CLINICAL VIGNETTE

Leg Edema as a Presenting Sign of Cushing's Disease

Amy Chow, MD and Neema Heivand, MD

Case Presentation

A 59-year-old postmenopausal woman with obesity s/p Roux-en-Y surgery, prediabetes, and hypertension presented with one-year of worsening bilateral lower extremity edema, bruising, weight gain, and hirsutism.

She had initially lost one hundred pounds over three years following her Roux-en-Y surgery. When she initially presented, she had gained back the weight with worsening bilateral leg edema, frequent cellulitis, easy bruising, and new hirsutism.

She had been previously seen by multiple specialists with extensive laboratory testing and imaging without identifying a diagnosis. They included CT scan of the abdomen and pelvis, lower extremity ultrasound, and echocardiogram. On presentation, her physical exam revealed moon facies, scattered ecchymoses over her arms and legs, purple striae, a buffalo hump, and bilateral lower extremity edema.

The patient was referred to Endocrinology for further evaluation. Her midnight salivary cortisol levels were elevated at 0.971 ug/dl and 1.628 ug/dl (≤ 0.112 ug/dl). Twenty-four-hour urine cortisol level was 221 ug/dl (<=45.0 ug/d) and dexamethasone suppression test showed cortisol level of 28 mcg/dl (≤ 1.8 mcg/dl). ACTH was 57 pg/ml (4-48 pg/ml). Pituitary MRI showed an 8 mm hypoenhancing left sellar lesion bordering the medial margin of the left cavernous sinus. She was diagnosed with Cushing's disease and underwent transsphenoidal surgery. Pathology confirmed mixed gangliocytoma-pituitary adenoma (corticotroph). Following surgery her symptoms improved and she lost thirty pounds.

Discussion

Bilateral lower extremity edema can be caused by many etiologies. However, this patient presented with worsening lower extremity edema as well as bruising, hirsutism, and weight gain. Based on the clinical history, Cushing's syndrome (CS) was be high on the initial differential diagnoses.

CS occurs from chronic exposure to excessive glucocorticoid which can be either exogenous or endogenous. Diagnosis may be challenging because few signs or symptoms are pathognomonic of CS, in isolation. Establishing the diagnosis of CS can be delayed for years, putting patients at greater risk for complications and mortality. In a meta-analysis that included 5367 patients, the mean time to diagnosis was 3, 2.5, and 1.3 years for pituitary, adrenal, and ectopic CS, respectively.[1]

CS can cause a myriad of symptoms. The more common symptoms are decreased libido, weight gain, round face, menstrual changes, hirsutism, hypertension, ecchymosis, lethargy, depression, dorsal fat pad, and abnormal glucose tolerance. Less common symptoms are electrocardiogram abnormalities, striae, edema, proximal muscle weakness, osteopenia or fracture, headache, backache, recurrent infections, and acne.[2-4] In adults, the most suggestive signs and symptoms are proximal muscle weakness, facial plethora, increased fat in the abdomen and face, wide purplish striae (>1cm wide), bruising with no history of trauma, and supraclavicular fat pads. An important clinical clue is the simultaneous development and increasing severity of these symptoms.[5-7]

According to the Endocrine Society guidelines, a patient should be tested for CS if there are unusual findings for their age (osteoporosis or hypertension in young adults), multiple progressive features of CS (those that are predictive for this disease such as facial plethora, proximal myopathy, striae and easy bruising), unexplained severe features (resistant hypertension, osteoporosis) at any age and adrenal incidentalomas.[6] It is also important to exclude exogenous glucocorticoid intake.[6]

If a person is suspected of having CS, initial testing includes one of the following first-line tests: late-night salivary cortisol (two measurements using the upper limit of the reference range), 24-hour urinary free cortisol (UFC) excretion (two measurement, three-fold above the upper limit of the normal for the assay) or the overnight 1 mg dexamethasone suppression test (serum cortisol concentration <1.8 mcg/dl as a cutoff for normal response) or longer low dose dexamethasone suppression test (2mg/d for 48 hours).[6]

After confirming hypercortisolism, it is important to determine if it is ACTH-dependent or independent. A low 8 am ACTH (<5 pg/ml) is evidence of ACTH-independent disease, and CT of the adrenal gland is the next step. If ACTH is over 20 pg/ml, it is ACTH dependent (Cushing's disease or ectopic Cushing's syndrome). Plasma ACTH between 5 and 20 pg/ml requires a Corticotropin Releasing Hormone (CRH) stimulation test. In a patient with ACTH-dependent CS, the final test is to determine

if ACTH is pituitary or ectopic by doing a high-dose dexamethasone suppression test and CRH stimulation test or pituitary MRI. Suppression of cortisol during dexamethasone administration coupled with increases in plasma ACTH and serum cortisol after CRH administration is consistent with the diagnosis of a pituitary adenoma (Cushing's disease).

Pituitary ACTH-dependent Cushing's syndrome is five to six times more common than Cushing's syndrome caused by both benign and malignant adrenal tumors.[8] Women are three to eight times more likely than men to develop Cushing's disease.[8] Cushing's disease occurs mainly in women aged 25 to 45 years.[8]

According to Endocrine Society guidelines, the initial treatment for CS is surgical resection of primary lesions underlying Cushing's disease for ectopic and adrenal etiologies.[6] Medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful.[6] Radiotherapy or bilateral adrenalectomy may also be needed to treat Cushing's disease.[6]

This case highlights the importance of obtaining a thorough clinical history and performing a comprehensive physical exam when initially evaluating a patient. For Cushing's syndrome, biochemical testing is important to facilitate making the diagnosis, but the first step is obtaining a thorough history and physical exam. When evaluating a patient who presents with numerous symptoms of unclear etiology, it is important to keep your differential diagnoses broad.

REFERENCES

1. **Rubinstein G, Osswald A, Hoster E, Losa M, Elenkova A, Zacharieva S, Machado MC, Hanzu FA, Zopp S, Ritzel K, Riester A, Braun LT, Kreitschmann-Andermahr I, Storr HL, Bansal P, Barahona MJ, Cosaro E, Dogansen SC, Johnston PC, Santos de Oliveira R, Raftopoulos C, Scaroni C, Valassi E, van der Werff SJA, Schopohl J, Beuschlein F, Reincke M**. Time to Diagnosis in Cushing's Syndrome: A Meta-Analysis Based on 5367 Patients. *J Clin Endocrinol Metab*. 2020 Mar 1;105(3):dgz136. doi: 10.1210/clinem/dgz136. PMID: 31665382.
2. **Howlett TA, Rees LH, Besser GM**. Cushing's syndrome. *Clin Endocrinol Metab*. 1985 Nov;14(4):911-45. doi: 10.1016/s0300-595x(85)80083-9. PMID: 3002679.
3. **Katayama M, Nomura K, Ujihara M, Obara T, Demura H**. Age-dependent decline in cortisol levels and clinical manifestations in patients with ACTH-independent Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1998 Sep;49(3):311-6. doi: 10.1046/j.1365-2265.1998.00551.x. PMID: 9861321.
4. **Terzolo M, Pia A, Alì A, Osella G, Reimondo G, Bovio S, Daffara F, Procopio M, Paccotti P, Borretta G, Angeli A**. Adrenal incidentaloma: a new cause of the metabolic syndrome? *J Clin Endocrinol Metab*. 2002 Mar;87(3):998-1003. doi: 10.1210/jcem.87.3.8277. PMID: 11889151.
5. **Ross EJ, Linch DC**. Cushing's syndrome--killing disease: discriminatory value of signs and symptoms aiding early diagnosis. *Lancet*. 1982 Sep 18;2(8299):646-9. doi: 10.1016/s0140-6736(82)92749-0. PMID: 6125785.
6. **Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM**. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008 May;93(5):1526-40. doi: 10.1210/jc.2008-0125. Epub 2008 Mar 11. PMID: 18334580; PMCID: PMC2386281.
7. **Nieman LK**. Cushing's syndrome: update on signs, symptoms and biochemical screening. *Eur J Endocrinol*. 2015 Oct;173(4):M33-8. doi: 10.1530/EJE-15-0464. Epub 2015 Jul 8. PMID: 26156970; PMCID: PMC4553096.
8. Diagnostic evaluation of endocrine disorders II. *Endocrinol Metab Clin North Am*. 1988 Sep;17(3):445-619. PMID: 3220055.