

## Corticomedullary Mixed Tumor of the Adrenal Gland

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Corticomedullary mixed tumors of the adrenal gland are quite rare, with only five well-documented cases reported in the literature.<sup>1-4</sup> Herein, we report the light microscopic and immunohistochemical features of two cases of this rare tumor. Patient 1 is a 34-year-old woman who presented with hypertension, hair loss, and amenorrhea of 1-year duration. Patient 2 is a 52-year-old woman who presented with flank pain and what appeared to be a renal mass on arteriogram with no history of hypertension, Cushing's syndrome, or other endocrine abnormalities. At surgery, the tumor was noted to arise from the adrenal gland rather than the kidney and adrenalectomy was performed. In both cases, the surgically resected specimens consisted of a well-circumscribed, single adrenal mass surrounded by a rim of uninvolved adrenal cortical tissue. The tumors were composed of adrenal cortical cells intimately admixed with pheochromocytes. Immunohistochemical studies highlighted these two cellular components. The pheochromocytes were strongly reactive with chromogranin and the sustentacular cells with S-100 protein, whereas the adrenal cortical cells reacted specifically with inhibin. Thus, we report two additional cases of mixed corticomedullary tumor of the adrenal gland.

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**Index Words:** Mixed tumor, corticomedullary tumor, adrenal gland

THE ADRENAL gland can be thought of as two separate organs, the adrenal cortex and the adrenal medulla, each with distinct structure, function, and embryologic origin. Neoplasms arise from both components and typically present with different clinical symptoms. Tumors of the adrenal cortex include adrenal cortical neoplasms such as adrenal cortical adenomas and carcinomas. Tumors of the medullary component typically present as pheochromocytomas. Tumors composed of both adrenal cortical and adrenal medullary tissue have rarely been reported.<sup>1-4</sup> To the best of our knowledge, the two cases described in this report represent the sixth and seventh cases of true mixed corticomedullary tumor of the adrenal gland.

There are a number of reports of synchronously occurring or coexisting adrenal cortical neoplasms and pheochromocytomas.<sup>5-11</sup> In the reported cases of true corticomedullary mixed tumors, including the two described herein, the adrenal cortical cells are intimately intermingled with the adrenal medullary component within a single tumor mass. Neither the cortical nor the medullary component show cytologic features of malignancy.

### Materials and Methods

The records of three patients with tumors diagnosed as "mixed corticomedullary adrenal tumors" were identified in the files of the Endocrine Registry at the Armed Forces Institute of Pathology from 1970 to 2001. One case was excluded as it had been previously reported.<sup>2</sup> Materials within the Institute's files were supplemented by a review of patient demographics (gender, age), symptoms and physical findings at presentation (including duration), and past medical and surgical history. We obtained follow-up information by direct communication with the pathologist and/or treating physicians. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research. Hematoxylin-eosin stained slides were examined in conjunction with immunohisto-

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chemical studies. Immunophenotypic analysis was performed on a single block by the standardized avidin-biotin method of Hsu et al<sup>12</sup> using 4 $\mu$ m-thick, formalin-fixed, paraffin-embedded sections. The panel of immunohistochemical stains included a cytokeratin cocktail (AE1/AE3/CK1; mouse monoclonal, 1:200 [AE1/AE3]; Dako, Carpinteria, CA and 1:40 [CK1] Boehringer-Mannheim, Indianapolis, IN), vimentin (mouse monoclonal, 1:800; Biogenex Laboratories, San Ramon, CA), S-100 protein (rabbit polyclonal, 1:800; Dako), chromogranin A (rabbit polyclonal, 1:100; Sanbio BV, Uden, Netherlands), synaptophysin (rabbit polyclonal, neat; Ventana, Tucson, AZ), inhibin (mouse monoclonal, 1:20; Serotec, Raleigh, NC), ACTH (rabbit polyclonal, 1:1600; Dako), calcitonin (mouse monoclonal, 1:50; Dako), serotonin (mouse monoclonal, 1:25; Dako) and somatostatin (rabbit polyclonal, 1:2000; Chemicon, Temecula, CA). When required, proteolytic antigen retrieval was performed by predigestion for 3 minutes with 0.05% Protease VIII (Sigma Chemical Co, St Louis, MO) in a 0.1-M phosphate buffer, pH of 7.8, at 37°C. Cellular conditioning to achieve antigen enhancement (recovery) was performed by using formalin-fixed, paraffin-embedded tissue treated with a buffered citric acid solution and heated for 20 minutes in a calibrated microwave oven. Afterward, the sections were allowed to cool at room temperature in a citric acid buffer solution for 45 minutes before continuing the procedure. Standard positive controls were used throughout, with serum used as the negative control.

### Case Reports

The first patient is a 34-year-old woman with known diabetes mellitus who presented with hypertension, weight gain, hirsutism, muscle weakness, and amenorrhea of 1-year duration. Laboratory evaluation showed elevated cortisol levels but normal catecholamine levels. A mass of the right adrenal gland was identified by ultrasound and magnetic resonance imaging. The patient remained hypertensive (210/125 mm Hg) despite therapy. She underwent surgical resection of the tumor and recovered uneventfully. The hypertension resolved and cortisol levels returned to normal postoperatively. The patient is well with no evidence of disease 4 months after surgery.

The second patient is a 52-year-old woman who presented with flank pain. During clinical evaluation, an arteriogram showed a nodule in the upper pole of the kidney. No other symptoms were reported; in particular, no hypertension, Cushingoid features, or other endocrine abnormalities were noted. At surgery, a mass was identified in the adrenal gland rather than the kidney and adrenalectomy was performed. The kidney was left intact, *in vivo*. The patient had an unremarkable postop-

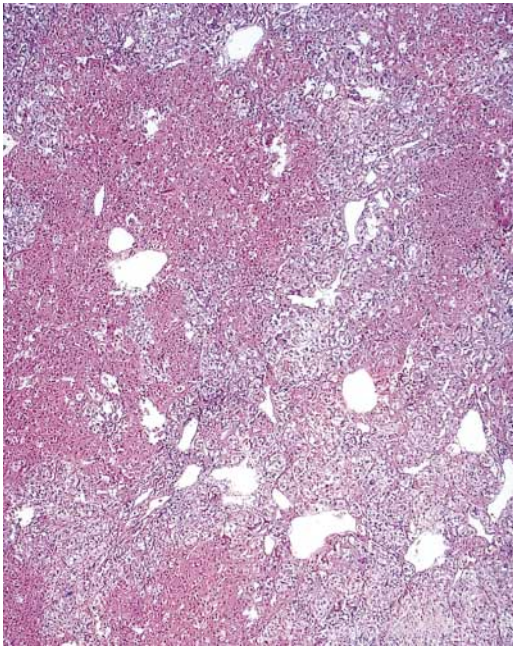
erative course and is alive and well with no sequelae of her disease nearly 30 years following surgery.

### Macroscopic and Microscopic Findings

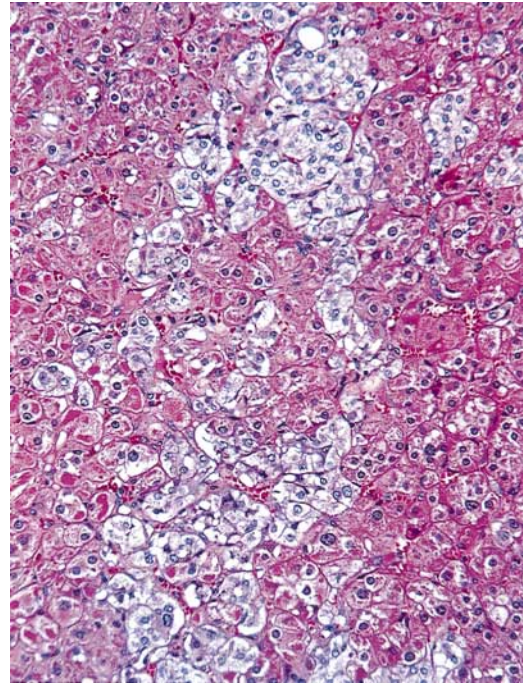
The tumor from patient 1 was an ovoid, circumscribed mass measuring 4.5 cm and weighing 28 gm. There was a rim of uninvolved adrenal tissue. The cut surface was fleshy in consistency and variegated in color, without macroscopic evidence of necrosis, hemorrhage, or cystic degeneration. The tumor was well circumscribed showing an attenuated fibrous capsule with focal areas in which the tumor blended with the remaining uninvolved adrenal tissue. The specimen from patient 2 consisted of an adrenal gland measuring 4.5 cm with a mass at one end measuring 2.5 cm. The lesion was yellowish-orange, well-circumscribed, homogenous, and solid throughout. This tumor had a thick, fibrotic capsule demarcating it from the remaining adrenal gland. Both tumors were composed of two distinct cell populations, adrenal cortical cells, and pheochromocytes, which were intimately admixed in a haphazard arrangement (Figs 1, 2). The adrenal cortical component consisted of enlarged cells with eosinophilic to microvacuolated cytoplasm growing in a solid or diffuse pattern. The nuclei of these cells were round to ovoid with smooth, regular nuclear membranes, homogeneous chromatin, and inconspicuous nucleoli (Fig 2). The pheochromocytes displayed an organoid growth pattern with the "zellballen" or alveolar appearance typically seen in pheochromocytomas. The cells were polygonal with finely granular, basophilic cytoplasm. The ovoid nuclei were central to eccentric, with a stippled chromatin pattern and small nucleoli (Fig 2). No mitotic activity was noted in either cell population. In case 1 the tumor showed an equal distribution of pheochromocytes and adrenal cortical cells in an intimately intermingled arrangement. In case 2 the pheochromocytoma component seemed to predominate but the adrenal cortical component was prominent enough with the cortical cells being enlarged relative to the adjacent uninvolved adrenal cortex and so intimately admixed within the tumor so as not to be considered entrapped cells.

### Immunohistochemical Findings

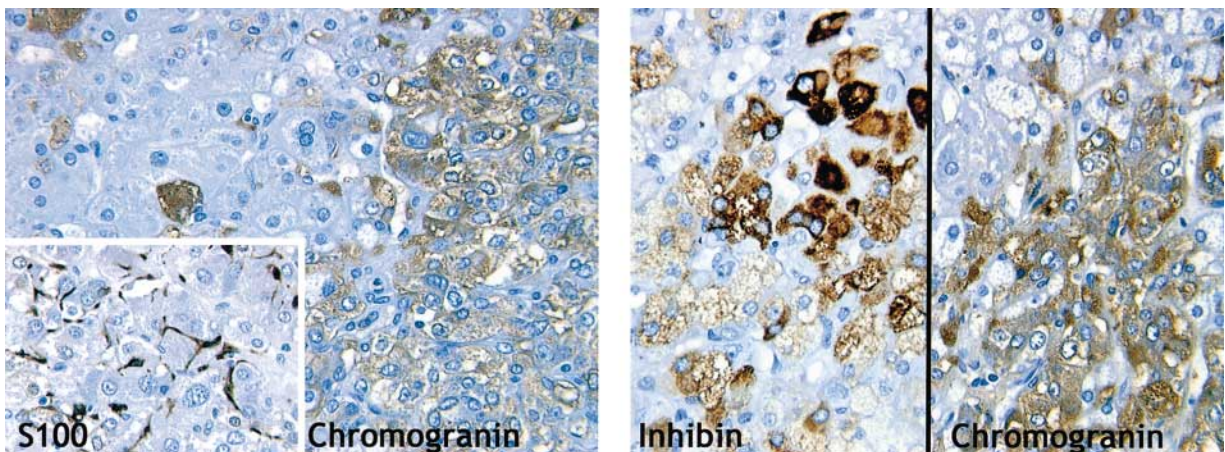
Immunohistochemical evaluation showed the pheochromocytes to be strongly reactive with chromogranin and synaptophysin (Fig 3, left). S-100 protein showed strong nuclear and cytoplasmic immunoreactivity of the supporting sustentacular cells as well as focal reactivity within a few paraganglia cells (Fig 3 left, inset). The adrenal cortical cells showed strong and diffuse reactivity to inhibin (Fig 3, right). No keratin or vimentin reactivity was present in either the adrenal cortical or pheochromocytoma component. ACTH, calcitonin, somatostatin, and serotonin were negative.



**Figure 1.** At low power, one can readily distinguish the eosinophilic adrenal cortical component from the more basophilic pheochromocytoma. The two cell components are intimately admixed within the tumor.



**Figure 2.** The adrenal cortical component is composed of enlarged cells with eosinophilic, slightly granular cytoplasm, round to oval nuclei with smooth regular nuclear membranes and inconspicuous nucleoli. The pheochromocytoma cells display an organoid growth pattern with finely granular, basophilic cytoplasm. The nuclei are larger and ovoid in shape with a stippled chromatin pattern and small nucleoli. The intimate association between the two cell types is again evident in these high-power views.



**Figure 3.** (Left) Immunohistochemical evaluation confirms the pheochromocytoma to be reactive for chromogranin. The adrenal cortical cells are distinctly negative. The inset highlights the S-100 positive sustentacular cells of the pheochromocytoma component. (Right) This split field contrasts the inhibin-positive cells of the adrenal cortical adenoma (left half) with the chromogranin positive cells of the pheochromocytoma (right half).

### Discussion

Mixed tumors involving the cortical and medullary components of the adrenal gland are quite rare. To the best of our knowledge the two cases herein reported represent only the sixth and seventh cases of true mixed corticomedullary tumor of the adrenal gland (Table 1).<sup>1-4</sup> The occurrence of composite tumors of the medullary component (ie, composite pheochromocytomas; ganglioneuroma, ganglioneuroblastoma, or neuroblastoma with pheochromocytoma), are well known. Composite pheochromocytomas with a malignant peripheral nerve sheath tumor component have rarely been described.<sup>13</sup> Several cases of synchronous or concurrent adrenal cortical adenoma and pheochromocytoma arising in the same gland have been described.<sup>6-11</sup> An interesting case of a composite pheochromocytoma-ganglioneuroma with adrenal cortical adenoma arising in the same gland also has been reported.<sup>5</sup> Based on our experience and review of the literature, we use the term corticomedullary mixed tumor to refer specifically to a *single* tumor mass of the adrenal gland composed of an intimately admixed population of both adrenal cortical cells and pheochromocytes which, when examined separately, show histologic features of their respective neoplasms (ie, adrenal cortical adenoma and pheochromocytoma). This essentially eliminates simultaneously concurrent adrenal cortical adenomas and pheochromocytomas arising in the same gland. There is a recent report by Delevaux et al<sup>14</sup> in the French literature of a single tumor mass of the adrenal gland composed of both adrenal cortical cells and pheochromocytes. However, the two components are described as distinctly separate

with a peripherally located adrenal cortical component and centrally located pheochromocytoma component.<sup>14</sup> We were unable to find any similar cases in the literature and did not include this case as a true corticomedullary mixed tumor as it appears to be histologically distinct from our case and the other previously reported cases.

The occurrence of adrenal cortical adenoma with medullary hyperplasia and the converse, pheochromocytoma with adrenal cortical hyperplasia, is also well-known. This distinction is important in making the diagnosis of true mixed corticomedullary tumors. By comparison, the cases described in this report consist of well-demarcated, well-circumscribed tumor masses, easily distinguished from the remaining adrenal cortical and medullary tissue. The tumor shows both components to be intimately admixed in a fairly equal distribution throughout the tumor. The fact that there was no overwhelmingly predominant cell component, that the two components were intricately intermingled throughout the tumor, and that each component examined individually on a cytologic basis was consistent with a neoplasm on its own (ie, adrenal cortical adenoma and pheochromocytoma) leads us to conclude that these neoplasms are true mixed corticomedullary tumors. As best we can tell from their descriptions, we believe that the five previously reported cases as noted in Table 1 also fit our criteria for mixed corticomedullary tumor of the adrenal gland. In fact, the first reported case was also seen at the Armed Forces Institute of Pathology, but is not included in this present report.<sup>2</sup> Follow-up information on this patient indicates

**Table 1. Review of the Literature of Mixed Corticomedullary Tumors of the Adrenal Gland<sup>1-4</sup>**

Case No.	Study	Year Reported	Age (yr)	Gender	Clinical Manifestations
1	Mathison and Waterhouse <sup>2</sup>	1969	39	F	Cushing's syndrome
2	Akai et al <sup>1</sup>	1993	61	F	Hypertension, hyperglycemia
3	Ohta et al <sup>4</sup>	1995	32	M	Cushing's syndrome
4	Michal and Havlicek <sup>3</sup>	1996	NR	NR	NR
5	Michal and Havlicek <sup>3</sup>	1996	NR	NR	NR
6	Current report	2001	34	F	Hypertension, hair loss, amenorrhea
7	Current report	2001	52	F	Flank pain, no other symptoms

Abbreviation: NR, not reported.

that she had no further recurrence of tumor and died of unrelated causes in 1991.

It is difficult to speculate on the origin of these tumors as the adrenal cortex and adrenal medulla have separate and distinct embryologic derivation, structure, and function. The simultaneous occurrence of separate adrenal cortical adenomas and pheochromocytomas is a bit easier to comprehend. Ectopic corticotropin production by a few pheochromocytomas is thought to be a mechanism leading to adrenal cortical hyperplasia,<sup>2</sup> which in turn may develop into an adrenal cortical adenoma. Additionally, catecholamines secreted by pheochromocytomas are thought to stimulate the anterior pituitary to secrete corticotropin,<sup>9</sup> which again may lead to adrenal cortical hyperplasia and/or adrenal cortical adenoma. It is not possible to extrapolate from these theories how a mixed corticomedullary tumor may develop. If both the adrenal cortical and adrenal medullary components of these tumors are neoplastic, which we believe they are, then perhaps the best explanation is to view these lesions as collision, composition, or combination tumors. The rarity of these lesions make further definitive conclusions difficult. Interestingly, none of the case reports, including our two cases, shows pathologic evidence of malignancy in either the adrenal cortical or pheochromocytoma components. This is supported by the clinical outcomes of these patients, who appear to have no significant clinical consequences from their tumors.

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