely rare seen in less than 1% cases. pHPT is mostly sporadic (95%) and 5% cases may be familial or associated with MEN syndromes.

Parathyroid glands, by virtue of parathyroid hormone production, are responsible mainly for maintaining calcium homeostasis in the body. Embryologically, superior parathyroid glands develop from 4th pharyngeal pouch and descend along with thyroid whereas inferior parathyroid glands develop from 3rd pharyngeal pouch and descend along with isthmus to ultimately reach near lower thyroid pole. There can be anatomic variations in location of parathyroid glands, particularly inferior ones due to their longer route of migration. Ectopic parathyroid glands (found in 15% of cases) may be one of the 4 standard parathyroid glands or a supernumerary gland and may be found anywhere from carotid bifurcation to pericardium.

Classical pHPT is characterized by chronic hypercalcemia causing skeletal changes (including osteopenia, cortical bone loss, osteitis fibrosa cystica), predisposition to renal stone formation, neuropsychiatric problems and other non-specific symptoms like anorexia, muscle weakness, nausea, vomiting, constipation and polyuria.

Surgery is the definitive treatment for pHPT and recommended for all symptomatic patient. Indications for surgery include serum calcium more than 1mg/dL above upper limit of reference range, Bone mineral density T score -2.5 at lumbar spine, hip, femoral neck or distal radius, history of vertebral fracture, creatinine clearance <60ml/min, 24 hours urinary calcium >400 mg/day, presence of nephrolithiasis or nephrocalcinosis and age less than 50.[1]

Surgery may be one of minimally invasive parathyroidectomy or bilateral neck exploration. The recent trend to shift from the classical bilateral neck exploration to focused or minimally invasive parathyroidectomy has placed a greater emphasis on the preoperative localization techniques. Hence, preoperative localization of hyperfunctioning parathyroid gland and differentiating single from multigland disease is crucial in deciding the surgical approach. Minimally invasive or focused parathyroidectomy done in cases of solitary adenoma, is associated with lower risk of complications, quick postoperative recovery, shorter hospital stay, greater patient satisfaction and better cosmetic outcomes. However minimally invasive parathyroidectomy in presence of MGD may increase risk of persistant/ recurrent disease. Re-surgery in cases of persistant disease is technically more challenging and associated with more complictaions. Owing to the short half-life of the PTH hormone (3-5minutes), intraoperative PTH monitoring (IOPTH) during minimally invasive parathyroidectomy can provide the necessary assurance that a focused parathyroidectomy has been adequately performed. 50% or more decline in IOPTH level at 5 mins postexcision from baseline and a normal or near-normal IOPTH level at 10 minutes defines successful cure. [2]

Current 1st line standard modality for preoperative localization is with cervical ultrasound and radionucleide scintigraphy, with combined sensitivity around 8195%. [3] Cervical ultrasonography is a cheap, non-invasive diagnostic modality, but highly operator dependent. Among radionucleide parathyroid scans, the single radiopharmaceutical dual-phase method using Tc-99m sestamibi is currently the method of choice for parathyroid localization. It is based on the differential washout rate of sestamibi from the thyroid and abnormal parathyroid glands. The reported sensitivity of this method ranges from 80% to 90%. It may also be helpful for ectopic or supernumerary glands, missed by ultrasound and may also help to choose gland with lowest uptake which may be partially preserved or autotransplanted in patients with MGD. Sensitivity is lower for multigland hyperplasia than solitary adenoma. The addition of single-photon emission computed tomography (SPECT) and more recently SPECT/CT improves the anatomical localization and helps in the differentiation of the parathyroid from the thyroid lesions (See figure below). [4]

Computed tomography (CT), and magnetic resonance, have been used for parathyroid localization providing excellent image resolution and contrast. These modalities, on the other hand, have inadequate and variable accuracy and they can't differentiate functional parathyroid tissue from other types of tissues. CT and magnetic resonance have similar range of sensitivity ranging from 46% to 76% and from 50% to 78% respectively.

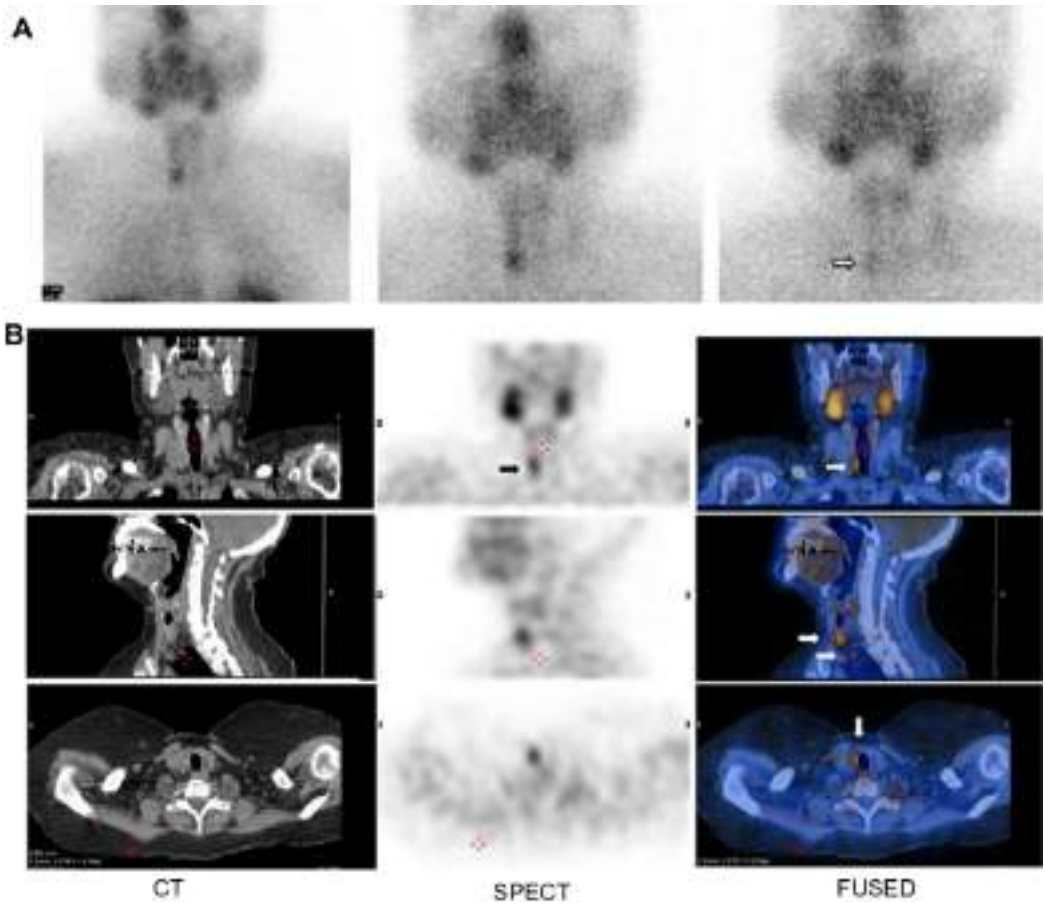


Figure: showing Tc-99m sestamibi study acquired at 15 and 120 minutes postinjection using parallel hole collimator.

Notes: Planar images (A) reveal a focus of increased uptake at the right lower pole seen on the early image and persisting on the delayed image (arrow) which showed further clearance of thyroid background activity. SPECT/CT study (B) was also obtained, showing the lesion with better contrast and anatomic localization (arrow).

In case of negative standard imaging, second-line imaging may be performed including [^{18}F] fluorocholine) PET/CT, so-called four-dimensional computed tomography (4D-CT), MRI, [^{18}F] fluorocholine PET/4D-CT or [^{18}F] fluorocholine PET/MRI. Combined [^{18}F] fluorocholine PET and 4D contrast-enhanced CT (4DCeCT) may be considered in pHPT patients with negative or inconclusive first-line imaging.

Invasive diagnostic procedures like selective venous sampling and selective arteriography may be considered in cases of prior unsuccessful parathyroid surgery and negative or equivocal non-invasive imaging studies. They are rarely utilized nowadays due to improved standard non-invasive imaging and because they carry certain risks for the patient.

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Laboratory Reference Ranges

Reference ranges very among laboratories. Conventional units are listed first with Sl units in parentheses.

Lipid Values

High-density lipoprotein (HDL) cholesterol

- Optimal ---------- >60 mg/dL (>1.55 mmol/L)
- Normal ---------- 40-60 mg/dL (1.04-1.55 mmol/L)
- Low ---------- <40 mg/dL (<1.04 mmol/L)

Low-density lipoprotein (LDL) cholesterol

- Optimal ---------- <100 mg/dL (<2.59 mmol/L)
- Low ---------- 100-129 mg/dL (2.59-3.34 mmol/L)
- Borderline-high ---------- 130-159 mg/dL (3.37-4.12 mmol/L)
- High ---------- 160-189 mg/dL (4.14-4.90 mmol/L)
- Very high ---------- ≥190 mg/dL (≥4.92 mmol/L)

Non-HDL cholesterol

- Optimal ---------- < 130 mg/dL (<3.37 mmol/L)
- Borderline-high ---------- 130-159 mg/dL (3.37-4.12 mmol/L)
- High ---------- ≥ 240 mg/dL (≥6.22 mmol/L)

Total cholesterol

- Optimal ---------- < 200 mg/dL (<5.18 mmol/L)
- Borderline-high ---------- 200-239 mg/dL (5.18-6.19 mmol/L)
- High ---------- ≥ 240 mg/dL (≥6.22 mmol/L)

Triglycerides

- Optimal ---------- < 150 mg/dL (<3.88 mmol/L)
- Borderline-high ---------- 150-199 mg/dL (3.88-5.15 mmol/L)
- High ---------- 200-499 mg/dL (5.18-12.92 mmol/L)
- Very high---------- ≥ 500 mg/dL (≥12.95 mmol/L)

Lipoprotein (a) ---------- ≤ 30 mg/dL (≤1.07 µmol/L)

Apolipoprotien B ---------- 50-110 mg/dL (0.5-1.1 g.L)

Hematologic Values

Erythrocyte sedimentation rate ---------- 0-20 mm/h

Haptoglobin ---------- 30-200 mg/dL (300-2000 mg/L)

Hematocrit ----------41 %-50% (0.41-0.51) (male); 35%-45% (0.35-0.45) (female)

Hemoglobin A_{1c} ---------- 4.0%-5.6% (20-38 mmol/mol)

Hemoglobin ---------- 13.8-17.2 g/dl (138-172 g/L) (male); 12.1-15.1 g/dL (121-151 g/L) (female)

International normalized ratio ---------- 0.8-1.2

Mean corpuscular volume (MCV) ---------- 80-100 μm^3 (80 -100 fL)

Platelet count ---------- 150-450 x $10^3/\mu L$ (150-450 x $10^9/L$)

Protein (total) ---------- 6.3-7.9 g/dL (63-79 g/L)

Reticulocyte count ---------- 0.5%-1.5% of red blood cells (0.005-0.015)

White blood cell count ---------- 4500-11,000/µL (4.5-11.0 x $10^9/L$)

Thyroid Values

Thyroglobulin --- 3-42 ng/mL (3-42 pg/L) (after surgery and radioactive iodine treatment: <1.0 ng/mL [<1.0 µg/L])

Thyroglobulin antibodies ---------- ≤ 4.o IU/mL (≤4.0 kIU/L)

Thyrotropin (TSH) ---------- 0.5-5.0 mIU/L

Thyroid-stimulating immunoglobulin ---------- ≤120% of basal activity

Thyroperoxidase (TPO) antibodies ---------- <2.0 IU/mL (<2.0 kIU/L)

Thyroxine (T_4) (fr ee) ---------- 0.8-1.8 ng/dL (10.30-23.17 pmol/L)

Thyroxine (T_4) (to tal) ---------- 5.5-12.5 µg/dL (94.02-213.68 nmol/L)

Free thyroxine (T_4) in dex ---------- 4-12

Triiodothyronine (T_3) (free) ---------- 2.3-4.2 pg/mL (3.53-6.45 pmol/L)

Triiodothyronine (T_3) (total) ---------- 70-200 ng/dL (1.08-3.08 nmol/L)

Triiodothyronine (T_3) r everse ---------- 10-24 ng/dL (0.15-0.37 nmol/L)

Triiodothyronine uptake, resin ---------- 25%-38%

Radioactive iodine uptake --- 3%-16% (6 hours); 15%-30% (24 hours)

Endocrine Values

Serum

Aldosterone ---------- 4-21 ng/dl (111.0-582.5 pmol/L)

Alkaline phosphatase ---------- 50-120 U/L (0.84-2.00 µkat/L)

Alkaline phosphatase (bone-specific) ---------- ≤ 20 µg/L (adult male): ≤ 14 µg/L (premenopausal female); ≤ 22 µg/L (postmenopausal female)

Androstenedione ---------- 65-210 ng/dL (2.27-7.33 nmol/L) (adult male); 80-240 ng/dL (2.79-8.38 nmol/L) (adult female)

Antimullerian hormone ---------- 0.7-19.0 ng/mL (5.0-135.7 pmol/L) (male, > 12 years);
0.9-9.5 ng/mL (6.4-67.9 pmol/L) (female, 13-45 years);
<1.0 ng/mL (<7.1 pmol/L) (female, >45 years)

Calcitonin ---------- < 16 pg/mL (<4.67 pmol/L) basal, male);
< 8 pg/mL (<2.34 pmol/L) (basal, female);
≤ 130 pg/mL (≤37.96 pmol/L) (peak calcium infusion, male);
≤ 90 pg/mL (≤26.28 pmol/L) (peak calcium infusion, female);

Carcinoembryonic antigen ---------- < 2.5 ng/mL (<2.5 µg/L)

Chromogranin A ---------- <93 ng/mL (<93 µg/L)

Corticosterone ---------- 53-1560 ng/dL (1.53-45.08 nmol/L) (>18 years)

Corticotropin (ACTH) ---------- 10-60 pg/mL (2.2-13.2 pmol/L)

Cortisol (8 AM) ---------- 5-25 µg/dL (137.9-689.7 nmol/L)

Cortisol (4 AM) ---------- 2-14 µg/dL (55.2-386.2 nmol/L)

C-peptide ---------- 0.9-4.3 ng/mL (0.30-1.42 nmol/L)

C-reactive protein ---------- 0.8-3.1 mg/L (7.62-29.52 nmol/L)

Cross-linked N-telopeptide of type 1 collagen ----------
5.4-24.2 nmol BCE/mmol creat (male);
6.2-19.0 nmol BCE/mmol creat (female)

Dehydroepiandrosterone sulfate (DHEA-S)

Patient Age	Female	Male
18-29 years	44-332 µg/dL (1.19-9.00 µmol/L	89-457 µg/dL (2.41-12.38 µmol/L)
30-39 years	31-228 µg/dL (0.84-6.78 µmol/L	65-334 µg/dL (1.76-9.05 µmol/L)
40-49 years	18-244 µg/dL (0.49-6.61 µmol/L	48-244 µg/dL (1.30-6.61 µmol/L)

Patient Age	Female	Male
50-59 years	15-200 µg/dL (0.41-5.42 µmol/L)	35-179 µg/dL (0.95-4.85 µmol/L)
≥ 60 years	(15-157 µg/dL) (0.41-4.25 µmol/L)	25-131 µg/dL (0.68-3.55 µmol/L)

Deoxycorticosterone ---------- < 10 ng/dL (<0.30 nmol/L) (>18 years)

1,25-Dihydroxyvitamin D3 ---------- 16-65 pg/mL (41.6-169.0 pmol/L)

Estradiol ---------- 10-40 pg/mL (36.7-146.8 pmol/L) (male);
10-180 pg/mL (36.7-660.8 pmol/L) (folicular, female);
100-300 pg/mL (367.1-1101.3 pmol/L) (midcycle, female);
40-200 pg/mL (146.8-734.2 pmol/L) (luteal, female);
<20 pg/mL (<73.4 pmol/L) (postmenopausal, female)

Estrone ---------- 10-60 pg/mL (37.0-221.9 pmol/L) (male);
17-200 pg/mL (62.9-739.6 pmol/L) (premenopausal female);
7-40 pg/mL (25.9-147.9 pmol/L) postmenopausal female)

a-Fetoprotein ---------- <6 ng/mL (<6 µg/L)

Follicle-stimulating hormone (FSH) ----------
1.0-13.0 mlU/mL (1.0-13.0 IU/L) (male);
<3.0 mIU/mL (<3.0 IU/L) (prepuberty, female);
2.0-12.0 mIU/mL (2.0-12.0 IU/L) follicular, female);
4.0-36.0 mIU/mL (4.0-36.0 IU/L) (midycycle, female);
1.0-9.0 mIU/mL (1.0-9.0 IU/L) (Iuteal, female);
>30 mlU/mL (>30 IU/L) (postmenopausal, female)

Free fatty acids ---------- 10.6-18.0 mg/dL (0.4-0.7 nmol/L)

Gastrin ---------- <100 pg/mL (<100 ng/L)

Growth hormone (GH) --- 0.01-0.97 ng/mL (0.01-0.97 (µg/L) (male);
0.01-3.61 ng/mL (0.01-3.61 µg/L) female)

Homocysteine ---------- ≤ 1.76 mg/L (≤ 13 umol/L)

ß-Human chorionic gonadotropin (b-hCG) ----------
<3.0 mIU/mL (<3.0 IU/L) nonpregnant female);
>25 mIU/mL (>25 IU/L) indicates a positive pregnancy test

ß-Hydroxybutyrate ---------- <3.0 mg/dL (<300 µmol/L)

17-Hydroxypregnenolone ---------- 29-189 ng/dL (0.87-5.69 nmol/L)

17a-Hydroxyprogesterone---<220 ng/dL (<6.67 nmol/L) (adult male);
<80 ng/dL (<2.42 nmol/L) (follicular, female);
<285 ng/dL (<8.64 nmol/L) (Iuteal, female);
<51 ng/dL (1.55 nmol/L) postmenopausal, female)

25-Hydroxyvitamin D -- < 10 ng/mL (<25.0 nmol/L) (Severe deficiency);
10-24 ng/mL (25.0-59.9 nmol/L) (mild to moderate deficiency);
25-80 ng/mL (62.4-199.7 nmol/L) (optimum levels);
>80 ng/mL (>199.7 nmol/L) toxicity possible)

inhibin B ---------- 15-300 pg/mL (15-300 ng/L)

Insulinlike growth factor 1 (IGF-1)

Patient Age	Female	Male
18 years	162-541 ng/mL (21.2-70.9 nmol/L)	170-640 ng/mL (22.3-83.8 nmol/L)
19 years	138-442 ng/mL (18.1-57.9 nmol/L)	147-527 ng/mL (19.3-69.0 nmol/L)
20 years	122-384 ng/mL (16.0-50.3 nmol/L)	132-457 ng/mL (17.3-59.9 nmol/L)
21-25 years	116-341 ng/mL (15.2-44.7 nmol/L)	116-341 ng/mL (15.2-44.7 nmol/L)
26-30 years	117-321 ng/mL (15.3-42.1 nmol/L)	117-321 ng/mL (15.3-42.1 nmol/L)
31-35 years	113-297 ng/mL (14.8-38.9 nmol/L)	113-297 ng/mL (14.8-38.9 nmol/L)
36-40 years	106-277 ng/mL (13.9-36.3 nmol/L)	106-277 ng/mL (13.9-36.3 nmol/L)
41-45 years	98-261 ng/mL (12.8-34.2 nmol/L)	98-261 ng/mL (12.8-34.2 nmol/L)
46-50 years	91-246 ng/mL (11.9-32.2 nmol/L)	91-246 ng/mL (11.9-32.2 nmol/L) .
51-55 years	84-233 ng/mL (11.0-30.5 nmol/L)	84-233 ng/mL (11.0-30.5 nmol/L)
56-60 years	78-220 ng/mL (10.2-28.8 nmol/L)	78-220 ng/mL (10.2-28.8 nmol/L)
61-65 years	72-207 ng/mL (9.4-27.1 nmol/L)	72-207 ng/mL (9.4-27.1 nmol/L)
66-70 years	67-195 ng/mL (8.8-25.5 nmol/L)	67-195 ng/mL (8.8-25.5 nmol/L)
71-75 years	62-184 ng/mL (8.1-24.1 nmol/L)	62-184 ng/mL (8.1-24.1 nmol/L)
76-80 years	57-172 ng/mL (7.5-22.5 nmol/L)	57-172 ng/mL (7.5-22.5 nmol/L)
≥80 years	53-162 ng/mL (6.9-21.2 nmol/L)	53-162 ng/mL (6.9-21.2 nmol/L)

Insulinlike growth factor binding protein 3 ---------- 2.5-4.8 mg/L

Insulin ----------1.4-14.0 µlU/mL (9.7-97.2 pmol/L)

Islet-cell antibody assay ---------- 0 Juvenile Diabetes Foundation units

Luteinizing hormone (LH) ---------- 1.0-9.0 mlU/mL (1.0-9.0 IU/L) (male);
<1.0 mIU/mL (<1.0 IU/L) (prepuberty, female);
1.0-18.0 mIU/mL (1.0-18.0 IU/L) (follicular, female);
20.0-80.0 mIU/mL (20.0-80.0 IU/L) (midcycle, female);
0.5-18.0 mIU/mL. (0.5-18.0 IU/L) (luteal, female);
>30 mIU/mL (>30 IU/L) (postmenopausal, female)

Metanephrines (plasma fractionated)

Metanephrine ----------<57 pg/mL (<289 pmol/L)

Normetanephrine---------- <148 pg/mL (<808 pmol/L)

75-g oral glucose tolerance test -- 60-100 mg/dL (3.3-5.6 mmol/L) (fasting)
Blood glucose values ---------<200 mg/dL (<11.1 mmol/L) (1 hour);
<140 mg/dL (<7.8 mmol/L) (2 hour)
Between 140-200 mg/dL (7.8-11.1 mmol/L) is considered impaired glucose tolerance or prediabetes. Greater than 200 mg/dL (11.1 mmol/L) is a sign of diabetes mellitus.

50-g oral glucose tolerance test for gestational diabetes ----------
<140 mg/dL (<7.8 mmol/L) (1 hour)

100-g oral glucose tolerance test for gestational diabetes ----------
<95 mg/dL (<5.3 mmol/L) (fasting);
<180 mg/dL (<10.0 mmol/L) (1 hour);
<155 mg/dL (<8.6 mmol/L) (2 hour);
<140 mg/dL (<7.8 mmol/L) (3 hour)

Osteocalcin ----------9.0-42.0 ng/mL (9.0-42.0 pg/L)

Parathyroid hormone, intact (PTH)---------- 10-65 pg/mL (10-65 ng/L)

Parathyroid hormone-related protein (PTHrP) 14-27 pg/mL (14-27 ng/L)

Progesterone ---------- ≤1.2 ng/mL (≤3.8 nmol/L) (male);
≤1.0 ng/mL (s3.2 nmol/L) (follicular, female);
2.0-20.0 ng/mL (6.4-63.6 nmol/L) (luteal, female);
≤1.1 ng/mL (≤3.5 nmol/L) (postmenopausal, female);
>10.0 ng/mL (>31.8 nmol/L) (evidence of ovulatory adequacy)

Proinsulin ----------26.5-176.4 pg/mL (3.0-20.0 pmol/L)

Prolactin ---------- 4-23 ng/mL (0.17-1.00 nmol/L) (male);
4-30 ng/mL (0.17-1.30 nmol/L) (nonlactating female);
10-200 ng/mL (0.43-8.70 nmol/L) (lactating female)

Prostate-specific antigen----------<2.0 ng/mL (<2.0 ug/L) (≤40 years);
<2.8 ng/mL (<2.8 µg/L) (≤50 years);
<3.8 ng/mL (<3.8 µg/L) (≤60 years);
<5.3 ng/mL (<5.3 µg/L) (≤70 years);
<7.0 ng/mL (<7.0 µg/L) (≤79 years);
<7.2 ng/mL (<7.2 µg/L) (≥80 years)

Renin activity, plasma, sodium replete, ambulatory -- 0.6-4.3 ng/mL per h

Renin, direct concentration ---------- 30-40 pg/mL (0.7-1.0 pmol/L)

Sex hormone-binding globulin------- 1.1-6.7 µg/mL (10-60 nmol/L) (male);
2.2-14.6 µg/mL (20-130 nmol/L) (female)

a-Subunit of pituitary glycoprotein hormones-------<1.2 ng/mL (<1.2 µg/L)

Testosterone (bioavailable)----------0.8-4.0 ng/dl. (0.03-0.14 nmol/L)
(20-50 years, female on oral estrogen);
0.8-10.0 ng/dL (0.03-0.35 nmol/L)
(20-50 years, female not on oral estrogen);
83.0-257.0 ng/dL (2.88-8.92 nmol/L) (male 20-29 years);
72.0-235.0 ng/dL (2.50-8.15 nmol/L) (male 30-39 years);
61.0-213.0 ng/dL (2.12-7.39 nmol/L) (male 40-49 years);
50.0-190.0 ng/dL (1.74-6.59 nmol/L) (male 50-59 years):
40.0-168.0 ng/dL. (1.39-5.83 nmol/L) (male 60-69 years)

Testosterone (free) ---------- 9.0-30.0 ng/dL (0.31-1.04 nmol/L) male):
0.3-1.9 ng/dL (0.01-0.07 nmol/L) (female)

Testosterone (total) ---------- 300-900 ng/dL (10.4-31.2 nmol/L) (male);
8-60 ng/dL (0.3-2.1 nmol/L) (female)

Vitamin B_{12} ---------- 180-914 pg/mL (180-914 ng/L)

Chemistry Values

Alanine aminotransferase ---------- 10-40 U/L (0.17-0.67 µkat/L)

Albumin ---------- 3.5-5.0 g/dL (35-50 g/L)

Amylase ---------- 26-102 U/L (0.43-1.70 µkat/L)

Aspartate aminotransferase ---------- 20-48 U/L (0.33-0.80 µkat/L)

Bicarbonate ----------21-28 mEq/L (21-28 mmol/L)

Bilirubin (total) ---------- 0.3-1.2 mg/dL (5.1-20.5 µmoi/L)

Blood gases
Po, art erial blood ---------- 80-100 mm Hg (10.6-13.3 kPa)
Pco_2, arterial blood ----------35-45 mm Hg (4.7-6.0 kPa)

Blood pH---------- 735-745

Calcium ---------- 8.2-10.2 mg/dL (2.1-2.6 mmol/L)

Calcium (ionized) ---------- 4.60-5.08 mg/dL (1.2-1.3 mmol/L)

Carbon dioxide ----------22-28 mEq/L (22-28 mmol/L)

CD_4cel l count ---------- 500-1400/µL (0.5-1.4 x 10^9/L)

Chloride ---------- 96-106 mEq/L (96-106 mmol/L)

Creatine kinase ----------50-200 U/L (0.84-3.34 µkat/L)

Creatinine ---------- 0.7-1.3 mg/dL (61.9-114.9 µmol/L) (male);
0.6-1.1 mg/dL (58.0-97.2 µmol/L) (female)

Ferritin---------- 15-200 ng/mL (33.7-449.4 pmol/L)

Folate ----------≥4.0 ng/mL (24.0 pg/L)

Glucose ---------- 70-99 mg/dL (3.9-5.5 mmol/L)

y-Giutamyltransferase ----------2-30 U/L (0.03-0.50 µkat/L)

Iron ---------- 50-150 µg/dL (9.0-26.8 µmol/L) (male);
35-145 µg/dL (6.3-26.0 µmol/L) (female)

Lactate dehydrogenase ---------- 100-200 U/L (1.7-3.3 µkat/L)

Lactic acid ---------- 5.4-20.7 mg/dL (0.6-2.3 mmol/L)

Lipase ----------~---------- 10-73 U/L (0.17-1.22 µkat/L)

Magnesium ---------- 1.5-2.3 mg/dL (0.6-0.9 mmol/L)

Osmolality ----------275-295 mOsm/kg (275-295 mmol/kg)

Phosphorus -----~----------2.3-4.7 mg/dL (0.7-1.5 mmol/L)

Potassium ----------3.5-5.0 mEq/L (3.5-5.0 mmol/L)

Prothrombin time---------- 8.3-10.8 s

Serum urea nitrogen ---------- 8-23 mg/dL (2.9-8.2 mmoi/L)

Sodium ---------- 136-142 mEq/L (136-142 mmol/L)

Transferrin saturation ---------- 14%-50%

Troponin | ---------- <0.6 ng/mL (<0.6 µg/L)

Tryptase ----------< 11.5 ng/mL (<11.5 µg/L)

Uric acid ----------3.5-7.0 mg/dL (208.2-416.4 µmol/L)

Urine

Albumin ---------- 30-300 µg/mg creat (3.4-33.9 µg/mol creat)

Albumin-to-creatinine ratio ---------- <30 mg/g creat

Aldosterone ----------3-20 µg/24 h (8.3-55.4 nmol/d)
(should be <12 µg/24 h [<33.2 nmol/d] with oral sodium loading—confirmed with 24-hour urinary sodium >200 mEq)

Calcium ---------- 100-300 mg/24 h (2.5-7.5 mmol/d)

Catecholamine fractionation
Normotensive normal ranges:
Dopamine ---------- <700 µg/24 h (<4567 nmol/d)
Epinephrine ---------- <35 µg/24 h (<191 nmol/d)
Norepinephrine---------- <170 µg/24 h (<1005 nmol/d)

Cortisol---------- 4-50 µg/24 h (11-138 nmoi/d)

Cortisol following dexamethasone suppression test --------- <10 µ9/24 h (<27.6 nmol/d) (low-dose: 2 day, 2 mg daily)

Creatinine ---------- 1.0-2.0 g/24-h (8.8-17.7 mmol/d}

Glomerular filtration rate (estimated) ---------- >60 mL/min per 1.73 m^2

5-Hydroxyindole acetic acid ----------2-9 mg/24 h (10.5-47.1 µmol/d)

Iodine (random)---------- >100 µg/L

17-Ketosteroids ----------6.0-21.0 mg/24 h (20.8-72.9 µmol/d) (male);
4.0-17.0 mg/24 h (13.9-59.0 µmol/d) (female)

Metanephrine fractionation
Metanephrine ---------- <400 µg/24 h (<2028 nmol/d)
Normetanephrine ---------- <900 µg/24 h (<4914 nmol/d)
Total metanephrine ---------- <1000 µg/24 h (<5260 nmol/d)

Osmolality ---------- 150-1150 mOsm/kg (150-1150 mmol/kg)

Oxalate ----------<40 mg/24 h (<456 mmol/d)

Phosphate ---------- 0.9-1.3 g/24 h (29.1-42.0 mmoi/d)

Potassium ----------17-77 mEQ/24 h (17-77 mmol/d)

Sodium ---------- 40-217 mEq/24 h (40-217 mmol/d)

Uric acid ---------- <800 mg/24 h (<4.7 mmol/d)

Saliva

Cortisol (salivary), midnight ---------- <0.13 µg/dL (<3.6 nmol/L

Semen

Semen analysis ---------- > 20 million sperm/mL: >50% motility

The End

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