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Ectopic ACTH-Secreting Cushing Syndrome of Pancreatic Origin: A Fatal Outcome Despite Early Diagnosis - A Case Report

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Abstract **Case Report**

Ectopic Cushing syndrome is a rare cause of ACTH-dependent hypercortisolism, with pancreatic neuroendocrine tumors representing an exceptional origin. We report the case of a 48-year-old woman presenting with severe Cushing syndrome, characterized by central obesity, hirsutism, secondary amenorrhea, and marked skin fragility. Laboratory evaluation confirmed pronounced ACTH-dependent hypercortisolism, and imaging revealed a suspicious pancreatic lesion. The patient was being prepared for surgical resection; however, her condition deteriorated rapidly, culminating in fatal septic shock before surgery. Pancreatic ectopic Cushing syndrome is associated with high morbidity due to metabolic, infectious, and cardiovascular complications. Diagnosis relies on elevated plasma ACTH, normal pituitary MRI, and targeted functional imaging. Optimal management involves surgical excision, with medical therapy to control hypercortisolism while awaiting intervention. This case underscores the potentially severe course of pancreatic ectopic Cushing syndrome and highlights the importance of early recognition and multidisciplinary management.

Keywords: Cushing syndrome, ectopic Cushing, ACTH, pancreatic neuroendocrine tumor, hypercortisolism, octreotide scan, early diagnosis, infectious complications.

INTRODUCTION

Cushing syndrome is an endocrine disorder characterized by chronic cortisol excess, most commonly due to exogenous glucocorticoid use or pituitary corticotroph tumors (Cushing disease) [1]. ACTH-dependent "ectopic" forms, caused by abnormal ACTH secretion from non-pituitary tumors, account for approximately 10–15% of cases [2].

Among ectopic causes, pancreatic neuroendocrine tumors (pNETs) are exceptionally responsible and represent a small minority of reported cases [3]. Diagnosis is often difficult due to the small size of the lesions and the absence of specific early symptoms.

Ectopic Cushing syndrome is frequently associated with rapid progression and severe complications, including metabolic disturbances, cardiovascular events, and infectious complications, contributing to a poor prognosis despite early recognition [4,5]. We report a case of ACTH-dependent Cushing syndrome secondary to a pancreatic neuroendocrine tumor with fatal evolution despite early diagnosis, highlighting the diagnostic and therapeutic challenges of this rare condition [6].

CASE REPORT

A 48-year-old woman with a two-year history of hypertension and recently diagnosed type 2 diabetes treated with metformin was referred for evaluation of suspected Cushing syndrome. She also had chronic cervical arthropathy with lumbar disc herniation and recurrent nodular panniculitis (Weber-Christian disease).

Clinical examination revealed rapid weight gain, central obesity, hirsutism, marked skin fragility with wide violaceous abdominal striae (Figure 1), and multiple ecchymotic and purpuric lesions on the lower limbs (Figure 2), consistent with severe hypercortisolism.

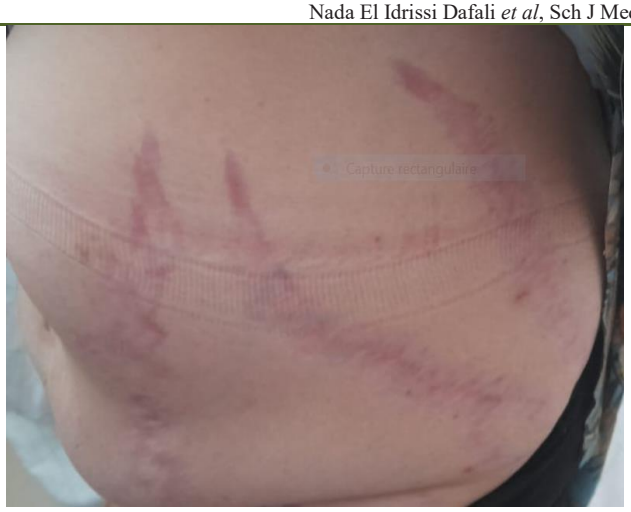

Figure 1: Wide violaceous abdominal striae associated with severe hypercortisolism

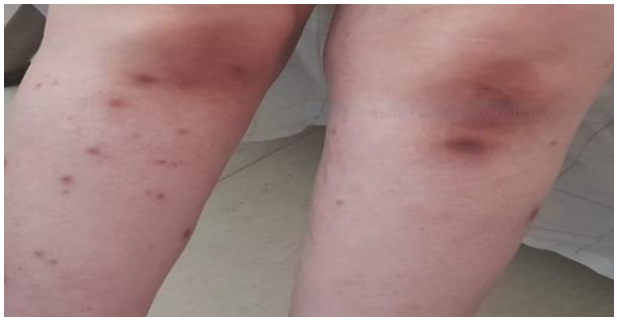

Figure 2: Multiple ecchymotic and purpuric lesions of the lower limbs reflecting marked skin fragility

Biological evaluation showed severe hypercortisolism with a non-suppressed overnight dexamethasone suppression test, morning plasma cortisol of 35.93 µg/dL, urinary free cortisol of 1988 µg/24 h, and elevated plasma ACTH of 203 pg/mL, consistent with ACTH-dependent Cushing syndrome.

Pituitary MRI was normal. Abdominopelvic CT revealed bilateral adrenal hypertrophy consistent with prolonged ACTH stimulation. Octreotide scintigraphy demonstrated abnormal uptake in the pancreatic body (Figure 3), and pancreatic MRI confirmed a suspicious nodular lesion compatible with an ACTH-secreting neuroendocrine tumor.

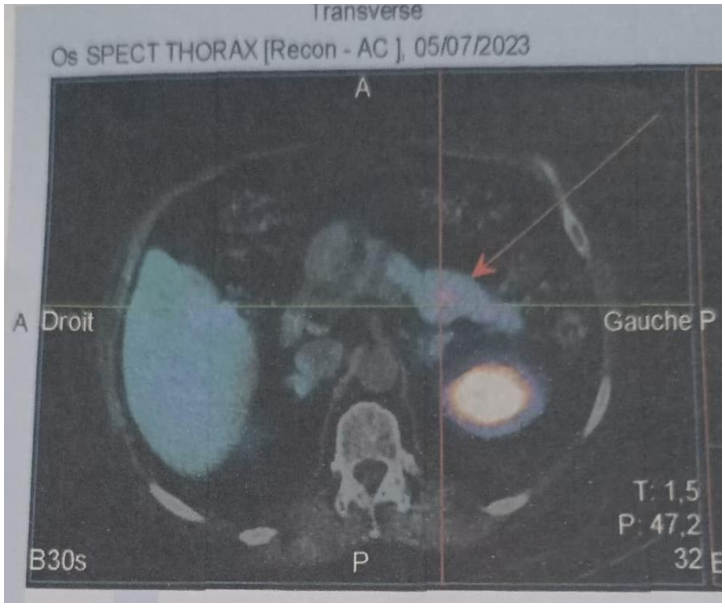

Figure 3: Hybrid SPECT/CT imaging demonstrating an intensely avid focus located in the pancreatic body, measuring 29.5 × 24.8 × 21.5 mm

The patient was being prepared for surgical resection; however, she developed rapid clinical deterioration with septic shock leading to death before surgery could be performed.

Discussion

Ectopic ACTH syndrome is a rare but severe form of ACTH-dependent hypercortisolism resulting from autonomous ACTH secretion by extra-pituitary tumors [2]. The most frequent sources are small-cell lung carcinoma and thymic tumors, whereas pancreatic neuroendocrine tumors represent an uncommon etiology, accounting for less than 5% of reported cases [3,4].

The pathophysiology involves sustained adrenal stimulation leading to markedly elevated cortisol levels and a profound catabolic state [1]. Excess cortisol induces insulin resistance, hypertension, protein catabolism, myopathy, skin fragility, and significant immune suppression. This immunosuppression predisposes patients to severe and opportunistic infections, which represent a major cause of mortality in ectopic Cushing syndrome [5]. The fatal septic shock observed in our patient illustrates the dramatic infectious risk associated with uncontrolled hypercortisolism.

The diagnostic workup relies on confirmation of ACTH-dependent hypercortisolism followed by localization of the source. Elevated plasma ACTH associated with a normal pituitary MRI strongly suggests an ectopic origin [6]. Functional imaging techniques such as octreotide scintigraphy or Ga-68 DOTATATE PET/CT play a crucial role in detecting neuroendocrine tumors that may not be easily visible on conventional imaging [7]. Bilateral adrenal hypertrophy, as observed in our case, reflects chronic ACTH stimulation and further supports the diagnosis [3].

Surgical resection remains the only potentially curative treatment for ACTH-secreting pNETs [8]. When surgery must be delayed, medical therapy aimed at controlling hypercortisolism is recommended. Steroidogenesis inhibitors such as ketoconazole, metyrapone, or mitotane may reduce cortisol levels and decrease the risk of acute complications [9]. In refractory or rapidly progressive cases, bilateral adrenalectomy may be considered as a life-saving option [10].

Despite early diagnosis, prognosis remains guarded in severe ectopic forms due to the high incidence of metabolic and infectious complications [4,5]. Early aggressive management, infection surveillance, metabolic stabilization, and close collaboration between endocrinologists, surgeons, radiologists, and intensivists are essential to improve outcomes.

Conclusion

Pancreatic ectopic ACTH syndrome is a rare but life-threatening condition. Even when diagnosed early, severe hypercortisolism can rapidly lead to metabolic decompensation and fatal infectious complications [4,5]. This case emphasizes the need for heightened clinical vigilance in rapidly progressive ACTH-dependent Cushing syndrome, prompt localization of the ectopic source using advanced imaging techniques [6,7], and immediate multidisciplinary management. Early initiation of cortisol-lowering therapy and careful monitoring for infectious complications are critical to improving prognosis in this challenging clinical entity [8,9].

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