



Review Article

Turner's Syndrome: Diagnosis and Management in 2005 (Part 1)

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Introduction

Turner's syndrome is a relatively common birth defect (~1 in 2000–3000 live female births) stemming from a chromosomal disorder associated with an absent or abnormal X-chromosome. Up to 10% of miscarriages carry a 45,XO karyotype (1). Turner's syndrome is typically characterized by the combination of physical features and cytogenetics in females with complete or partial absence of a second sex chromosome. Most affected patients have a 45,XO monosomy, but the presence of an abnormal chromosome, or mosaicism of 45,X with another cell line can also fulfill the criteria (2, 3). Turner's syndrome is associated with a 3-fold increase in mortality and shortened life expectancy of up to 13 yr (4). This review is designed to provide the basis for diagnosis and management decisions at key stages of development, treatment, and follow-up from birth to adulthood.

Diagnosis

The presenting clinical features can vary widely among affected individuals. Consequently, whereas short stature and gonadal dysgenesis are almost universal in Turner's syndrome, many other organ systems are affected to varying degrees and at different stages of life. The absence of a second sex chromosome is associated with the most abnormal phenotype, which includes four cardinal features:

female phenotype, short stature, sexual infantilism owing to rudimentary gonads, and a variety of associated somatic abnormalities. In addition, embryonic death is also a common outcome.

Whereas the diagnosis of Turner's syndrome may be made *in utero* or at birth, it may be delayed into late childhood, adolescence, or even adulthood because of failure to recognize the significance of poor growth (98%) or gonadal failure (95%) with subsequent pubertal delay (5). The majority of girls

of at least 50 cells is required to identify low-level mosaicism and the presence of other chromosomal abnormalities associated with Turner's syndrome.

A karyotype analysis for a definitive diagnosis should be considered in any girl with unexplained growth failure or pubertal delay. Other findings that may point to Turner's syndrome, and should thus lead to karyotyping, include newborn edema of feet or hands, nuchal folds, coarctation of the aorta or hypoplastic left heart, low hairline, low set ears, cubitus valgus, nail dysplasia, and multiple pigmented nevi. Congenital dislocation of the hip and elevated circulating FSH levels in infancy or adolescence indicate gonadal failure and may point to Turner's syndrome.

Isochromosome X, designated as 45,X/46,ξ(Xq), is the second most common karyotype and is also associated with autoimmune disease, deafness, hypothyroidism, and inflammatory bowel disease (2, 6). In addition, the spectrum

of Turner's syndrome also includes karyotypes with Y-chromosome material present (such as 45,X/46,XY). SRY, the testis-determining gene normally located on the Y-chromosome, can be probed during cytogenetics and aids in detecting occult Y-chromosome material in females with Turner's syndrome (7). The presence of this Y-chromosome material

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The first gene for Turner's syndrome to be identified was the SHOX gene.

with Turner's syndrome do not have other phenotypic features. Other phenotypic features, *e.g.* neck webbing (25%) and marked cubitus valgus (47%) occur in a minority of girls.

Chromosomal Analysis/Genetics/SHOX Box

Deletion of the whole or part of one X-chromosome will invariably lead to the definitive diagnosis. Examination



LETTER FROM THE PRESIDENT

Since the inception of the Endocrine Fellows Foundation in 1990, I have always been amazed by the willingness of physicians and other health care professionals to help the EFF in presenting programs and carrying out projects to help endocrine fellows.

Whether it has been speaking at one of our scientific meetings, reviewing research grant proposals, writing articles for our web page or our newsletter, *EndoTrends*, or participating as a mentor in one of our preceptorship programs, the response to our request has been overwhelmingly positive.

It seems that there is a desire to "give back" from those who have moved on in their careers, and the eagerness and enthusiasm to learn shown by all of you stimulates a mutually satisfying experience.

At most scientific meetings, speakers will remain for a short time after their presentations to answer questions. Although this also occurs at the EFF meetings, there is an interesting extension of this interaction that has fascinated me. Speakers will sit at a dinner table with a group of fellows and, after the meal, will remain on and spend hours chatting about medical issues and career issues until the lights are turned off.

The preceptorship programs have been a life-changing experience for many of those privileged to attend. The faculty/fellow communication is intense and ongoing during the 2 weeks with mentors, and the post-preceptorship connection remains between the attendees and the faculty.

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EndoTrends

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When it comes to evaluating grant proposals, most organizations find it challenging to get reviewers who will commit and complete reviews. The EFF response from reviewers is over 95%—an extraordinarily high percentage.

My hope, and the hope of each of the members of the EFF Board of Directors, is that the tradition of helping those who follow you will become part of your “after-training” behavior as well. The gratification and the return are more than you will expect.

We at EFF have already been rewarded when some of our fellows have volunteered to serve as mentors when they complete their training.

It has also been extremely exciting for EFF to have one of the first recipients of an EFF Research Grant become part of the faculty of several scientific forums and to serve as a preceptor in one of our preceptorships.

You can do it too!

Sherman M. Holvey, M.D.
President, The Endocrine Fellows Foundation

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increases the risk of gonadoblastoma/dysgerminoma. Therefore, probing for Y-chromosome material should be undertaken, and if present, a gonadectomy should be performed before puberty.

The first gene for Turner's syndrome to be identified was the SHOX gene. When mutated, the SHOX gene (short stature homeobox-containing gene) leads to short stature (8). It is located on the X and Y short arms in the pseudoautosomal (a gene that occurs on both sex-determining chromosomes) regions of these chromosomes. Two full copies of

the gene are needed for full expression, and the loss of one of the SHOX genes in an individual is responsible, at least in part, for the short stature in patients with Turner's syndrome, probably by affecting the epiphyseal plate (9).

Differential Diagnosis of Turner's Syndrome

Gonadal dysgenesis

Gonadal dysgenesis is a term used to encompass all forms of defective gonadal development (including Turn-

er's syndrome). 46,XY gonadal dysgenesis is a rare condition, characterized by abnormalities of testis differentiation. This group can be further subdivided into complete (or pure) gonadal dysgenesis and partial gonadal dysgenesis. Complete gonadal dysgenesis is characterized by normal female external genitalia and well-developed Müllerian structures. The gonads consist of streaks of fibrous tissue. As the name suggests, 46,XY partial gonadal dysgenesis is characterized by partial testis development and a normal XY karyotype without

mosaicism. Internal ducts usually consist of a mixture of Wolffian and Müllerian ducts. Affected individuals exhibit varying degrees of ambiguous external genitalia, which correlate with the extent of testicular differentiation (10).

Turner's syndrome can often have a similar presentation to Noonan's Syndrome, in which case there is a normal karyotype, either 46,XX or 46,XY. Noonan's syndrome is an autosomal dominant inherited disorder that is characterized by dysmorphic facial features, short stature (in about 50% of cases), and heart disease (most commonly valvular pulmonic stenosis and hypertrophic cardiomyopathy). The phenotype also includes webbing of the neck, chest deformities giving a square appearance of the thorax, cryptorchidism, mild mental retardation, and a host of bleeding problems (11).

Puberty and Bone Health

Importance of estrogen

Estrogens are used for induction of puberty and bone maturation in Turner's syndrome females. The majority (>90%) of girls with Turner's syndrome have gonadal failure, but up to one third can go through spontaneous puberty. Most of these girls will subsequently develop gonadal failure. Therefore, almost all girls with Turner's syndrome will require either pubertal induction and/or later maintenance estrogen therapy.

Initiation of estrogen therapy

Estrogen replacement should be initiated at a time that will minimize the negative effect on final height by closing the epiphyses, while inducing puberty at a normal age. Early treatment (before 12 yr), especially without GH therapy, will compromise final height (12). If GH therapy is started early (average age 8.2 yr), and GH is administered in adequate doses, estrogen treatment could be initiated at a puberty-appropriate time (average age 12.7 yr) without compromising adult height (13).

In a general consensus, estrogen should be started around age 12–13 yr in girls undergoing GH therapy and no later than age 14–15 yr without GH treatment (3). Measurement of gonadotropin levels is also recommended before introduction of estrogens to confirm gonadal failure with an elevated FSH. If the serum FSH level is normal, consider performing a pelvic ultrasound to determine whether follicles are visible and measuring uterine size and thickness, which may aid in prediction of spontaneous puberty.

Dose of estrogen

Start with a low dose of estrogen and adjust according to the response with the aim of completing feminization in 2–3 yr. Estrogen therapy is summarized in Table 1. If an induction dose is not stated in Table 1, one sixth to one fourth of the adult dose is generally used for induction. Doses can be increased gradually at 3- to 6-month intervals. Continuous estrogen-only preparations may be preferable over oral contraceptives to avoid symptoms of estrogen withdrawal during the estrogen-free week (6). In addition, ethinyl estradiol, a commonly used estrogen in contraceptive pills, may increase the hypertensive risk in girls with Turner's syndrome (who are already at increased risk for hypertension) and has been associated with increased liver abnormalities. Therefore, transdermal preparations are also an option. Recently, a percutaneous estradiol gel was successful in the gradual development of secondary sexual characteristics and uterine growth, mimicking natural puberty (15).

Approximately two thirds of girls with Turner's syndrome will achieve Tanner 3 breast stage after 12 months of estrogen therapy. Patients should be advised that breakthrough bleeding may occur with estrogen therapy alone. After vaginal bleeding first occurs or after 12–24 months of unopposed estrogen therapy, a progestin should be added in a cyclical or continuous dose to prevent development of endometrial carcinoma (3, 6, 9). Once a woman with Turner's syn-

drome has reached menopausal age, a decision to continue or stop hormone replacement therapy should be made on an individual basis.

Skeletal Health

Skeletal maturation in girls with Turner's syndrome is normal or slightly delayed in childhood and lags further in adolescence as a result of gonadal steroid deficiency (16). Patients not treated with estrogen often develop a severe form of the postmenopausal type of osteoporosis and may develop fractures and vertebral collapse. The prepubertal decrease in bone mineral density normalized with puberty and menarche, suggesting that optimizing bone mass in patients with Turner's syndrome may require earlier pubertal induction than is currently recommended to achieve optimal bone mass (17).

As in puberty, continuing estrogen replacement therapy in adults with Turner's syndrome is necessary to prevent osteopenia and osteoporosis and to decrease fracture risk. The bone mineral density of the lumbar spine and hips correlates with the number of years on hormone replacement therapy in patients with Turner's syndrome (3). Therefore, initiation of estrogens, early detection of osteopenia, and improvement in general measures for adequate bone mass (calcium intake and physical activity) should be considered mandatory for the skeletal health in these patients.

In addition to decreased bone mineral density, approximately 10% of girls with Turner's syndrome develop scoliosis (18). Once diagnosed, these cases should be referred to and followed by an orthopedic surgeon. **(To be continued in Issue 4)**

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Table 1
Recommended Hormone Replacement Therapy in Women with Turner's Syndrome

A. Estrogen preparation	Regimen	
Micronized estradiol (esterified estrogens) E2 valerate (oral) Conjugated estrogens (oral) (Premarin) Estradiol (Ortho-est) Ethinyl estradiol (see warning in text) E2 transdermal patch ^a (Estraderm) Estradiol matrix patch ^a (Climara)	Maintenance: 0.625–1.25 mg daily Maintenance: 2 mg daily Induction: 0.3 mg/d. Maintenance: 0.625–1.25 mg/d. Induction: dose not established. Maintenance: 0.625–1.25 mg Induction: 2–5 µg/d. Maintenance: increase dose to 10–20 µg/d if needed. Induction: dose not established. Maintenance: 50–100 µg/24 h. New patch applied twice a week. Induction: dose not established. Maintenance: one patch once a week.	
B. Progestagen	Cyclical dose: d 1–12, 15–21, 15–25, or 15–28.	Continuous daily dose: (used with daily estrogen, leads to amenorrhea)
Medroxyprogesterone acetate (Provera) Norethindrone (Aygestin) ^b Combination regimens Oral contraceptive regimens Cojugated estrogens (CE) and medroxyprogesterone acetate (MA) combination (Prempro)	5–10 mg 0.7–1.0 mg No cyclical dose available.	2.5–5 mg Dose not available. A low dose oral contraceptive can be used for maintenance. Maintenance: 0.625–1.25 mg. Conjugated estrogens with 2.5–5 mg MA daily.
^a Because estrogen doses are difficult to adjust with patches, it is recommended to begin with oral estrogens at lower doses, and if needed, equivalent doses of patches may be started at a later time.		
^b May be slightly more androgenic and lead to higher lipid levels.		

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Childrens Hospital Los Angeles Preceptorship



Left to right: Linda Burkett, Elizabeth Parker, Christy Bollinger, Stephanie Drobac, Jacky Salazar, Diane Hatcher, Deborah Goldstein, Nicole Matthews, Irina Kazachkova, and Dr. Geffner.

Under the direction of Dr. Mitchell Geffner, Professor of Pediatrics at the Keck School of Medicine of the University of Southern California, the third annual Endocrine Fellows Foundation Preceptorship in Pediatric Endocrinology at Childrens Hospital Los Angeles (CHLA) took place on April 11–22, 2005. Selected fellows included: Stephanie Drobac, M.D. (University of Chicago, Chicago, IL); Irina Kazachkova, M.D. (Maimonides Medical Center, Brooklyn, NY); Nicole Matthews, M.D. (Maimonides Medical Center, Brooklyn, NY); and Elizabeth Parker, M.D. (National Institutes of Health, Bethesda, MD). In addition, for the first time, four advanced practice pediatric nurse practitioners in pediatric endocrinology, under the sponsorship of the Pediatric Endocrine Nurses' Society (PENS), also participated in the program. They included: Christy Bollinger, R.N., M.S., C.P.N.P. (Texas Children's Hospital, Houston, TX); Deborah Goldstein, N.D., F.N.P. (Stroger Hospital, Chicago, IL); Diane Hatcher, B.S.N., M.S., C.P.N.P., C.D.E. (Walter Reed

Army Medical Center, Washington, DC); and Jacky Salazar, B.S.N., M.S.N., A.R.N.P. (Melbourne Internal Medicine Associates, Melbourne, FL).

The highlights of Week 1 included: Introduction to EFF Program (Geffner); CHLA: Past, Present, and Future (Robert Adler, M.D.); Saban Research Institute at CHLA (Emil Bogenmann, Ph.D.); Outcomes Research: How to Work within New Federal Regulations Using Databases and Repositories (Mary Halvorson, R.N., M.S.N., C.D.E.); Update in Diabetes Technology: Sensors, Pens, Insulins, and other Devices (Halvorson); Motivational Interviewing (Halvorson and Sue Carpenter, R.N.); Self-Paced Competency Education Program and Competency Tools (SPCT) in Diabetes Management (Halvorson); Pre-Clinic Teaching Conference (Geffner); Bone Density: Hands-On Approach to Measurement (Vicente Gilsanz, M.D., Ph.D.); Endocrinology Clinic (Geffner and Gertrude Costin, M.D.); Pre-Bone Clinic Teaching Conference and Bone Clinic (Pisit Pitukcheewanont, M.D.); Diabetes Camps in Latin

America (Barry Conrad, M.P.H., R.D., C.D.E. and Roshi Monzavi, M.D.); Plenary Lecture 1: Uri Alon, M.D. (Children's Mercy Hospital, University of Missouri-Kansas City School of Medicine). "What's New in Hypophosphatemic Rickets?"; KidsNFitness Symposium: Program Design and Outcomes and Hands-On Participation in Weekly Session (Daina Dreimane, M.D. and staff); Pediatric Surgery Mini-Symposium: Ambiguous Genitalia (Donald Shaul, M.D.), Cryptorchidism (Andrew Hwang, M.D.), Pituitary (Mark Krieger, M.D.) and Thyroid/Parathyroid (Dennis Maceri, M.D.); Childhood Osteoporosis (Pitukcheewanont); and Bone Case Discussions: Methodology, Diseases, and Management (Pitukcheewanont).

The highlights of Week 2 included: Pump Class (Carpenter and staff); a trip to Esoterix Laboratories (Walt Chandler, Ph.D.); The CHLA Diabetes Experience (Kevin Kaiserman); Living with Diabetes (Patrice Yasuda, Ph.D. and Kaiserman); Pre-Clinic Teaching Conference (Geffner); Plenary Lecture 2: Fran Kaufman, M.D. "Diabetes in the 21st Century"; Pathology of the Pituitary Gland and Sellar Region (Ignacio Gonzalez-Gomez, M.D.); Symposium on Stem Cells in Diabetes Research: Donald Kohn, M.D., Gay Crooks, M.D., and Carolyn Lutzco, Ph.D.; Faculty Case Presentations (Geffner); Plenary Lecture 3: Scott Rivkees, M.D. (Chief, Section of Development Endocrinology and Biology, Director, Yale Child Health Research Center Yale University School of Medicine); "Treatment of Graves' Disease in Children: Controversy and Fact"; Review of Your Simulated Diabetes Life Experience (Yasuda and Kaiserman); Plenary Lecture #4: Geffner: "Hormone Resistance: A Sensitive Subject"; and Fellows' Research Presentations (visiting and CHLA fellows).

Finally, social events included dinners at Asia de Cuba and P. Shaw's Bistro and wine and hors d'oeuvres at the Geffner's. Support for the 2-wk program was provided by EFF.

Metabolic Bone Preceptorship for 2005



Left to right: Matthew Drake, John Lindsay, Jennifer Sipos, Azeez Farooki, Dr. Bilezikian, Harvey Chiu, Bridgett Sinnott, Jennifer Klinke, and Nikheel Kolatkar.

lege of Physicians and Surgeons. For 2 wk, eight selected Endocrinology Fellows were taught by a faculty of over 25 experts on a broad and diverse set of skeletal conditions. These included primary hyperparathyroidism, osteoporosis, vitamin D abnormalities, renal osteodystrophy, Paget disease of bone, metastatic bone disease, hypoparathyroidism, and unusual metabolic bone diseases. Bone densitometry and histomorphometry of the skeletal system were also featured topics. In addition to general considerations about postmenopausal osteoporosis, the Fellows were presented with issues in premenopausal women who have low bone mass, organ transplantation-related osteoporosis, race and ethnic issues in skeletal health, male osteoporosis, and skeletal metabolism in diabetes mellitus. Pictured with Dr. Bilezikian are the attendees from this year.

In June, the Metabolic Bone Preceptorship, directed by Dr. John Bilez-

ikian, was conducted at the Metabolic Bone Diseases Unit at Columbia's Col-



Successful Third Diabetes Training Forum

To help recognize the risks and diagnosis criteria for metabolic syndrome; to study the link between diabetes and heart disease and the appropriate therapies for each;

To identify patient educational needs and corresponding referral resources;

To implement an integrated approach to care for the patient with metabolic syndrome or diabetes . . .

These and a number of other learning objectives were provided to the fortunate

Endocrine Fellows who attended the Third Diabetes Training Forum in Chicago. During this program, they had the opportunity to hear from a renowned faculty of diabetes thought leaders who spoke on the metabolic syndrome and team care of the diabetic patient. The Fellows participated in workshops that allowed for personal interactive learning. The attendees' evaluations confirmed that they are being provided with educational opportunities vital to their careers.

These on-going programs, generously supported by an educational grant from

AstraZeneca, are organized and presented through a partnership between DM Strategies, Inc. and the Endocrine Fellows Foundation. The fourth Forum was held on September 17 and 18 in Chicago and will be reviewed in Issue 4 of *EndoTrends*.

We are pleased to inform Endocrine Fellows that these Forums will continue in 2006 and 2007, once again thanks to support from AstraZeneca. Invitations for the Spring 2006 Diabetes Training Forum will be sent next January.

MEDICINE AROUND THE WORLD



Random Thoughts from a Traveler

Derek LeRoith, M.D., Ph.D.

Endocrine Fellows Foundation, Member of the Board

I have been traveling to South Africa for the past 20 yr, having emigrated after completing my training as an internist and endocrinologist. This report will describe the changes that I have encountered and highlight some of the issues involved in medicine in that country over the past two decades.

South Africa has some unique issues related to the practice of medicine. Despite its being the wealthiest country in Sub-Saharan Africa, of the black population of over 30 million the unemployment rate remains at almost 40% and poverty is rampant. This impacts on the types of diseases that affect the poorer elements and their medical care. Rates of malnutrition, especially protein-calorie malnutrition, are still high (parenthetically, that was the topic of my Ph.D. studies), and the life expectancy of infants is reduced, as is that of adults. Infectious diseases, particularly tuberculosis, is still high, and the National Institutes of Health of the U.S. funds tuberculosis research in South Africa for this reason. The incidence of HIV/AIDS, as is commonly pointed out in the popular press, is 20%, and retrovirals are not being widely used as of 2004. In addition, South Africa's Indian population shares the same diabetes prevalence and cardiovascular risk as do Indians in India. Thus, more needs to be done with education of patients in their disease management.

Most medical schools and academic medical centers focus on training of physicians for private or community practice: there is little basic research in the field of medicine, owing to limited resources. Many of the research programs focus on clinical research and are quite extensive given the numbers of cases that are seen with the disease I have described. Physicians and nurses in these centers describe the extremely high prevalence of HIV/AIDS in all cases they treat, irrespective of the reason for admission of the patient. This fact often impacts on the treatment outcome and decision making by the physicians. The physicians are highly qualified and up to date with the latest knowledge, either because of travel to overseas meetings, particularly to Europe, or by bringing specialist to their own Society meetings. This year, two members of the EFF board were invited to The Endocrine Society meeting in South Africa! In addition, web-based learning is quite an important technique.

Those in practice tend to gravitate to the urban centers where the more affluent members of the population live and the facilities in private hospitals and clinics outshine those in the government hospitals due to funding discrepancies. For internists and endocrinologists in private practice, the rewards, both financial and intellectual, are very similar to the situa-

tion in the U.S., as described to me during my recent attendance at the Annual South African Endocrinology and Diabetes Conference. The set-up in practice is much the same as in the U.S. Primary care physicians refer their complicated cases to specialists in practice or to the academic medical centers for specialized care. For those in hospital practice, the rewards are much less financial but more related to a feeling of "giving" to the poorer elements of the population and of course even more intellectual owing to the breadth of diseases that are encountered. In the urban areas, the large state-funded hospitals are overcrowded. For example, in Johannesburg, Baragwaneth Hospital, the largest in South Africa, often has over 200% occupancy; classically described as having one patient on the bed, one in the chair, and one on the floor. Private hospitals are more similar to what we know in the U.S. In the rural areas, the hospital facilities are even more primitive, underfunded, and understaffed. In fact, medical students after qualifying are or will be required to "return to the state" a 2-yr period of service in the more remote areas of the country.

It seems that during the 30 yr since I emigrated for "greener fields" in academic endocrinology, very little has changed!

HIGHLIGHTS FROM THE FIFTH ANNUAL EFF/ADA ENDOCRINE FELLOWS FORUM—“ADVANCES IN THE DIAGNOSIS AND TREATMENT OF DIABETES”

On June 9, 2005, the Fifth Annual EFF/ADA Forum was held at The Marriott Hotel and Marina in San Diego, CA. The Forum featured an outstanding faculty from across the country who presented various didactic lectures and presided over a wide spectrum of workshops.

Like the first four collaborative efforts, these presentations provided a unique opportunity for the Fellows to hear well-known experts in various fields discuss updates on the latest in diabetes clinical management, including inpatient management, hypoglycemia, and new treatment options. It also provided practical applications for improving patient outcomes.

This Forum also offered the 100 Fellows the opportunity to attend the 65th ADA Scientific Sessions, which followed the Forum. The Fellows were sponsored through a generous grant from Sanofi-Aventis.

This Forum offered an additional, unique learning experience while at the ADA Sessions. The ADA and the EFF developed a list of clinical topics and questions related to particular symposia, issues, and abstracts at the Sessions that provided a learning framework for the Fellows. They were assigned to workgroups of ten with each group assigned a particular question/area of focus. On Sunday, June 12, the 100 Fellows met with the Board of the EFF and representatives of the ADA and Sanofi-Aventis with each group, through a selected presenter, reporting on their specific assignments. The Fellows' presentations will be a special feature of Volume 12, Issue 4 of *EndoTrends*.

Following are the abstracts of some of this year's speakers.

Inpatient Management

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Perhaps no area in clinical diabetes is as topical as the inpatient management of the patient with diabetes. This is an area that has been a concern for many for decades, but only recently do we have data showing meticulous control, particularly in the critically ill patient, can improve outcomes. There is more recent controversy from The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 and Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE)/Estudios Cardiologicas Latin America Study Group (ECLA) studies that did not show a benefit of a glucose-insulin-potassium infusion during acute MI; unfortunately, glucose control compared with other studies was not achieved in these reports. The cellular mechanism for improved outcomes appears to be that a combination of hyperinsulinemia with euglycemia suppresses both free fatty acids and inflammatory cytokines, whereas hyperinsulinemia with hyperglycemia does the opposite. The

data showing the improvement in outcomes have resulted in national recommendations for glycemic management in the hospital. These recommendations require endocrinologists to be familiar with all of the tools used in the hospital for the treatment of diabetes. We will review eight cases of diabetes management for hospitalized patients with diabetes.

Type 2 Diabetes in Children: The Beginnings of a New Epidemic

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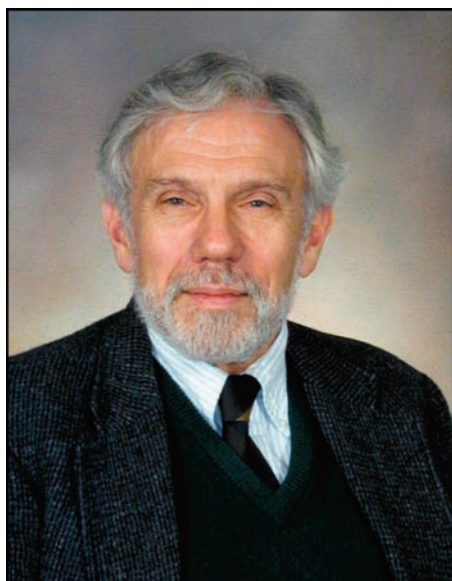
An estimated 100 million people worldwide currently suffer from type 2 diabetes mellitus (T2DM). The incidence of T2DM is steadily escalating throughout the world in people from a wide range of ethnic groups and all social and economic levels. Recent projections suggest that by the year 2010, there will be more than 230 million diabetic individuals in the world. Parallel with the global epidemic of T2DM in adults, an “emerging epidemic” of T2DM has been observed in youth over the last decade. Research and clinical experience in adults have estab-

lished that insulin resistance is a major risk factor for developing T2DM. However, insulin resistance alone is not sufficient to cause diabetes, which will develop only if insulin secretion by β -cells is inadequate.

Our experience in youth with T2DM suggests that the early abnormality is insulin resistance compounded later with β -cell failure. The basis for this proposition is the recognition that all the clinical characteristics of youth with T2DM share a common feature, which is insulin resistance. The clinical characteristics of youth with T2DM are: 1) obesity, 2) high-risk family history of T2DM, 3) age of onset at mid-puberty around 13.5 years, 4) high-risk minority ethnicity, 5) female gender, and 6) "syndrome X." In this lecture, data will be presented on how these features impact insulin sensitivity and secretion in childhood ultimately leading to T2DM. Therapeutic options, starting with lifestyle modification and followed with pharmacotherapy that is approved in children with T2DM, will be discussed. Finally, T2DM in children may represent the tip of the iceberg of the cluster of "syndrome X," the driving force of which is increasing rates of obesity and socio-culture factors. Future efforts must target prevention strategies starting early in life.

New Treatment Options

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Treatment of diabetes continues to evolve, with addition of new therapeutic agents and new tactics for use of older ones. There are new ways of controlling both basal and postprandial hyperglycemia with both older and newer agents. The distinction between basal and postprandial hyperglycemia has been shown to be relevant in several ways. Basal hyperglycemia (overnight and between meals) is quantitatively more important to the total glycemic burden when glucose control is poor (e.g. when A1c is over 8%), and postprandial increments become clinically important as A1c approaches 7%. Also, pharmacotherapy generally targets one or the other. That is, sulfonylureas, metformin, thiazolidinediones, and basal insulins mainly control basal glycemia, whereas α -glucosidase inhibitors, rapid-acting secretagogues, and short and rapid-acting insulins are meant to improve postprandial increments. Treatment of basal hyperglycemia has generally been more effective. The newest agents, long-acting insulin analogs and agents affecting gastrointestinal peptide physiology, should be able to improve both basal and postprandial control, respectively. Systematic use of basal insulins using "treat-to-target" methods has been shown to allow reduction of fasting plasma glucose to 100–120 mg/dl, and A1c to about 7% in typical patients with type 2 diabetes, and evidence to date suggests that the long-acting insulin analogs, glargine and detemir, can do so with less hypoglycemia. The remaining challenge is to control glycemic increments after meals. In addition to prandial insulin doses, two other options are likely to be used in the near future. Pramlintide, an analog of the second β -cell hormone, amylin, has just been approved for use in insulin-requiring diabetes. Exenatide, a molecule with similarities to human glucagon-like peptide-1, is under review. Although these agents will be used for different populations of patients, early studies indicate they both greatly reduce postprandial hyperglycemia without causing weight-gain. Tactics for using these agents are currently under study.

Adipocytes and Insulin Resistance

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Adipose tissue has recently received a lot of attention due to the discovery of a number of adipocyte-derived factors that have profound effects on metabolism, inflammation, and cancer. The physiological characterization of these factors has greatly profited not only from the availability of knockout mice lacking these specific factors, but also from mouse models that either partially or completely lack adipocytes.

A number of adipocyte-derived factors have been implicated as modulators of insulin sensitivity, inflammation, and atherosclerosis. Specifically, resistin has been shown to cause decreased sensitivity in hepatocytes. In contrast, the adipocyte-derived secretory factor adiponectin has a potent insulin-sensitizing activity on hepatocytes. Several studies have shown that the circulating levels of adiponectin are directly proportional to systemic insulin sensitivity and are lowered in diabetics and patients suffering from cardiovascular disease.

Adipocytes that are insulin resistant and/or exposed to hyperglycemic conditions display a number of changes within the secretory pathway. These changes affect the overall rate of se-

cretion of a number of essential adipocyte-specific secretory products as well as the assembly and the release of specific complexes of these

proteins. Insulin-sensitizing agents such as peroxisome proliferator-activated receptor (PPAR) γ agonists restore these functions in the secre-

tory pathway through the up-regulation of specific chaperones as well as through PPAR γ -independent effects on mitochondria.



Challenging Characteristics of Generalized Lipodystrophy

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Introduction

Lipodystrophies first described in 1885 are a heterogenous group of adipose tissue disorders. Their characteristic is selective loss of fat (lipoatrophy) from various parts of the body and should be differentiated from other disorders that can lead to fat loss or fat redistribution (Table 1) (1). Lipodystrophies can be congenital or acquired, partial, or generalized (Table 2) (1–3). The extent of adipose tissue loss correlates with the severity of the metabolic abnormalities, namely insulin resistance, hypertriglyceridemia, diabetes, and fatty liver (1). We report a patient with generalized lipodystrophy.

Case Report

The patient is a 22-yr-old African-American male with history of hyperten-

Table 2 Classification of Lipodystrophies
<p>Familial or genetic types:</p> <ul style="list-style-type: none"> • Congenital generalized lipodystrophy (Berardinelli-Seip syndrome) <ul style="list-style-type: none"> Type 1 (seipin gene) Type 2 (AGPAT2 gene) Other • Familial partial lipodystrophies <ul style="list-style-type: none"> Dunnigan variety Kobberling variety Associated with PPARγ gene mutations Mandibuloacral dysplasia variety • Other types <p>Acquired types</p> <ul style="list-style-type: none"> • Acquired generalized lipodystrophy (Lawrence syndrome) <ul style="list-style-type: none"> Panniculitis variety Autoimmune variety Idiopathic variety • Acquired partial lipodystrophy (Barraquer-Simons syndrome) • Lipodystrophy in HIV patients • Localized lipodystrophies <ul style="list-style-type: none"> Drug induced Pressure induced Panniculitis variety Centrifugal variety Idiopathic

The patient has a body mass index of 19.5, curly hair, prominent mandible, enlarged hands and feet, acanthosis, absence of sc fat in upper extremities, lower extremities and trunk, a small umbilical hernia, and hepatosplenomegaly. His last laboratory work-up revealed triglycerides of 3104 mg/dl (0–200), HDL (high-density lipoprotein) of 5 mg/dl and total cholesterol of 211 mg/dl. Creatinine was 0.9 mg/dl, and microalbuminuria was present. Electrolytes, bilirubin, albumin, and coagulation profile were all in the normal range and transaminases were twice the upper level of normal. Hepatitis and HIV profile were negative. HbA1c was 11.1%, and TSH was normal. C-peptide concentration was 0.5 ng/ml with serum glucose of 330 mg/dl, indicating insulin deficiency. Leptin was 1.1 ng/ml (reference range 0.7–5.3). Computerized tomography (CT) of the abdomen (Fig. 1) revealed hepatosplenomegaly, inhomogeneous enhancement of the liver with fatty infiltration, and absence of sc and intraabdominal fat.

Discussion

Generalized lipodystrophies can be congenital (Berardinelli-Seip syndrome) or acquired (Lawrence syndrome).

Congenital generalized lipodystrophy (CGL) is an extremely rare autosomal recessive disorder that affects all ethnic groups. About 250 patients have been reported, and the estimated prevalence is one case in 10 million people. Metabolically active adipose tissue (sc, intraabdominal, intratho-

tion, severe hypertriglyceridemia, diabetes with high insulin requirements, chronic pancreatitis, and sickle cell trait. He was diagnosed with diabetes in puberty. During the same time, he had episodes of severe acute pancreatitis. Since then, he had multiple hospital admissions for hyperglycemia and epigastric pain.

His insulin requirements have been increasing since the diagnosis of diabetes. He is currently taking U-500 insulin, 500 U twice a day. Despite markedly increased appetite and oral intake, he is underweight. He denies family history of diabetes, hyperlipidemia, cardiac disease, or autoimmunity.

Table 1 Differential Diagnosis of Lipodystrophies
<ul style="list-style-type: none"> • SHORT syndrome (short stature, hyperextensibility of joints, ocular depression, ocular and dental Reiger anomaly and teething delay) • Werner syndrome • Leprechaunism (Donahue syndrome) • Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome) • Severe weight loss (loss of muscle mass in addition to fat) <ul style="list-style-type: none"> Malnutrition Anorexia nervosa Malabsorption syndromes Uncontrolled diabetes mellitus Thyrotoxicosis Adrenocortical insufficiency Cancer cachexia HIV-associated wasting Chronic infections • Multiple symmetric lipomatosis • Cushing's syndrome

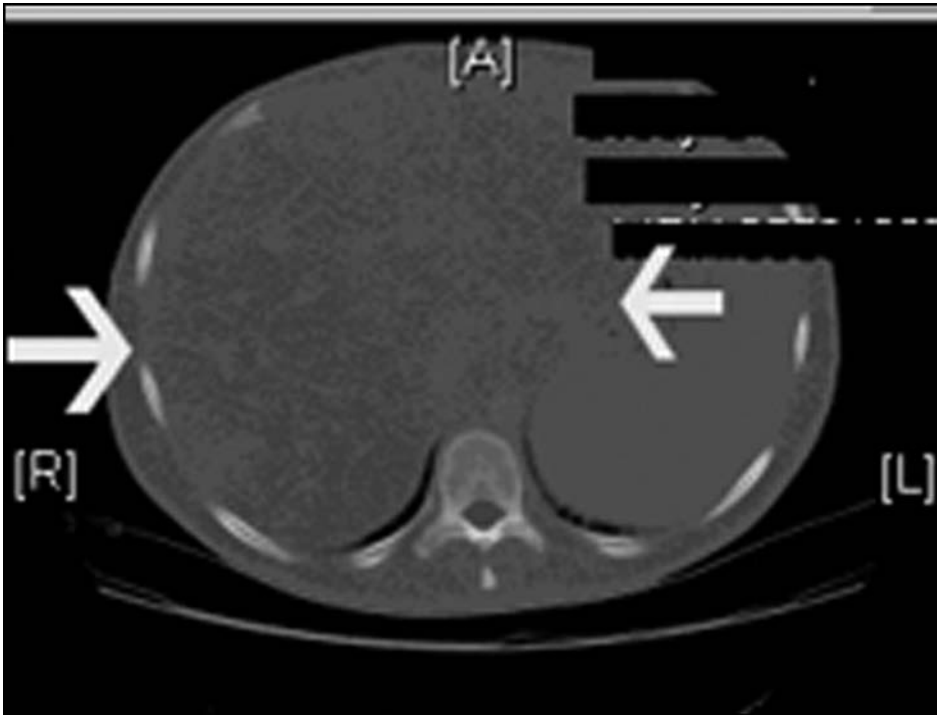


Figure 1. CT of the abdomen of the patient revealed enlarged liver with fatty infiltration (white arrows) and absence of sc and intraabdominal fat.

racic, bone marrow, and parathyroidal) is absent from birth, resulting in a generalized muscular appearance. Mechanical adipose tissue is present in normal amounts (4). Childhood is characterized by accelerated growth, voracious appetite, increased metabolic rate, and advanced bone age with normal or slightly above normal final height. Acanthosis nigricans usually appears by the age of 8 and might be widespread. Usual accompanying features include umbilical hernia, hepatosplenomegaly, and slight enlargement of the hands, feet, and mandible, resulting in acromegaloïd appearance. Severe hyperinsulinemia and high-serum triglycerides might be seen as early as in infancy, frequently causing chylomicronemia, eruptive xanthomas, and acute pancreatitis. Low HDL is common (1). Abnormal glucose tolerance and diabetes usually appear during puberty (1) and accelerated atherosclerosis as well as diabetic nephropathy and retinopathy can occur during adulthood. Fatty infiltration of the liver occurs early and may lead to cirrhosis. Postpubertal patients might exhibit focal lytic bone lesions. Plasma leptin and adiponectin levels are expected to be low (5). Resis-

tance to ketoacidosis has been reported. Genetic studies have identified two different loci (BSCL2 and AGPAT2) that are responsible for CGL, but other genes might also be involved. The identified loci map to chromosomes 11q13 and 9q34, respectively. The first gene encodes the protein seipin, which has

Generalized lipodystrophy: genetics, clinical and metabolic picture, classification, and differential diagnosis. Learning points from a case and review of the literature.

unknown function, and the second encodes the enzyme 1-acyl-glycerol-3-phosphate-acyltransferase-b, which is involved in the synthesis of triglycerides.

Acquired generalized lipodystrophy (AGL) was first described by Ziegler in 1928, and since then fewer than 80 patients have been reported in the

literature (2). It is three times more common in women than in men (2). Essential differentiating criterion from CGL is the age of onset: congenital occurs at birth, whereas AGL during childhood or adolescence (1). The loss of sc fat affects the face, neck, trunk, and extremities including the palms and soles (1). Clinical and laboratory features are similar with CGL. AGL has been subclassified into three different varieties (2):

- The panniculitis variety: It comprises 25% of AGL cases characterized by tender and inflamed sc nodules during childhood with fat loss upon healing.
- The autoimmune variety: Patients have past or present evidence of autoimmune diseases without preceding panniculitis.
- The idiopathic variety: Patients do not have evidence of panniculitis or autoimmune disease. This type appears to be the most common, accounting for about 50% of the AGL cases.

Diagnostic criteria for CGL and AGL have been proposed in 2000 (1) and 2003 (2), respectively.

Although our patient has generalized lipodystrophy, it is unclear whether this is congenital or acquired. He exhibits generalized loss of body fat, which is the essential criterion of both generalized lipodystrophy categories, but whether this feature was present at birth is unknown. He has hypertriglyceridemia with low HDL, low leptin levels, diabetes with high insulin requirements, and resistance to ketoacidosis. Intraabdominal fat is absent by CT scan. He does not have hyperinsulinemia as evidenced by the low C-peptide levels, probably a result of repeated episodes of pancreatitis. Clinically he has acanthosis, hepatosplenomegaly, absence of sc fat, muscular appearance, and acromegaloïd features. It is not obvious on clinical grounds whether there is absence of fat from palms and soles, and at imaging it is unclear whether he has presence or absence, of bone marrow fat. He has no evidence of other autoimmune disease or

panniculitis, and his family history does not point to a genetic cause.

Treatment of lipodystrophy-induced hyperglycemia has included insulin, sulfonylureas, metformin, and thiazolidinediones. Many patients like our own require extremely high doses of insulin. Rigorous glycemic control is important because it can improve dyslipidemia and also prevent long-term complications of diabetes. Fibrates, sometimes in combination with statins, have been used as lipid-lowering treatments. Niacin is not recommended due to exacerbation of insulin resistance (1). N-3 polyunsaturated fatty acids can also be added to the regimen. Experimental treatments include IGF-I, which has led to improvement of insulin resistance in short-term studies (6), adiponectin that ameliorated metabolic abnormalities in mice models of lipo-

dystrophy (7), and sc leptin that achieved significant decreases in HbA1c, insulin requirements, serum triglycerides, liver volume, caloric intake, and resting metabolic rate in nine affected individuals (8).

In conclusion, generalized lipodystrophies are rare disorders characterized by absence of metabolically active adipose tissue, which leads to deleterious metabolic and clinical sequelae. They pose a diagnostic and therapeutic challenge to the clinician.

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Case Report

Thyroid Papillary Carcinoma Presenting with Breast Metastases to the Same Thyroid Gland

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Introduction

Metastases to the thyroid gland is considered uncommon (1, 2). The incidence in autopsy series varies widely from 1.25% in unselected autopsy reports to 24% in series of patients with widespread neoplasm (3–10). Usually, the metastases to the thyroid gland is not clinically apparent and is also not frequently sought because more classic sites of metastases are often detected first.

The simultaneous occurrence of breast carcinoma metastatic to the thyroid gland and primary thyroid cancer within the same gland has not been reported in the current literature. Although some previous studies have suggested that there is an association between breast cancer and thyroid carcinoma, no scientific expla-

nations for this association have been discovered yet (11, 12).

In this report, we describe a case of papillary thyroid carcinoma presenting with metastases to the same thyroid gland from a breast carcinoma.

In this report, we describe a case of papillary thyroid carcinoma presenting with metastases to the same thyroid gland from a breast carcinoma.

Case Report

A 59-yr-old woman presented to the endocrinology department for evaluation of a thyroid mass found on computed tomography (CT) scan. This woman was treated in 1989 for a breast carcinoma (T₂N₁M₀), for which she underwent mastectomy, radiation therapy, and chemotherapy. She was free of disease until 2001, when she developed mediastinal and lung metastases, for which she received Tamoxifen with good response initially.

During follow-up with CT scan of the thorax and abdomen, progression of the disease was found in 2003, showing progression of the

lungs and mediastinal metastases, as well as new lesion in the left adrenal gland and a mass in the left lobe of the thyroid gland. Tamoxifen was stopped, and Arimidex was started. Hormonal evaluation confirmed the nonfunctionality of the adrenal nodule. A positron emission tomography (PET) scan was done to evaluate the adrenal mass, which was hypermetabolic, consistent with breast metastases with similar captation to the remaining breast carcinoma lesions. In the neck region, an intense hypermetabolic lesion was seen, corresponding to the mass seen on CT scan over the left thyroid lobe. A fine needle aspiration biopsy was performed, and the material was suspicious for a papillary carcinoma. Total thyroidectomy was undertaken according to the favorable prognostic predicted by her oncologist. The pathology report confirmed the presence of a papillary thyroid carcinoma within the left thyroid lobe ($1.5 \times 1.5 \times 1.5$ cm) as well as breast carcinoma implants within the opposite lobe, which were not seen on CT scan nor on PET scan because of the small size of these implants (all less than 0.8 cm). A radioactive iodine ablation treatment was performed after thyroidectomy.

Discussion

PET scan is more and more used in the follow-up of patients with neoplasms because various type of malignancies show increased glucose utilization when compared with normal tissues. Its frequent use has led to the evaluation of incidentalomas found on PET scan. In fact, when compared with ultrasound evaluation where the prevalence of thyroid incidentalomas ranges around 19–46% and where the associated risk of cancer is considered low, ranging 1.5–10% (13–15), the largest PET scan report showed a prevalence of thyroid incidentalomas of 2.2%, with a much higher rate of neoplasm, 26.7% of the lesions being cancerous (16). The stan-

dard uptake value can help distinguishing benign and malignant lesions because there seems to be a proportional relationship between higher standard uptake value and the risk of malignancy (16).

Even though metastases to the thyroid gland seem to be uncommon, they appear to be more frequent than primary thyroid cancer. The more frequent primary tumor sites are kidney, lung, breast, and esophagus (17). Some studies have suggested a correlation between breast and thyroid cancer, but to date no explanations have been found to confirm this correlation. Exposure to radiation is a well-known risk factor for both breast and thyroid cancer, so radiation therapy used to treat the first malignancy may contribute to the subsequent development of the second neoplasm. However, recent data failed to demonstrate a role of radiation therapy used to treat the first tumor in the risk of developing the second neoplasm (12). Furthermore, hereditary factors do not seem to be responsible for the correlation between breast and thyroid cancer. In fact, family history evaluation of women with both primary breast and thyroid cancer did not show an increased risk of developing these cancers in the patients' relatives, neither a mutation on the genes BRCA1, BRCA2, and PTEN was found to explain this association (11).

In conclusion, there seems to exist an association between breast and thyroid cancers, but no explanations have been discovered yet. The association of these two cancers may be a result of two frequent cancers affecting women. Are there hormonal factors predisposing women to develop these two cancers? We know it is true for breast, but it is still hypothetical for thyroid cancer. Explanation for this association is therefore still to be discovered. To our knowledge, this is the first report of a simultaneous occurrence of a primary

thyroid cancer and breast metastases to the same thyroid gland.

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The Misleading Neck Mass

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Introduction

Neck masses are a relatively common clinical finding, and frequently the reason for referral to the endocrinologist. The differential diagnosis of neck masses covers a broad spectrum of diseases including tumors (benign or malignant), lymph nodes, and cysts. We report the case of a young woman with an unusual cause of neck mass.

Case Report

A 34-yr-old African-American female presented to the Parkland Hospital Endocrine Clinic with a 3-month history of a right neck mass. The mass was first noted by her work-based doctor. Because she was asymptomatic, she pursued no further work-up. Over the next 2 months, the mass doubled in size. One month before her presentation to us, she was diagnosed with a thyroid nodule by physical exam. Thyroid function tests were normal. A fine needle aspiration was performed before our consultation and showed numerous bland follicular-like clusters and macrophages with no significant amount of colloid. The immunostains for thyroglobulin and thyroid transcription factor were negative but were positive for PTH.

The week before her visit, she noted sudden development of hoarse voice. She denied any fatigue; dyspepsia; nausea; constipation; dysuria; hematuria; ache of the bone, muscle, or abdomen; or memory problems. She had no history of kidney stones or bone fractures. She had no personal or family history of any endocrine disorders or malignancies of any kind. On physical examina-

tion she had a right neck oval-shaped mass, 4 × 6 cm, lying in close proximity to the right thyroid. The mass was nontender, of solid consistency, and mobile with swallowing movement.

Laboratory tests showed serum creatinine of 0.9 mg/dl, Ca 9.4 mg/dl, phosphate 3.2 mg/dl, PTH 120 (12–72) pg/ml. A contrast CT scan of her neck (Fig. 1) showed a nonenhancing mass (3.6 × 3 cm) posterior to the right thyroid lobe, displacing it, also displacing the trachea to the left. The lesion abutted the

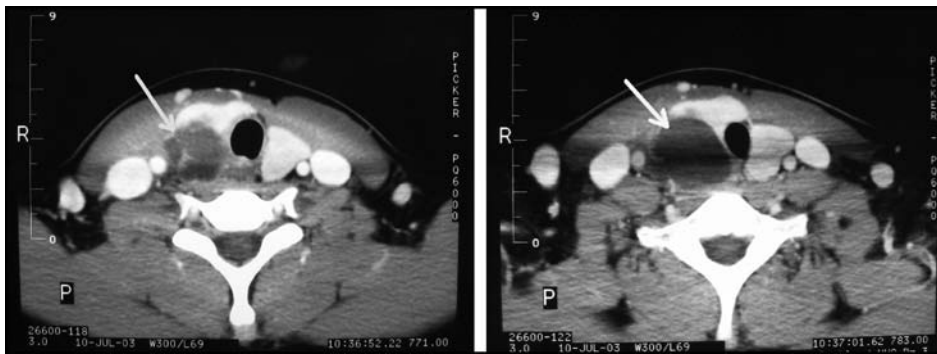


Figure 1. Contrast CT scan showing the nonenhancing right neck mass (arrow), posterior to the right thyroid lobe. The mass was deviating the trachea.

trachea and esophagus and surrounded the medial half of the right carotid artery. No pathologic lymphadenopathy was noted. Further blood work on 15 July 2003 showed ionized Ca of 5.1 mg/dl and 25 hydroxyvitamin D of 14 ng/ml. A repeat calcium level was 9.4 mg/dl, and 24 h calcium excretion was 58 mg.

A parathyroid origin mass was suspected, and she underwent surgery 2 wk later. The right recurrent laryngeal nerve was densely adhering to the capsule of the mass. En-block resection of the mass and right thyroid lobe was performed, with preservation of the right inferior parathyroid gland and the right recurrent laryngeal nerve. The surgeons described the procedure as very difficult because of extensive adhesions, and they made a preliminary di-

agnosis of parathyroid carcinoma based on the intraoperatively noted features of the mass. Postsurgery calcium level was 8.1 mg/dl.

The pathology report described a partly cystic mass (2.1 cm), with patchy desmoplasia, adherent to adjacent thyroid tissue, containing almost uniformly clear cells. Foci of hemorrhage and necrosis were seen. No significant atypia, mitoses, vascular invasion, or thyroid invasion were noted. Immunostain was diffusely positive for PTH (Fig. 2). The parathyroid gland was not easily dissected from the thyroid gland. All surgical margins were negative for tumor. The one resected lymph node was negative for tumor.

Her hoarseness slowly improved. She was treated with calcium and

vitamin D supplementation because of a very low vitamin D level and in an attempt to eliminate any stimulus for PTH secretion. One month after surgery, serum calcium was 10.0 mg/dl, TSH 1.5 μ UI/ml, ionized Ca 5.1 mg/dl, and PTH 189 pg/ml. Two months after the surgery, serum calcium level was 10.1 mg/dl, phosphorus 3.9 mg/dl, albumin 4.8 g/dl. Six months after surgery, her laboratory work shows: PTH, 70 pg/ml; serum calcium, 9.4 mg/dl; phosphorus, 2.7 mg/dl; TSH, 2.5 μ UI/ml; and normal albumin, creatinine, alkaline phosphatase, and magnesium. A surveillance Tc^{99m} sestamibi scan of the neck performed 6 wk after the surgery was negative. Two years after the surgery, she continues to be free of symptoms, and there is no recurrence of the mass. Her most recent laboratory reports included cal-

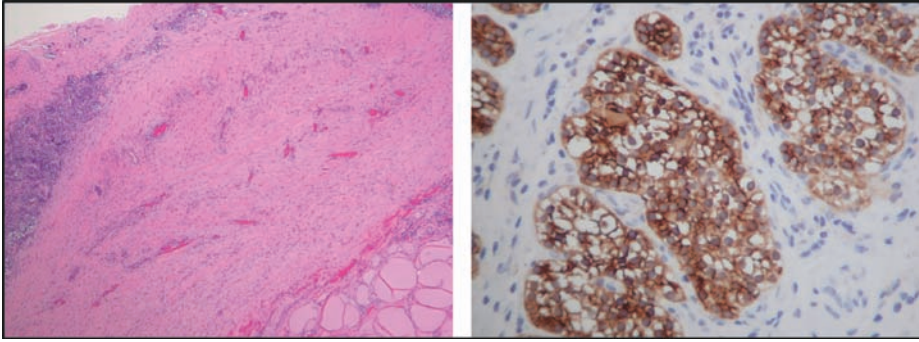


Figure 2. Histopathology of the tumor, showing desmoplasia and sheets of clear cells (left panel) and the PTH stain uptake (right panel).

cium 8.9 mg/dl, phosphate 2.9 mg/dl, and PTH 50 pg/ml.

Discussion

Parathyroid carcinoma is a rare malignancy of the parathyroid glands. Approximately 400 cases of parathyroid carcinoma were reported in the English literature since 1920. Because of its rarity and little experience with this disease, there are poorly defined diagnostic criteria and treatment algorithms, and data on prognosis and survival are scant. This makes treatment decisions for an individual case challenging, and counseling of the patient and family is difficult.

The etiology of parathyroid cancer is unknown. No clear pattern of predisposing factors has emerged in the cases described to date (1). Over the past decade, evidence for the involvement of mutations of both oncogenes and tumor suppressor genes in the development of parathyroid tumors has accumulated. No single gene has been documented, however, to be a definite participant in the pathogenesis of parathyroid cancer. New research suggests that HRPT2 mutation may be an early event that may lead to parathyroid malignancy and suggests that intragenic mutation of HRPT2 as a marker of malignant potential in both familial and sporadic parathyroid tumors (2).

The clinical features of parathyroid carcinoma are due primarily to the effects of excessive secretion of PTH by the functioning tumor rather than to infiltration of vital organs by tumor mass (1). No preoperative test currently is available to

reliably distinguish parathyroid cancer from benign primary hyperparathyroidism. Diagnosis should be suspected based on the clinical features and laboratory findings consistent with severe hyperparathyroidism including serum Ca more than 14 mg/dl and serum intact PTH more than five times the upper limit of normal. Fine needle aspiration is seldom diagnostic and should be avoided because there are reports of needle track seeding with recurrence. Imaging procedures are not useful to differentiate carcinoma from adenoma.

No preoperative test currently is available to reliably distinguish parathyroid cancer from benign primary hyperparathyroidism.

As is the case with many endocrine neoplasms, the histopathological distinction between benign and malignant parathyroid tumors is very difficult (1). Surgical frozen sections concur with the final diagnosis from the permanent sections in little over half of the cases. Even after review of permanent sections, the diagnosis is not always conclusive, and the confirmation is done retroactively based on subsequent clinical outcome. All too often, the diagnosis of parathyroid carcinoma is made in retrospect when hypercalcemia recurs

because of local spread of tumor or distant metastases. This is why new techniques are continuously searched to improve the diagnostic accuracy.

Parathyroid carcinoma is an indolent, albeit tenacious, tumor with rather low malignant potential. It tends to recur locally at the operative site and spread to contiguous structures in the neck (1). Metastases occur usually late in the course of the disease, by both lymphatic and blood stream spread. Cervical nodes (30%) and lung (40%) are involved most commonly, followed by liver (10%) (1). The cause of death is rarely because of the mass of primary tumor and metastases, but rather from metabolic complication of hyperparathyroidism.

The single most effective therapy for parathyroid carcinoma is complete resection of the primary lesion at the time of the initial operation when extensive local invasion and distant metastases are less likely (1). Radiation and chemotherapy have been unsuccessful to date. When parathyroid carcinoma has become widely disseminated and surgical resection is no longer effective, the prognosis is poor. However, even at this juncture relatively prolonged survival is possible with control of the hypercalcaemia (1). Because of the extremely elevated PTH levels and the intensity of the associated bone resorption, this may be a difficult and frustrating task (1). The average time between surgery and the first recurrence is approximately 3 yr, although intervals of up to 20 yr have been reported (1). Five-year survival rates vary from 40–86% (1), and 10-yr survival varies between 13 and 35%, and the mean survival rate is 6–7 yr from the time of diagnosis.

A small percentage of parathyroid carcinomas are of the nonfunctioning type. Because of the difficulty in diagnosing and classifying nonfunctioning tumors, there has been a tendency to exclude them from discussions of parathyroid carcinoma. In the English literature, over 400 cases of functioning and 17 cases of nonfunctioning parathyroid

carcinoma have been reported. These percentages should be interpreted with caution because of the relatively small number of cases, and reporting bias. Clinical detection of nonfunctioning parathyroid malignancies preoperatively is primarily based on symptoms of an expanding neck mass. This ominous complaint is typically accompanied with an advanced stage of the disease at initial diagnosis. Hence, parathyroid carcinoma should be considered in every patient evaluated for a neck mass regardless of the blood calcium and blood PTH level. Treatment of the nonfunctioning variant is the same, with prognosis being worse because of the delayed diagnosis, often when metastases are already present (3).

The lack of demonstrable endocrine activity remains unexplained. Four possible hypotheses have been postulated: lack of hormone synthesis, impairment

of cellular hormone secretion, synthesis of an abnormal hormone with defective endocrine activity, or synthesis of an insufficient amount of PTH to cause hypercalcaemia. Recent case reports with parathyroid cancer suggested the presence of an abnormal fragment of PTH, which is recognized by the whole PTH but not the intact PTH assay. Identification and characterization of this newly recognized form of whole PTH, and assessment of its potential biological activity, could provide insights into the mechanisms of abnormal PTH processing as well as further in our understanding of the biology of parathyroid cancer (4).

Conclusion

Our patient's diagnosis is still unclear. Her clinical presentation and intraoperative findings strongly support the diagnosis of nonfunctioning parathyroid carcinoma, but the pathology report

was unable to confirm this suspicion. This is a common dilemma when trying to diagnose parathyroid carcinoma. Molecular markers, like HRPT2, may prove to be useful diagnostic tools in the future. Meanwhile, we are closely following our patient to detect early any potential recurrences or metastases.

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continued from back page

Bariatric Surgery and the Endocrinologist

published meta-analysis showed 64–100% improvement or resolution of diabetes (2). An earlier study indicated that more than 90% of gastric bypass patients may be able to discontinue insulin therapy, more than 90% may stop all drug therapy, and more than 80% may achieve normal serum insulin and A1_c levels (3). Gut

hormones are thought to play a large role by promoting improved insulin sensitivity (4). Whereas these changes may ameliorate type 2 diabetes, recent reports indicate a potential serious complication—changes in gut hormone secretion may lead to nesidioblastosis in some patients, causing hypoglycemia

and requiring partial resection of the pancreas (5). Although it is a relatively rare complication, it illustrates the potential for as-yet-unidentified complications of the surgeries. Additional research is required to fully understand the benefits and risks of these procedures.

Table 1
Bariatric Surgeries and Selected Outcomes

Surgery	Vertical Banded Gastroplasty	Gastric Banding	Roux-en-Y Gastric Bypass	Biliopancreatic Diversion/ Diversion with Duodenal Switch
(All surgeries create a small stomach pouch)	Stomach stapled front to back wall. Pouch restricted by a polypropylene band.	Band around upper stomach. Sub-q port for band adjustment.	Pouch created by band/ stapling. Pouch connects to Roux limb of jejunum.	Limited gastrectomy. Pouch connects to transected ileum. Switch-sleeve gastrectomy, maintaining pylorus. Distal bowel connects to duodenum.
Restrictive, malabsorptive, or both	Restrictive	Restrictive	Both	Both
Excess weight loss, % (>2 yr) (10–12)	30–50	36–87	60–80	70–80
Nutritional side effects (10–12)	Nausea and vomiting	Nausea and vomiting	Nausea, vomiting and diarrhea, protein malnutrition, vitamin/mineral malabsorption	Nausea, vomiting, diarrhea, dumping syndrome, protein malnutrition, vitamin/mineral malabsorption
Cholelithiasis	Observed with any rapid weight loss, regardless of process			
% Diabetes resolution (10–12)	72	54–65	80–100	80–100

Table 2
Suggested Follow-Up of the Bariatric Surgery Patient^a (Adapted with Permission from Ref. 13)

	1 Month	3 Months	6 Months	12 Months	18 Months	24 Months	Yearly
BMP	X	X	X	X	X	X	X
Mg	X	X	X	X	X	X	X
CBC	X	X	X	X	X	X	X
Fe studies	X	X	X	X	X	X	X
PTH				X	X	X	X
Bone density				X	X ^b		X ^b
Vitamin D		X ^c	X ^c	X	X	X	<i>Biannually</i>
Alkaline phosphatase				X ^d		X ^d	X ^d

Adaptations are *italicized*.

^a Recommendations for follow-up will depend on the type of surgery performed. Many of these studies may not be necessary for patients of purely restrictive procedures.

^b If the patient is found to have abnormally low bone density, or decreasing bone density, then measure bone density annually.

^c This author's recommendation.

^d See Ref. 6.

Risks and Benefits of Bariatric Surgery

Table 1 lists selected outcomes of common bariatric surgeries. Especially important to the endocrinologist are the effects on diabetes and bone health. In the short term, hypoglycemic agents must be adjusted immediately following surgery due to drastic reduction in intake and, in malabsorptive surgeries, changes in secretion of gut hormones. Duration of diabetes is an important determinant of medication adjustment—patients with residual β -cell function may require discontinuation of all hypoglycemic agents. As weight loss progresses, patients still on hypoglycemic agents may require additional medication adjustment. Hypoglycemia may be due to dumping syndrome or medication and may be treated by dietary counseling or dose adjustment. Nesidioblastosis should be considered if other causes are excluded (5).

Any significant weight loss decreases bone density. Bariatric surgery also increases the risk of inadequate intake and absorption of nutrients vital to bone health (calcium and vitamin D). This problem is compounded when the patient is lost to follow-up by the surgeon. Dietary adequacy and supplement intake is then not monitored or reinforced, and tests to screen for complications not done. Goldner *et al.* (6) published a case report of a woman who had undergone bariatric surgery 17 yr prior, had previously presented with symptoms and diagnostic test results indicating osteomalacia, yet her complaints were *misdiagnosed* and osteomalacia *undiagnosed* for many years.

Table 2 lists the micronutrients that must be supplemented after bariatric surgery and suggests a schedule of tests to assess nutritional adequacy. Shuster *et al.* (7) published a comprehensive discussion of nutritional concerns related to the Roux-en-Y gastric bypass—a good resource for practitioners interested in nutritional sequelae of malabsorptive bariatric surgeries. Patients who have had malabsorptive surgery may require calcium and vitamin D supplementation in doses higher than those generally recommended for the healthy adult (8). Recommendations for the frequency of assessment of vitamin D status vary. Many obese patients have low serum 25-hydroxyvitamin D levels, presumably because vitamin D is sequestered in adipose tissue (9). Intake of vitamin D may change over time, or as weight loss progresses vitamin D might be more available for circulation (less stored in adipose tissue), but the only way to assess adequacy is to assess vitamin D levels routinely and frequently. I suggest that vitamin D levels be assessed before surgery, at 2- to 3-month intervals until after the first year after surgery, and every 6 months thereafter. Dietary intake of calcium and vitamin D should also be assessed at each office visit and appropriate diet changes and/or supplementation reinforced. [See previous *EndoTrends Back Page News* articles by Stuber (14–16) for food sources of calcium and vitamin D.]

Conclusion

Gastric bypass surgery may be an effective treatment for obesity and intervention for type 2 diabetes. When performed

by experienced surgeons, surgical risks are reduced and as risks decrease, patient interest increases. Further study is needed to determine which surgeries provide optimal outcomes (weight loss, reduction of surgical complications, and improvement of comorbidities of obesity) and to identify the unknown long-term complications. Indicators of known risks must be consistently assessed. It is vitally important for patients to be seen in follow-up to monitor nutritional status and prevent complications from vitamin/mineral deficiencies. Before surgery, patients must fully understand the risks and what is required to minimize these risks. Referring physicians must counsel their patient about the risks and the importance of routine follow-up. The endocrinologist must be actively involved in the glycemic management of the patient undergoing bariatric surgery. Evaluation of new patients must include a thorough medical history, including specific questions about weight and surgical histories. It is important to know which surgical procedure was performed—only then can clinical and laboratory results be interpreted and appropriate treatment provided.

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THE ENDOCRINE FELLOWS FOUNDATION ANNOUNCES ITS RESEARCH GRANT RECIPIENTS FOR THE SPRING CYCLE OF 2005

Derek LeRoith, M.D., Ph.D., Director, Grants Program

The Endocrine Fellows Foundations received 52 grant applications for the spring cycle. Awardees receive \$7,500 to facilitate their research. Applications were received from over 38 different institutions and included the entire spectrum of endocrinology: thyroid, diabetes, metabolism, water balance, reproductive endocrinology, metabolic bone diseases, adrenal, and pediatric endocrinology. The applications covered basic and clinical research. Among the 45 experts who were asked to review these applications, over 96% completed the reviews for this cycle, a remarkably high percentage. The average grant received four separate reviews. Using an NIH-based priority system, many grants were very favorably received. We are pleased to announce that nine grants were approved for funding. The awardees are noted below:

Paul Bernard, M.D.

Washington University
“The Mechanism of p38 Dependent Glucocorticoid Modulation of Inflammation in the Macrophage”
Program Director—Louis Muglia, M.D., Ph.D.

Ian De'Boer, M.D.

University of Washington
“Central Obesity, Sex and Nephropathy in Type 1 Diabetes Mellitus”
Program Director—John Brunzell, M.D.

Ines Donangelo, M.D.

Cedars-Sinai Medical Center
“Molecular Analysis of *in Vivo* Pituitary Tumor Transforming Gene (PTTG) Function”
Program Director—John Adams, M.D.

Adriana Ioachimescu, M.D.

The Cleveland Clinic Foundation
“Plasma Free Fatty Acids Endothelial Dysfunction, and the Role of Nitric Oxide Synthase (NOS) Pathway in Subjects with and without Insulin Resistance”
Program Director—S. Sethu Reddy, M.D.

Michelle Lee, M.D.

Columbia University
“Effects of The Melanocortin System on Adiposity and Hepatic Steatosis”
Program Director—John P. Bilezikian, M.D.

Jordan Pinsker, M.D.

Uniformed Service Health Sciences
“Regulation of Gene Expression and Protein Phosphorylation by Thyroid Transcription Factor-2”
Program Director—Gary Francis, M.D.

Jessica R. Smith, M.D.

Children's Hospital of Boston
“Prediction of Remission of Children & Adolescents with Graves' Disease: Utility of Assessing Thyrotrophin (TSH) Receptor Antibody and Heterogeneity”
Program Director—Joseph Majzoub, M.D.

Marie S. Thearle, M.D.

Columbia University
“Effects of Exercise on Hepatic Steatosis in Murine Modules of Obesity”
Program Director—John P. Bilezikian, M.D.

Julia Warren-Ulanch, M.D.

Children's Hospital of Pittsburgh
“Obesity, Insulin Resistance and Bone Metabolism in Adolescents with PCOS: Effects of Insulin Sensitizers vs. Oral Contraceptives”
Program Director—Silva Arslanian, M.D.