MEN-2A in a pregnant female during the COVID pandemic: A double whammy?

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INTRODUCTION

Multiple Endocrine Neoplasia (MEN) 2A is an autosomal dominant syndrome characterized by medullary thyroid carcinoma (MTC), pheochromocytoma (PCC) and parathyroid tumors.[1-4] Caused by germ-line mutation in the RET proto-oncogene located on chromosome 10, MEN-2A is a subtype of the MEN-2 syndrome and is the more commonly encountered clinical variant (accounting for 75% cases) as opposed to MEN-2B.[5,6] Almost 90% afflicted individuals manifest with MTC while PCC and parathyroid tumors are noted in upto 40-50% and 20-30% cases respectively. As the disease may present with polyglandular involvement, screening of other endocrine organs is imperative once any single organ involvement is detected. Current literature on diagnosis and management of MEN-2A syndrome in pregnancy is scant and largely comprises case series or case reports. Most patients were incidentally detected to have hypertension during routine antenatal screening and found to have an underlying pheochromocytoma. The limitations imposed by pregnancy both in terms of restricted imaging options due to radiation exposure to the fetus and restricted period of surgical intervention in the second trimester makes the management of this situation challenging in most cases. We share our experience of a young woman with MEN 2A syndrome who became pregnant immediately post adrenalectomy for pheochromocytoma and had to undergo surgery for medullary thyroid carcinoma in second trimester during a nationwide lockdown due to the ongoing COVID pandemic. The case highlights the various challenges we faced in patient management, surgical intervention, post-operative care and follow up amidst travel restrictions during the lockdown along with how these challenges were overcome through multidisciplinary teamwork, teleconsultation services and shared decision making with the patient which led us to a successful outcome in a difficult clinical scenario, in such challenging times.

METHODS AND RESULTS

Our patient was a 20-year-old lady who had initially presented to the medicine outpatient services at an outside hospital in September 2019 for recurrent episodes of palpitations, headaches and abdominal pain. On imaging she had been detected to have bilateral adrenal masses. Due to the high prevalence of tubercular adrenalitis in India, she had been given a trial of empirical anti-tubercular therapy, which had been unsuccessful and she was subsequently referred to the Medicine department of our institute for further evaluation. Review of her clinical history and imaging led us to suspect the possibility of a pheochromocytoma which was confirmed by the elevated catecholamine levels noted in her urine along radiological evidence with 68Ga-DOTANOC PET/CT [68Ga-Labeled(1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraaceticacid)-1-NaI3-octreotide- positron emission tomography/computed tomography] which were consistent with bilateral pheochromocytoma (Table S1 and Figure 1, S2).

Considering the occurrence of bilateral pheochromocytoma at a young age (seen in only 10% cases), the

possibility of MEN syndrome was kept, and further evaluation was performed. Ultrasound (USG) neck revealed bilateral thyroid nodules and parathyroid adenoma. Fine needle aspiration cytology (FNAC) of the thyroid nodules revealed MTC thus completing the classical triad of MEN 2A syndrome. In light of these findings, the patient's family history was reviewed but was noncontributory.

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The patient was reviewed by the surgery and endocrinology services at our centre and was planned for bilateral adrenalectomy followed by total thyroidectomy for definitive management of her condition in two sittings. The patient underwent a laparoscopic transperitoneal adrenalectomy with a plan to perform a thyroidectomy for MTC in the next sitting. Histopathological examination of the adrenal glands confirmed the diagnosis of pheochromocytoma. However, India entered a nationwide lockdown from 24th March 2020 in view of the COVID-19 pandemic and massive reorganization occurred in the government healthcare system. Outpatient services were restricted and largely replaced by teleconsultation services were offered to outpatients. All elective surgeries were deferred and only emergency procedures were being performed with a large number of physicians being diverted to centres dedicated to the management of the burgeoning load of patients afflicted with COVID-19 pneumonia.[7] Considering the exceptional situation at hand the patient was discharged and asked to follow up through teleconsultation for her second surgery. She was kept on glucocorticoids (Tablet Prednisolone 5 mg once a day) and mineralocorticoids (Tablet Fludrocortisone 100 mcg once a day). However, she conceived in her subsequent menstrual cycle in April 2020. This posed a unique challenge of delivering appropriate antenatal care and following up with the patient closely to optimize her for surgery, which was now deferred to the second trimester of her pregnancy. These services were provided by a multidisciplinary team comprising her treating obstetricians, endocrinologists and surgeons. Her first trimester was uneventful and she successfully underwent a near total thyroidectomy with level IV lymph node dissection and right inferior parathyroid adenectomy in October 2020 at 24 weeks period of gestation (POG). The histopathology revealed bilateral medullary thyroid carcinoma each measuring 0.5 x 0.5 x 0.3 cm with lympho-vascular invasion and no lymph node involvement along with right parathyroid adenoma (1 x 0.5 x 0.5 cm). Post-operative period was uneventful and she was discharged on thyroid replacement therapy (Tab Thyroxine sodium 75 mcg/day). Coincidentally there was a gradual downregulation of travel restrictions at this time which made it easier for the patient to access healthcare services provided at our centre. Unfortunately, in the postoperative period she developed a mild COVID-19 infection at 27 weeks and was admitted at our COVID facility, where close maternal and fetal surveillance was done by a dedicated obstetric team. Her recovery was uneventful and she continued to follow up with the treating team post COVID through teleconsultation. She sought confinement at 36 weeks of gestation with pre-eclampsia without severe features, intrahepatic cholestasis of pregnancy (ICP) and late onset fetal growth restriction and a decision was taken to terminate her pregnancy by cesarean section at 37 weeks of gestation due to fetal bradycardia. She delivered a healthy female child weighing 2380 grams (appropriate for gestational age) with an APGAR score of 9, 9. She received an intravenous stress dose of hydrocortisone during peripartum

period.

OUTCOME AND FOLLOW-UP

Both mother and baby were discharged in healthy condition and the patient has undergone genetic testing, the results of which are awaited.

COMMENTS

MEN 2 is an autosomal dominant disorder with an estimated prevalence of 2.5 per 100,000.[8] Activating germline mutations of the RET proto-oncogene are present in 98% of the families of MEN-2 patients. There is a strong genotype- phenotype correlation between a specific RET mutation and its clinical course, with some genotypes being associated with aggressive disease. The overall rarity of this syndrome along with scant literature available on its management in pregnancy posed significant challenges for the treating team. This was further compounded by the COVID-19 pandemic and diversion of healthcare resources for managing those afflicted which made it very difficult to provide individualized care, which is mandated in such cases. To the best of our knowledge, ours is the first case of pregnancy in a patient with MEN-2A syndrome to be successfully managed and reported.

The primary step is management of pheochromocytoma, which, if left untreated, may have devastating consequences and is associated with high maternal and fetal morbidity and mortality. As it presents with hypertension, it is often misdiagnosed as pre-eclampsia in the earlier stages of pregnancy[9] Most cases of MEN 2A in pregnancy reported till date presented with PCC crisis mandating the need to undergo adrenalectomy. Our patient was fortunately diagnosed prior to conception and underwent adrenalectomy prior to an unplanned conception. These patients need glucocorticoid and mineralocorticoid replacement therapy as received by our patient postoperatively.

MTC is the next challenge to tackle owing to the aggressive and malignant nature of the disease. The impact of newly diagnosed MTC in pregnancy is unknown and no major guidelines are available to guide management of the same in pregnancy.[10] Our patient conceived spontaneously while awaiting surgery for MTC, which forced us to delay our surgical intervention till the second trimester. During this time, we followed up out patient with serial serum calcitonin levels which is generally used in postoperative follow up as recommended by ATA.[11] However, it is important to highlight that a rise in calcitonin or even its doubling time must be interpreted with caution in pregnant females due to physiological increase in calcitonin during pregnancy.[12] Delays in management of MTC are known to be associated with poorer outcomes. This, along with the difficulty in monitoring pre-operatively with serum calcitonin values, led us to pursue the surgery in the second trimester.[10] Planning an elective surgery during the ongoing pandemic where the entire healthcare infrastructure was restructured for COVID management posed several logistic issues which were dealt with successfully by the treating team and administration services of our centre.

Tewari et al (2001) described a case report of a 22-year-old primigravida who was diagnosed with MEN 2A in her first trimester and underwent adrenalectomy followed by thyroidectomy during her second trimester and had successful maternal and fetal outcome at term.[13]*Sarathi et al* in 2011 described a 21-year-old primigravida presenting with PCC crisis at 12 week's gestation and was diagnosed with MEN 2A and RET mutation (C634W).[14] She successfully underwent bilateral adrenalectomy followed by thyroidectomy during her second trimester with calcitonin levels 713 pg/ml preoperatively and 32.6 pg/ml postoperatively. A larger case series of ten patients with pheochromocytoma in pregnancy was described by *Donatini et al* in 2018, out of which three patients had MEN 2A. Two of them had undergone thyroidectomy for MTC prior to pregnancy and one patient had PCC crisis at 27 weeks POG, for which she underwent unilateral adrenalectomy along with total thyroidectomy and central neck dissection at 28 week's gestation. Her Ctn levels before and after surgery were 311 pg/ml and 95.7 pg/ml respectively.[15]

A majority of the cases of MEN 2A in pregnancy reported so far where surgery for MTC had to be undertaken during pregnancy were either diagnosed for first time during pregnancy or presented with PCC crisis leading to a diagnosis of MEN 2 and mandating the need for simultaneous adrenalectomy and thyroidectomy. This

case merits special attention not only for highlighting the rarity of this syndrome during pregnancy but also for the numerous challenges in management that were overcome to deliver a successful outcome, which included a pandemic, an unplanned pregnancy, second trimester surgery in a high-risk pregnancy, uneventful COVID, pre-eclampsia at term culminating in an emergency cesarean section!

This case posed a multitude of challenges in management which were overcome by a well-coordinated multidisciplinary teamwork and the effective utilization of teleconsultation services which proved to be crucial in providing antenatal and postoperative services during such testing times. It would be amiss to not recognize the courage of our patient and the support provided by her family who braved such a difficult pandemic to continuously remain in touch with us and also for actively assisting us in decision making at several points of her tumultuous course in hospital.

LEARNING POINTS/TAKE HOME MESSAGES

- Preconception and contraception counseling is very important in women of reproductive age group diagnosed with any medical disorder to avoid unplanned pregnancy. Optimization of condition before pregnancy is ideal.
- Teleconsultation can be a very useful tool for managing high risk pregnancy if judiciously used in a pandemic like situation.
- A well-coordinated interdisciplinary team approach can bring about successful outcome in pregnancy complicated by this rare syndrome.

FIGURE LEGENDS

Figure 1: Computed tomography (CT) image and corresponding fused PET (positron emission tomography)/CT at the level of lower pole of thyroid showing bilateral uptake (1A, B); Thyroid gland marked by asterisk

Figure S1: Coronal images Computed tomography (CT) image and corresponding fused PET/CT of the suprarenal masses (2A, 2B).

Well-defined hetero-dense lesions with solid and cystic components noted in both adrenals measuring ˜5.5 x 4.4 x 6.2 cm on right side and ˜7.2 x 5.5 x 6.7 cm on left side with increased radiotracer uptake in the solid component

Right adrenal gland marked by broad arrow, left adrenal gland marked by narrow arrow

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Contribution to authorship

Aarti Chitkara: Conception and design of primary draft, acquisition of data

Anubhuti Rana: Revision of manuscript and critical analysis of data

Setu Gupta: Drafting and critical analysis of Endocrine part of the manuscript

Vidushi Kulshrestha: Critical revision and conceptualization of the final draft of manuscript

ArunRaj Sreedharan Thankarajan: Imaging inputs and interpretation of the nuclear imaging pertaining to the case

Vatsla Dadhwal: Critical revision of the final draft with significant input in confirming the accuracy and integrity of the manuscript

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Table S1: Investigations for pheochromocytoma, MTC and hyperparathyroidism as part of MEN 2A syndrome

Component of MEN 2A	**Before Surgery**	**Before Surgery**	**After Surgery**	**After Surgery**

	Biochemical Findings	**Imaging**	**Histopathology**	**Imaging/ biochemical findings**
Pheochromocytoma *(Pre-pregnancy)*	**24-hour Urine Adrenaline:** 81.74 ug/day (Normal < 20ug/day) **Noradrenaline:** 197.66 ug/day (Normal < 90 ug/day) **Urinary Free Cortisol:** 76ug/day (Normal <120 ug/day) **S. DHEAS:** 210 ug/dL	*CECT abdomen:* Bilateral enlargement of adrenal gland, with heterogenous mass with areas of necrosis and cystic changes Size: 7.6 X 5.4 cm on right side and 5.5 X 4.4 cm on left side *68-Ga-DOTANOC Scan:* Uptake in the solid component of the lesions bilaterally	Bilateral pheochromocytoma; PASS-4	None
Medullary Thyroid Carcinoma	**S.Calcitonin** *(Pre-pregnancy)*: 20 pg/ml (Normal < 5 pg/ml) **S.Calcitonin** *(At 22 weeks POG):* 42.1pg/ml	**USG Neck:** *(pre-pregnancy)* A TIRADS 5 nodule on right lobe (5.8 x 3.7 mm). Two TIRADS 5 on left lobe of thyroid (8 x 5 mm); *USG Neck (At 22 weeks POG, repeated before surgery)* Right thyroid nodule (6.5 x 4.8 mm) and left thyroid nodule (6.2 x 5 mm)	Medullary thyroid carcinoma	**USG Neck:** (*At 32 weeks POG)*: No residual Lesion
Hyper-parathyroidism	**S. Calcium** *(Pre-pregnancy):* 12.1mg/dL (Normal- 8.2-10.4 mg/dL **iPTH** *(Pre-pregnancy):* 226 pg/ml (Normal < 65 pg/ml)	*USG Neck: (Pre-pregnancy)* A right inferior parathyroid adenoma (9 x 5.2 mm); repeat imaging: 8 x 6 mm *USG Abdomen: (Pre-pregnancy)* Bilateral nephrocalcinosis, right moderate hydronephrosis	Parathyroid adenoma	**S. Calcium:** *(At 24 weeks POG)* 9.1 mg/dL **iPTH:** *(At 24 weeks POG)* 8 pg/ml