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

David M. Sherer, M.D.,1 Mudar Dalloul, M.D.,1 Ghadir Salame, M.D.,1 Tana Shah, M.D.,1 Eli Serur, M.D.,1 Harry L. Zinn, M.D.,1 and Ovadia Abulafia, M.D.1

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

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.

1Divisions of Maternal-Fetal Medicine and Gynecologic Oncology, Departments of Obstetrics and Gynecology and Radiology, State University of New York, Downstate Medical Center, Brooklyn, New York.

Address for correspondence and reprint requests: David M. Sherer, M.D., Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, State University of New York, Downstate Medical Center, 445 Lenox Road, Box 24, Brooklyn, NY 11203-2098 (e-mail: dmsherer@aol.com).

Am J Perinatol Rep 2011;1:59–64. Copyright © 2011 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

Received: December 2, 2010. Accepted after revision: March 6, 2011. Published online: June 9, 2011. DOI: http://dx.doi.org/10.1055/s-0031-1280572. ISSN 2157-6998.
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/m². Her thyroid gland was diffusely enlarged and mobile and measured ~10 × 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 × 10⁹/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 × 2.4 × 3.0 cm) with a large heterogeneous nodule in the mid to upper pole measuring 3.1 × 1.6 × 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 × 1.6 × 2.7 cm, and contained two adjacent nodules measuring 2.3 × 1.2 × 1.9 cm and 2.8 × 1.2 × 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 × 3.1 × 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 pheochromocytoma

Figure 1  Sagittal image of the right thyroid lobe. Heterogenous mass with microcalcifications is outlined by electronic calipers.
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. Ultrasound is an established tool in the evaluation of thyroid nodules and detection of thyroid carcinoma. Sonographic features associated with thyroid carcinoma include...
hypoechogenicity, irregular or microlobulated calcifications, hypoechoic halo, disrupted eggshell calcifications (Figs. 1 to 4), and abundant vascularity.\textsuperscript{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.\textsuperscript{8,13,14} Approximately one-quarter of all medullary thyroid carcinomas are determined genetically due to a mutation in the RET proto-oncogene.\textsuperscript{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.\textsuperscript{15,16} However, controversy remains regarding the ideal timing and extent of prophylactic thyroidectomy due to the wide spectrum of clinical presentation.\textsuperscript{17}

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

---

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

**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-oncogene.⁸

Most authors agree that in the second half of pregnancy, α-adrenergic blockade with phenoxycarbamide 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.¹⁰ 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.¹¹

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., 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.

REFERENCES

1. Thakker RV. Multiple endocrine neoplasia. Horm Res 2001; 56(Suppl 1):67–72
2. Ahn JT, Hibbard JU, Chapa JB. Atypical presentation of pheochromocytoma as part of multiple endocrine neoplasia IIa in pregnancy. Obstet Gynecol 2003;102(5 Pt 2):1202–1205
3. Langerman A, Schneider JA, Ward RP. Pheochromocytoma storm presenting as cardiovascular collapse at term pregnancy. Rev Cardiovas Med 2004;5:226–230
4. Kim J, Reutrakul S, Davis DB, Kaplan EL, Refetoff S. Multiple endocrine neoplasia 2A syndrome presenting as peripartum cardiomyopathy due to catecholamine excess. Eur J Endocrinol 2004;151:771–777
5. Moraca-Kvapilova L, Op de Coul AA, Merkus JM. Cerebral hemorrhage in a pregnant woman with a multiple endocrine neoplasia syndrome (type 2A or Sipple’s syndrome). Eur J Obstet Gynecol Reprod Biol 1985;20:257–263
6. Sherer DM, Dallool M, Salame G, Kalidas P, Zinn HL, Abulafia O. Gestational diabetes leading to diagnosis and management of multiple endocrine neoplasia type 2a. Obstet Gynecol 2010;115(2 Pt 2):455–457
7. Wattanachanya L, Bunworasate U, Plengpanich W, et al. Bilateral pheochromocytoma during the postpartum period. Arch Gynecol Obstet 2009;280:1055–1058
8. Danese D, Centanni M, Farsetti A, Andreoli M. Diagnosis of thyroid carcinoma. J Exp Clin Cancer Res 1997;16:337–347
9. Kim BM, Kim MJ, Kim EK, et al. Sonographic differentiation of thyroid nodules with eggshell calcifications. J Ultrasound Med 2008;27:1425–1430
10. Yoon DY, Lee JW, Chang SK, et al. Peripheral calcification in thyroid nodules: ultrasonographic features and prediction of malignancy. J Ultrasound Med 2007;26:1349–1355; quiz 1356–1357
11. Kakkos SK, Scopa CD, Chalmoukis AK, et al. Relative risk of cancer in sonographically detected thyroid nodules with calcifications. J Clin Ultrasound 2000;28:347–352
12. Saller B, Moeller L, Gorges R, Janssen OE, Mann K. Role of conventional ultrasound and color Doppler sonography in the diagnosis of medullary thyroid carcinoma. Exp Clin Endocrinol Diabetes 2002;110:403–407
13. Hahm JR, Lee MS, Min YK, et al. Routine measurement of serum calcitonin is useful for early detection of medullary thyroid carcinoma in patients with nodular thyroid diseases. Thyroid 2001;11:73–80
14. Mayr B, Brabant G, von zur Mühlen A. Incidental detection of familial medullary thyroid carcinoma by calcitonin screening for nodular thyroid disease. Eur J Endocrinol 1999;141:286–289
15. Schellhas E, König C, Frank-Raue K, Buhr HJ, Hotz HG. Long-term outcome of “prophylactic therapy” for familial medullary thyroid cancer. Surgery 2009;146:906–912
16. Lau GS, Lang BH, Lo CY, et al. Prophylactic thyroidectomy in ethnic Chinese patients with multiple endocrine neoplasia type 2A syndrome after the introduction of genetic testing. Hong Kong Med J 2009;15:326–331
17. Puñaes MK, da Rocha AP, Meotti C, Gross JL, Maia AL. Clinical and oncological features of children and young adults with multiple endocrine neoplasia type 2A. Thyroid 2008;18:1261–1268
18. Martellini P, Marotti GM, Pasquali D, et al. Genetic prenatal RET testing and pregnancy management of multiple endocrine neoplasia type II A (MEN2A): a case report. J Endocrinol Invest 2004;27:357–360
19. Nader S. Other endocrine disorders of pregnancy. In: Creasy RK, Resnik R, Iams JD eds. Maternal Fetal Medicine, Principles and Practice. 5th ed. Philadelphia: Saunders; 2004:1083–1107

SONOGRAPHIC FINDINGS OF MEDULLARY THYROID CARCINOMA/SHERER ET AL