Juxtaglomerular Cell Tumor

A Clinicopathologic Study of Four Cases and Review of the Literature

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Abstract

We studied 4 new cases of juxtaglomerular cell tumor and compared their morphologic and immunohistochemical features with 2 renal hemangiopericytomas and 5 cutaneous glomus tumors. The juxtaglomerular tumors were resected from 2 males and 2 females (mean age at diagnosis, 23 years). Three patients manifested with severe hypertension. Tumors ranged from 2.2 to 8.0 cm and were well circumscribed. The tumors consisted of solid sheets and nodules of variably sized tumor cells with round, oval, and spindled nuclei alternating with edematous microcystic foci. Nuclear atypia, present in all tumors, was a prominent feature in 2. Mitotic activity was not identified. All cases showed hemorrhage, numerous mast cells, and thick-walled blood vessels. Unusual features included coagulative tumor necrosis, a hemangiopericytoma-like vascular pattern, and hyalinized stroma. All tumors were immunoreactive for CD34 and actin. Ultrastructural analysis revealed the presence of rhomboid-shaped renin protogranules. Patients were treated by partial or radical nephrectomy and followed up for 14 to 48 months. There were no recurrences or metastases. The characteristic clinical and morphologic features of juxtaglomerular cell tumor permit distinction from renal hemangiopericytoma and other renal tumors.

Juxtaglomerular cell tumor of the kidney is a rare renal neoplasm that was first described by Robertson et al[1] in 1967. This tumor typically is found in young adults, with a peak incidence in the second and third decades.[2-4] Patients have hypertension, hyperaldosteronism, and hypokalemia secondary to tumor renin secretion.[5,6] In addition to the typical light microscopic findings, these tumors contain characteristic rhomboid-shaped renin protogranules that are evident by electron microscopy,[7-9] and renin also has been demonstrated by immunofluorescence[5,6,10-12] and immunoperoxidase methods.[13-15] There have been 66 previously reported cases in the English literature, the vast majority as single case reports.[1-62] Because of their rarity, the immunohistochemical profile and morphologic features of this tumor have not been clearly established. We report the clinicopathologic features of 4 cases of juxtaglomerular cell tumor of the kidney that to the best of our knowledge is the largest series of these rare tumors reported in the pathology literature. We reviewed the literature to better define the morphologic and immunohistochemical profile of juxtaglomerular cell tumor. In addition, we compared the immunophenotypic findings of juxtaglomerular cell tumor with 2 renal hemangiopericytomas and 5 cutaneous glomus tumors, both tumors that share morphologic features with juxtaglomerular cell tumor.

Materials and Methods

Four cases of renal juxtaglomerular cell tumor were identified in a search of the Mayo Clinic (Rochester, MN)

Table 1
Antibodies Used in Immunohistochemical Staining

Antibody	Source	Clone	Dilution
Keratin	Roche, Indianapolis, IN	AE1/AE3	1:400
CAM 5.2	Becton Dickinson, San Jose, CA	CAM 5.2	1:50
Smooth muscle actin	DAKO, Carpinteria, CA	1A4	1:150
Muscle-specific actin	DAKO	HHF 35	1:50
Desmin	DAKO	DER 11	1:100
S-100	DAKO	Polyclonal	1:800
HMB-45	DAKO	HMB-45	1:100
CD34	Becton Dickinson	HPCA	1:20
CD31	DAKO	JC/70a	1:200
c-kit	Santa Cruz Technology, Santa Cruz, CA	Polyclonal	1:600
Synaptophysin	ICN, Costa Mesa, CA	SY38	1:40
Chromogranin	Roche	LK2H10	1:1000
Factor VIII	DAKO	Polyclonal	1:1000

Table 2
Clinicopathologic Features of Four Cases of Juxtaglomerular Cell Tumor

Case No./Sex/Age (y)	Hypertension (level)	Symptoms	Tumor Size (cm)	Nephrectomy	Follow-up (mo)
1/F/15	Yes (150/110)	Headache	2.2	Partial	Alive, well (48)
2/M/16	Yes (200/140)	None	3.0	Partial	Alive, well (42)
3/F/44	Yes (190/110)	None	8.0	Radical	Alive, well (24)
4/M/18	Yes (not available)	Pain, vomiting	5.5	Radical	Alive, well (14)

surgical pathology files (1 case) and consultation files (3 cases) for the years 1985 to 2001. Four-micrometer-thick, formalin-fixed, paraffin-embedded sections were stained with H&E for routine microscopic examination, and a mean of 3.5 slides per case (range, 2-5) were examined. Tumors were assessed for growth pattern, nuclear atypia, mitotic activity, and necrosis. Nuclear atypia was defined as greater than 3-fold variation in nuclear size. Mitotic activity was determined by counting 50 consecutive high-power fields (×400). Paraffin blocks were available for all cases for immunohistochemical study. In addition, 2 renal hemangiopericytomas and 5 cutaneous glomus tumors were selected for immunohistochemical analysis. All cases were immunostained with the following antibodies using standard avidin-biotin complex techniques: smooth muscle actin, muscle-specific actin, desmin, cytokeratins (CAM 5.2, AE1/AE3), S-100, HMB-45, CD34, CD31, c-kit, synaptophysin, chromogranin, and factor VIII–related antigen **Table 1**. Slides were processed using a Biotek autostainer (Ventana Medical Systems, Tucson, AZ). Ultrastructural analysis was performed in all cases using glutaraldehyde-fixed tissues. Electron microscopy was performed on 3 cases at the Mayo Clinic and at 1 outside submitting institution.

Information about clinical manifestations and follow-up was obtained by reviewing the medical records or by correspondence with outside physicians.

Results

Clinical Features

There were 2 male and 2 female patients **Table 2**. The mean age at initial examination was 23 years (range, 15-44 years), and 3 of the tumors occurred in patients younger than 20 years. Three patients had severe hypertension (mean systolic/diastolic blood pressure, 180/120 mm Hg) at diagnosis that in 1 case was accompanied by frequent headaches. The fourth patient had left flank pain, nausea, and vomiting at initial examination, but also had a 6-year history of hypertension that had been well controlled with medication. Two patients were treated with radical nephrectomy and 2 with partial nephrectomy. Patients were followed up for 14 to 48 months (mean, 32 months), and no tumors recurred or metastasized. One patient continues to have mild hypertension that is well controlled with antihypertensive therapy, and the remaining patients are normotensive postoperatively.

Gross Findings

Gross features were available from the surgical pathology reports in all cases. Two of the tumors were located in the right kidney and 2 in the left kidney. The tumors ranged in size from 2.2 to 8.0 cm (mean, 4.7 cm). Gross examination revealed that all tumors were solitary, well circumscribed, and partially surrounded by a fibrous

Image 1 Typical gross appearance of juxtaglomerular cell tumor showing a well-circumscribed tumor with a hemorrhagic cut surface.

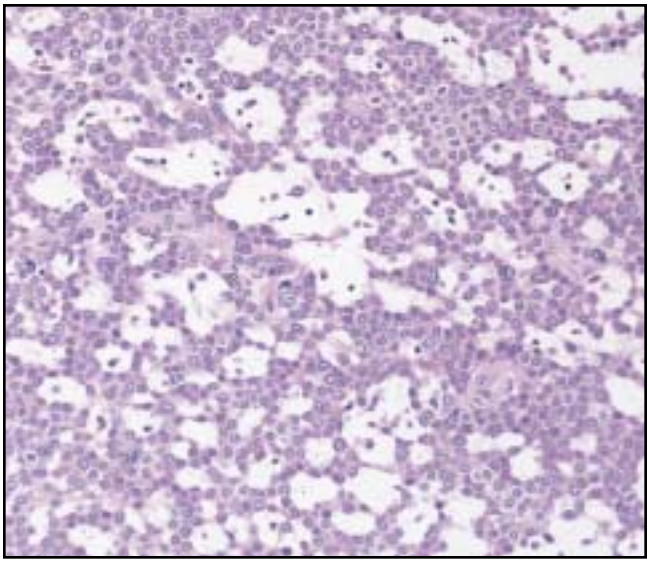

Image 2 Juxtaglomerular cell tumor exhibiting the microcystic pattern that was present in all cases (H&E, ×40).

capsule **Image 1**. The cut surface was yellow to gray-tan. Hemorrhage was present in all cases and was extensive in one tumor. One of the cases was partially cystic. Grossly, necrosis was not present in any case, nor was there invasion of the renal vein, perirenal fat, or renal pelvic fat.

Histologic Findings

The tumors were well circumscribed and at least partially invested by a thick fibrous capsule. Low-power examination showed that 2 tumors had a multinodular appearance with incomplete fibrous septa separating large nodules of tumor cells. In all tumors, there were foci in which individual cells were separated by intercellular edema imparting a microcystic pattern **Image 2**. Stroma was scanty and when present typically consisted of a hypocellular edematous fibrous tissue containing occasional fibroblasts and scattered mast cells. One case contained a prominent eosinophilic hyalinized stroma that surrounded tumor cells individually and in small clusters **Image 3**.

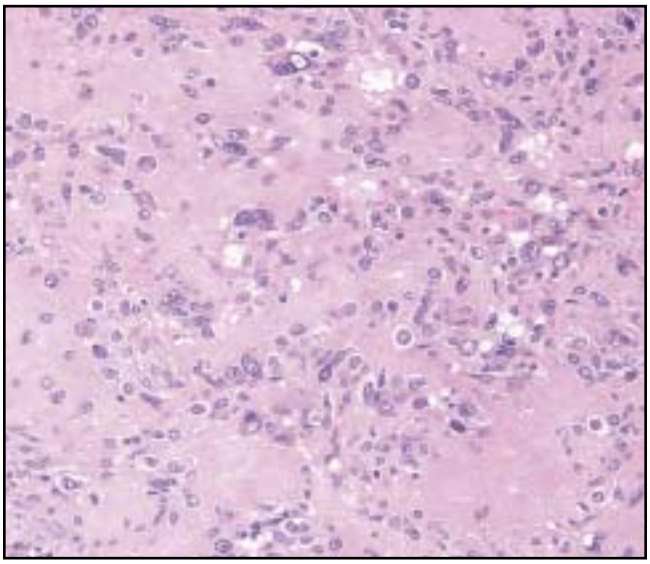

Image 3 Juxtaglomerular cell tumor with abundant hyalinized stroma separating small clusters of tumor cells. Note the presence of nuclear atypia (H&E, ×200).

Three tumors (cases 1-3) consisted of polygonal to elongated cells with variable amounts of lightly eosinophilic cytoplasm and ill-defined cell borders. The nuclei were variable in size and were round to oval to spindled with inconspicuous nucleoli **Image 4A**. The other tumor (case 4) consisted predominantly of uniform polygonal cells with a moderate amount of eosinophilic cytoplasm, well-defined cell borders, and round, uniformly spaced nuclei, imparting a strong resemblance to glomus tumor **Image 4B**. All tumors exhibited nuclear atypia that was a prominent feature in 2 cases **Image 5**. Mitotic activity was not identified in any of the tumors with examination of 50 high-power fields (×400) over multiple tissue sections. Focal coagulative tumor necrosis was identified in 1 case that showed otherwise typical morphologic features **Image 6**. Three tumors contained entrapped renal tubules at the periphery of the tumor **Image 7**. In addition, numerous mast cells were scattered throughout the tumors at a ratio of approximately 1 mast cell for every 10 tumor cells.

The vasculature was well developed in all cases and consisted predominantly of uniformly distributed thin-walled vessels. Thick-walled blood vessels also were present and often

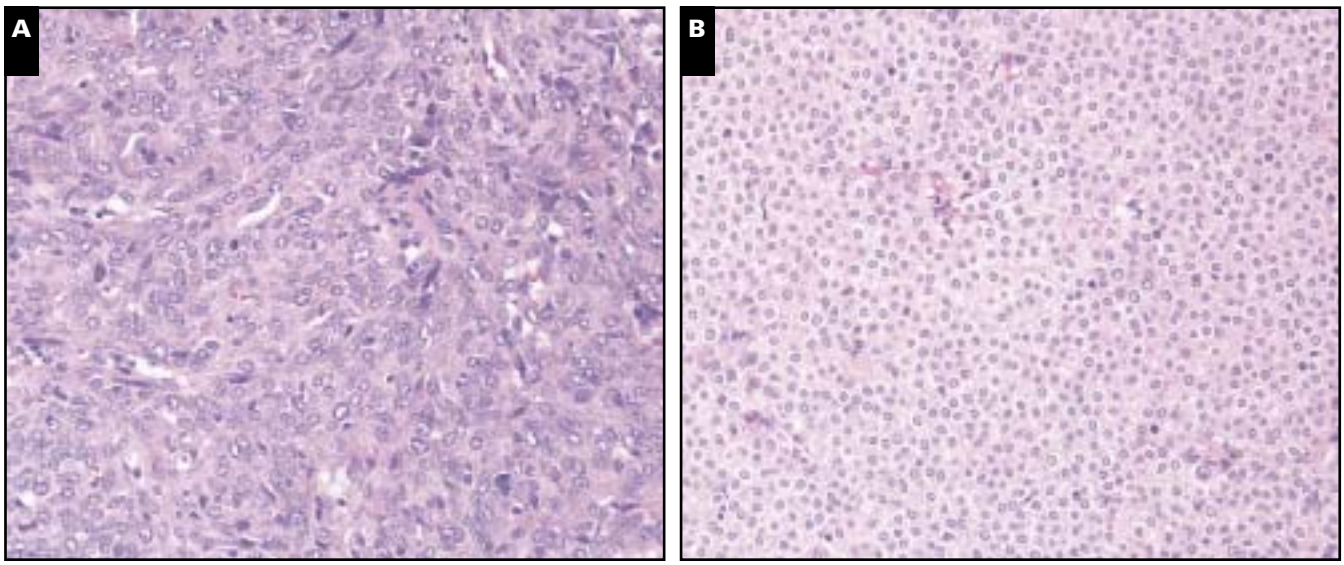

Image 4 Two examples of juxtaglomerular cell tumor. **A**, Case 1 showing tumor cells with oval to spindled nuclei and indistinct cell borders. This was the predominant growth pattern in 3 cases (H&E, ×200). **B**, Case 4 consisted almost entirely of uniform polygonal cells with round, evenly spaced nuclei and well-defined cell borders (H&E, ×200).

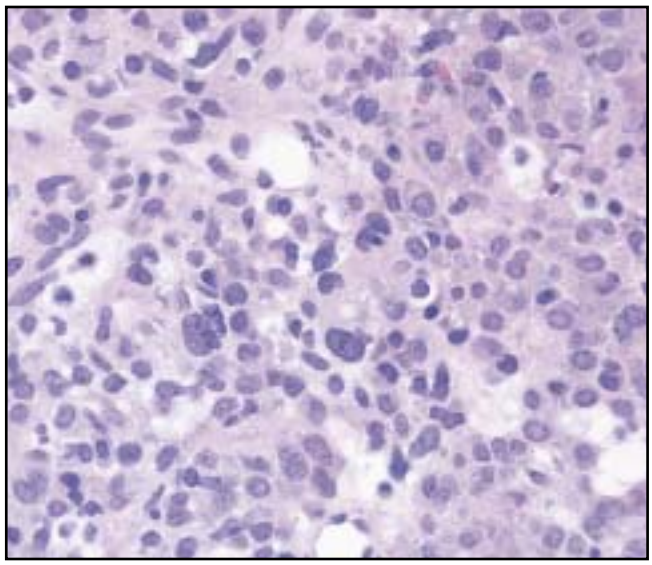

Image 5 Juxtaglomerular cell tumor with prominent nuclear atypia that was not associated with mitotic activity (H&E, ×300).

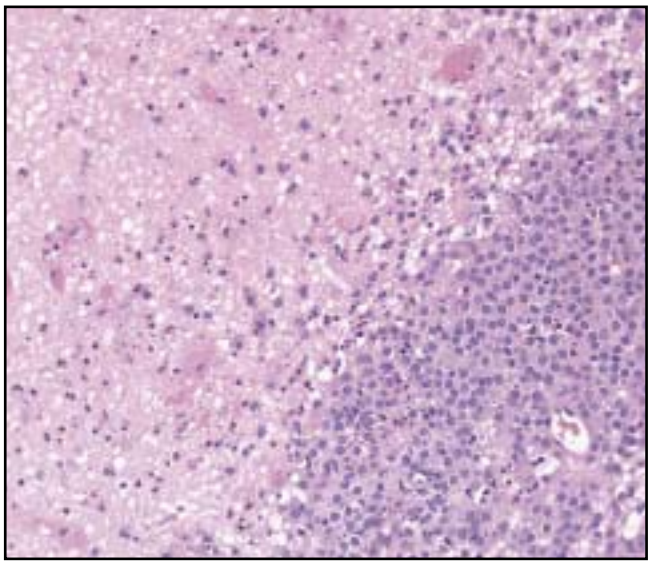

Image 6 Focus of coagulative tumor necrosis in an otherwise typical juxtaglomerular cell tumor (H&E, ×40).

were grouped in small clusters **Image 8A**. Hyalinization of the walls of these thick-walled vessels was observed in 2 cases. One case exhibited an irregular branching vascular pattern resembling hemangiopericytoma **Image 8B**. All cases showed areas of hemorrhage that varied from focal to extensive.

Immunohistochemical Findings

Immunohistochemical studies were performed in all cases **Table 3**. All tumors were positive for actin **Image 9**. Of 4 cases, 3 were strongly positive for muscle-specific actin and smooth muscle actin, with more than 25% of the cells staining in each case. One tumor exhibited only focal staining (<5% of the neoplastic cells were positive) for smooth muscle actin. All cases showed strong and diffuse positivity for CD34 **Image 10**. Immunohistochemical stains for the cytokeratin intermediate filaments were negative but highlighted the entrapped renal tubules at the periphery of 3 tumors. CD31 and factor VIII–related antigen also were negative but stained the endothelial cells of the numerous thin-walled vessels. The numerous mast cells showed cytoplasmic positivity for c-kit.

Two cases of renal hemangiopericytoma and 5 cases of cutaneous glomus tumor were stained with the same panel of

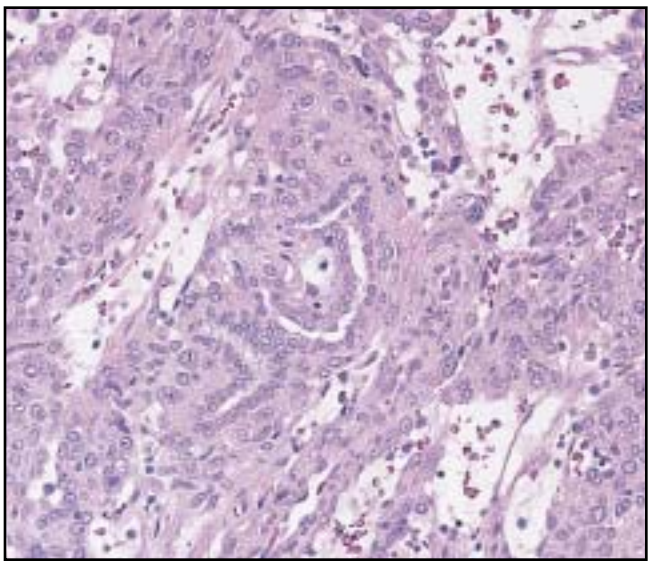

Image 7 Branching tubules lined by bland cuboidal epithelium were present at the periphery of 3 of the tumors (H&E, ×240).

Table 3
Immunohistochemical Findings in Juxtaglomerular Cell Tumors, Glomus Tumors, and Renal Hemangiopericytoma*

	Juxtaglomerular Cell Tumor (n = 4)	Glomus Tumors (n = 5)	Renal Hemangio-pericytoma (n = 2)
CAM 5.2	0 (0)	0 (0)	0 (0)
AE1/AE3	0 (0)	0 (0)	0 (0)
Smooth muscle actin	4 (100)	5 (100)	0 (0)
Muscle-specific actin	3 (75)	5 (100)	0 (0)
Desmin	0 (0)	0 (0)	0 (0)
S-100	0 (0)	0 (0)	0 (0)
HMB-45	0 (0)	0 (0)	0 (0)
CD34	4 (100)	3 (60)	0 (0)
CD31	0 (0)	0 (0)	0 (0)
Factor VIII	0 (0)	0 (0)	0 (0)
c-kit	0 (0)	0 (0)	0 (0)
Synaptophysin	0 (0)	0 (0)	0 (0)
Chromogranin	0 (0)	0 (0)	0 (0)

* Data are given as number (percentage).

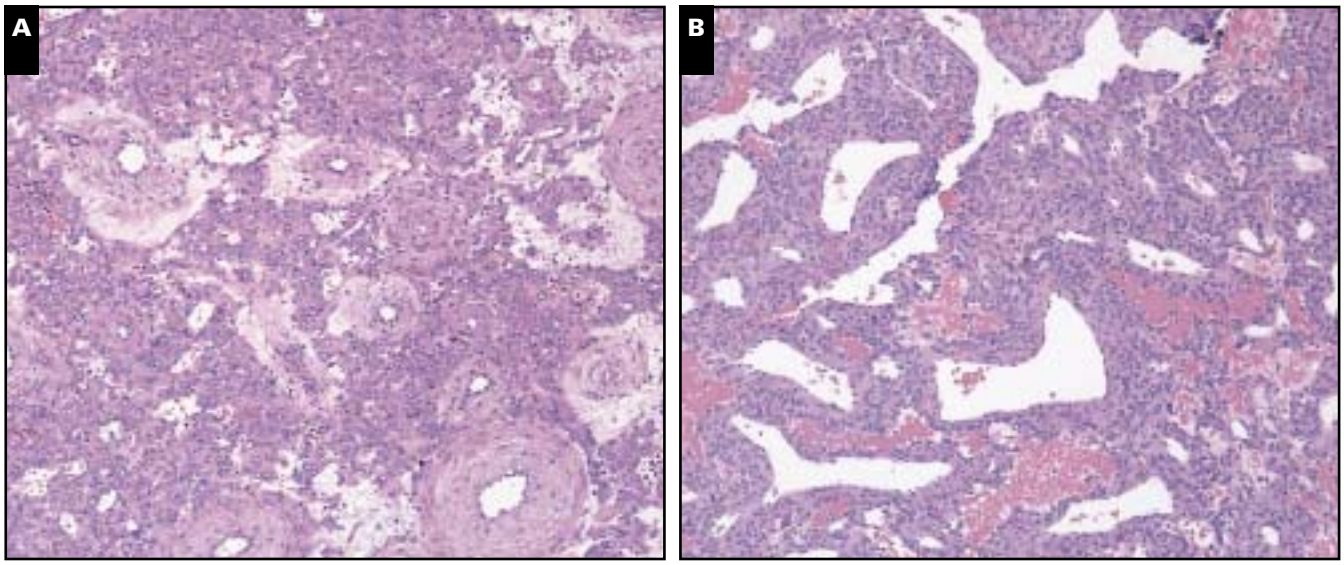

Image 8 Vascular patterns of juxtaglomerular cell tumor (JGCT). **A**, Clusters of thick-walled blood vessels were present in all tumors (H&E, ×40). **B**, JGCT with branching, gaping vasculature similar to that seen in hemangiopericytoma (H&E, ×40).

antibodies (Table 3). Both cases of renal hemangiopericytoma were negative for all antibodies tested, including muscle-specific actin, smooth-muscle actin, and CD34. All 5 cases of glomus tumor were strongly positive for both smooth-muscle actin and muscle-specific actin, and 3 of 5 glomus tumors also showed strong staining for CD34.

Ultrastructural Findings

Electron microscopic examination revealed the presence of polygonal cells with round to oval nuclei containing dispersed chromatin. The cytoplasm contained abundant rough endoplasmic reticulum and prominent Golgi apparatuses. In all cases, rhomboid-shaped renin protogranules were identified in the cytoplasm of the tumor cells **Image 11**.

Discussion

Juxtaglomerular cell tumor is a rare benign renal neoplasm, and our study confirms that these tumors have characteristic clinical, morphologic, immunohistochemical, and ultrastructural features. Our study of 4 cases is, to the

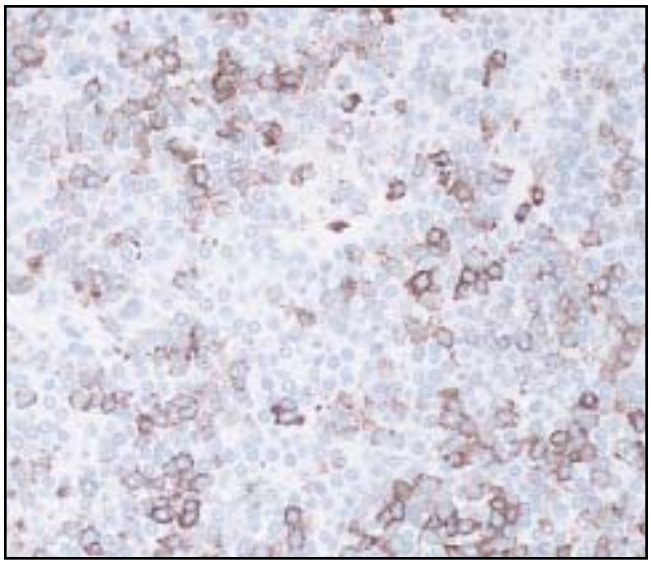

Image 9 Juxtaglomerular cell tumor (JGCT) showing strong cytoplasmic positivity for smooth muscle actin in many of the tumor cells. This staining pattern was typical of JGCT in that only a portion of the tumor was positive for actin (smooth muscle actin, ×100).

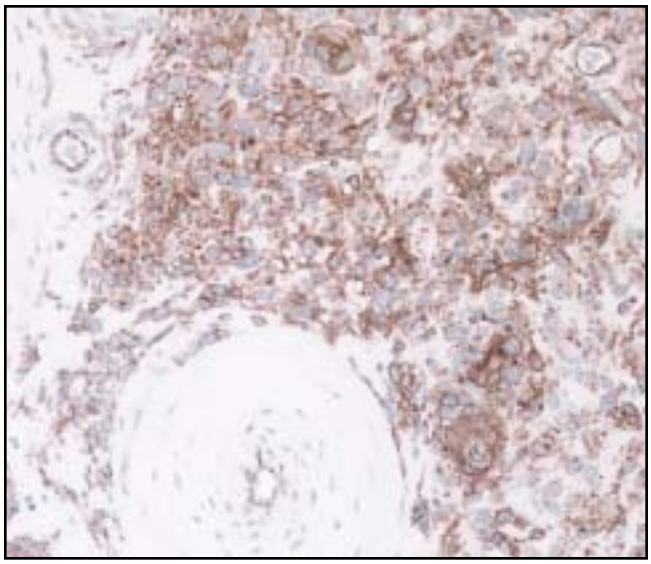

Image 10 Juxtaglomerular cell tumor showing strong diffuse positivity (CD34, ×200 magnification).

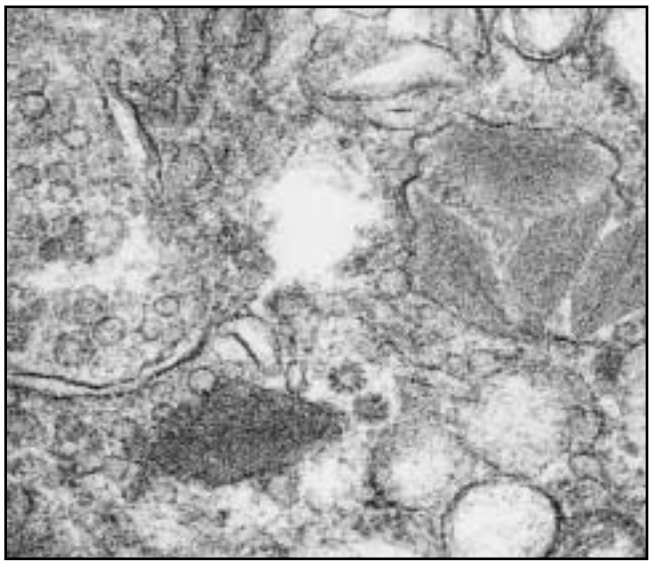

Image 11 Electron microscopy of juxtaglomerular cell tumor demonstrating the characteristic cytoplasmic rhomboid-shaped protogranules (×45,000).

best of our knowledge, the largest series reported in the pathology literature. The clinicopathologic features of the previously reported 66 cases are summarized in **Table 4**.[1-62] Clinically, these tumors typically occur in young adults (mean age, 26.8 years) with a slight female predominance (F/M ratio, 1.9:1). In our series, the mean age at diagnosis was 23 years, and 3 cases occurred in patients younger than 20 years. Despite the tendency to occur in young adults, these tumors have been reported in children and older adults. Thirteen reported cases of juxtaglomerular cell tumor have occurred in adults older than 40 years, including our case diagnosed in a 44-year-old woman, and 3 tumors have been reported in children younger than 10 years.

Patients almost invariably are hypertensive at initial examination due to renin secretion by the tumor. This elevated plasma renin activity results in hyperaldosteronism with subsequent hypokalemia in the majority of patients.[15,16,31] The hypertension may be present for several years before the discovery of the renal tumor,[7,12,20,40,56] and in 1 reported case, hypertension was present for 17 years before diagnosis.[46] There does not seem to be a correlation between tumor size and duration or degree of hypertension.[2] Despite the near constant association of juxtaglomerular cell tumor and hypertension, there is a single case report of a "nonfunctioning" juxtaglomerular cell tumor not associated with hypertension that was discovered incidentally during an ultrasound examination.[27,35] Other commonly reported symptoms include headache, polyuria, nocturia, dizziness, and vomiting.

All reported cases of juxtaglomerular cell tumor have behaved in a benign manner, and no recurrences or metastases have occurred with either radical or partial nephrectomy. There have not been any reports of hypertensive crises precipitated by surgical manipulation and no reported cases of surgical morbidity or mortality. Approximately 10% of patients are mildly hypertensive following resection of the tumor, although the hypertension is always markedly decreased from preoperative levels.[17,20,31,51,61] Bonsib and

Table 4
Clinicopathologic Features of the 66 Reported Cases of Juxtaglomerular Cell Tumor

Characteristic	Previously Reported (n = 66)	Current Series (n = 4)
Female/male	1.9:1	1:1
Mean (range) age (y)	26.8 (6-69)	23.3 (15-44)
Mean systolic/diastolic blood pressure (mm Hg)	195/125	180/120
Diagnosed preoperatively	41/55 (75%)	2/4 (50%)
Mean (range) tumor size (cm)	3.1 (0.8-9.0)	4.7 (2.2-8.0)
Mean (range) follow-up (mo)	34 (3-204)	32 (13-48)
No. (%) with postoperative hypertension	5/60 (8)	1/4 (25)

Hansen[20] described a patient who, in addition to long-standing severe hypertension, was noted to have renal insufficiency on initial examination. Despite tumor resection, the patient eventually required renal transplantation owing to progressive renal failure.[20] Gherardi et al[30] reported a case of a juxtaglomerular cell tumor that was initially discovered at autopsy in a patient who died of massive intracerebral hemorrhage secondary to severe hypertension. To our knowledge, this is the only case of juxtaglomerular cell tumor that directly resulted in patient death.

Gross examination of these neoplasms reveals a well-circumscribed cortical mass confined to the kidney. Most tumors are less than 4.0 cm in diameter, but tumors up to 9 cm in diameter have been reported.[41] The mean tumor size in our series was 4.7 cm, and the largest tumor was 8 cm in diameter. The cut surface of these neoplasms usually is yellow to tan-gray, with areas of hemorrhage. Interestingly, despite the patient's hypertension and the tumor's vascularity and propensity for intratumoral hemorrhage, only 1 patient was diagnosed as a result of spontaneous intratumoral hemorrhage.[25]

Microscopically, juxtaglomerular cell tumors are well circumscribed and partially or fully surrounded by a thick fibrous capsule. Although not identified in our series, capsular invasion has been described[13] but does not correlate with aggressive behavior. The tumors are composed of variably sized cells with round, oval to spindled nuclei and variable amounts of lightly eosinophilic cytoplasm. The tumors contain a prominent vasculature that consists of numerous small, thin-walled vessels and clustered thick-walled vessels that may be hyalinized. Entrapped renal tubules were identified in 3 of our cases and have been identified in approximately half of the reported cases.[58] All cases in our study showed nuclear atypia that was a prominent feature in 2 cases. The atypia was not accompanied by mitotic activity. Cytologic atypia associated with mitotic activity has been described in juxtaglomerular cell tumors in some cases.[20]

Immunohistochemically, all of our cases showed actin positivity, which stained only a subset of the tumor cells. These results are consistent with those observed by Kodet et al[13] and Bonsib and Hansen[20]; however, our study is the first to demonstrate CD34 immunostaining in juxtaglomerular cell tumors, which was strong and diffuse in all of our cases. Juxtaglomerular cell tumors do not stain for cytokeratin, chromogranin, synaptophysin, HMB-45, S-100, c-kit, CD31, factor VIII, or desmin. The immunohistochemical profile of juxtaglomerular cell tumors is identical to that of glomus tumors, with both neoplasms exhibiting actin and CD34 positivity.

In juxtaglomerular cell tumors, the cell of origin is the modified smooth muscle cell that comprises the vascular component of the juxtaglomerular apparatus. This cell exhibits ultrastructural features of both endocrine and smooth muscle cells and, therefore, has been termed a *myoendocrine* cell.[63] In addition to the rhomboid-shaped renin protogranules, smooth muscle microfilaments have been observed in the cytoplasm of several cases.[2,18,23] Similarly, the glomus cell is a modified smooth muscle cell localized within the adventitia of a specialized dermal arteriovenous anastomosis involved in temperature regulation. Although glomus and juxtaglomerular cells share an origin from smooth muscle cells, glomus cells seem to lack an endocrine function.

Several histologic features identified in the present study are worth noting owing to the potential for confusion with other renal neoplasms. One of our cases showed a prominent hemangiopericytoma-like vascular pattern with large, branching, thin-walled vessels. Originally, juxtaglomerular cell tumors were classified as hemangiopericytomas because of their prominent vascular network.[13,15,27] However, renal hemangiopericytomas are cellular tumors with characteristic and consistent gaping, thin-walled vessels surrounded by spindled cells with oval nuclei and scant cytoplasm. Hemangiopericytomas lack the thick-walled vessels and polygonal cells with abundant eosinophilic cytoplasm seen in juxtaglomerular cell tumors.[64-66] In addition, hemangiopericytomas lack immunoreactivity for actin. Although CD34 positivity has been described in a few cases of hemangiopericytoma, this finding is suggestive of solitary fibrous tumor.[64,65,67] Importantly, hemangiopericytoma typically does not cause hypertension, a key feature of the juxtaglomerular cell tumor.[66,68]

The presence of thick-walled, hyalinized blood vessels; polygonal eosinophilic cells; and actin positivity in juxtaglomerular cell tumor mimics epithelioid angiomyolipoma.[69-71] Juxtaglomerular cell tumors lack an intermingling adipose tissue component, although Bonsib and Hansen[20] described 1 juxtaglomerular cell tumor with a very small component of fat. Juxtaglomerular cell tumors also lack the fascicular

growth pattern and muscular differentiation of angiomyolipoma. Immunohistochemically, juxtaglomerular cell tumors are negative for HMB-45, a finding that is typical of angiomyolipoma.[20,69-71]

The nuclear atypia, prominent vascularity, entrapped tubules, and focal necrosis of juxtaglomerular cell tumor could result in an erroneous diagnosis of renal cell carcinoma. Juxtaglomerular cell tumors also can display a papillary architecture mimicking papillary renal cell carcinoma.[58] Hypertension is present in approximately a third of patients with renal cell carcinoma, and renin has been identified in the cells of renal cell carcinoma.[72,73] Although there are superficial similarities of juxtaglomerular cell tumor and renal cell carcinoma, the histologic features of the tumors are sufficiently distinctive to allow separation. If necessary, immunohistochemical analysis can readily differentiate these tumors.

Juxtaglomerular cell tumors are rare benign renal neoplasms that typically occur in young adults who have severe hypertension at initial examination. The tumors have characteristic pathologic features, including actin and CD34 positivity, and the presence of renin crystals that is revealed by ultrastructural analysis. Most of these tumors are readily diagnosed owing to their characteristic clinical and morphologic features; however, in cases with atypical clinical manifestations or histologic features, immunohistochemical demonstration of actin and CD34 positivity in conjunction with cytokeratin negativity will lead to the correct diagnosis.

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