Sonographic Findings of Medullary Thyroid Carcinoma Leading to Diagnosis of Multiple Endocrine Neoplasia Type 2a during Pregnancy

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ABSTRACT

Multiple endocrine neoplasia (MEN) type 2a (Sipple's syndrome) is characterized by medullary thyroid carcinoma and pheochromocytoma, and in a smaller percentage of cases, multiglandular parathyroid hyperplasia. This autosomal-dominant syndrome is due to a mutation in the rearranged during transfection (RET) proto-oncogene located on chromosome 10cen–10q11.2 and rarely complicates pregnancy. We present an unusual case in a patient with an enlarged thyroid with sonographic findings characteristic of thyroid cancer, which led to diagnosis and subsequent management of RET proto-oncogene-positive MEN type 2a complicating pregnancy.

KEYWORDS: Pregnancy, ultrasound, thyroid carcinoma, pheochromocytoma, multiple endocrine neoplasia type 2a

Multiple endocrine neoplasia (MEN) type 2a (Sipple's syndrome) is characterized by medullary thyroid carcinoma and pheochromocytoma, and in a smaller percentage of cases, multiglandular parathyroid hyperplasia.[1] This autosomal-dominant syndrome is due to a mutation in the rearranged during transfection (RET) proto-oncogene located on chromosome 10cen–10q11.2 and rarely complicates pregnancy.[1–7]

We present an unusual case in a patient with an enlarged thyroid with sonographic findings characteristic of thyroid cancer, which led to diagnosis and subsequent management of RET proto-oncogene-positive MEN type 2a complicating pregnancy.

CASE REPORT

A 34-year-old Caucasian woman, para 5, was followed during her current pregnancy at State University of New York (SUNY) Downstate Medical Center. Her medical history was unremarkable, and she specifically denied previous hypertension or symptoms suggestive or consistent with pheochromocytoma. She was a late registrant for prenatal care at SUNY at 28 weeks' gestation, at which time fetal ultrasound depicted normal anatomy and amniotic fluid volume. At 34 weeks' gestation, the patient complained of palpitations, and she was hospitalized due to the presence of an enlarged thyroid gland and tachycardia of 110 beats per minute.

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On admission, she was afebrile her blood pressure was 101/62 mm Hg, pulse 108 beats per minute, respiratory rate 20 breaths per minute, and body mass index 22.8 kg/m^2. Her thyroid gland was diffusely enlarged and mobile and measured $\sim 10 \times 5$ cm. Heart sounds were normal, and her lungs were clear. Her abdomen was soft and nontender, and fundal height was appropriate for gestational age. Hemoglobin was 10.4 g/dL, hematocrit 29.6%, white blood cells 10.04×10^9/L. Serum creatinine, blood urea nitrogen, and electrolytes were normal. Thyroid function tests were within normal limits. Ultrasonography depicted a singleton, vertex-presenting fetus with an estimated fetal weight of 2603 g, with fetal biometry appropriate for gestational age. Fetal heart rate was reactive and reassuring. Electrocardiogram disclosed sinus tachycardia, and cardiac enzymes were negative. Echocardiography showed a normal-sized heart with a left ventricular ejection fraction of 72%. Ultrasound assessment of the thyroid was suspicious for malignancy, depicting an enlarged right lobe ($6.5 \times 2.4 \times 3.0$ cm) with a large heterogeneous nodule in the mid to upper pole measuring $3.1 \times 1.6 \times 2.3$ cm and containing several microcalcifications (Figs. 1 and 2). Color Doppler imaging depicted marked internal vascularity within this nodule. The left lobe was similarly enlarged, measuring $5.2 \times 1.6 \times 2.7$ cm, and contained two adjacent nodules measuring $2.3 \times 1.2 \times 1.9$ cm and $2.8 \times 1.2 \times 2.1$ cm, respectively (Figs. 3 and 4). Both nodules were heterogeneous and contained microcalcifications and internal and peripheral vascularity. Serum calcitonin was 3097 pg/mL (markedly elevated). Parathyroid hormone was elevated (98.4 pg/mL), and serum total calcium was low 7.5 mg/dL (normal levels ranging between 8.4 and 10.2 mg/dL). Serum levels were not adjusted for pregnancy. Cytology (both smears and ThinPrep), obtained at fine-needle aspiration of the thyroid confirmed medullary thyroid carcinoma. Immunohistochemistry results of the cytology specimen were positive for calcitonin, chromogranin, and carcinoembryonic antigen, polyclonal.

With the concern for possible MEN type 2a, Magnetic resonance imaging of the abdomen was performed and depicted a homogeneous mass in the right adrenal gland measuring $2.6 \times 3.1 \times 2.0$ cm (Figs. 5 and 6). With 24-hour urine metanephrine levels of 2870 μg/24 hours (markedly elevated), the mass was considered consistent with an adrenal pheochromocytoma. Nucleotide sequence analysis of the RET proto-oncogene was positive. Following consultation with the Endocrinology and Surgery Departments, α-receptor blockade treatment with oral phenoxybenzamine 10 mg/d was initiated. At 36 weeks' gestation, following the onset of spontaneous labor, cesarean delivery was performed through a transverse lower uterine segment incision under general anesthesia.

The female neonate weighed 2920 g and was assigned Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. Umbilical artery pH was 7.30, and base excess was -0.8. During the immediate uneventful postpartum course, phenoxybenzamine 10 mg/d was continued. Following the presence of sustained tachycardia to 130 beats per minute on postoperative day 2, β-receptor blockade treatment with propranolol 10 mg/d was administered. Resection of the pheochromcytoma

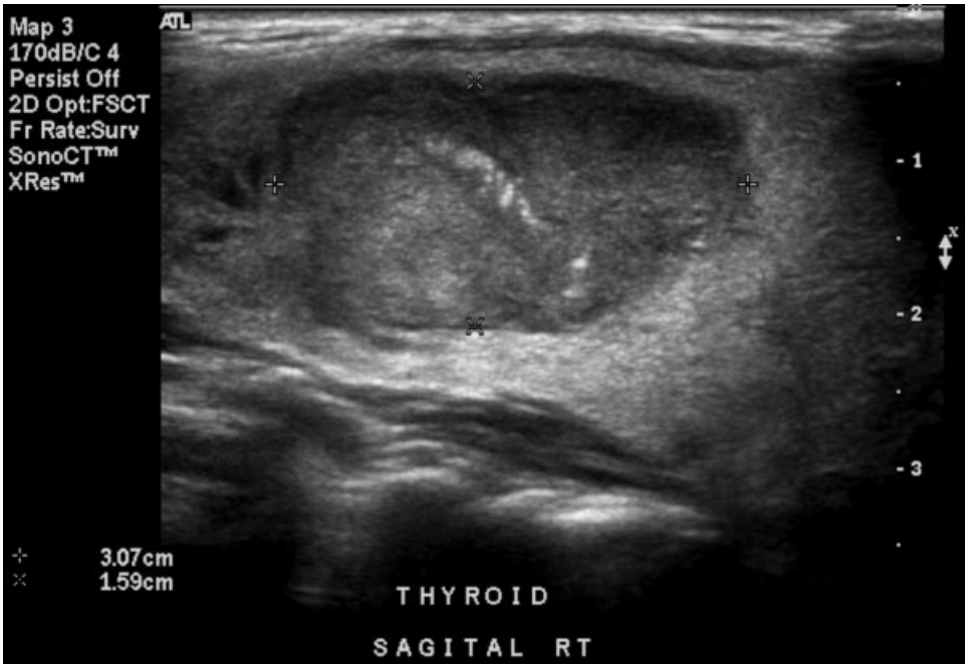

Figure 1 Sagittal image of the right thyroid lobe. Heterogenous mass with microcalcifications is outlined by electronic calipers.

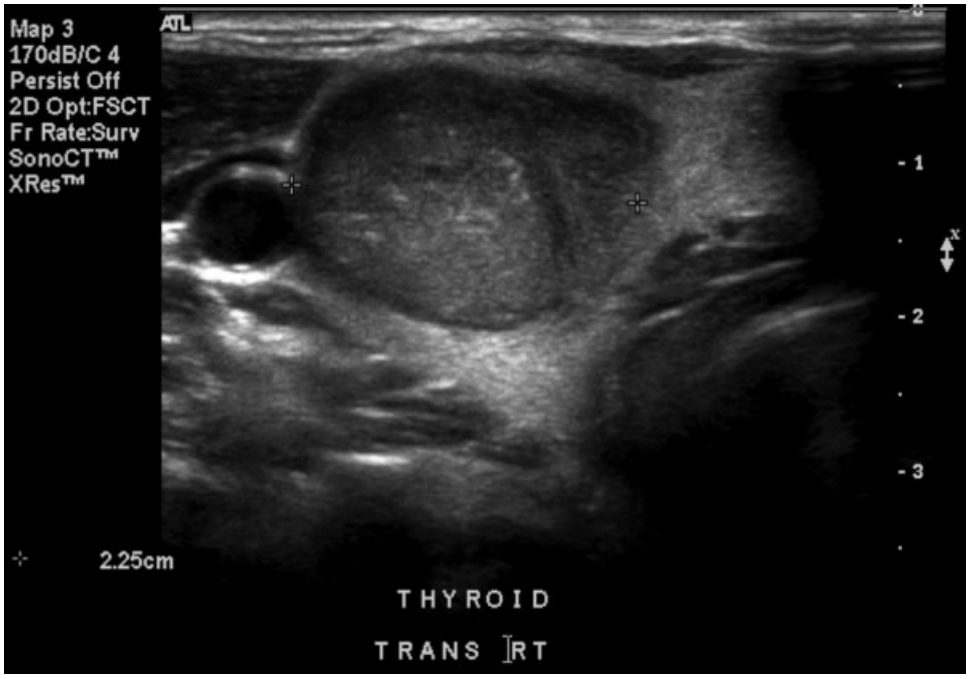

Figure 2 Transverse image of the mass depicted in Figure 1.

and thyroidectomy were planned. Three months after delivery, the patient and her infant were both well. Despite extensive, repeated counseling with maternal–fetal medicine, endocrinology, and surgery consultants, the patient declined surgical management of both the medullary thyroid carcinoma and pheochromocytoma. Similarly, the parents declined RET proto-oncogene testing of the infant.

DISCUSSION

Despite being one of the most frequent neoplasms occurring in the endocrine system, thyroid carcinoma is a relatively rare event, accounting for 0.5 to 1.5% of all malignant tumors in humans.[8] Ultrasound is an established tool in the evaluation of thyroid nodules and detection of thyroid carcinoma.[9–12] Sonographic features associated with thyroid carcinoma include

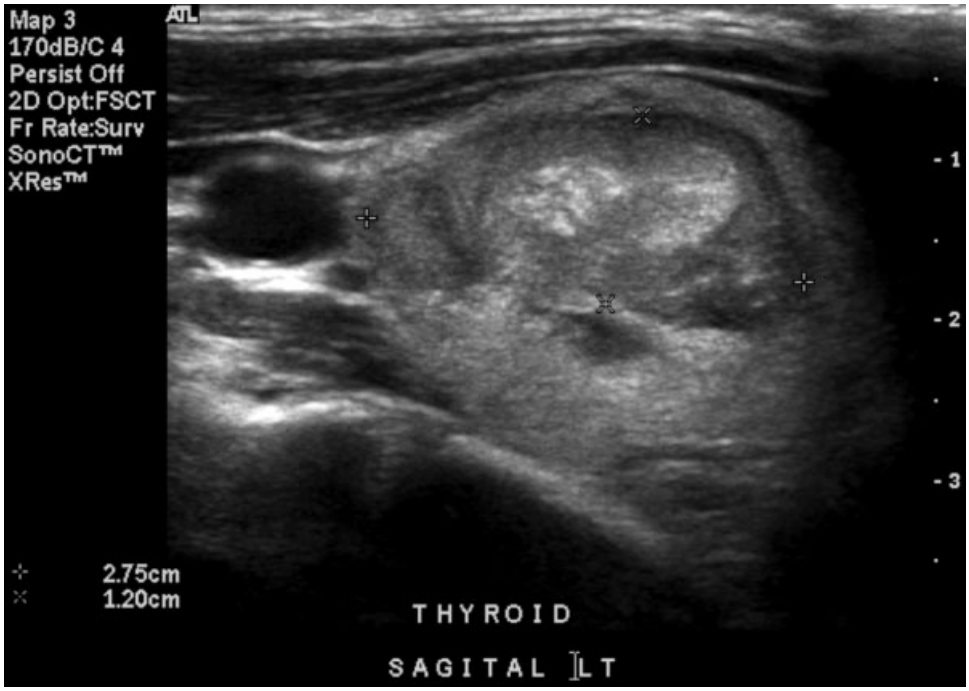

Figure 3 Sagittal image of the left thyroid lobe. Heterogenous mass with microcalcifications is outlined by electronic calipers.

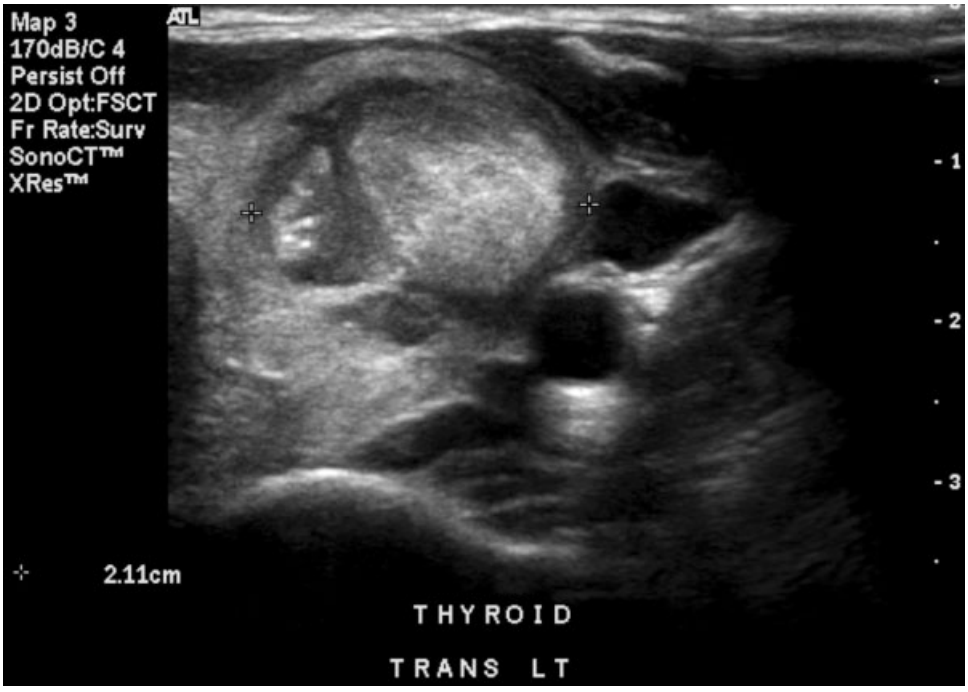

Figure 4 Transverse image of the mass depicted in Figure 3.

hypoechogenicity, irregular or microlobulated calcifications, hypoechoic halo, disrupted eggshell calcifications (Figs. 1 to 4), and abundant vascularity.[9,12] Routine measurement of serum calcitonin has been recommended as a supplement to fine-needle aspiration (considered the "most discriminating investigation" and "technique of choice") in the early detection of medullary thyroid carcinoma among patients with nodular thyroid diseases.[8,13,14] Approximately one-quarter of all medullary thyroid carcinomas are determined genetically due to a mutation in the RET proto-oncogene.[15] Interestingly, genetic testing has been advocated to replace conventional biochemical and radiological modalities to identify asymptomatic MEN type 2a carriers, for potential prophylactic thyroidectomy.[15,16] However, controversy remains regarding the ideal timing and extent of prophylactic thyroidectomy due to the wide spectrum of clinical presentation.[17]

Unrecognized MEN type 2a complicating pregnancy has been associated with severe life-threatening

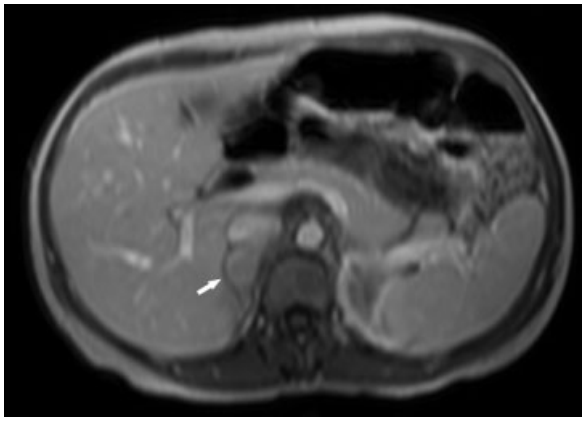

Figure 5 T1-weighted postgadolinium axial magnetic resonance imaging depicting a large soft tissue mass of the right adrenal gland (arrow).

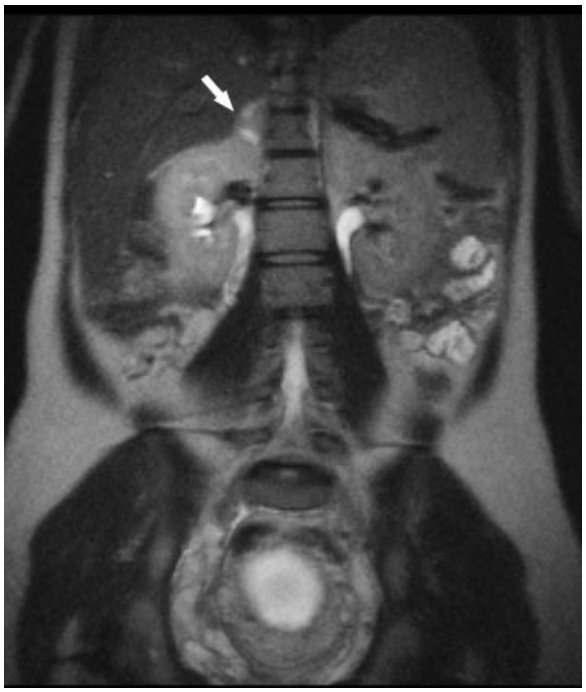

Figure 6 T2-weighted coronal image depicting the right adrenal gland mass (arrow). Note bilateral physiological hydronephrosis of pregnancy.

sequelae including myocardial infarct, cardiovascular collapse at term, peripartum cardiomyopathy, and intracranial hemorrhage.[2–5] The importance of maintaining a high suspicion for this uncommon occurrence is highlighted by the recent report of fatal adrenergic crisis in a postpartum patient with unrecognized MEN type 2a despite her established history of medullary thyroid carcinoma. Autopsy revealed the presence of previously undetected bilateral pheochromocytoma.[7]

Recently, first-trimester prenatal RET testing utilizing chorionic villus sampling and polymerase chain reaction and DNA sequence analysis was reported in a pregnant patient with MEN type 2a, excluding the possibility that the fetus was bearing the same maternal mutation of RET proto-oncongene.[18]

Most authors agree that in the second half of pregnancy, α-adrenergic blockade with phenoxybenzamine is the treatment of choice, 10 mg orally twice daily, gradually increasing by 10 to 20 mg daily until hypertension is controlled.[9] When fetal maturity is achieved, Cesarean delivery should be performed with simultaneous or subsequent excision of the tumor.[19] Clearly, in patients with pheochromocytoma or MEN type 2a syndrome, β-blockade should not be used without prior α-blockade, as unopposed α-adrenergic activity may lead to generalized vasoconstriction and a steep rise in blood pressure.[18]

A systematic English literature search (PubMed, MEDLINE) of works between 1966 and 2010 utilizing the search terms "pregnancy," "multiple endocrine neoplasia," "Sipple syndrome," "medullary cell thyroid carcinoma," and "ultrasound" reveals that this is the first report of sonographic findings of medullary cell thyroid carcinoma leading to the diagnosis of MEN type 2a during pregnancy. Our case and the report by Wattanachanya et al,[7] describing postpartum adrenergic crisis-associated death with unrecognized MEN type 2a, despite the presence of known medullary thyroid carcinoma, emphasize the importance of considering MEN type 2a in pregnant patients with medullary thyroid carcinoma.

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