Cushing's syndrome (CS) is the result of excess chronic glucocorticoid exposure of the body. This leads to local overproduction of growth factors resulting in complications affecting the cardiovascular system, metabolic disorders, psychiatric dysfunction, osteoporosis, and hematologic impairment [1]. CS has an incidence of 39.5 Per million Person Years with a skewed propensity to females with a ratio of 9:1 [2]. It could be the result of endogenous secretion or exogenous administration of glucocorticoids.

Exogenous administration is the most common cause of hypercortisolism, which primarily occurs via the oral route, but could also result from intraarticular, intramuscular, inhalation, or topical application. Endogenous CS spans three general domains: (1) abnormal hormone secretion within the hypothalamic-pituitary axis (also known as Cushing's Disease (CD); 60-70%), (2) an ectopic tumor (10%), and (3) excess corticoid production from the adrenal glands (20%) [1,3,4]. Although the most common cause of endogenous hypercortisolism is CD, it is rare, affecting only 40 in 1 million individuals with favoritism to female gender (F:M ratio 3.5:1). These tumors are rarely associated with genetic syndromes [1,3] and could have a significant impact on infectious morbidity and mortality of the patient.

**Case Report**

We present the case of a 26-year-old female with morbid obesity and poorly controlled diabetes, admitted with necrotizing soft tissue infection of the lower anterior abdominal wall. She underwent wide excisional debridement with a resultant large soft tissue defect, which extended over bilateral groins and occupied over 50% of her lower abdominal wall. Despite aggressive management and wound care, she had poor granulation tissue formation and delayed wound healing. Due to her cushingoid features endocrine workup was conducted revealing hypercortisolism and a pituitary macroadenoma on brain MRI. Inferior petrosal sinus sampling showed significant central-to-peripheral gradient confirming pituitary origin. The patient underwent trans-sphenoidal endoscopic tumor resection and pathology confirmed corticotrophic adenoma. Postoperatively, patient's glycemic control improved dramatically and her rate of wound healing and granulation improved.

**Conclusion:** Cushing's syndrome is a rare disease that could be challenging to diagnose. Elevated serum glucocorticoid levels may have remarkable immunosuppressive effects, predisposing to infectious complications as well as impaired wound healing. High clinical suspicion and appropriate workup is imperative to timely diagnosis and treatment in surgical patients to prevent complications and reduce morbidity and mortality.
Emergency Department three times during the course of a week for left calf erythema (presumably traumatic in nature), a fungal rash on her right thigh, evolving erythema of the lower abdominal wall, and progressively worsening pain, accentuating redness, and swelling of the right thigh and lower abdominal wall. In the interim, she was treated with a multitude of systemic and topical antimicrobial agents including trimethoprim-sulfamethoxazole, cephalaxin, fluconazole, topical clotrimazole, and doxycycline with no clinical improvement.

On her third presentation, she was febrile to 102°F, tachycardic, with a normal perfusion pressure. On exam, she was noted to have ecchymosis on her arms, hirsutism, diffuse nodular acne, an obese abdomen, diffuse abdominal striae, and tender edema and erythema of the RLQ extending to the suprapubic area and the right thigh. She also had bilateral lower extremity edema and thick whitish malodorous matter underneath her perianal skin. Initial laboratory evaluation was consistent with leukocytosis (white blood cell count of 14.3 with 21.7% bands), serum glucose of 254, proteinuria, and glycosuria. CT scan of the abdomen and pelvis revealed extensive subcutaneous emphysema of lower right abdominal wall that extended to her mons pubis and right upper thigh, suggestive of a necrotizing soft tissue infection. The patient was admitted to surgical service, resuscitated, started on broad spectrum antibiotics, and emergently taken to the operating room for wound exploration and wide surgical debridement. Intraoperative cultures were suggestive of a polymicrobial etiology with predominance of Proteus mirabilis and Peptostreptococcus anaerobius. She completed a 10 day course of Cefepime, Vancomycin, and Unasyn. Subsequently, had multiple planned take backs for wound exploration and further debridement, with a resultant gaping abdominal and inguinal wound measuring 30cm in lateral dimension, 8cm in cranio-caudal dimension, and 8cm in depth. The wound was managed with negative pressure dressing. The patient showed progressive clinical improvement, however, her abdominal wound had no trace of granulation tissue with no significant signs of healing and contraction. Two weeks later, the wound base was deemed appropriate for an attempted closure by plastic surgery that was successful with advancement flaps. The lower extremity wound was covered with split thickness skin graft. She was subsequently discharged to a facility for ongoing wound care and rehabilitation. Four days later, she presented to the outpatient clinic with dehiscence of the abdominal closure, gross contamination of the wound with purulent debris and fibrinous slough, in addition to evolving cellulitis along the edges of the wound. She underwent urgent wound exploration and further excisional debridement, with a resultant defect measuring 50cm x 10cm and 8 cm in depth. Cultures at the time grew Pseudomonas aeruginosa, Klebsiella pneumonia, and Corynebacterium, and she had a short course of Cefepime, Vancomycin, and Flagyl. Negative pressure dressing reapplied over the area.

Patient had a prolonged hospital course mainly due to poor progression of wound healing. In the interim, she underwent an MRI of her spine for worsening back pain, revealing multiple nondisplaced compression fractures of her lumbar vertebrae. Her functional status continued to deteriorate with significant muscle wasting and impaired mobility. Due to her Cushingoid features and issues with wound healing, endocrine workup was conducted. Her random cortisol, 24-hour urine cortisol, and serum ACTH levels were found to be elevated. Dexamethasone suppression testing was suggestive of a hypothalamic-pituitary etiology. Moreover, an MRI of the pituitary gland revealed a 17mm x 10mm x 14mm cystic structure in the pituitary gland with a 5mm nodular enhancing component along the anterior floor of the sella, suspicious of a cystic pituitary adenoma. Furthermore, bilateral inferior petrosal sinus sampling with cosyntropin releasing hormone stimulation, demonstrated an elevated central to peripheral ACTH and Prolactin levels, confirming an ACTH secreting pituitary adenoma, further localizing the tumor to the left hemisphere. The patient underwent an endoscopic endonasal transsphenoidal resection of the pituitary adenoma under BrainLAB guidance. Postoperative reticulin stain showed widespread disruption of the normal compartmentalized pituitary architecture, supporting the diagnosis of adenoma. She had considerable improvement in her CD, yet no resolution evident by persistent elevation of serum cortisol levels in the 20's, requiring Mifepristone to antagonize the effects of cortisol. Her overall metabolic status improved allowing reduction in her insulin and antihypertensive medication requirements. The wound base continued to granulate and she underwent split thickness skin grafting of the wound three months later.

**Discussion**

Hypercortisolism may present with a wide spectrum of systemic manifestations, significantly increasing morbidity and mortality. The most commonly reported symptom is weight gain due to characteristic centripetal, supraclavicular, and dorsocervical fat deposition [1]. Depending on severity, the changes in habitus could range from subtle to drastic. Other symptoms are the resultant of an abnormally high catabolic state such as osteoporosis from bone wasting, purple striae on the abdomen, proximal muscle wasting and weakness, easy bruising from atrophy of the skin and platelet dysfunction, and lower extremity edema due to increased capillary permeability. Decreased bone density presents in up to 80% of patients with CS, increasing the risk of vertebral body compression fractures [1]. Other nonspecific features of CS include Congestive Heart Failure, opportunistic infections, thrombotic complications, hirsutism, menstrual dysfunction and infertility, in addition to a myriad of psychiatric disturbances like cognitive impairment, depression, manic disorders, delusions/hallucinations, and suicidality. If left untreated, CS could be life threatening, with a median survival of 4.6 years.

When hypercortisolism is suspected based on history and physical exam findings, workup is imperative in accordance with the endocrine society guidelines. Two of the following three criteria are required for diagnosis: (1) elevated 24-hour urine free cortisol (UFC) levels more than three to fourfold the upper limit of normal, (2) loss of normal diurnal rhythm in cortisol secretion with a late-night salivary cortisol >4 nmol/L (repeated twice), and (3) loss of feedback inhibition (>1.8 ug/dl) with an overnight or 48-
hour low-dose dexamethasone suppression test (DST) [3].

Once the diagnosis of CS is established, further workup can elucidate the source of aberrant glucocorticoid secretion. Measurement of plasma ACTH levels differentiate between ACTH dependent (values >10-15 pg/mL) and ACTH independent (<5pg/mL) mechanisms [1,5]. ACTH independent CS could result from adrenocortical tumors, dysplasia, or hyperplasia. Causes of ACTH dependent CS include ACTH secreting adenoma of the pituitary gland or CD, Corticotrophin Releasing Hormone (CRH) secreting tumor within the hypothalamus, and ectopic ACTH syndrome with concomitant bilateral adrenal hyperplasia (5-10%).

Oversecretion of ACTH occurs due to the lack of a functioning negative feedback inhibition from circulating glucocorticoids, resulting in excess production of cortisol, adrenal androgens, and 11-deoxycorticosterone [1]. To assist in appropriate treatment planning, it is important to further assess the source of ACTH oversecretion with high-dose DST. Hypothalamic-pituitary (HP) axis adrenals retain sensitivity to glucocorticoid negative feedback inhibition. A 48-hour high-dose DST is considered positive if the morning/fasting serum cortisol is <50% of the basal value. If results are inconclusive, brain MRI and bilateral inferior petrosal sinus sampling (IPSS) can be conducted to confirm suspicions of a pituitary adenoma. In patients with ACTH dependent CS, high-dose DST alone has a sensitivity of 85% whereas combined with IPSS, sensitivity increases to about 95%; therefore, it's highly recommended that both high-dose DST and IPSS are conducted together [1,5]. When catheterizing the inferior petrosal sinuses bilaterally, both prolactin and ACTH levels can be measured and compared with their respective peripheral or baseline serum levels to localize the tumor to the right or left hemisphere. According to Sharma et. al, combined ACTH and Prolactin measurements lead to better localization than prolactin alone [6]. An IPSS measurement is considered positive if the central-to-peripheral ratio of ACTH is ≥2 and/or Prolactin ≥1.3 prior to cosyntropin releasing hormone stimulation.

If the high-dose DST is suggestive of an ectopic ACTH secreting tumor, CXR, CT, MRI, and Radiolabeled PET scans may be utilized to identify the tumorous tissue. Pulmonary paraneoplastic syndromes caused by small-cell lung cancer and bronchial carcinoid tumors make up the majority of ectopic CS sources; therefore, imaging should be focused within the intrathoracic cavity for every ectopic source encountered [5]. If the plasma ACTH level suggest an ACTH independent mechanism, CT scan of the adrenal glands with bilateral adrenal venous sampling under CT guidance should conducted to further elucidate an adrenal aberrancy.

Both medical and surgical modalities are available to manage CS. The most definitive treatment in surgical resection of the offending tumor, and hence the most common intervention. Surprisingly, remission rate is dependent more upon complete surgical removal of the tumor mass vs. characteristics of the tumor [7]. On average, 60-70% of patients with CD have a microadenoma <10 mm on MRI, which requires transsphenoidal hypophysectomy [1]. As a first line therapy, hypophysectomy carries a remission rate of 60-90%, which varies highly depending on the skill set of the surgeon, size of tumor, and degree of metastasis. The recurrence rate at 5 and 10 years is 5-10% and 10-20% respectively [8]. In patients with CD who fail transsphenoidal surgical resection, long term medical management, pituitary radiotherapy, or bilateral adrenalectomy with lifelong glucocorticoid and mineralocorticoid replacement may be the next best option [6]. Often, successful adenomectomy results clinical remission and/or transient corticotroph deficiency requiring steroid replacement. Such cases still require prolonged follow-up as Bansal et al, discovered that patients with cortisol levels <3 ug/dl and ACTH levels within normal limits were found to have recurrent CD within 2–5 years of successful adenomectomy. Medical treatment includes steroidogenesis inhibitors, modulators of ACTH release, and glucocorticoid receptor blockers. Radiotherapy can also be utilized to control cortisol levels in up to 8 months in patients who are poor surgical candidates; it is accompanied with a 20% relapse rate [6,8]. These classes of treatments can be used in combination or independently to normalize the plasma cortisol levels and should be considered as a case by case basis. For ACTH secreting ectopic tumors, surgical resection of the primary tumor or bilateral adrenalectomy are the mainstays of treatment.

Cushing's Disease could be associated with significant immune issues and infectious complications. In the presented case, the patient developed extensive polymicrobial necrotizing soft tissue infection of the anterior lower abdominal wall and groins, also suffering problems with granulation tissue formation and wound healing inherent to her metabolic disorder. The repetitive soft tissue infections, despite appropriate empiric antibiotic therapy and aggressive excisional debridement were likely precipitated by the immunosuppressive effects of CD. In the setting of massive fluid resuscitation with severe sepsis and septic shock, it might be challenging to appreciate certain features in relation to an endocrinopathy; her cushingoid features became precipitated by the immunosuppressive effects of CD. In the setting of massive fluid resuscitation with severe sepsis and septic shock, it might be challenging to appreciate certain features in relation to an endocrinopathy; her cushingoid features became

This case represents a rare phenomenon as to the best of our knowledge; currently there are no reported cases of concomitant CD and necrotizing fasciitis. It also highlights the magnitude of impaired tissue healing and compromised immunity imposed by hypercortisolism, leading to severe life-threatening infectious complications reported in 42% of patients [9]. The reported mortality of patients with necrotizing fasciitis ranges from 10–80% [10]. Associating the patient's source of infection to an endocrinopathy caused by a brain tumor proved challenging considering her multiple pre-existing comorbidities. Especially as
symptoms of hypercortisolism may also result from major depression, alcoholism, pregnancy, chronic renal failure, or stress in a class of symptoms known as pseudo-Cushing’s syndrome. Studies have linked necrotizing fasciitis with numerous co-morbidities such as diabetes mellitus, cancer, chronic alcoholism, immunosuppression, and vascular insufficiencies. In a study conducted by Cheng et al. assessing risk factors for necrotizing fasciitis, diabetes was identified to be a major comorbid condition present in 44.5–72.3% of patients in Necrotizing Fasciitis [11]. Moreover, diabetic patients with NF were found to be at a higher risk of limb loss directly related to the necrotizing infection. As CD and diabetes also have a strong association, it is very likely, that Cushing's Disease is also a major risk factor for necrotizing soft tissue infections, due to the associated immunodeficiency and comorbidities.

**Conclusion**

Diagnosing Cushing’s disease is a unique challenge. Expedient diagnosis is imperative as patients have a 9-year remission rate of up to 76.5% following surgical resection of the offending adenoma according to Ntali et al. [12]. High index of suspicion in conjunction with multidisciplinary collaboration of specialists to ensure conduction of appropriate diagnostic workup is imperative to timely treatment and prevention of complications in hopes of reduced mortality. It may be simple to attribute the patient’s physical features to other more common comorbidities, such as obesity, diabetes, and so forth, losing sight into the underlying endocrinopathy. Clinical curiosity in search for alternate diagnoses to explain the situation in hand might be the key to save a life.

**References**