Composite Pheochromocytoma—A Rare Clinical Entity: A Case Series

Pushkar Sharma1, Supriya Sen2, Paul M Jacob3, Santosh Raj4, Elanthenral Sigamani5, Marie T Manipadam6

ABSTRACT

Background: Composite pheochromocytoma is a rare entity with tumor comprising both pheochromocytoma and neuroblastic elements. The clinical outcome of such a composite tumor is not fully understood. In this case series, we report three cases of composite pheochromocytoma managed at our institute from 2016 to 2021.

Results: We had three patients with MEN2A syndrome with composite tumor who underwent adrenalectomy, all of which were ganglioneuroma with pheochromocytoma. None of the three cases had recurrence or metastasis associated with composite adrenal tumor on 13-month mean follow-up.

Conclusion: We noticed a higher incidence of syndromic association in composite adrenal tumors. The clinical and radiological presentation was dominated by the pheochromocytoma component.

Keywords: Adrenal, Composite Pheochromocytoma, Ganglioneuroma, Multiple endocrine neoplasia.

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BACKGROUND

Composite pheochromocytoma is a rare entity, which refers to pheochromocytoma admixed with tumors of neuroblastic origin like ganglioneuroma, neuroblastoma, ganglioneuroblastoma, or rarely schwannoma.1,2 The occurrence of neural tissue along with pheochromocytoma has been attributed to their common embryological origin from the neural crest cells.3 The clinical outcome and impact of such a composite tumor is yet to be fully understood as a limited data set exists for the same. Here, we present a case series of three cases of composite pheochromocytomas managed at our institute between 2016 and 2021.

RESULTS

In our case series, all our patients had syndromic association. The following tables described below summarize our results.

Table 1 depicts the demographic data of all the patients. Table 2 depicts the clinical presentation of all three cases. Table 3 depicts the evaluation and management of the cases. Figure 1 depicts the imaging characteristics of the cases. Table 4 depicts the tumor characteristics on histopathological examination. Figure 2 depicts the histopathological findings of the composite tumor. Table 5 depicts the outcome of the three cases.

DISCUSSION

Composite adrenal tumors are rare tumors with components of both neuroendocrine and neuroblastic differentiation. The chromaffin cells and sympathogonia have a common origin from the neural crest cells, which explains the etiology behind composite tumors. Though adrenal gland is the most common site for composite tumors, extra-adrenal composite tumors have been reported in the literature in the retroperitoneum, urinary bladder, and cauda equina.4

The neuroblastic components arising from primitive sympathogonia in their order of incidence include5:

- Ganglioneuroma (65%)
- Neuroblastoma (16%)

The occurrence of neural tissue along with pheochromocytoma has been attributed to their common embryological origin from the neural crest cells. The clinical outcome and impact of such a composite tumor is yet to be fully understood as a limited data set exists for the same. Here, we present a case series of three cases of composite adrenal tumors managed at our institute from 2016 to 2021.

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- Ganglioneuroblastoma (11%)
- Schwannoma (1%)

The incidence of composite pheochromocytoma has been reported to be around 3 to 9% in the literature.1,5,7 In our institute, the incidence of composite adrenal tumor was noted to be 1.4%.

In our case series, all patients were male, and the mean age at presentation was 43.6 years. This is similar to what is quoted in the literature; however, no gender predilection is reported in the literature.5,6,8

Most common presentation in our case series was with hypertension (66.7%) followed by abdominal pain (33.3%). In our case series, the pheochromocytoma component predominated the clinical presentation with raised catecholamine levels. Two-thirds had increased 24-hour urinary metanephrines and normetanephrines, and one-third had increased normetanephrine levels alone. The neuroblastic component of composite tumors is mostly non-secretory; however, a few cases of composite tumors presenting with the secretion of vasoactive intestinal peptide (VIP) with WDHA syndrome have been reported in the literature.

The ganglioneuroma and ganglioneuroblastoma component, including pheochromocytoma, have been reported to produce VIP3–14.
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In our study, all three cases (100%) had syndromic association with all having mutation in RET (rearranged during transfection proto-oncogene) Cys 634 codon at exon 11, suggestive of MEN2A syndrome. Literature review suggests that one-third of composite pheochromocytoma conditions are associated with a underlying genetic syndrome, out of which the most common association is noted with neurofibromatosis type 1 (19%), followed by MEN2A (4%).

In our case series, all three patients underwent contrast enhanced computed tomography (CECT) as part of preoperative workup. The imaging showed the characteristic features of pheochromocytoma. The ganglioneuroma component did not seem to alter the imaging characteristics. One patient in our case series had computed tomography (CT) imaging, which showed indeterminate bilateral enhancing nodules (HU—40–60), who underwent Ga68 dotatate positron emission tomography/ computed tomography (DOTATE PET CT), which showed uptake in bilateral adrenal glands. MIBG scan was done for another patient, which showed the uptake in bilateral adrenal glands. All three of our patients were blocked preoperatively with the selective alpha1 blockade. One out of three patients in our case series underwent open adrenalectomy in view of large size, and all three patients underwent bilateral adrenalectomy due to the bilateral involvement.

All three patients in our case series were noted to have ganglioneuroma as the composite component, which is reported to be the most common neuroblastic component in literature. The mean tumor size was noted to be 3.86 cm. Literature review suggests a larger size of composite tumors when compared to pheochromocytoma alone.

Two out of three cases (66.7%) in our case series had composite tumor on the right, while one had it on the left side. Literature review suggests a higher incidence of composite tumor on the right side (56%).

Two-thirds of cases in our case series had PASS score, suggestive of low malignant potential, while one-third had a GAPP score, suggestive of moderately differentiated type of pheochromocytoma.

Table 1: Demographic data

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Age at presentation (years)</td>
<td>32</td>
<td>59</td>
</tr>
</tbody>
</table>

Table 2: Clinical presentation

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Syndromic association</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Hypertension*</td>
<td>MEN 2A†</td>
</tr>
<tr>
<td>Case 2</td>
<td>Hypertension</td>
<td>MEN 2A</td>
</tr>
<tr>
<td>Case 3</td>
<td>Abdominal pain</td>
<td>MEN 2A</td>
</tr>
</tbody>
</table>

*With medullary thyroid carcinoma (MTC) with lung, bone metastasis status post-total thyroidectomy with bilateral neck dissection; †Multiple endocrine neoplasia (MEN)

Table 3: Evaluation and management

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Alpha blockade</th>
<th>Surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>CECT</td>
<td>Ga68 dotatate PET</td>
</tr>
<tr>
<td>Case 2</td>
<td>CECT</td>
<td>MIBG</td>
</tr>
<tr>
<td>Case 3</td>
<td>CECT</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Combined bilateral retroperitoneoscopic adrenalectomy; †Underwent left cortical sparing and right adrenalectomy

Figs 1A to C: Contrast-enhanced computed tomographic images showing bilateral adrenal lesions: (A) case 1; (B) case 2; (C) case 3
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Pheochromocytomas are known to have a metastatic potential; however, ganglioneuroma component of composite tumors is noted to have a benign course. However, ganglioneuroma and neuroblastoma have been reported to have a malignant course as per the literature. Further studies are required to fully understand the behavior and outcome of composite adrenal tumors.

**Conclusion**

In our case series, we saw a higher incidence of syndromic association with composite tumors. There were no clinical or radiological differences noted due to the ganglioneuroma component associated with pheochromocytoma. In composite tumors, as pheochromocytoma determines the outcome, the cases with malignant potential warrant a close follow-up. As described in the literature, in our case series also the composite pheochromocytoma was a histological surprise.

**Table 4: Tumor characteristics**

<table>
<thead>
<tr>
<th>Composite tumor component</th>
<th>Tumor size (cm)</th>
<th>Laterality</th>
<th>GAPP/PASS score</th>
<th>Ki-67 index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 GN + Pheo</td>
<td>1.8</td>
<td>Right</td>
<td>PASS score-3</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Case 2 GN + Pheo</td>
<td>2</td>
<td>Left</td>
<td>PASS score-1</td>
<td>NA</td>
</tr>
<tr>
<td>Case 3 GN + Pheo</td>
<td>7.8</td>
<td>Right</td>
<td>GAPP score-5</td>
<td>1%</td>
</tr>
</tbody>
</table>

1Ganglioneuroma; 2Pheochromocytoma; *Grading of Adrenal Pheochromocytoma and Paraganglioma (GAPP); 1Pheochromocytoma of Adrenal gland Scaled Score (PASS)

**Table 5: Outcome and follow-up**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Follow-up</th>
</tr>
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<tbody>
<tr>
<td>Case 1</td>
<td>No recurrence*</td>
</tr>
<tr>
<td></td>
<td>No metastasis</td>
</tr>
<tr>
<td>Case 2</td>
<td>No recurrence</td>
</tr>
<tr>
<td></td>
<td>No metastasis</td>
</tr>
<tr>
<td>Case 3</td>
<td>No recurrence</td>
</tr>
<tr>
<td></td>
<td>No metastasis</td>
</tr>
</tbody>
</table>

*Left pheochromocytoma recurrence at the site of cortical sparing adrenalectomy with progressive MTC lung, bone metastasis; †Lost to follow-up

Mean duration of follow-up was 13 months in our case series. On follow-up, none of the three cases had recurrence or metastasis from the composite adrenal tumor. One patient with MEN2A with metastatic MTC at the presentation had the progression of metastatic disease on 1-year follow-up with the calcitonin doubling time of about 3 months. Patient had recurrence of pheochromocytoma at the site of cortical sparing adrenalectomy after 1 year. Patient was planned for further treatment; however, he was lost to follow up.

Pheochromocytomas are known to have a metastatic potential; however, ganglioneuroma component of composite tumors is noted to have a benign course. However, ganglioneuroma and neuroblastoma have been reported to have a malignant course as per the literature. Further studies are required to fully understand the behavior and outcome of composite adrenal tumors.

**Figs 2A to F:** (A) H&E stain showing Zellballen pattern of pheochromocytoma at 40×; (B) Pheochromocytoma at 100×; (C) H&E showing areas of both pheochromocytoma and ganglioneuroma; (D) H&E staining of ganglioneuroma; (E) Immunohistochemistry (IHC) synaptophysin highlighting the ganglion cells; (F) S100 highlighting the sustentacular cells (arrow)
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REFERENCES