Composite Pheochromocytoma-Ganglioneuroma: A Rare Tumour of the Adrenal Gland with Distinctive Clinicopathologic Features

Anum Rashid, Sameen Afzal, Samina Zaman and Fizza Jahangir

Department of Histopathology, Chughtai Institute of Pathology, Lahore, Pakistan

ABSTRACT

Composite adrenal neoplasms comprise a mixture of different cell types. Such tumours are very rare. Composite pheochromocytoma-ganglioneuroma is an uncommon tumour with a small number of cases reported in the literature. Pheochromocytoma arises from chromaffin cells, and ganglioneuroma is derived from neural crest cells. The authors present a case of a 35-year male with right-sided lumbar pain. His adrenalectomy was performed, and microscopic findings revealed composite pheochromocytoma-ganglioneuroma.

Key Words: *Composite pheochromocytoma, Adrenal neoplasms, Chromaffin cells, Ganglioneuroma*.

How to cite this article: Rashid A, Afzal S, Zaman S, Jahangir F. Composite Pheochromocytoma-Ganglioneuroma: A Rare Tumour of the Adrenal Gland with Distinctive Clinicopathologic Features. *JCPSP Case Rep* 2025; **3**:408-410.

INTRODUCTION

Composite pheochromocytoma (CP), being a rare adrenal tumour, has more than 130 reported cases in the literature. Most CPs are incidentally found on radiological investigations.[1] They are more prevalent during the sixth decade of life with a median age of 53 years (ranging from 12 to 86 years).[2] About 75% of composite tumours are pheochromocytoma-ganglioneuroma, which are more common in females (F: M ratio: 1.5 to 1). Mixed adrenal tumours have more than one cell type. They comprise pheochromocytoma and an embryologically related neurogenic tumour, such as ganglioneuroma, ganglio-neuroblastoma, neuroblastoma, or malignant peripheral nerve sheath tumour (MPNST). According to the WHO guidelines, the diagnostic criterion is the presence of at least 5% of any of the components. Composite pheochromocytoma-gangioneuroblastoma and pheochromocytoma-neuroblastoma account for more than 10% of composite tumours. Rarely, pheochromocytoma-MPNSTs and pheochromocytoma-neuroendocrine carcinoma have also been reported.[3] Composite paragangliomas are rare, with composite paraganglioma-ganglioneuroma usually seen in adults, and half of composite paragangliomas-neuroblastomas are seen in the paediatric age group, with the youngest described case at the age of 15 months.

Correspondence to: Dr. Anum Rashid, Department of Histopathology, Chughtai Institute of Pathology, Lahore, Pakistan
E-mail: anumrashid66@yahoo.com

Received: November 21, 2024; Revised: May 03, 2025; Accepted: July 23, 2025
DOI: https://doi.org/10.29271/jcpspcr.2025.408

Most CPs are sporadic, with no known predisposing factors. However, 20% of tumours are associated with underlying hereditary syndromes. The most common genetic predisposition is neurofibromatosis type I, accounting for approximately 70% of the hereditary cases.[4] In literature, three composite pheochromocytomas-ganglioneuromas and one composite pheochromocytoma-ganglioneuroblastoma were reported in patients with multiple neuroendocrine neoplasia type 2A (MEN 2A),[5] three composite pheochromocytomas-ganglioneuromas have been reported in von Hippel-Lindau (vHL) syndrome and one in multiple neuroendocrine neoplasia type 2B (MEN 2B). Patients with pheochromocytoma show catecholaminergic and hypertensive symptoms,[6] whereas patients with ganglioneuroma are usually asymptomatic, as it is a non-metabolically active tumour. Therefore, the detection of CP is mainly based on histopathology. The authors recently diagnosed a normotensive patient with composite pheochromocytoma-ganglioneuroma.

CASE REPORT

A 35-year male presented in the urology OPD of a teaching hospital with complaints of right-sided lumbar pain for the last six months, which was gradual in onset, severe in intensity, and associated with episodes of vomiting. He gave no personal or family history of headache, palpitations, or hypertension.

A subsequent abdominal CT scan showed a right adrenal cystic mass measuring 10.0 × 9.6 × 7.4 cm with internal septations in the right suprarenal region. It was seen extending into the subhepatic region. A 24-hour urine metanephrine test was carried out, which revealed elevated urinary metanephrines, *i.e.*, 607.15 µg/24 hours.

Given the size of the adrenal mass, right adrenalectomy was planned and performed. Gross pathological examination revealed a circumscribed mass measuring 10.0 × 9.0 × 5.2 cm

showing solid-cum-cystic cut surface with speckled gelatinous areas and haemorrhagic foci. Two separately present tan-brown fragments of adrenal tissue measuring 5.0 × 2.0 × 1.0 cm in aggregate were also present in the jar.

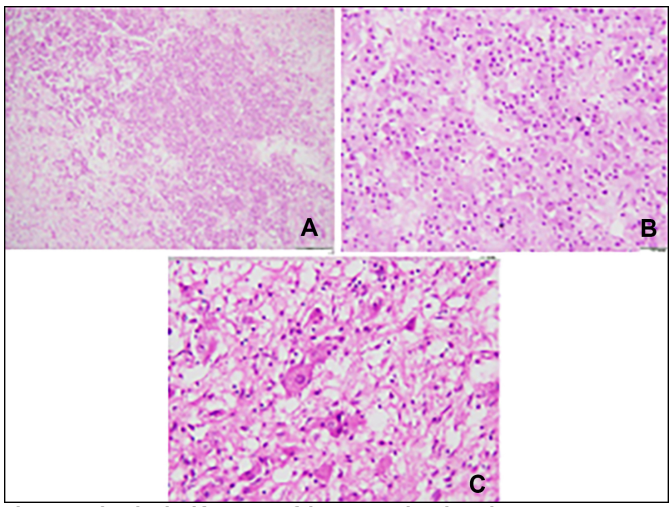

Figure 1: Histological features of the composite pheochromocytoma-ganglioneuroma. (A) Pheochromocytoma with an interspersed ganglioneuroma component. (B) Atypical polygonal cells with abundant eosinophilic cytoplasm consistent with pheochromocytoma. (C) Sheets of the mature ganglion cells consistent with ganglioneuroma components.

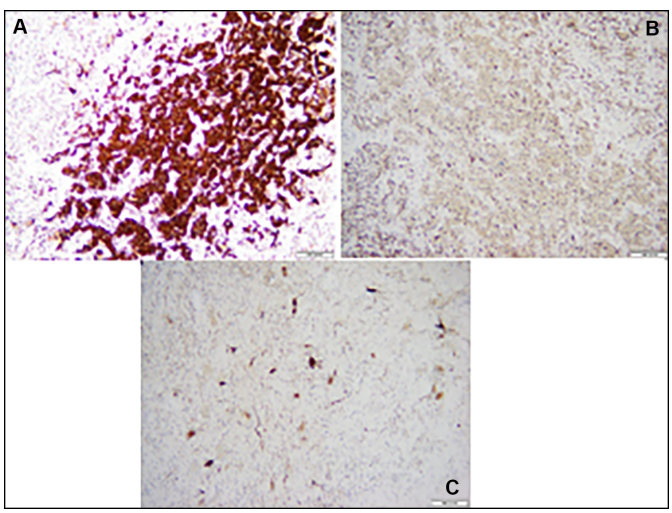

Figure 2: Immunohistochemistry performed on composite pheochromocytoma-ganglioneuroma. (A) Synaptophysin is diffusely positive in the component of pheochromocytoma (Synaptophysin ×10). (B) S-100 highlighting the intervening sustentacular cells (S-100, ×4). (C) Calretinin highlighting the ganglion cells of ganglioneuroma (Calretinin, ×4).

Microscopic examination revealed a tumour comprising polygonal cells arranged in delineated nests encircled by a fine fibrovascular stroma. The atypical cells showed a moderate-to-abundant amount of granular eosinophilic cytoplasm with round to oval nuclei and prominent nucleoli. Few areas revealed sheets of mature ganglion cells with surrounding fascicles of Schwann-like cells (Figure 1). Areas of haemorrhage, dense fibrocollagenous tissue, and mixed inflammatory cell infiltrate were also appreciated. Separately submitted tissue fragments showed unremarkable adrenal gland tissue. No primitive neuroblastic cells were identified in the extensively sampled specimen. Based on histomorphological findings, a preliminary diagnosis of composite pheochromocytoma-ganglioneuroma was made.

For confirmation, an immunohistochemical workup was performed. Synaptophysin was diffusely positive in the cellular component of pheochromocytoma, S-100 was positive in the intervening sustentacular cells, and calretinin highlighted the ganglion cells of the composite ganglioneuroma. This immunoprofile confirmed the provisional diagnosis (Figure 2).

DISCUSSION

Composite pheochromocytoma-ganglioneuroma emerges from chromaffin cells and sympathetic ganglion cells. Both of these cells are known to arise from primitive neuroectodermal cells of the neural crest. If there is any abnormality in the development or migration of these neuroectodermal cells, it may lead to the origin of composite tumours.[2]

The clinical representation of a tumour depends upon its functionality and non-functionality. Pheochromocytoma is made up of chromaffin cells, which produce catecholamines. Paroxysmal hypertension, headache, or sweating usually occurs in patients with pheochromocytoma.[7] In this case, the patient was normotensive despite elevated urinary metanephrines. No definitive manifestation of catecholamine hypersecretion was identified before diagnosis. Immunohistochemically, these tumours express the same immunomarkers as they would in their pure tumour form. The markers include Synaptophysin, Chromogranin A, and GATA3. Out of these, GATA3 shows expression in 70% of cases.[8] S-100 is expressed in the nuclei and cytoplasm of sustentacular cells and some pheochromocytes throughout the tumour.

CPs are mostly sporadic, while 20% cases show association with genetic syndromes, such as Neurofibromatosis 1(NF1),[4] MEN types 2A and B, vHL syndrome, and watery-diarrhoea hypokalaemia-achlorhydria syndrome. So, clinical or molecular screening for NF1, RET, vHL, and MAX mutations can be performed in selected cases.[9] This patient did not show any association with any of these syndromes.

Preoperative radiographical investigations, including computed tomography (CT) imaging, show well-circumscribed heterogenous mass with significant contrast enhancement and a potential cystic component. Clinically and radiographically, composite tumours are very similar to adrenal pheochromocytomas.[1] Final diagnosis is made after the pathological evaluation. Histology shows features of both components. Similar histomorphological features were observed in this case.

The treatment of choice is adrenalectomy, with a good prognosis if removed early. The prognosis of CP is dependent on the highest grade component present. Roughly, 13% of these tumours metastasise. Generally, 60% of patients die with a median survival of 2 years.[10] In composite pheochromocytomas-ganglioneuromas, 6% of the cases metastasise, while in composite pheochromocytomas-ganglioneuroblastomas/neu-

roblatomas, metastasis is more common and present in one fourth of cases. The highest risk is seen in composite pheochromocytoma-MPNSTs, and they are most often metastatic at presentation. The common metastatic sites include the contralateral adrenal gland, lymph node, retroperitoneum, and rarely, the liver, lungs, and bones.

In conclusion, composite tumours of the adrenal gland, though very rare, do exist and can present in diverse ways with or without the definitive clinical symptoms of catecholamine hypersecretion. Therefore, a clinico-radiological and histopathological correlation is required to recognise these composite tumours.

PATIENT'S CONSENT:
Informed consent was taken from the patient.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AR: Design, reviewing of the literature, and writing of the manuscript
SA: Design and interpretation.
SZ, FJ: Review of the manuscript.
All authors approved the final version of the manuscript to be published.

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