Case Report

# Hidden diagnosis of multiple endocrine neoplasia-1 unraveled during workup of virilization caused by adrenocortical carcinoma

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## ABSTRACT

Multiple endocrine neoplasia-1 (MEN1) is an autosomal dominant syndrome with classic triad of parathyroid hyperplasia, pancreatic neuroendocrine tumors, and pituitary adenomas. Other recognized manifestations include carcinoid, cutaneous or adrenocortical tumors. It is commonly presented with clinical features related to parathyroid, pancreas or pituitary lesions. Here, we have presented a case that had virilization and biochemical Cushing's syndrome due to adrenocortical carcinoma as presenting feature of MEN1. Cushing's syndrome in MEN1 is an extremely rare and usually late manifestation and most cases are due to corticotropin-producing pituitary adenomas. Although Cushing's syndrome generally develops years after the more typical manifestations of MEN1 appear, it may be the primary manifestation of MEN1 syndrome particularly when related to adrenal adenoma or carcinoma.

**Key words:** Adrenocortical carcinoma, Cushing's syndrome, multiple endocrine neoplasia-1, virilizing syndrome

## Introduction

Multiple endocrine neoplasia-1 (MEN1) is an autosomal dominant syndrome described for the first time in 1954 by Moldawers and colleagues and Wermer separately.[1] It is a rare syndrome with prevalence of 1 in 30,000.[2] It is caused by mutations of MENIN gene located on Chromosome 11q13.3.[3] Germline mutations in this gene lead to development of one or more components of the classic triad of parathyroid hyperplasia (90%), pancreatic neuroendocrine tumors (PET) (60%), and pituitary adenomas (40%).[4] Other recognized manifestations of MEN1 include carcinoid tumors of the bronchus, thymus and gastrointestinal tract; and cutaneous tumors such as lipomas, angiofibromas, collagenomas, and adrenocortical tumors. Incidence of adrenal involvement in MEN1 has been reported to be between 9 and 45% and incidence of adrenocortical carcinoma in MEN1 is around 2.6-6%.[3] Most of the cases of MEN1 presents with symptoms related either to hyperparathyroidism or pancreatic neuroendocrine tumors. Here, we report a case of MEN-1 in a 43-year-old female presented with features of rapidly progressive virilization and during workup was detected to have parathyroid adenoma, pancreatic tumors and adrenocortical carcinoma.

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## Case Report

A 43-year-old lady presented to periphery hospital with history of amenorrhea for last 1 year, coarse hair growth over face, upper lip, trunk, arms and thighs, for which her abdominal computerized tomography (CT) scan was done which revealed adrenal mass of 4.3 × 3.4 cm. In view of this patient was referred to our tertiary care hospital as a case of hirsutism with adrenal lesion. She also complained of loss of scalp hairs, change in voice, proximal muscle weakness for last 1 year. Examination revealed hypertension (156/98 mm of Hg). She had normal body habitus (body mass index - 21.58 kg/m$^2$, waist-hip ratio 0.72). She had temporal

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baldness, hirsutism (Ferriman-Gallway score – 26/36), facial plethora, acne over face and upper chest and back, and multiple bruise marks. Her systemic examination was normal except proximal muscle weakness at shoulder and hip joints (power at both joints was $4^{+}/5$). Laboratory investigations detected diabetes mellitus (Oral Glucose Tolerance Test – 156/298 mg/dl; A1C – 7.4%). Her serum sodium and potassium were in normal range. Her lipid profile was normal (triglyceride – 119; total cholesterol – 170, LDL cholesterol – 109 and HDL cholesterol – 37 mg/dl). Electrocardiogram revealed left ventricular strain pattern and echocardiography showed left ventricular hypertrophy. She had nonsuppressible cortisol levels with overnight dexamethasone (Serum cortisol – 33.2 μg/dL) and low dose dexamethasone suppression test (Serum cortisol – 22.66 μg/dL). Her ACTH level was 7.7 pg/ml (normal 10-67 pg/ml). High doses dexamethasone decreased cortisol value only by 34% of basal value (31.08 to 21.56 μg/dL). She had raised testosterone levels (6 ng/ml; normal <0.6 ng/ml), and DHEAS levels (445 μg/dl; normal 30-335). Her twenty four urinary metanephrine and normetanephrine levels were normal (80 and 40 μg/day respectively). Her dynamic MRI abdomen and pelvis revealed one 3.3 × 3.6 × 4.2 cm heterogeneously hyperintense lesion with small fat containing foci with possibility of benign adrenal adenoma. There were two well-defined space occupying lesions (SOLs) were seen in pancreas; one in body of 16 mm and other in tail was 13 mm in size. Also multiple collocated subcapsular space occupying lesions in segment V of liver were noted and there was one 18 mm aortocaval lymph node. $^{18}$F-deoxy glucose (FDG) PET-CT scan showed right adrenal mass of 4.1 cm × 3.7 × 3.5 cm (SUV – 7.3) and 1.5 cm aortocaval lymph node of 1.5 cm with SUV of 3.8 with possible diagnosis of adrenocortical carcinoma with lymph node metastasis [Figure 1]. In view of clinical, biochemical and imaging studies, she was diagnosed as a case of adrenocortical carcinoma with metastasis in lymphnode, liver and pancreas. She denied any history of similar illness or malignancy in her family.

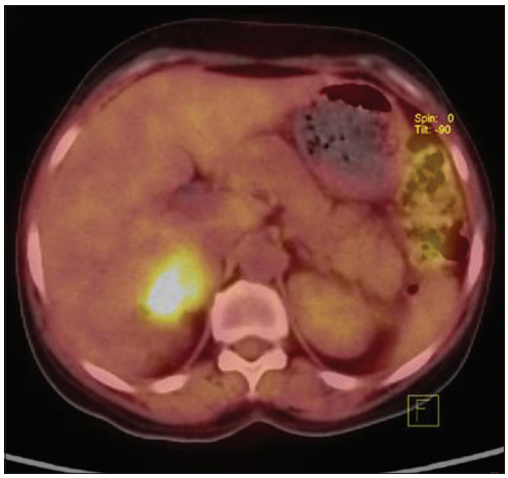


**Figure 1:** PET-CT showing FDG avid lesion in right adrenal region

Her investigation had incidental and surprising finding of hypercalcemia, which was confirmed on repeat testing (Serum calcium – 12.7, 13.5 mg/dl) with hypophosphatemia (1.8 mg/dl) in presence of normal serum albumin (4 g/dl) and magnesium levels (1.8 mg/dl). Her 24 hour urinary calcium measurement revealed hypocalciuria (135 mg/dl in presence of hypercalcemia). Though, Cushing's syndrome particularly due to adrenal carcinoma, can cause hypercalcemia but is associated with hypercalciuria, but our patient has hypocalciuria, indicating another underlying cause. Second possibility considered was humoral hypercalcemia of malignancy, where parathyroid hormone (PTH) levels are low. Hence, a serum PTH level was measured and to our second surprise it was detected to be raised (1003.8 pg/ml; normal–15-68 pg/ml). A possibility of ectopic secretion of PTH was considered. Literature search revealed only 12 cases of ectopic PTH secretion and none was related to adrenal gland.[5] She was evaluated for primary hyperparathyroidism and technetium sestamibi scan revealed left inferior parathyroid adenoma [Figure 2], but her ultrasonography of neck was normal. Bone mineral density measurement by DXA showed osteoporosis with low T- and Z-score at spine L1-L4 (T score -3.0; Z score -2.7), femur neck T score was -3.2; Z score -2.8 and radius T score was -3.6; Z score -3.0. Clinical dilemma faced was, whether it is sporadic parathyroid adenoma with adrenocortical carcinoma with metastasis, or is it that we are dealing with MEN1 with parathyroid adenoma and pancreatic tumor and associated adrenocortical carcinoma with metastasis. There were no symptoms suggestive of acid peptic disease, watery diarrhea, weight gain, and hypoglycemia. Biochemically her serum gastrin levels were raised (486 pg/ml; 13-115) strongly suggesting possibility of MEN1. Her upper gastrointestinal endoscopy was done to look for duodenal gastrinoma which was normal. MRI brain showed normal pituitary

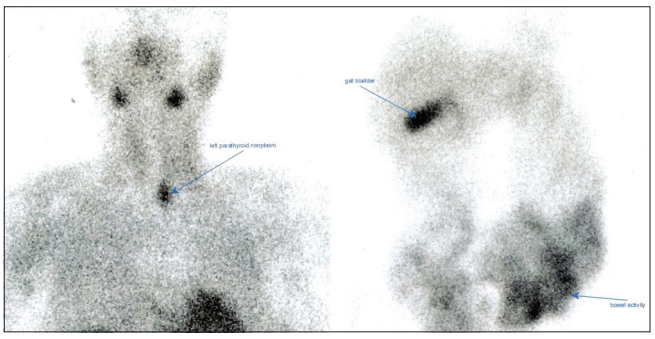


**Figure 2:** Technetium sestamibi scan showing left inferior parathyroid adenoma

gland. She had normal baseline pituitary functions (thyroid profile (FT3 – 2.99 pg/ml; FT4 – 1.43 ng/ml; TSH – 4.76 μIU/ml) prolactin (26 ng/ml) and suppressible growth hormone (0.65 ng/ml) levels). Nuclear imaging for neuro-endocrine tumor was not done as it was unavailable at our institution.

Her hypercalcemia was managed with saline diuresis and injection zoledronic acid. She was vaccinated with pneumococcal, meningococcal and H. Influenza vaccine in view of lesion in tail of pancreas which were to be excised, which are associated with risk of splenic injury and subsequent splenectomy. She underwent surgical excision of parathyroid adenoma with excision of all four parathyroids and half of one parathyroid gland was transplanted in left arm. In the same sitting, oncosurgeons operated her for pancreatic lesion. Her intra-operative ultrasound revealed three additional SOL in pancreas. Pancreatic lesion in head of pancreas was enucleated with resection of tail of pancreas for distal lesions along with splenectomy. Her adrenal lesion was excised in total with removal of aortocaval lymph node. Her postoperative recovery was uneventful.

Histopathology revealed parathyroid hyperplasia in all four parathyroid glands with left inferior parathyroid adenoma and neuroendocrine tumor in pancreas and liver. Immunohistochemistry (IHC) [Table 1] showed similar pattern of positivity in pancreatic tumor and liver metastasis - cytokeratin, synaptophysin and chromogranin A. Adrenal lesion was seen as adrenocortical carcinoma which expressed vimentin, synaptophysin, S-100 and inhibin; all of these were shared by aortocaval lesion [Figure 3]. Finally, patient had parathyroid hyperplasia with pancreatic neuroendocrine tumor with liver metastasis and adrenocortical carcinoma with lymphnode metastasis confirming the diagnosis of sporadic form of MEN1 with adrenocortical carcinoma. Her postoperative PTH ratio in transplanted arm to non transplanted arm was ~ 3 (27.35/9.74). Her testosterone value got (0.33 ng/ml) normalized post operatively. She developed primary adrenal insufficiency as evidenced by her low basal cortisol on fifth post operative day (0.9 μg/dl). She has been started on replacement doses of hydrocortisone and she is planned for chemotherapy and regular follow up for periodic assessment of recovery of hypothalamic adrenal axis.

Thus, this case presented with rapidly progressive virilization with adrenal mass which during workup was detected to have parathyroid adenoma and asymptomatic pancreatic neuroendocrine lesions with liver metastasis leading to final diagnosis of clinical MEN1 syndrome with adrenocortical carcinoma.

## Discussion

MEN1 is an autosomal dominant syndrome known for long and like all other polyendocrine syndromes, has been a fascinating syndrome to diagnose and manage for physicians and surgeons. MEN1 is caused by mutations in a tumor suppressor gene, MENIN, located at chromosome 11q13.3.[4] Development of MEN1 syndrome has been explained by Knudson's two hit hypothesis of tumorigenesis where first mutation is inherited while second mutation is acquired from environmental causes.[6] Sporadic *clinical* MEN1 is characterized by the occurrence of primary tumors involving two of the three main MEN1 related endocrine tissues within a single patient, while *familial* MEN1 is defined as at least one MEN1 case plus at least one first degree relative with one of those three tumors, and *genetic* MEN1 by the presence of mutation in the individual irrespective of clinical features.[7] Thus our patient full filled the clinical criteria for diagnosis of MEN1; however, genetic analysis was not performed due to cost constraints.

Most common and usually the earliest manifestation of MEN1 is hyperparathyroidism, which usually involves around 95% of cases,[4] but our case presented with virilization and ACTH independent Cushing's syndrome related with adrenal carcinoma. Management of symptomatic or hypercalcemic hyperparathyroidism is by surgical means as was done in our case. Mostly all four parathyroid glands are removed and half of one parathyroid is transplanted on to non dominant arm. Functioning of this graft is ascertained by calculating PTH gradient between two arms which if >1.5 towards transplanted arm indicate functioning of transplanted parathyroid tissue as was seen in our case.[8]

Pancreatic tumors occur in about 30-75% of MEN1 patients and are the second commonest clinical manifestation of MEN1.[9] Pancreatic tumors associated with MEN1 are characterized by an early onset, multiplicity of lesions, variable expression of the tumors, and propensity for

**Table 1: Immunohistochemistry results of pathology specimens**

| Lesion | Vimentin | Synaptophysin | Chromogranin | S100 | Inhibin | Cytokeratin | EMA | ACTH |
|---|---|---|---|---|---|---|---|---|
| Adrenal | + | + | – | + | + | + | – | – |
| LN | + | + | – | – | + | – | – | – |
| Pancreas | – | + | + | + | – | + | + | + |
| Liver | – | + | + | – | – | + | + | + |

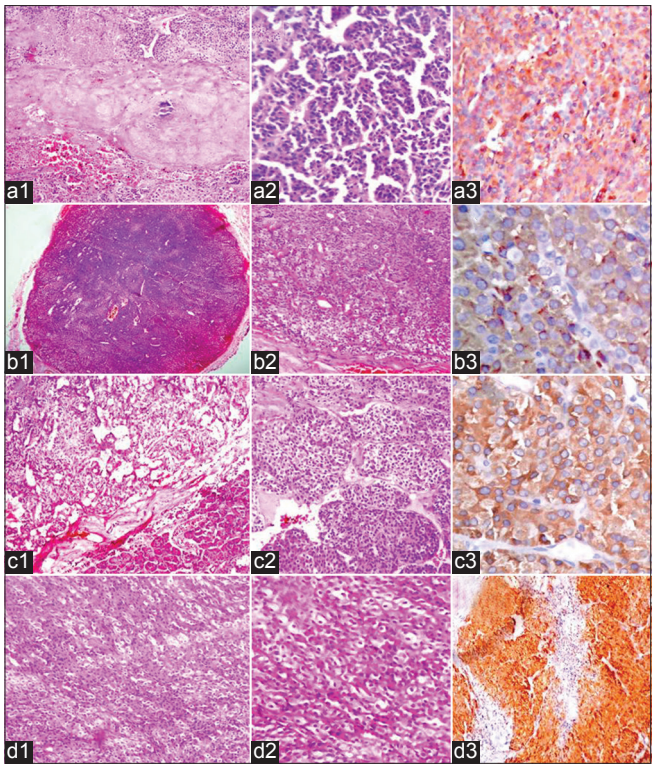


**Figure 3:** 1 = H and E ×40; 2 = H and E ×100; 3 = IHC ×40. (a1) Adrenal neuroendocrine neoplasm with areas of necrosis and calcification, (a2) Sheets of monomorphic cells in a nested pattern with high N : C ratio, scant cytoplasm and stippled nuclear chromatin, (a3) Positivity for Inhibin, (b1) Deposits of neuroendocrine carcinoma aortocaval lymph node, (b2) Sheets of monomorphic neuroendocrine cells, (b3) Positivity for Inhibin, (c1) Pancreas with neuroendocrine tumor,(c2) Sheets of monomorphic neuroendocrine cells, (c3) Positivity for chromogranin, (d1) Deposits of Neuroendocrine carcinoma in liver, (d2) Cords of hepatocytes with monomorphic neuroendocrine cells, (d3) Positivity for chromogranin

malignant degeneration. One third of pancreatic tumors are non-functioning and clinically silent, but the majority of them produce excessive amounts of hormones such as gastrin, insulin, glucagon, somatostatin, neurotensin or vasoactive intestinal polypeptide and are associated with distinct clinical syndromes.[9] The incidence of non functional pancreatic tumors is nowadays increasing because of advancement of radiological techniques. In our case, though biochemically gastrin levels were raised, but clinically pancreatic tumors were silent and UGI endoscopy was normal, gastric acid output was not assessed. Though, surgical excision is usually not warranted in sporadic gastrinomas associated with MEN1 initially along with parathyroidectomy. Because we were not sure about nature of pancreatic tumor and liver SOLs preoperatively, surgery was planned with aim to obtain excision biopsy of pancreatic and liver SOLs when undergoing removal of adrenocortical tumor with aortocaval lymph node. Triponez *et al.*,[10] reporting the experience of the French Endocrine Tumor Study Group involving 108 patients with MEN1, observed a correlation between the size of the tumors and their malignant potential, with a critical diameter of 1.5 to 2 cm significantly marking increased risk of malignant involvement. In our case pancreatic tumors were confirmed on histopathological and immunohistochemical analysis as neuroendocrine tumor with metastasis to liver.

Pituitary lesions are third most common lesions occurring in about 40% cases.[4] However, our case had no clinical or biochemical evidence of pituitary hyperfunction and MRI showed normal pituitary.

Adrenal involvement in MEN1 has been variable from 9-41%.[3] In a study conducted on 66 genetically confirmed cases of MEN1 syndrome adrenal lesions were seen in 26.8% of cases, the most common being non functional tumors (10 cases), followed by adenomas (3) and then adrenocortical carcinomas (4 cases; 3 functional and 1 non functional) and pheochromocytoma (1 case).[11] Waldmann *et al.* prospectively screened 38 cases of MEN1 syndrome for adrenal tumors with use of computed tomography and endoscopic ultrasonography for a median follow-up period of 48 months (range, 12 to 108). In 21 patients, adrenal lesions developed during a mean follow-up of 6.9 years after the initial diagnosis, of which only 3 lesions were functional (1 pheochromocytoma, 1 bilateral Cushing syndrome, and 1 adrenocortical carcinoma).[12] On an average, adrenal lesions occur around 5 years after hyperparathyroidism or pancreatic lesions. From the molecular biologic point of view, it remains unclear whether the development of MEN1-related adrenal tumors is directly caused by inactivation of the MENIN gene. No mutations (somatic or germline) of the MEN1 gene have been identified in adrenal lesions of MEN1 syndrome. Based on these results it is suggested that adrenocortical tumors are not primary component of MEN1 syndrome. Current research indicate the relevance of cAMP signaling in the pathogenesis of adrenocortical disease and point to the *Wnt* signaling pathway as a potential important mediator of tumorigenesis related to increased cAMP or PKA signaling (or both).[13] The study of relation between menin protein and cAMP pathway may unravel this mystery.

Though adrenocortical carcinomas have been reported in MEN1 syndrome, and there is a single case report of Cushing's syndrome due to adrenal adenoma as presenting feature of MEN1.[4] To the best of our knowledge, virilization with biochemical Cushing's syndrome due to adrenocortical carcinoma as initial presenting feature of MEN1 has not been reported in the literature.

## Conclusion

MEN1 is commonly presented with clinical features related to parathyroid, pancreas or pituitary lesions. Here, we have

presented a case that had virilization and biochemical Cushing's syndrome due to adrenocortical carcinoma as presenting feature of MEN1. Cushing's syndrome is an extremely rare and usually late manifestation and most cases are due to corticotropin-producing pituitary adenomas. Although Cushing's syndrome generally develops years after the more typical manifestations of MEN1 appear, it may be the primary manifestation of MEN1 syndrome particularly when related to adrenal adenoma or carcinoma.[4]

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