



Composite Pheochromocytoma – Ganglioneuroma as Adult Incidentaloma

**Ancuta Augustina
Gheorghisan-
Galateanu**

Department of Cellular and Molecular Medicine, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

Mara Carsote

Department of Endocrinology, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

Dana Terzea

Monza Hospital, Oncoteam, Bucharest, Romania

Sorin Paun

Floreasca Emergency Hospital, Bucharest, Romania

Catalina Poiana

Department of Endocrinology, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Adrenal incidentalomas underline exceptional tumors as composite pheochromocytoma. Clinical phenotype does not correlate with radiological features and the definite diagnosis is histological. 48-year Caucasian female accused a mild lumbar pain. The computed tomography pointed a right adrenal tumor of 6 by 4.2 centimeters. Mild elevation of the plasma metanephrines and serum chromogranin A were found. Transperitoneal anterolateral right laparoscopic adrenalectomy was performed. Macroscopic, the encapsulated tumor was of 7 by 6 centimeters. A composite pheochromocytoma - ganglioneuroma was confirmed. Immunohistochemistry pointed S100+ve, chromogranin A+ve, Ki67 of <2%. Composite elements did not induce any specific symptoms or imagery clues but they might interfere with the catecholamines metabolism since no typical elevation was registered as in classical pheochromocytomas. The large dimensions might involve a malignant behavior that was not confirmed. The prognosis and the long term management in mixed pheochromocytomas depend on different factors but this is still an open issue.

KEYWORDS : incidentaloma, composite pheochromocytoma, ganglioneuroma, chromogranin A, metanephrines

Background

The adrenal tumors comprise a wide area. The term of “incidentaloma” is used for accidentally discovered tumors. [1] The true incidence of adrenal incidentaloma varies depending on criteria; recently there is an increasing incidence because of the widespread use of imaging techniques. Pheochromocytoma might be displayed as an adrenal incidentaloma. The symptoms are not always presented but there is a large area as sustained arterial hypertension or paroxysms of high blood pressure, etc. [2] The clinically silent pheochromocytomas also need surgical approach and the adequate hemodynamic control including before, during and after surgery. [3] The “rule of four” was suggested: overall, 4% of the population performing an abdominal computed tomography scan might have an adrenal incidentaloma; 4% of them are pheochromocytomas, and the cutoff of 4 cm is mandatory for the surgical approach, regardless the endocrine profile. [4] The high dimensions are very suggestive for malignant behavior, including pheochromocytomas with a 10-year survival rate of 40%. [5]

The composite (mixed) pheochromocytoma is an extremely rare tumor (<3% of pheochromocytomas). [6,7] The adrenal tumor originates from neural crest derived cells and associates both pheochromocytoma and non-pheochromocytoma elements (as ganglioneuroma, ganglioneuroblastoma, neuroblastoma, neuroblastomatosis-I, rhabdomyosarcomatous differentiation, schwannoma, neuroendocrine carcinoma, metastatic squamous cell carcinoma). [6,8,9,10,11] A mixed case with an adrenal cortical adenoma (a part from ganglioneuroma elements) was also reported. [1] Malignancy might be seen; also extraadrenal tumors (composite paraganglioma or retroperitoneal pheochromocytoma) are described. [13,14] Pediatric forms are exceptional. [15] Genetic syndromes might be involved as MEN-2A or NF-1. [8,16] The specific protocol of management and follow up even in aggressive forms (like neuroblastoma) is still uncertain. [17]

The composite pheochromocytoma – ganglioneuroma associates adrenal chromaffin cells and autonomic ganglion cells. Both types

of cell originate from neural crest cells and migrate to somatic areas. [18] Defects in normal migration, differentiation, and development of these cells cause the tumor. Either of cells might cause hormonal secretion and the pathologic features are similar, thus the composite aspect of the tumor might be under diagnosed before surgery and pathological examination. [8] An analysis published up to 2010 reported 45 cases of composite pheochromocytoma (70% with ganglioneuroma component which is considered up to this moment the most frequent composite element). [19]

We present a fifth decade female case accidentally discovered with an adrenal tumor that was confirmed as a mixed pheochromocytoma. The informed and written consent of the patient was obtained.

Case report. 48-year old Caucasian female accused in October 2013 a mild lumbar pain for a few days. An abdominal ultrasound, and then a computed tomography scan confirmed a solid, right adrenal tumor of 6 by 4.2 centimeters. (Figure 1.A)



Figure 1.A. Computed tomography (before surgery): right well shaped adrenal tumor of 6 by 4.2 cm, normal left adrenal tumor;

She was referred to endocrinology for further evaluation. On admission, in November 2013, no other obvious medical causes of lumbar pain were found. Her medical history revealed menopause at age of 45 years, and some skin allergies. The medical family history was irrelevant. The general and endocrine physical exam was normal. The biochemistry tests were within normal limits. The endocrine profile pointed a mild elevation of the plasma metanephrines with normal plasma normetanephrines. The serum chromogranin A was more than twice upper the normal limit of normal. (**Table 1**)

Table 1. Hormonal profile (baseline, and after adrenalectomy)

Hormone	Baseline (November 2013)	3 Months after surgery (February 2014)	6 Months after surgery (May 2014)	Normal levels
Plasma Free Metanephrines (pg/mL)	168 (repeated 112)	67	27	10-90
Plasma Free Normetanephrines (pg/mL)	154 (repeated 156)	89	46	15-180
Chromogranin A (ng/mL)	267	41	71	20-100

The patient was referred to surgery. Transperitoneal anterolateral right laparoscopic adrenalectomy was performed in December 2013 without any cardiovascular incidents and the patient was discharged within 7 days. The peritoneal drainage catheter was extracted within 48 hours, and the digestive tolerance was rapidly re-established. Grossly, the tumor was encapsulated, and the diameters were 7 by 6 by 6 centimeters. (**Figure 2**)



Figure 2. Macroscopic aspect: right adrenal tumor of 7 by 6 by 6 centimeters

Histologically, the tumor showed a mixed phenotype, with two distinct patterns. One pattern, with high cellularity, was consistent with pheochromocytoma (**Figure 3.A**)

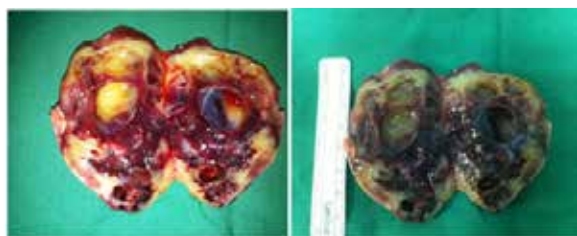


Figure 3. Histopathological and immunohistochemical features:

It was composed of nest-like clusters of chromaffin cells (or pheochromocytes) with sustentacular cells at the periphery of the clusters, demonstrable only by immunostaining. The chromaffin cells were pleomorphic small cells, with granular cytoplasm, round to oval nuclei and sometimes prominent nucleoli. The other pattern with a relatively loose wavy with fibrous stroma, was consistent with ganglioneuroma (**Figure 3.B**). It was composed of large ganglion cells scattered or aggregated within the proliferating nerve bundles and Schwann cells. The two components were merged into each other. Areas of hemorrhage were also seen within the tumor. The necrosis or mitotic figures were not found. No histopathological feature suggestive of malignancy was seen. Immunohistochemically, the indi-

vidual components of these tumors are the same as they would be in pure tumors of the same type. The chromaffin cells which contained neurosecretory granules, were strongly and diffusely positive for chromogranin A (**Figure 3.C**), while the sustentacular cells of the pheochromocytoma component and the Schwann cells of ganglioneuroma component were immunoreactive with S-100 protein. (**Figure 3.E,F**) The cellular marker for proliferation, the Ki-67 protein (also known as MKI67) was positive <2% in the pheochromocytoma areas. (**Figure 3.D**) The final histopathological diagnosis of composite pheochromocytoma/ ganglioneuroma was made. Three months after surgery (in February 2014), the patient was reevaluated. She felt well and the hormonal profile was normal, including the plasma metanephrines and normetanephrines, as well as the serum chromogranin A. (**Table 1**) The RET mutation (PCR) was negative. The clinical and hormonal parameters were also normal six months after surgery (in May 2014), as well as computed tomography. (**Figure 1.B**) Close follow-up was recommended.

Discussions

We presented an exceptional situation that may be found behind an adult adrenal incidentaloma: a composite pheochromocytoma. The case was clinically silent and some unspecific local pain was most probably related to the tumor itself, unlikely to the endocrine or histological features. The asymptomatic well shaped tumor with benign appearance and no genetic background seems to be the common phenotype in most reports regarding composite pheochromocytoma which mostly are limited series of cases. The composite elements do not induce any specific symptoms or imagery clues. [20] The differential diagnostic is mainly due to the pathological examination since endocrine or radiological examination is not specific. [20] The non-pheochromocytoma elements were suggestive for ganglioneuroma based on histological and immunohistochemistry findings. More than two thirds of the composite cases published in the literature are related to the mixed tumors with ganglioneuroma elements. [19] Some reported that in composite pheochromocytoma the female / male ratio is one; the most frequent age interval is 40-60 years, and means diameters are between 4 and 6 centimeters. [19] In our case, we performed limited genetic tests: only RET gene mutation was negative. No significant diseases were registered in the family of the fifth decade patient. In the literature, 13 susceptibility genes were found to be related to pheochromocytoma and paragangliomas. [21] One of the most common mechanisms related to the majority of these genes includes abnormal apoptosis but some data indicate that other genes (yet unknown) might be actually involved. [22] The adult ganglioneuroma associates a slow growth and an asymptomatic appearance with no specific imaging features. The radiological findings are not suggestive (some cases with very high diameters have been reported), and the definite diagnosis is provided by pathological exam. [23] While the pheochromocytoma is mostly metabolic active, the ganglioneuroma is rather not. A composite tumor with both pheochromocytoma and ganglioneuroma elements may associate symptoms related to their endocrine profile, but they are exceptional compare to standard pheochromocytomas. The radiological appearance indicates that composite pheochromocytoma have a tendency to be larger than classical tumor. [24] In case of composite tumors, the correlation with clinical-radiological aspects is poor. [25] As in our case, the tumor had a diameter >4 centimeter which is the "warning" level in order to perform a surgical approach and displayed a mild elevation of the plasma free metanephrines in a completely asymptomatic adult female (a silent composite pheochromocytoma). There are not enough evidence based medicine data to explain if the presence of the composite elements may impair the classical metabolism of catecholamines as seen in non-mixed pheochromocytoma. The adrenal tumor may suggest a malignant behavior based on increased diameters but the definite diagnosis was provided by the pathological report which found no atypical or malignant components. Thus, no correlation between pre-operative status and the histological exam was found. We recommended surgery primarily based on the tumor dimensions, and secondary based on the increased serum chromogranin A and plasma free metanephrines. No supplementary dynamic tests were used for the confirmation of the pheochromocytoma before surgery, as some centers encourage to be used. [26] The normal cardiovascular exam remained so during and 6 months after surgery. No classical event as seen in peri-operative management of classical pheochromocytomas was registered. [26,27] Even the immunochemistry points a large panel of reactions, the composite pheochromocytoma – ganglioneuroma is mostly nonfunctional regarding the clinical symptoms and the labo-

ratory tests. [29] The S100 protein and chromogranin A were positive and the proliferation marker Ki67 was low.

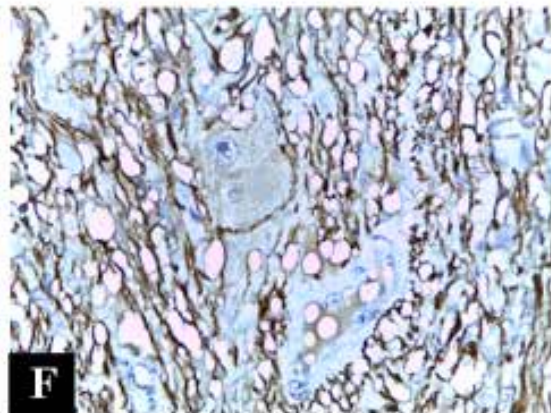
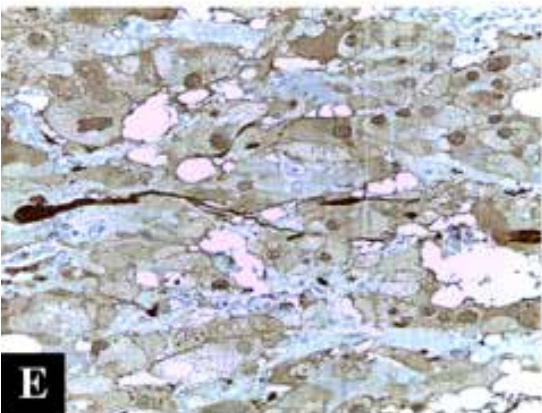
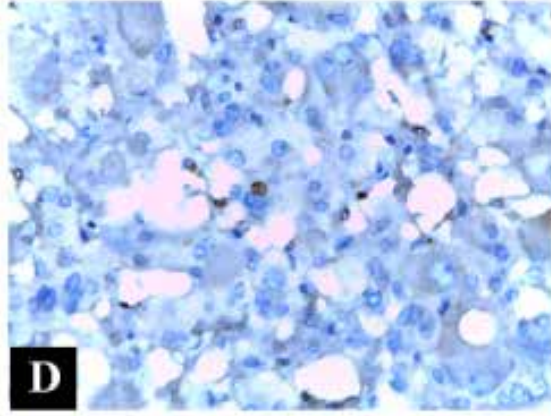
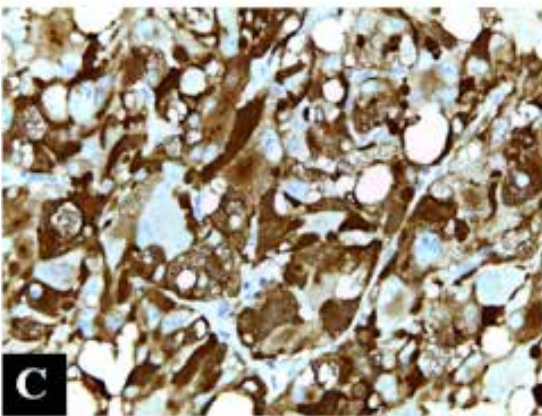
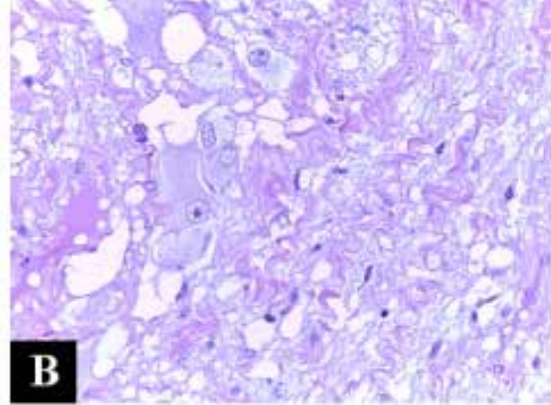
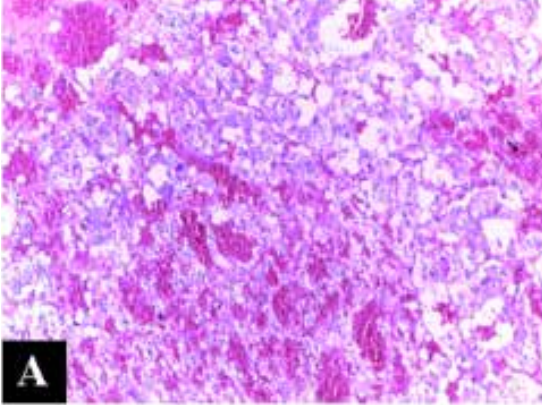
The prognosis in mixed pheochromocytomas depends on the malignancy features. There are not enough published data to indicate whether the composite pheochromocytoma needs a more aggressive approach related to classical pheochromocytoma or ganglioneuroma and whether the mixed tumor associates a more severe prognosis. Molecular studies for example using N-myc amplification pointed that composite type is a histological variant of ordinary pheochromocytoma. [30]

Conclusions

We conclude with some key points: the composite pheochromocytoma may embrace an adult incidentaloma medical presentation; the abnormal (also not according to the standard criteria for pheochromocytoma) hormonal profile associates a disturbance in the adrenal

medulla hormones metabolism which is difficult to be appreciated as caused by the composite elements; the essential role of the histological and the immunochemistry report with the major contribution in the exact diagnosis (the composite elements representing an extremely rare "incidental" event); more data are necessary to highlight the long term follow-up and the prognosis in mixed pheochromocytomas versus classical pheochromocytomas; such cases represent an argument for a multidisciplinary approach between endocrinology, pathology, radiology, and surgery.

pheochromocytoma HE stain x100 (A) and ganglioneuroma, HE stain x400 (B) Immunohistochemical staining for chromogranin A was strongly and diffusely positive in the chromaffin cells x400 (C). Ki-67 protein was positive < 2% in the chromaffin cells x400 (D). Immunohistochemical staining for S-100 protein was positive in sustentacular cells x400 (E), and Schwann cells x400 (F).



Competing Interest: None.

Acknowledgements. We thank to the patient and the medical team.

REFERENCES

1. Prinz RA, Brooks MH, Churchill R, Graner JL, Lawrence AM, Paloyan E, Sparagana M: Incidental asymptomatic adrenal masses detected by computed tomographic scanning. Is operation required? *JAMA* 1982, 248:701-704. | 2. Young WF: The Incidentally Discovered Adrenal Mass. *The New England Journal of Medicine* 2007, 356(6):601-610. | 3. Shen SJ, Cheng HM, Chiu AW, Chou CW, Yang CY, Chen SY: Clinically Silent Pheochromocytoma in Adrenal Incidentaloma: A Case Report and Review of Literature. *J Intern Med Taiwan* 2003, 14:248-254. | 4. Alexandraki K, Grossman A: Adrenal incidentaloma: "the rule of four". *Clinical Medicine* 2008, 8(2):201-204. | 5. Kopf D, Goretzki PE, Lehnert H: Clinical management of malignant adrenal tumors. *J Cancer Res ClinOncol* 2001, 127:143-155. | 6. Rao RN, Singla N, Yadav K: Composite pheochromocytoma-ganglioneuroma of the adrenal gland: A case report with immunohistochemical study. *Urology Annals* 2013, 5(2):115-118. | 7. Linnoila RI, Keisser HR, Steinberg SM, Lack EE: Histopathology of the benign versus malignant sympathoadrenal paragangliomas: Clinicopathologic study of 120 cases including unusual histologic features. *Hum Pathol* 1990, 21:1168-1180. | 8. Juarez D, Brown RW, Ostrowski M, Reardon MJ, Lechago J, Truong LD: Pheochromocytoma associated with neuroendocrine carcinoma. A new type of composite pheochromocytoma. *Arch Pathol Lab Med* 1999, 123:1274-1279. | 9. Moore PJ, Biggs PJ: Compound adrenal medullary tumour. *South Med J* 1995, 88:475-478. | 10. Pathmanathan N, Murali R: Composite pheochromocytoma with intratumoural metastatic squamous cell carcinoma. *Pathology* 2003, 35:263-265. | 11. Gupta R, Sharma A, Arora R, Vilayarghavan M: Composite pheochromocytoma with malignant peripheral nerve sheath tumour and rhabdomyosarcomatous differentiation in a patient without von Recklinghausen disease. *J ClinPathol* 2009, 62(7):659-661. | 12. Lay SK, Chu PG, Weiss LM: Mixed cortical adenoma and composite pheochromocytoma-ganglioneuroma: an unusual cortico/medullary tumor of the adrenal gland. *Ann DiagnPathol* 2011, 15(3):185-189. | 12. Lay SK, Chu PG, Weiss LM: Mixed cortical adenoma and composite pheochromocytoma-ganglioneuroma: an unusual cortico/medullary tumor of the adrenal gland. *Ann DiagnPathol* 2011, 15(3):185-189. | 13. Chang H, Jeong H, Kim Y, Park SH, Kim A: Composite Pheochromocytoma or Paraganglioma of Adrenal Gland: A Case Report with Immunohistochemical Studies and Electron Microscopic Examination. *The Korean Journal Of Pathology* 2011, 45:306-310. | 14. Hu J, Wu J, Cai L, Jiang L, Lang Z, Qu G, Liu H, Yao W, Yu G: Retroperitoneal composite pheochromocytoma-ganglioneuroma: a case report and review of literature. *Diagnostic Pathology* 2013, 8(63): 1-5. | 15. Lee Thiel E, Trost B, Tower R: A Composite Pheochromocytoma/Ganglioneuroblastoma of the Adrenal Gland. *Pediatr Blood Cancer* 2010, 54:1032-1034. | 16. Menon S, Mahajan P, Desai SB: Composite adrenal medullary tumor: A rare cause of hypertension in a young male. *Urology Annals* 2011, 3(1):36-38. | 17. Steen O, Fernando J, Ramsay J, Prebtani APH: An Unusual Case of a Composite Pheochromocytoma With Neuroblastoma. *J EndocrinolMetab* 2014, 4(1-2):39-46. | 18. Weston JA: The migration and differentiation of neural crest cells. *AdvMorphol* 1970, 8:41-114. | 19. Khan AN, Solomon SS, Childress RD: Composite pheochromocytoma - ganglioneuroma: a rare experiment of nature. *Endocrine Practice* 2010, 16(2):291-299. | 20. Shawa H, Elsayer KM, Javadi S, Sircar K, Jimenez C, Habra MA: Clinical and Radiological Features of Pheochromocytoma/Ganglioneuroma Composite Tumors: A Case Series with Comparative Analysis. *Endocr Practice* 2014;18:1-19. | 21. King KS, Pacak K: Familial pheochromocytomas and paragangliomas. *Mol Cell Endocrinol.* 2014, 386(1-2):92-100. | 22. Opocher G, Schiavi F: Genetics of pheochromocytomas and paragangliomas. *Best Pract Res Clin Endocrinol Metab.* 2010, 24(6):943-56. | 23. Kacagan C, Basaran E, Erdem H, Tekin A, Kayikci A, Cam K: Case report: Large adrenal ganglioneuroma. *International Journal of Surgery Case Reports.* 2014, 5:253-255. | 24. Rai R, Gajanthody S, Jayaram J, Chaudhry RK: Composite pheochromocytoma. *South Asian Journal of Cancer* 2012, 1(2):98-99. | 25. Bowen JS, Parker A, Bellur SS, Anikumar B, Dove D, Sadler GP, Srinivas-Shankar U: Management of adrenal incidentaloma: size still matters. *BMJ Case Report* 2011; doi:10.1136/bcr.08.2011.4709-1-4 | 26. Darr R, Lenders JW, Stange K, Kindel B, Hofbauer LC, Bornstein SR, Eisenhofer G: Diagnosis of pheochromocytoma and paraganglioma: the clonidine suppression test in patients with borderline elevations of plasma free normetanephrine. *Dtsch Med Wochenschr.* 2013, 138(3):76-81. | 27. Fishbein L, Orlowski R, Cohen D: Pheochromocytoma/Paraganglioma: Review of perioperative management of blood pressure and update on genetic mutations associated with pheochromocytoma. *J Clin Hypertens (Greenwich).* 2013, 15(6):428-34. | 28. Mannelli M, Dralle H, Lenders JW: Perioperative management of pheochromocytoma/paraganglioma: is there a state of the art? *Horm Metab Res.* 2012, 44(5):373-8. | 29. Gong J, Wang X, Chen X, Chen N, Huang R, Lu C, Chen D, Zeng H, Zhou Q: Adrenal and extra-adrenal nonfunctioning composite pheochromocytoma/paraganglioma with immunohistochemical ectopic hormone expression: comparison of two cases. *UrolInt* 2010, 85(3):368-372. | 30. Comstock J, Willmore-Payne C, Holden J, Coffin C: Composite Pheochromocytoma. A Clinicopathologic and Molecular Comparison with Ordinary Pheochromocytoma and Neuroblastoma. *American J ClinPathol* 2009, 132:69-73. |