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Case Report

Adrenal Liposarcoma: A Novel Presentation of Multiple Endocrine Neoplasia Type 1

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ABSTRACT

Background/Objective: Multiple endocrine neoplasia type 1 (MEN1) syndrome results from genetic sequence variations of the tumor suppressor MEN1 gene, which codes for the protein menin. Individuals with MEN1 are prone to developing multiple tumors involving the endocrine and nonendocrine organs. MEN1 associated with liposarcomas has not been documented previously. We highlight a case of MEN1 presenting with a metastatic adrenal liposarcoma.

Case Report: A 41-year-old Hispanic man with a history of nephrolithiasis and skin lesions presented to the emergency department with abdominal pain. He was found to have a right adrenal mass measuring 7.9 cm with extension into the liver and primary hyperparathyroidism. He had multiple paternal first-degree relatives with similar skin lesions, hypercalcemia, and tumors of the brain, thoracic cavity, abdomen, and thyroid. The mass was identified as a metastatic pleiomorphic adrenal liposarcoma on surgical pathology. Genetic testing revealed a germline pathogenic sequence variation of the MEN1 gene.

Discussion: Liposarcomas are rare malignant tumors with an annual incidence of 2.5 cases per 1 million. Although lipoma formation is a commonly described manifestation of MEN1, liposarcomas have not been associated with MEN1 previously. A potential mechanism of this association is through the role of menin in inducing adipocyte differentiation via peroxisome proliferator–activated receptor-γ activation, a highly expressed protein in liposarcomas.

Conclusion: Liposarcomas should be included in the differential of MEN1-related tumors.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) syndrome results from genetic sequence variations of the tumor suppressor MEN1 gene which codes for the protein menin. It is inherited as an autosomal dominant disorder with high penetrance or can occur sporadically. The diagnosis of MEN1 is made based on clinical, familial, or genetic criteria.[1] Clinical criteria require 2 or more MEN1-associated tumors (pituitary adenomas, parathyroid adenomas, and enteropancreatic tumors). Familial criteria require 1 MEN1-associated tumor and a first-degree relative with confirmed MEN1. Genetic criteria require a germline MEN1 sequence variation in an individual who may be asymptomatic. Individuals with MEN1 are prone to developing multiple tumors involving the pituitary, parathyroid, and enteropancreatic organs. However, other associated tumors include angiofibromas, collagenomas, adrenal tumors, various neuroendocrine tumors, meningiomas, and lipomas.[1] We describe a case of MEN1 associated with a metastatic adrenal liposarcoma.

Case Report

A 41-year-old Hispanic man with a medical history of recurrent nephrolithiasis presented to the emergency department with acute, right-sided abdominal pain. He had not routinely sought medical attention prior to this; therefore, the reported medical history was limited, and he had no laboratory tests in our system prior to this presentation. He had multiple paternal first-degree relatives with skin nodules; tumors of the brain, thoracic cavity, abdomen, and thyroid gland; and hypercalcemia. The patient had 3 biologic children without any known medical conditions.

Abbreviations: MEN1, multiple endocrine neoplasia type 1; PPAR-γ, peroxisome proliferator–activated receptor-γ.

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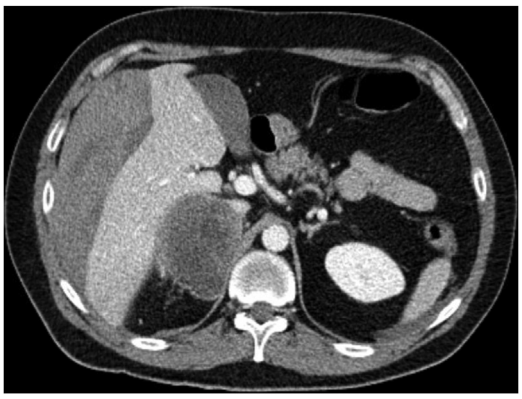

Fig. 1. Computed tomography scan with contrast: 7.9-cm heterogeneous hypoattenuating right adrenal mass and hepatic subcapsular hematoma.

Highlights

- Individuals with multiple endocrine neoplasia type 1 (MEN1) syndrome are prone to developing multiple tumors involving the pituitary, parathyroid, and enteropancreatic organs
- Adrenal liposarcomas may be associated with MEN1
- Although rare, it is important to keep MEN1 in the differential diagnosis of patients with adrenal tumors and other suggestive characteristics of the disease, such as hyperparathyroidism, pituitary adenoma, enteropancreatic tumor, and a significant family history of such manifestations.

Clinical Relevance

To our knowledge, this is the first documented case associating multiple endocrine neoplasia type 1 (MEN1) with liposarcomas. We believe that this article is of interest to a broad audience because it is a tumor that should be in the differential diagnosis of a patient with MEN1 presenting with an adrenal or intra-abdominal mass.

On physical examination, multiple brown, subcentimeter cutaneous nodules were noted on his torso. He had a 1-cm pedunculated nodule noted on his right arm. His body habitus was lean, and he had no cushingoid features. Computed tomography of the abdomen and pelvis with contrast revealed a 7.9-cm heterogeneous, hypoattenuating right adrenal mass, an 11-cm right posterior hepatic mass, and a hepatic subcapsular hematoma (Figs. 1 and 2). He was admitted to surgical oncology for urgent surgical intervention.

At the time of the patient's admission, the laboratory results were the following: (1) total calcium level, 11.7 mg/dL (8.4-10.4 mg/dL); (2) albumin level, 3.6 g/dL (3.4-4.7 g/dL); (3) calcium corrected for albumin level, 12 mg/dL (8.4-10.4 mg/dL); (4) parathyroid hormone level, 181 pg/mL (18-84 pg/mL); (5) 25-hydroxyvitamin D level, 19 ng/mL (>29 ng/mL); (6) creatinine level, 0.97 mg/dL (0.62-1.66 mg/dL); (7) estimated glomerular filtration rate, 97 mL/minute/1.73 m^2 (>60 mL/minute/1.73 m^2); (8) magnesium level, 2.0 mg/dL (1.4-2.6 mg/dL); (9) phosphorus level, 1.0 mg/dL (2.3-5.6 mg/dL); and (10) 24-hour urine calcium level, 482 mg/24 hours (42-353 mg/24 hours). Based on these levels, he was diagnosed with primary hyperparathyroidism. Prior to surgery, the 24-hour urine metanephrine, 24-hour urine normetanephrine, plasma metanephrine, and plasma normetanephrine levels were 261 μg/day (55-320 μg/d), 1098 μg/day (114-865 μg/day), 0.17 nmol/L (0.00-0.49 nmol/L), and 0.94 nmol/L (0.00-0.89 nmol/L), respectively. The 24-hour urine free cortisol level was 364.6 μg/day (≤60 μg/day), and the 1-mg dexamethasone suppression test showed a serum cortisol level of 10.1 μg/dL (<1.8 μg/dL), baseline adrenocorticotropic hormone level of 9 pg/mL (0-46 pg/mL), dehydroepiandrosterone sulfate level of 41 μg/dL (80-56 μg/dL), androstenedione level of 0.816 ng/mL (0.230-0.890 ng/mL), 17-hydroxyprogesterone level of 95.97 ng/dL (≤138.00 ng/dL), renin level of 8.7 ng/mL/hour (0.2-1.6 ng/mL/hour), and aldosterone level of 13.9 ng/dL (≤16.0 ng/dL).

Based on the aforementioned evaluations, suspicion for pheochromocytoma and adrenocortical carcinoma was low. Autonomous cortisol secretion could not be accurately assessed in the acute inpatient setting. He underwent a right adrenalectomy and received postoperative stress doses of hydrocortisone. Pathology revealed a high-grade pleomorphic liposarcoma involving the right adrenal gland that extended into the liver parenchyma. Magnetic resonance imaging showed T-spine lesions, and the patient was classified as having stage IV disease.

Because the suspicion for MEN1 was high because of his family history and primary hyperparathyroidism, the patient consented to proceed with genetic testing. A pathogenic sequence variation (c.2T>A, p.Met1?) of the MEN1 gene was discovered within a gene panel of 67 genes analyzed. He was retested for hypercortisolism 4 months after surgery with a 24-hour urine free cortisol, of which the level was 33.1 μg/day (≤60 μg/day), and 3 midnight salivary cortisol test results showing 0.037, 0.044, and 0.055 μg/dL (n <0.112 μg/dL). He was taken off hydrocortisone and did not have clinical evidence of adrenal insufficiency or glucocorticoid withdrawal syndrome. For the treatment of the liposarcoma, chemotherapy with doxorubicin, ifosfamide, and mesna was started, and cinacalcet was initiated to manage hypercalcemia while on chemotherapy. Parathyroidectomy was being considered on completion of chemotherapy. Unfortunately, he had disease progression on doxorubicin, ifosfamide, and mesna therapy, and he was placed on eribulin for palliative treatment.

Discussion

This is the first reported case of MEN1 associated with the development of an adrenal liposarcoma. Liposarcomas are rare malignant tumors with an annual incidence of 2.5 cases per 1

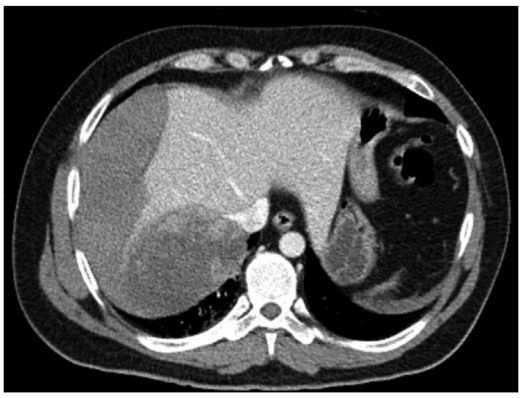

Fig. 2. Computed tomography scan with contrast: 11-cm right posterior hepatic mass and hepatic subcapsular hematoma.

million.[2] Although lipoma formation is a commonly described manifestation of MEN1, liposarcomas have not been associated with MEN1 previously. Menin is a nuclear scaffold protein that regulates gene transcription and acts as a tumor suppressor in endocrine organs.[3,4] It has been shown that menin can act as a coactivator of peroxisome proliferator–activated receptor-γ (PPAR-γ). PPAR-γ is expressed in adipocyte cells, and its stimulation has been shown to induce cell differentiation. A loss of function of menin has been shown to decrease PPAR-γ stimulation, and this is the proposed mechanism for lipoma formation in patients with MEN1.[5] PPAR-γ is also expressed in high levels in liposarcomas.[6] Thus, it can be postulated that the development of liposarcomas in the setting of MEN1 may share a similar mechanism, although there have been no studies reported in the literature examining this entity. Treatment with PPAR-γ agonists, such as pioglitazone, has been shown to induce cell differentiation, emerging as a potential treatment for liposarcomas.[7,8]

The incidence of MEN1 has been estimated to be 0.25%, and 1% to 18% of patients with primary hyperparathyroidism are found to have MEN1.[1] Although hypercalcemia is the most common initial presenting finding in patients with MEN1, this patient had not previously sought routine medical care aside from emergent care for nephrolithiasis, and therefore, this presenting feature went unidentified. Rather, he presented with a constellation of endocrine abnormalities and evidence of a metastatic liposarcoma, signifying advanced disease from delayed diagnosis. A potential missed opportunity for earlier diagnosis of this patient would have been further workup of his multiple skin nodules, which he shared with many of his relatives and had since childhood. Multiple cutaneous manifestations, including cafe au lait macules and nodules, have been associated with MEN1 and have even been used to increase the pretest probability of positive genetic testing for the relatives of patients with MEN1.[9] Regarding the concern for hypercortisolism in the patient's initial testing, it is difficult to definitively determine if it was physiologic or pathologic. First, the patient had no cushingoid features, and the pretest probability for Cushing syndrome was low. However, both the 1-mg dexamethasone suppression and 24-hour urine free cortisol test results were abnormal. Unfortunately, these tests are not reliable in the setting of acute stress owing to false positives and cannot solely be relied on to make the diagnosis of Cushing syndrome.[10] The facts that the patient did not require long-term glucocorticoids postoperatively and that pathology was not suggestive of cortisol-producing cells, point toward physiologic hypercortisolism due to stress rather than a cortisol-producing liposarcoma.

Conclusion

In conclusion, it is important to keep MEN1 in the differential diagnosis in patients who present with a history of nephrolithiasis and evaluate early for the presence of hypercalcemia. This case further highlights the importance of obtaining a thorough family history in such patients because the tumors associated with MEN1 can portend significant morbidity and mortality for patients and their families.

References

1. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*. 2012;97(9):2990–3011.
2. Henze J, Bauer S. Liposarcomas. *Hematol Oncol Clin North Am*. 2013;27(5):939–955.
3. Matkar S, Thiel A, Hua X. Menin: a scaffold protein that controls gene expression and cell signaling. *Trends Biochem Sci*. 2013;38(8):394–402.
4. Chen YX, Yan J, Keeshan K, et al. The tumor suppressor menin regulates hematopoiesis and myeloid transformation by influencing Hox gene expression. *Proc Natl Acad Sci U S A*. 2006;103(4):1018–1023.
5. Dreijerink KM, Varier RA, van Beekum O, et al. The multiple endocrine neoplasia type 1 (MEN1) tumor suppressor regulates peroxisome proliferator-activated receptor gamma-dependent adipocyte differentiation. *Mol Cell Biol*. 2009;29(18):5060–5069.
6. Tontonoz P, Singer S, Forman BM, et al. Terminal differentiation of human liposarcoma cells induced by ligands for peroxisome proliferator-activated receptor gamma and the retinoid X receptor. *Proc Natl Acad Sci U S A*. 1997;94(1):237–241.
7. Somaiah N, Beird HC, Barbo A, et al. Targeted next generation sequencing of well-differentiated/dedifferentiated liposarcoma reveals novel gene amplifications and mutations. *Oncotarget*. 2018;9(28):19891–19899.
8. Frapolli R, Bello E, Ponzo M, et al. Correction: combination of PPARγ agonist pioglitazone and trabectedin induce adipocyte differentiation to overcome trabectedin resistance in myxoid liposarcomas. *Clin Cancer Res*. 2020;26(5):1199.
9. Vidal A, Iglesias MJ, Fernández B, Fonseca E, Cordido F. Cutaneous lesions associated to multiple endocrine neoplasia syndrome type 1. *J Eur Acad Dermatol Venereol*. 2008;22(7):835–838.
10. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93(5):1526–1540.