East African Medical Journal Vol. 96 No. 6 June 2019
CAUDA EQUINA PARAGANGLIOMA IN PREGNANCY: CASE PRESENTATION AND REVIEW OF LITERATURE
Dr. Michael Chukwugoziem Nweke. M.B.B.S, FMC Path, Lecturer/Consultant Anatomic Pathologist, Department of Anatomic Pathology, University of Medical Sciences Teaching Hospital Complex, PMB 536 Ondo Town, Ondo State. Nigeria, Dr. Mojisola Olutayo Udoh, M.B.B.S, MHPM, FMC Path, Senior Lecturer/Consultant Anatomic Pathologist, Department of Anatomic Pathology, University of Benin Teaching Hospital, PMB 1111, Ugbowo Road, Benin-City, Nigeria, Dr. Emmanuel C. Obeta. M.B.B.S, FWACS, FACS, Consultant Neurosurgeon, Department of Surgery, University of Benin Teaching Hospital, PMB 1111, Ugbowo Road, Benin City, Nigeria, Dr. Nosakhare Osasere Enaruna, M.B.B.S, FWACS, FMCOG, Associate Professor and Honorary Consultant Obstetrician/Gynaecologist, Department of Obstetrics & Gynaecology, University of Benin Teaching Hospital, PMB 1111, Ugbowo Road, Benin City, Nigeria.

Corresponding author: Dr. Michael Chukwugoziem Nweke, Dept of Anatomic Pathology, University of Medical Sciences Teaching Hospital, PMB 536, Ondo Town, Ondo State, Nigeria. Email: goziemnweke@gmail.com

CAUDA EQUINA PARAGANGLIOMA IN PREGNANCY. CASE PRESENTATION AND REVIEW OF LITERATURE

M. C. Nweke, M. O Udoh, E. C. Obeta and N. O Enaruna

ABSTRACT

Extra-adrenal Paragangliomas (EAP) are a subset of neuroendocrine tumours. They may arise in a variety of locations in the body. Paragangliomas in the cauda equina region are uncommon, more so is their occurrence during pregnancy. We present a cauda equina paraganglioma arising in a young pregnant female who presented with back pain, constipation and paraparesis. The MRI showed a lumbosacral intradural extramedullary mass. She underwent surgery - a laminectomy, and the mass was removed. Histology with Immunohistochemistry confirmed the diagnosis of Paraganglioma. This article highlights multidisciplinary management of low back pain coexisting with neurological deficits in pregnancy. It is emphasized that early diagnosis and appropriate management significantly reduce maternal and fetal mortality

INTRODUCTION

Paragangliomas are neuro-endocrine tumours arising from para-ganglia cells[1]. These are neural crest cell derived neuroendocrine cells, closely associated with the autonomic nervous system. They are divided into adrenal and extra-adrenal categories. Tumours of these cells arising outside the adrenal glands are called Extra-adrenal paragangliomas (EAPs) and are very similar to their adrenal gland counterparts called pheochromocytomas.

Extra-adrenal paragangliomas often simply referred to as 'paragangliomas', are rare neoplasms that can occur in any locations within the body in which benign paraganglia are known to occur. The

majority are seen in the carotid body, jugular foramen, middle ear, aorticopulmonary region, posterior mediastinum, and abdominal para aortic region[1,2]. The incidence of spinal paragangliomas in the general population is reported to be 0.07% per 100,000[3]. Most spinal paragangliomas are located in the intradural extra-medullary compartment, at the level of the cauda equina and the filum terminale, followed by the thoracic and cervical regions. Extra-adrenal Paragangliomas occurring in the cauda equina make up 3.5 - 4% of all neoplasms in that region[1,4,5]. The clinical presentation of these tumours depend on the degree of compression of the filum terminale [6]. Index of suspicion for the diagnosis is when a patient presents due to bilateral sciatica, dorsal feet flexion weakness or other neurological deficits.

Extra-adrenal Paragangliomas occur in all races, most commonly between 30 and 50 years of age. They appear to show roughly equal sex predilection, though most authors report more males than females; head and neck Paragangliomas however appear to be more common in females [2,6–8]. Paragangliomas are mostly sporadic but up to 30% may exhibit a familial pattern associated with neurofibromatosis type 1, Tuberous sclerosis, Von Hippel-Lindau disease, Multiple Endocrine Neoplasia IIA or IIB, and Carney's triad.[2,9]

Extra-adrenal Paragangliomas could be hormone producing or non-producing. Excess catecholamine secretion are rare when tumours occur on the head and neck region but occur frequently in the thorax and abdomen [2]. However, most tumours are benign but malignant forms do occur and have been known to metastasize. The incidence of malignant paragangliomas tend to form wide local invasion. Distant metastases varies from 2% to 36% depending on the series [2]. The histologic criteria for malignant paraganglioma, except the presence of metastases are also not well-defined [2]. The use of the term 'neuroendocrine neoplasm' -with a qualifier (well differentiated, moderately differentiated or poorly differentiated)- is advocated in the reporting of paragangliomas [10]. This qualifier reflects the estimated metastatic risk based on specific clinico-morphologic indicators[10]. Common sites of metastases include regional lymph node, bone, liver, and lung [2].

CASE REPORT

A 33-year-old right-handed female hairdresser with low back pain of a year's duration and inability to walk for over a month presented to the emergency room, in her 5th month of pregnancy. The back pain was insidious in onset and associated with recurrent of moderate intensity and radiating to both lower limbs. The pain predated pregnancy. It was initially attributed to long hours of standing and bending associated with her job and was aggravated by prolonged standing. It was also later believed to have been aggravated by pregnancy. It was initially relieved by analgesics, but progressively worsened till she was no longer able to walk without support. There was no history of trauma to the back. She also complained of constipation with bowel motions reduced to once a week.

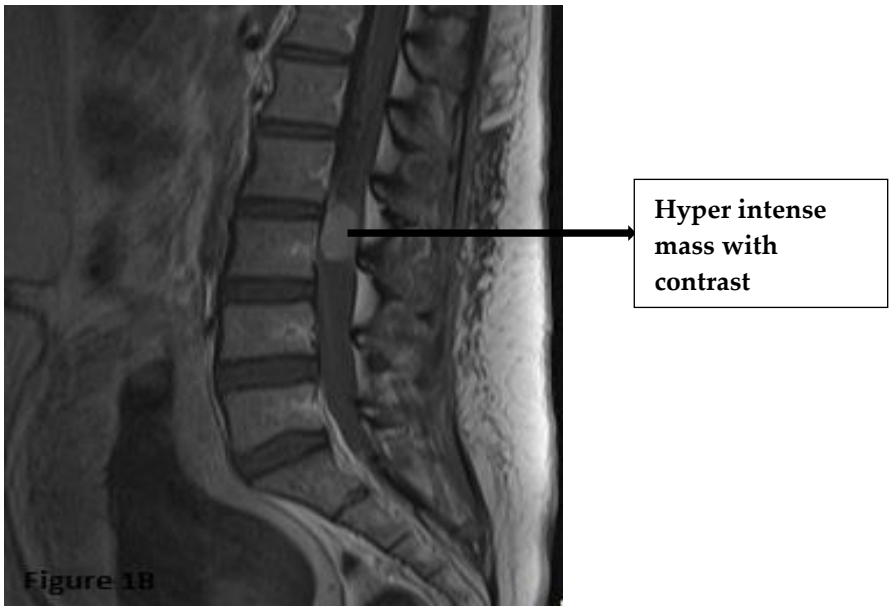
Examination

General examination revealed a young woman in good general physical condition with vital signs all within normal limits. Neurologic examination revealed lower limb paraparesis power grade 3 across the hip flexors, grade 4+ across the knee extensors, grade 4 across ankle dorsiflexes, grade 3 across the big toe extensors and grade 4 power in both ankle plantar flexors. Muscle tone was reduced across all the lower limb muscle groups. The knee jerk and ankle jerk were both depressed. Plantar response was

flexor bilaterally. There was impaired light touch and pain sensation across the L4, L5 and S1 dermatomes. Muscle bulk tone, power and reflexes were normal in both upper extremities. Mental state and cranial nerve examinations were normal and there were no signs of meningeal irritation. Abdominal examination revealed, no organ enlargement or tenderness. Per abdominal examination revealed fundal height of 18 weeks. A clinical assessment of 'Lumbar Canal Stenosis? cause', was made.

Investigations

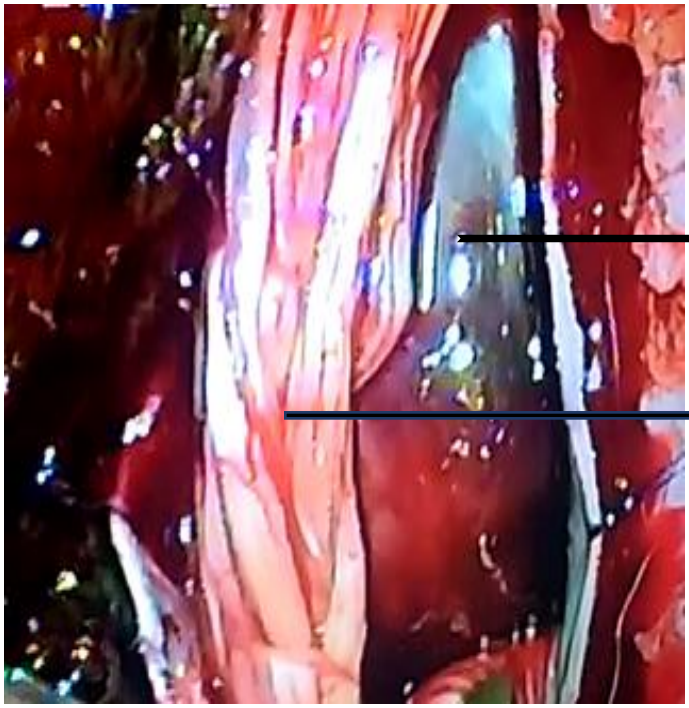
Her full blood count parameters were normal. Serum beta hCG was positive and obstetric ultrasound scan confirmed a single live intra-uterine gestation at an approximate gestational age of 16 weeks and 6 days. A lumbosacral spine MRI showed a well circumscribed slightly hyper intense T2 lesion within the thecal sac dorsal to the vertebral bodies and at the L2/L3 level. The lesion was also slightly hyper-intense on T1 imaging and enhanced brightly with contrast. Review of the neuroimaging lead to a diagnosis of 'Lumbar Canal Stenosis secondary to an Intradural mitotic lesion'.



Surgery

Patient was counselled for surgery and consent obtained for an L2 and L3 laminectomy with excision of the intradural cauda equina mass. She was operated the day after presentation, under general anesthesia with intravenous ceftriaxone 1g stat, and skin preparation with cetrimide and iodine.

Laminectomies of the L2 and L3 were performed, followed by a mid-line longitudinal durotomy with "en-bloc" excision of a well circumscribed firm, dark red mass attached to the filum terminale , using a combination of blunt and sharp dissection.



Histopathology

Gross examination revealed a tumor of 2.5cm x 2cm x 2cm; that was hemorrhagic, dark brown in appearance, and soft in consistency, with grey-white cut surface. Histology showed a relatively well circumscribed neoplasm composed of proliferating uniformly sized cells in "zellballen" pattern, with relatively uniform nests. The tumour cells had oval vesicular nuclei with stippled salt and pepper chromatin and moderate eosinophilic cytoplasm. There was paucity of mitoses and no areas of capsular or vascular invasion.

Immunohistochemistry showed diffuse positivity for NSE and chromogranin. There was positive staining by the supporting sustentacular cells for S100. There was negative staining for AEL/AE3 which ruled out the possibility of a metastatic carcinoma or ependymoma. Overall histomorphology and immunohistochemistry features established the diagnosis of a caudal equina paraganglioma.

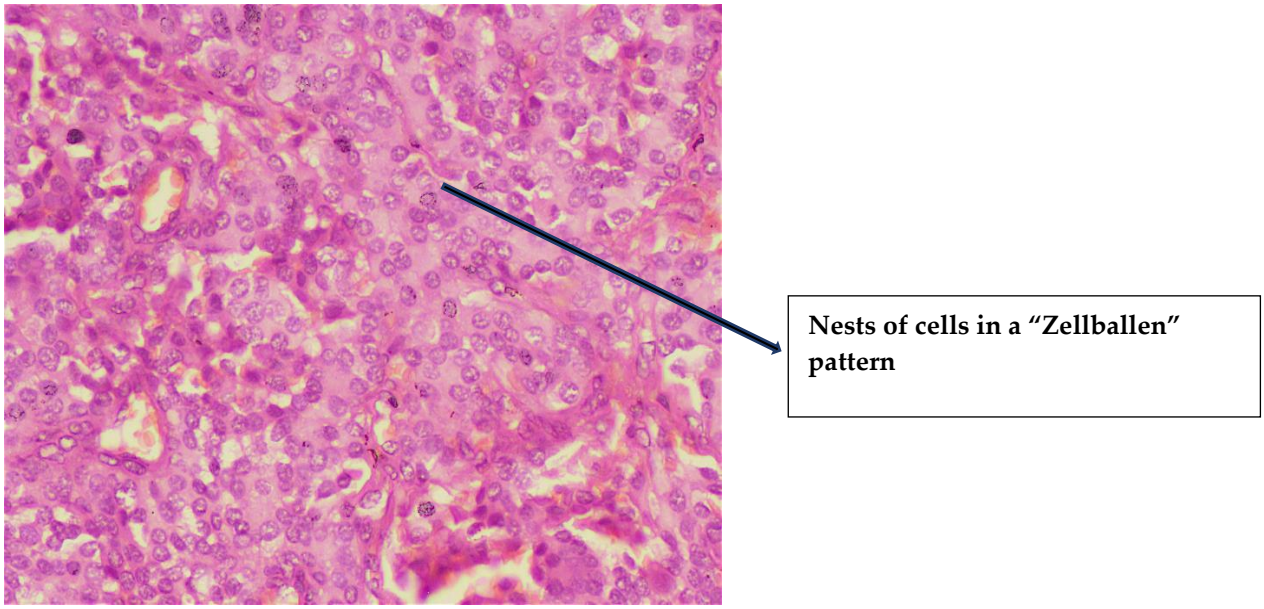


Figure 3A (x100): **Photomicrographs showing a well differentiated neoplasm composed of nests of relatively monomorphic tumour cells with salt and pepper chromatin pattern disposed in nests and interspersed by vascular channels within the fibro-collagenous stroma.**

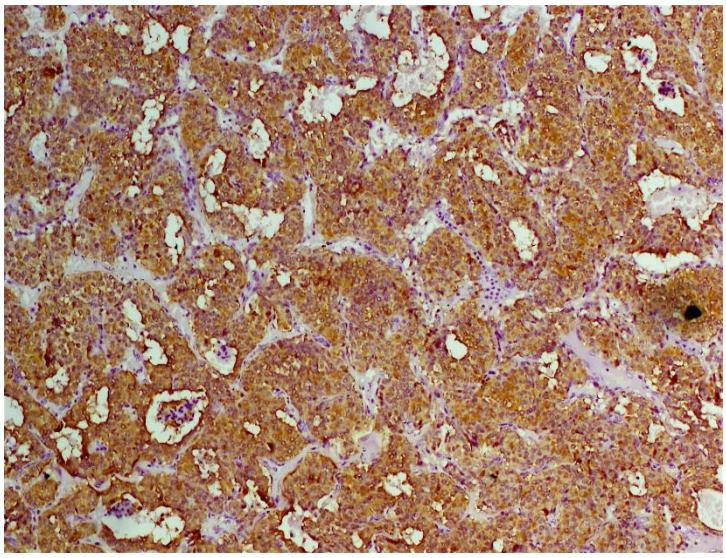


Figure 3B(X100): **Photomicrograph showing positive expression of chromogranin immunohistochemical monoclonal antibody by the neoplastic cells, thus confirming neuroendocrine differentiation/origin of the neoplasm.**

Follow-up

The Immediate post-op period was uneventful. Sutures were removed on the 10th day post-op with the patient subsequently discharged for follow up in clinic. Power in both lower limbs remained unchanged in the immediate post-op period but was fully regained in all limbs along with normal bowel habits and control, by two weeks post-surgery. She carried the pregnancy uneventfully to term and was delivered of a live male infant by elective caesarean section. Her postpartum period was normal. She was subsequently followed

up in clinic for six months post-surgery prior to being transferred to a center closer to her home for continued expert care. Patient remains symptom free 2 years post excision. Baby is alive and well.

DISCUSSION

Spinal paragangliomas were first recognized as a distinct clinical and pathologic entity by Lerman et al in 1972[11]. Majority of spinal paragangliomas (87%) present with low back pain as seen in our patient; with or without sciatica which is observed in 74% of patients [12]. Also common are signs of cord compression, which include constipation as seen in our patient. Clinically spinal paragangliomas are difficult to distinguish from degenerative lumbar spondylosis, such that diagnosis is often delayed until substantial growth occurs [13]. In our patient, the nature of her job and her pregnant state were factors that contributed to the delay in seeking medical help to determine the cause of her low back pain.

Low back pain occurs in up to 56% of pregnancies [6]. While the most common spinal problem in pregnancy is a prolapsed intervertebral disc, but rarely pregnancy can cause osteoporotic compression fractures or worsen symptoms of spinal tumors as in this case [6].

Pregnancies complicated by a paraganglioma are very rare, paragangliomas being estimated to occur in only 0.007% of all pregnancies [14]. The PGLs have been estimated to account for 15-19% of chromaffin cell tumors occurring in pregnancy, with pheochromocytomas accounting for the majority of tumors [15,16].

Paragangliomas may be functioning, or non-functioning. Functioning paragangliomas may present symptoms of excess catecholamine production like paroxysmal or sustained hypertension, headaches, sweating, and palpitations. These symptoms are similar to features of variants of hypertensive disorders of pregnancy [15–17]. The similarity to other conditions and the rarity of the disease contributes to delays in recognition and diagnosis. The presence of labile hypertension or hypertension in the first 20 weeks of pregnancy, especially if refractory to conventional antihypertensive treatment should however, raise the suspicion of pheochromocytomas or paraganglioma[18]. Catecholamine secreting paragangliomas carry high risks of fetal and maternal mortality, especially if undiagnosed till delivery [15,16] Excessive maternal levels of catecholamine are associated with increased risk of fetal growth restriction, placental abruption, and fetal hypoxia and anaemia [20]. Main causes of death include cardiac arrhythmias, cerebrovascular disease and pulmonary oedema. Maternal and fetal mortality in undiagnosed and untreated cases may be as high as 40-50%. Early diagnosis and appropriate management can reduce maternal and fetal mortality to less than 5% and 15% respectively[9]. There are aspects to point to the diagnosis such as finding of elevated levels of 24hr urine catecholamine and their metabolites, vanillylmandelic acid; confirms the diagnosis of a functioning neuroendocrine tumor [19].

Concerns however are the approximately 10–15% of Paragangliomas that do not secrete hormones are referred to as non-functioning, and another 10% may have, but not clinically manifest hormone activity [20]. Most reported cauda equina paragangliomas are non-functioning as in this patient.[13] Non-functional paragangliomas are difficult to diagnose due to the absence of typical symptoms of excess catecholamine secretion, though they may produce symptoms related to compression of neighboring structures pain or paralytic ileus[20]. If the patient is symptomatic and a tumour is suspected as in this patient, localization of the tumour is usually by MRI or ultrasound scan [19].

Otherwise if the tumour is clinically silent it may be detected incidentally during evaluation of the patient for unrelated symptoms [2]. Non-functioning paragangliomas tend to become locally invasive and are often associated with local recurrence [20]

Complete surgical resection is the treatment of choice for paragangliomas where possible. When a tumour is unresectable, its size may be reduced using chemotherapy, radiation therapy or embolization [20]. Adjuvant radiotherapy is given for incompletely excised tumours[21]. The optimal management guidelines for women with pheochromocytomas or Paraganglioma in pregnancy is not well established, due to the rarity of pheochromocytomas and PGLs in pregnancy. The recommended management for mother and baby is based on case reports, small case series, and expert opinions[14]. The decision to surgically intervene is influenced by gestational age at time of diagnosis [17,22]. Current recommendations are that if the condition is diagnosed in the first 24 weeks of gestation, the tumor should be removed preferably by a laparoscopic approach in the second trimester, but when discovered in the third trimester, surgical excision should be delayed until the fetus is viable and preferably delivered through a cesarean section' with the tumor being removed either immediately after delivery or at a later date [9,14]. In our patient, the tumour was completely excised in the second trimester through a laminectomy and no further treatment was considered necessary based on her pregnant state, as well as clinico-morphologic parameters.

Definitive diagnosis of paraganglioma is by histology [23]. Histology is essential to the differentiation of paragangliomas from other tumors occurring in the cauda equina region. It is particularly important in the diagnosis of non-functioning tumors in which a diagnosis of a paraganglioma might not be considered until histology reveals it. The primary histological hallmark of a paraganglioma is the "zellballen" nesting of the cell groups with a prominent vascular network [23]. Ancillary immunohistochemical staining for Chromogranin and Neuron Specific Enolase (NSE) confirm the neuro-endocrine nature of the tumour. Peripheral positivity to S-100 in the lining sustentacular cells also supports the diagnosis[23]. The Negative staining for AE1/AE3 helps rule out the possibility of a metastatic lesion.

Paragangliomas have some degree of metastatic potential. An approach to metastatic risk stratification developed in Japan, referred to as the Grading System for Adrenal Pheochromocytomas and Paraganglioma (GAPP)[24,25]; involves grading Paragangliomas into a three-tiered grading system (well differentiated, moderately differentiated and poorly differentiated neuroendocrine neoplasms) reflecting a continuum of metastatic risk based on Ki-67 immunohistochemistry and hormone data[24]. Paragangliomas with paucity of mitotic figures and no evidence of catecholamine hormone expression as seen in our patient have good prognosis with a reported risk of metastasis of 3.6%, and a 5-year survival rate in of 100%[24].

CONCLUSION

Spinal paragangliomas may present in similar fashion to, or be masked by other medical conditions including pregnancy. It should be considered in the differential diagnosis of any back pain in pregnancy. Diagnosis may be easier in hormone secreting tumours, Imaging coupled with histologic assessment of any tissue obtained at surgery will establish diagnosis of tumors. Early diagnosis and multidisciplinary management offer the best outcome.

REFERENCES

1. Miliaras GC, Kyritsis AP, Polyzoidis KS. Cauda equina paraganglioma: a review. 2003:177-190.

2. Lee YJ, Yong H-S, Oh Y-W, Lee KY, Kang E-Y, Kim KA. Extraadrenal Paragangliomas of the Body: Imaging Features. *Am J Roentgenol*. 2006;187(August):492-504.

3. Corinaldesi R, Novegno F, Giovenali P, Lunardi T, Floris R, Lunardi P. Paraganglioma of the cauda equina region. *Spine J*. 2015;15(3): e1-e8.

4. Warrier S, Owler B, Besser M. Case Report on paraganglioma and paragangliomatosis of the Cauda Equina. 2006:1033-1037.

5. Gelabert-Gonzalez M. Paragangliomas of the lumbar region. *J Neurosurg Spine*. 2005; 2:354-365.

6. Fernando J, Pinheiro JV, Hernández DP, Blanco JFB. International Journal of Surgery Case Reports Cauda equina syndrome during pregnancy: A condition to consider. *Int J Surg Case Rep*. 2018; 49:14-16.

7. Corinaldesi R, Novegno F, Giovenali P, Lunardi T, Floris R, Lunardi P. Paraganglioma of the cauda equina region. *Spine J*. 2015;15(3): e1-e8.

8. Williams MD. Paragangliomas of the Head and Neck: An Overview from Diagnosis to Genetics. *Head Neck Pathol*. 2017;11(3):278-287.

9. Lenders JWM. Pheochromocytoma and pregnancy: A deceptive connection. *Eur J Endocrinol*. 2012;166(2):143-150.

10. Rindi G, Klimstra DS, Sylvia BA, et al. A common classification framework for neuroendocrine neoplasms: An International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. 2018;(November 2017):1770-1786.

11. Lerman R, Kaplan E, Daman L. Ganglioneuroma-paraganglioma of the intradural filum terminale. *J Neurosurg*. 1972; 36:1-7.

12. Aghakhani N, George B, Parker F. Paraganglioma of the cauda equina region - Report of two cases and review of the literature. *Acta Neurochir (Wien)*. 1999;141(1):81-87.

13. Walsh JC, O'Brien DF, Kumar R, Rawluk D. Paraganglioma of the cauda equina: A case report and literature review. *Surgeon*. 2005;3(2):113-116.

14. Wing LA, Conaglen J V., Meyer-Rochow GY, Elston MS. Paraganglioma in pregnancy: A case series and review of the literature. *J Clin Endocrinol Metab*. 2015;100(8):3202-3209.

15. Dusitkasem S, Herndon BH, Paluzzi D, Kuhn J, Small RH, Coffman JC. From Bad to Worse: Paraganglioma Diagnosis during Induction of Labor for Coexisting Preeclampsia. *Case Rep Anesthesiol*. 2017; 2017:1-5.

16. Biggar MA, Lennard TWJ. Systematic review of phaeochromocytoma in pregnancy. *Br J Surg*. 2013;100(2):182-190.

17. Radfar MH, Shakiba B, Afyouni A, Hoshyar H. Laparoscopic management of paraganglioma in a pregnant woman: A case report. *Int Braz J Urol*. 2018;44(5):1036-1041.

18. Combs CA, Easterling TR, Schmucker BC, Benedetti TJ. Hemodynamic observations during paroxysmal hypertension in a pregnancy with pheochromocytoma. *Obstet Gynecol*. 1989;74(3).

19. Weerd K Van Der, Noord C Van, Loeve M, Knapen MFCM, Visser W. Pheochromocytoma in pregnancy: case series and review of literature. *Eur J Endocrinol*. 2017;177: R49-R58.

20. Gannan E, Veenendaal P Van, Scarlett A, Ng M. Retroperitoneal non-functioning paraganglioma: A difficult tumour to diagnose and treat. *Int J Case Reports*. 2015; 17:133-135.

21. Hénaux P, Zemmoura I, Riffaud L, François P. Surgical treatment of rare cauda equina tumours. *Acta Neurochir*. 2011;(153):1787-1796.

22. Doo AR, Kim D, Cha KN, Han YJ, Kim DC. Anesthetic management of a pregnant woman undergoing laparoscopic surgery for pheochromocytoma -A case report-. *Korean J Anesthesiol*. 2013;64(4):373-375.

23. Moran CA, Rush W, Mena H. Primary spinal paragangliomas: a clinicopathological and immunohistochemical study of 30 cases. *Histopathology*. 1997:167-173.

24. Kimura N, Takekoshi K, Naruse M. Risk Stratification on Pheochromocytoma and Paraganglioma from Laboratory and Clinical Medicine. *J Clin Med*. 2018:1-11.

25. Koh J, Ahn SH, Kim H, et al. Validation of pathological grading systems for predicting metastatic potential in pheochromocytoma and paraganglioma. *PLoS One*. 2017; 40:1-14.