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Renal Medullary Carcinoma

The Seventh Sickle Cell Nephropathy

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Over the last 22 years, we have encountered 34 examples of a highly aggressive neoplasm with a microscopic morphology that is highly predictive of finding sickled erythrocytes in the tissue. With the exception of one patient, all are believed to have had sickle cell trait or, in one case, hemoglobin SC disease. These 33 patients are the subject of this report and, where their race was known, they were all blacks between the ages of 11 and 39 years. Between the ages of 11 and 24 years, males predominated by 3 to 1. Beyond age 24, however, the tumors occurred equally in men and women. The dominant tumor mass was in the medulla and ranged from 4 to 12 cm in diameter. Mean size was 7 cm; median, 6 cm. Peripheral satellites in the renal cortex and pelvic soft tissues, as well as venous and lymphatic invasion, were usually present. The lesions exhibited a reticular, yolk sac–like, or adenoid cystic appearance, often with poorly differentiated areas in a highly desmoplastic stroma admixed with neutrophils and usually marginated by lymphocytes. The tumors had usually metastasized when first discovered, and none was confined to the kidney at the time of nephrectomy. The mean duration of life after surgery was 15 weeks. These tumors probably arise in the calyceal epithelium in or near the renal papillae, the same site that produces the more familiar picture of unilateral hematuria in patients with sickle cell trait. We have concluded that renal medullary carcinoma represents another example of renal disease associated with sickle cell disorders. The other six are unilateral hematuria, papillary necrosis, nephrotic syndrome, renal infarction, inability to concentrate urine, and pyelonephritis.

Key Words: Renal carcinoma—Sickle cell trait—Renal pelvic carcinoma—Collecting duct carcinoma—Hemoglobin S disorders—Renal medulla.

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Berman, in 1974, enumerated the six nephropathies seen in patients with sickle cell disease (SCD) or trait (SCT) (1). All of them could be attributed to the vascular stagnation associated with the sharp-pointed sickle cells or the reduced oxygen pressure and interstitial hypertonicity of the renal medulla that are associated with them. Gross hematuria, the most common, occurs more often with the trait and is chiefly due to bleeding immediately beneath the renal pelvic epithelium. The second nephropathy is papillary necrosis. Nephrotic syndrome, the third, is poorly understood, but a form of membranoproliferative glomerulonephritis or focal glomerular sclerosis are most often described. Renal infarction, the fourth, is likely precipitated by vascular stagnation. An inability to concentrate the urine is ascribed to alterations of the countercurrent mechanism, and pyelonephritis, the sixth, presumably is due to an increased susceptibility to bacterial growth.

In the middle or late 1970s, we began to suspect that there might be a seventh in the form of a highly aggressive neoplasm. Carcinoma of the renal pelvis is a very uncommon tumor in patients younger than 40 years, and it was becoming obvious that a significant number of these were in patients who were black. Also, the more or less repetitive character of the tumor histology in these patients was such that one could usually anticipate when a search of the peripheral renal tissue would reveal sickled erythrocytes.

A study of this group of tumors is the subject of this article, and the objective was to determine whether or not young patients with sickle cell disorders may develop carcinomas with specific morphologic features.

MATERIALS AND METHODS

All cases coded as renal pelvic carcinoma in patients younger than 40 years since 1969 were re-

trieved from the files for initial review. There were 55 cases. Twenty-one of these were typical examples of transitional cell carcinoma, and the other 34 presented the microscopic features that prompted this study. Except for one case with one microscopic slide, we had available for study from four to 22 slides, and for most cases, there were also paraffin blocks.

In addition to hematoxylin and eosin (H&E)-stained slides, a variable number of cases were studied with mucicarmine or periodic acid–Schiff (PAS)-diastase, keratin, epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA).

The immunostains were prepared following the biotin–avidin–peroxidase method developed by Hsu (6), and the reaction product was visualized with diaminobenzidine (DAB). Pooled monoclonal antibodies AE1 and AE3, recognizing a wide spectrum of acidic and basic subfamilies of keratin, were obtained from Boehringer, Mannheim (Indianapolis, IN, U.S.A.) and applied at a dilution of 1:1,280. Monoclonal antibody for EMA and polyclonal antibody to CEA were obtained from Dakopatts (Carpinteria, CA, U.S.A.) and both applied at dilutions of 1:1,280. Negative controls were nonimmune mouse and rabbit serum.

RESULTS

The 21 cases of transitional cell carcinoma were classified as papillary (14 patients) or infiltrating (seven patients). Twelve of these were men and 9 were women. The ages of this group ranged from 18 to 39 years with a progressively increasing incidence through the 20s and 30s. In 13 of the 21, the patient's race was known: 12 were white, and one was black. The latter patient was a 34-year-old man with a papillary and infiltrating transitional cell carcinoma, grade III, and, interestingly, he had sickled erythrocytes. There was no reason to suspect analgesia abuse or Balkan nephropathy in any of these patients, and they were not further studied.

One patient, a 31-year-old white woman, had a renal tumor indistinguishable from those to be described, but she did not have sickled erythrocytes. We are aware that she died of her disease, but she is not included in the following data. This case obviously rules out the possibility that renal medullary carcinoma is seen only in patients with hemoglobin S disorders.

Thirty-three patients were identified as having the type of renal tumor under study. Their ages ranged from 11 to 39 years (Fig. 1). The median and mean ages were 21 and 22 years, respectively. Twenty-two were males, and 11 were females. In females, ages ranged from 16 to 39, and males, 11 to 35. After age 25, the sexes were equally affected, but before that, males predominated by 3:1. To date, we have not seen carcinomas of this type in older patients. With respect to race, this information was not provided for eight patients, but the other 25 were black. Nine patients were known to have sickle cell trait; one had hemoglobin SC disease. In all patients, drepanocytes were identified microscopically.

The presenting symptoms were available for 25 patients (Table 1), and most commonly these consisted of gross hematuria (15 cases) or abdominal or flank pain (12 cases). In one instance, the hematuria was described as massive. Significant weight loss had occurred in six patients, and this ranged from 15 to 40 pounds over periods of 1 to 5 months. Three had a palpable mass, and one had an enlarged cervical lymph node. Information about the duration of the presenting symptoms was available for

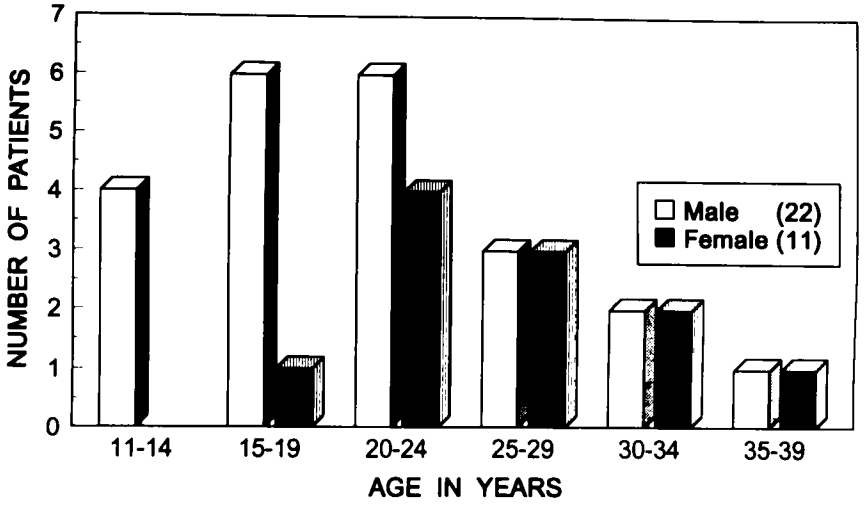

FIG. 1. Renal medullary carcinoma: age and sex of patients.

TABLE 1. *Renal medullary carcinoma: clinicopathological features*

Age & sex	Presenting symptoms	Duration of symptoms	Extent of tumor at diagnosis	Survival after diagnosis
20 M	Pain, fever, wt loss	6 wks	Perinephric[a] and rt pleural effusion	3 wks
16 M	Hematuria	3 mos	Nodes,[b] RV	?
20 F	Hematuria, pain	?	Nodes	?
11 M	Hematuria	3 mos	Nodes, adrenal	4 mos
17 M	?	?	Nodes	4 wks
27 M	Fever, wt loss	4 wks	Cervical node	4 mos
15 M	Hematuria, pain	?	Lung mets 1 wk postop	?
16 M	Palpable mass	?	Nodes, liver	4 mos
21 M	?	?	Perinephric disease	?
22 F	?	?	Nodes	~12 mos
20 M	?	?	Nodes, peritoneum	?
19 M	Hematuria	?	Nodes, massive retroperitoneal disease	4 mos
21 M	Hematuria, wt loss, pain	5 mos	Liver, extensive perinephric disease	8 mos
12 M	Hematuria, pain	5 wks	Nodes, liver, adrenal	2 mos (lung mets)
27 M	Hematuria	?	Nodes	4 mos (lung mets)
19 M	Hematuria	1 wk	Nodes, adrenal	5 mos
32 M	?	?	Perinephric disease	6 wks, (lung and peritoneal mets)
35 M	?	?	Nodes	9 wks, extensive retroperitoneum
21 M	Nausea, vomiting, pain	?	Nodes, liver, lungs	?
14 M	Wt loss, pain	3 mos	Pericaval, lungs	10 wks
21 F	Massive hematuria, pain	?	Nodes, RV, mesentery	8 wks, (general mets: lungs, liver, thyroid, others)
33 M	Hematuria	?	Perinephric disease	3 mos
23 F	?	?	Nodes, lung	?
16 F	Wt loss, fever	2 mos	Nodes, adrenal, lungs	?
23 M	Pain	2 mos	Nodes, liver	3 mos
29 F	Hematuria, mass	?	Nodes, adrenal	7 wks, (lung, liver mets)
27 M	Weight loss	4 mos	Nodes, adrenal, lungs	3 mos
11 M	Pain	2 mos	Nodes, RV, lungs, liver	?
28 F	Pain, mass	2 mos	Nodes, RV, adrenal	?
39 F	?	?	Nodes	?
34 F	Hematuria, pain, acute retention	"Few weeks"	Extensive retroperitoneal disease	?
32 F	Hematuria	?	Nodes	?
27 F	Hematuria	?	Nodes, adrenal, lungs	?

Wt, weight; RV, renal vein; METS, metastasis.
[a] Perinephric refers to soft tissue peripheral to the kidney or renal pelvis.
[b] Nodes refers to those in or near renal hilum and adjacent retroperitoneum.

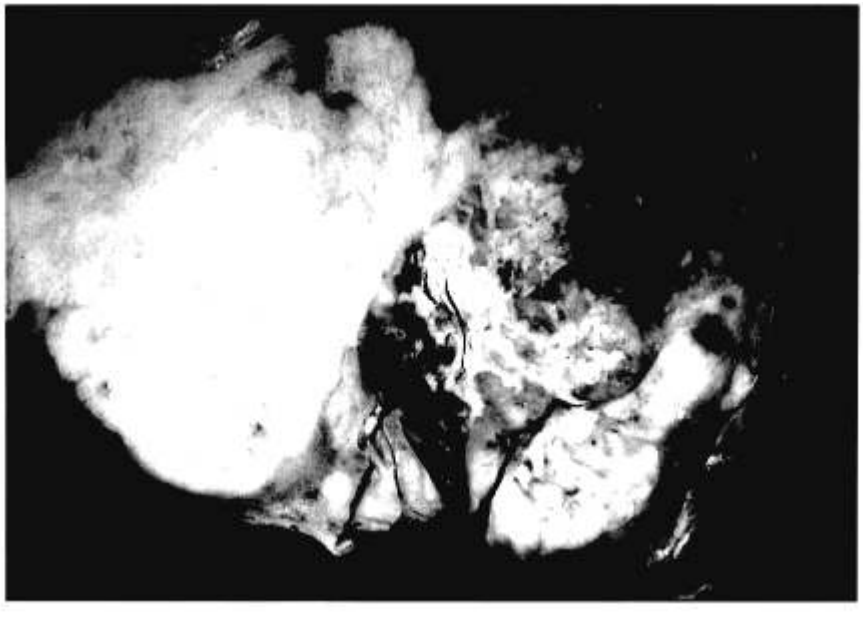

FIG. 2. Renal medullary carcinoma, 21-year-old man. Note irregular tumor margin and extension into perinephric tissue.

FIG. 3. Renal medullary carcinoma, 27-year-old woman. The tumor–renal margins are blurred because of interstitial growth pattern and associated inflammation.

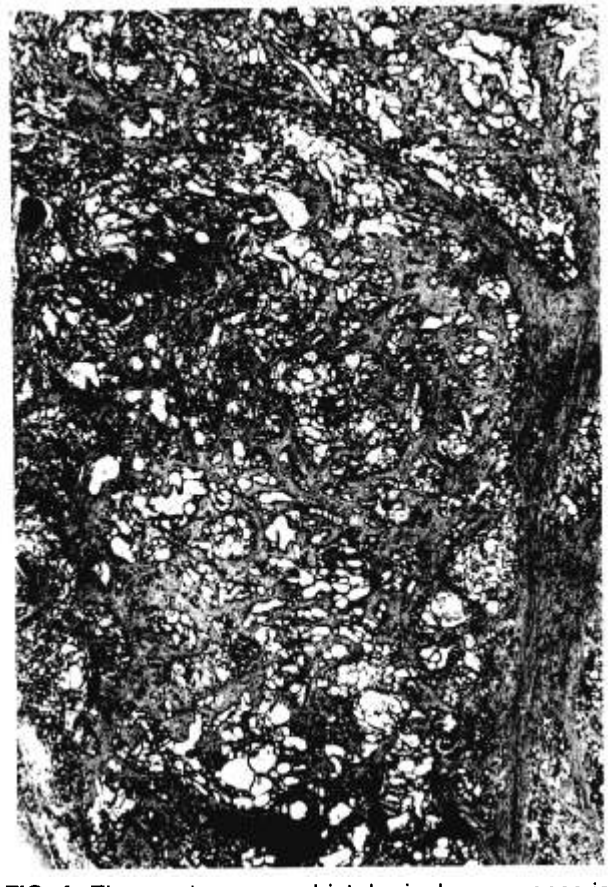

FIG. 4. The most common histological appearance is a loose, reticular pattern of growth reminiscent of the testicular yolk sac tumor.

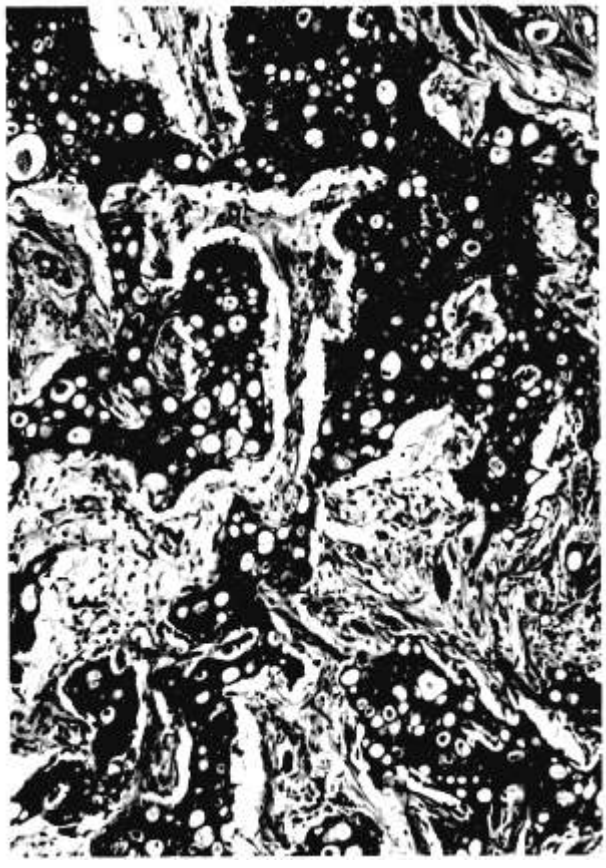

FIG. 5. A more compact adenoid–cystic growth pattern is usually associated with the reticular morphology shown in Fig. 4.

13 patients. It ranged from 1 to 20 weeks with a median and mean both of 8 weeks.

PATHOLOGICAL FINDINGS

Gross Pathology

The tumor was in the right kidney in 23 cases, in the left in eight, and the location of the other two is unknown. They were ill-defined or poorly circumscribed lesions occupying most or a large part of the renal parenchyma, with extension or protrusion into the calyces or pelvis (Fig. 2). Most exhibited smaller satellite nodules in the renal cortex, in addition to extension into the perinephric and peripelvic soft tissue (Fig. 3). The best composite description would be of a lobulated neoplasm occupying chiefly the renal medulla, firm or rubbery, tan to gray, with variable hemorrhage and necrosis. Several were said to be mucoid. Tumor size was given for 24 tumors and ranged from 4 to 12 cm, with 18 between 6 and 8 cm. Mean size was 7 cm; median, 6 cm. In two cases, the dominant medullary tumor mass was cavitary.

Microscopic Pathology

The most characteristic picture was that of a reticular pattern of growth (Fig. 4), in which tumor cell aggregates formed spaces of varied size, reminiscent of the more familiar yolk sac testicular tumors of reticular type. Transitions were seen to a more compact adenoid cystic appearance (Fig. 5) or, less often, the cell aggregates exhibited an open, microcystic pattern, usually with micropapillations (Fig. 6). Most cases also contained poorly differentiated areas in the form of solid sheets of cells (Fig. 7). In four cases, this was the dominant histological pattern, and in three others, it was the only pattern, although one of these was a case with limited sampling. Five cases had spindling of tumor cells in a few fields (Fig. 8). Tubular, trabecular, and discrete glands were other growth patterns occasionally found.

The tumor cells had dark cytoplasm, clear nuclei, and usually prominent nucleoli (Figs. 7 and 9). In five cases, the cells had a squamoid appearance in areas, and in two tumors, we found intercellular bridges. Mucin droplets in cells with intercellular bridges were noted in one case, but keratinization was never seen. It was not uncommon to see cells with a rhabdoid or a vaguely plasmacytoid appearance (Fig. 10), but no lesion resembling a transitional cell carcinoma was evident in any of the tumors. It should also be noted that these lesions have no resemblance to yolk sac tumors except under the scanning objective of the microscope.

FIG. 6. In scattered areas, the tumor may have a microcystic appearance with mural papillations.

FIG. 7. Poorly differentiated area of tumor showing the characteristic cellular features. Note neutrophils within the tumor and lymphocytes at its periphery (top).

Stromal desmoplasia was prominent in all cases and composed a considerable bulk of the tumor. This usually had a mucoid, myxoid, or edematous appearance and tended to be hypocellular (Fig. 11). In nine cases, there were also areas in which the stroma was more densely collagenous (Fig. 12), and in only one was it entirely collagenous.

Hemorrhage

Most tumors had multiple hemorrhagic areas, and in only four cases did we see little or none.

Necrosis

Two tumors did not show necrosis microscopically, and in four others there were only a few small

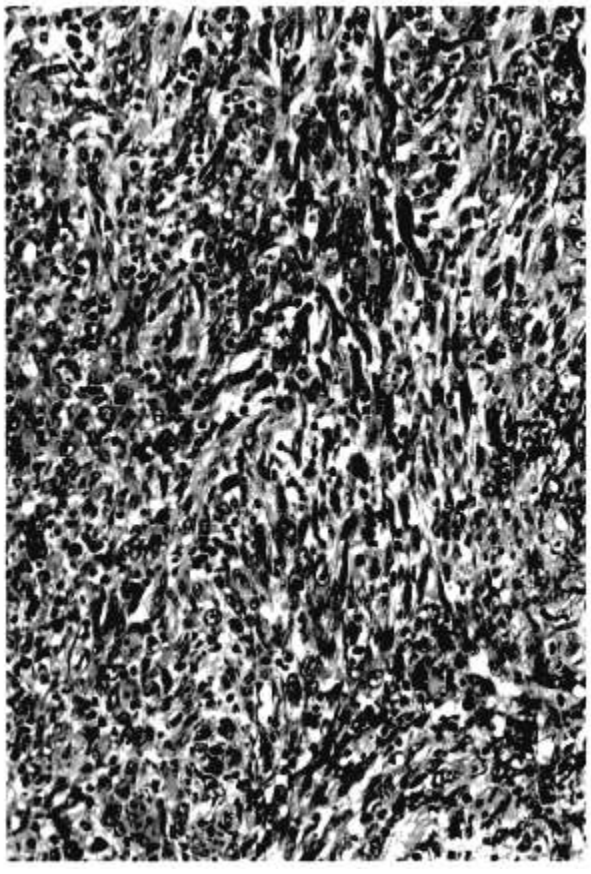

FIG. 8. Five cases had focal spindling of cells in poorly differentiated areas.

foci. All of the others showed extensive necrosis, which appeared to be geographic in configuration (three cases), ischemic (six cases), comedo (two cases), or suppurative. The latter was one of the characteristic features of these lesions because it was present in most cases and typically resembled microabscesses within the epithelial aggregates (Fig. 13).

As with stromal desmoplasia, a prominent inflammatory element was a constant observation. Most microscopic fields of tumor were infiltrated with polymorphonuclear leukocytes (Figs. 7 and 9). Peripheral to the advancing margins of the tumor, and around the satellites, it was usually possible to find a band of lymphocytes (Figs. 7 and 14). The 39-year-old female patient had an absence of neutrophils in many fields and very few lymphocytes, but the tumor was otherwise typical.

Satellites

Peripheral to the main tumor mass in the medulla, smaller aggregates of tumor were found in the renal cortex and/or the adjacent peripelvic soft tissue in all but two cases, and in one of the latter, we had only a small sampling of the lesion. These aggregates often proved to represent venous or lymphatic invasion (Fig. 14).

Tumor extent

All tumors contained lymphatic or vascular invasion or both, and in four, the lesion invaded into the main renal vein. When perinephric tissue was available for review, the tumor could be demonstrated in the perinephric or peripelvic soft tissue, and in eight, it was in or around the adrenal gland. When nodal tissue was available, it contained tumor, and we saw this 19 times. None of the tumors was stage I (Table 1).

Special stains

Fifteen cases were stained with PAS-diastase and 12 with mucicarmine. In general, the tumors contained less epithelial mucin than had been suspected from the appearance of the H&E sections. In four cases, both stains were negative, but the others contained variable numbers of cytoplasmic mucin

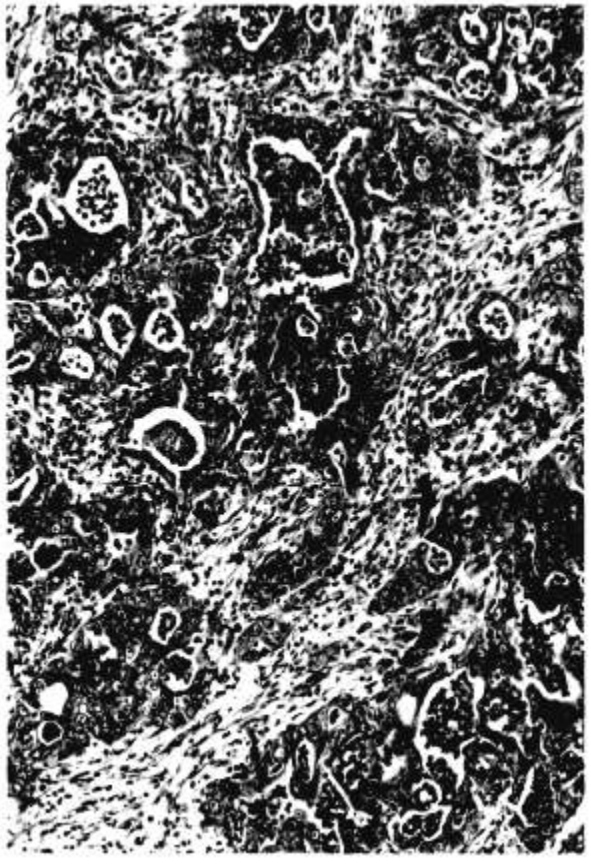

FIG. 9. Typical medullary carcinoma with adenoid–cystic features, dark cells with prominent nucleoli, stromal proliferation, and admixed neutrophils.

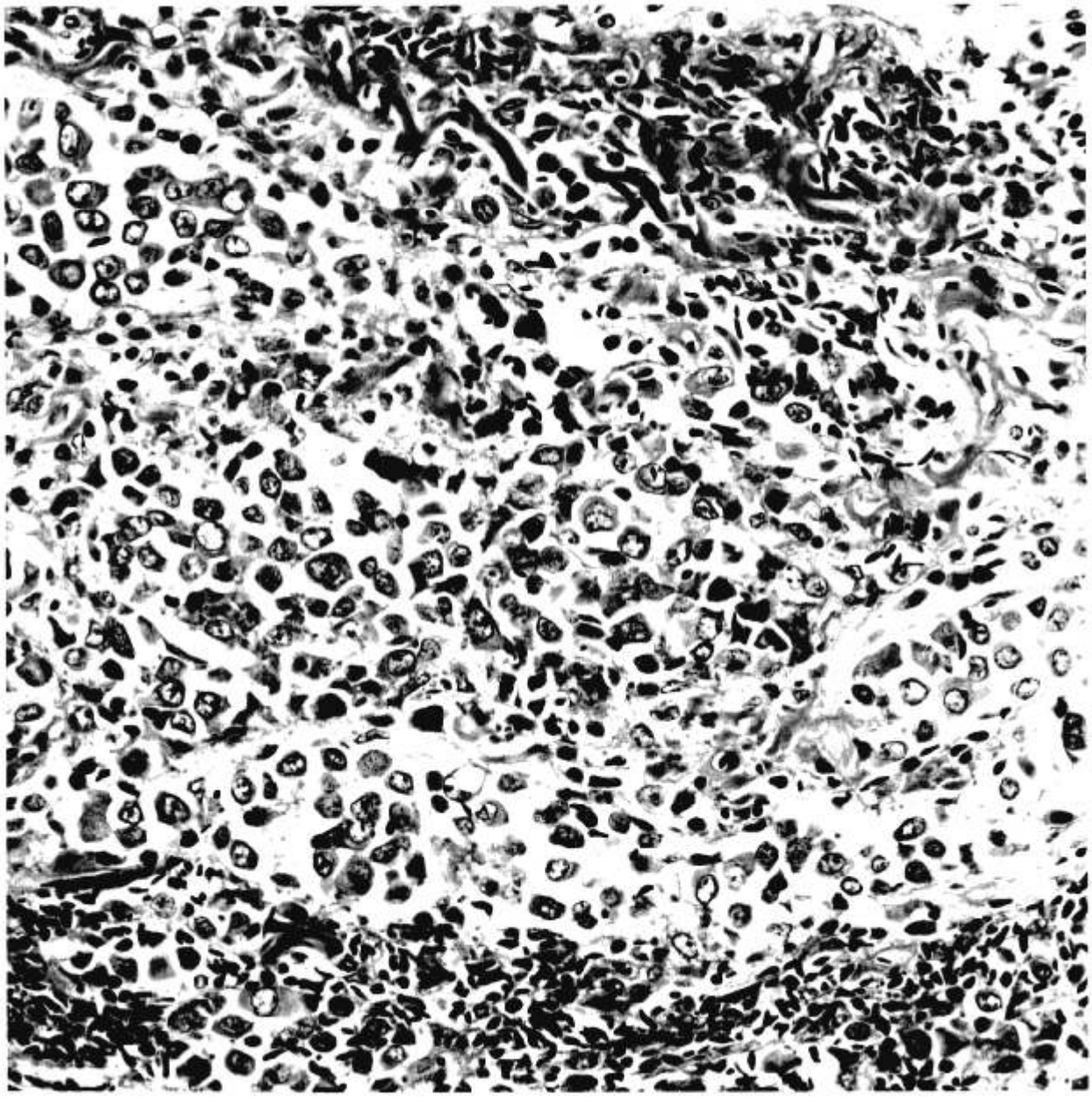

FIG. 10. Renal medullary carcinoma in sickle cell trait. In poorly differentiated areas, tumor cells often had a rhabdoid appearance. Most of the red cells in the upper right field and at the bottom are sickled.

droplets (Fig. 15). Mucicarmine occasionally stained luminal mucin and sometimes the stroma. Eight tumors were evaluated for CEA, and the result was negative three times. The other cases varied from most cells showing reactivity to very few. Keratin immunostains were performed on 10 cases, and in nine of them, the result was strongly positive, meaning that most or all of the tumor cells appeared to be reactive. The other case, a poorly differentiated tumor, was negative. The EMA was positive in that case, as it was in the other three cases tested. In the latter three cases, the keratin was much more strongly and diffusely reactive than was the EMA.

In two patients, we found scars indicative of remote papillary necrosis, but there was no other evidence, pathologically or in the clinical records, that the patients had previously had problems with any of the other sickle cell nephropathies.

BIOLOGICAL BEHAVIOR

At the time of diagnosis (surgery), 25 patients are known to have had metastases to one or more

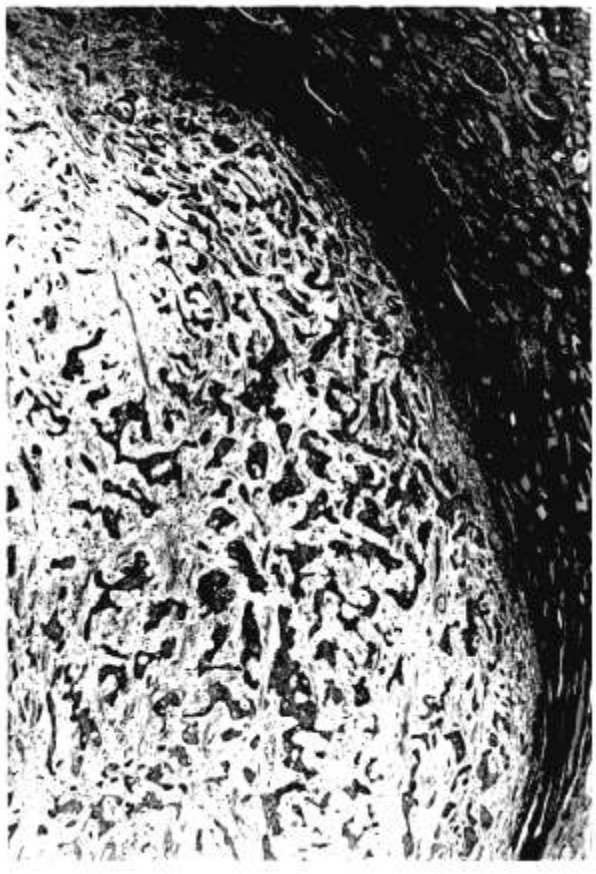

FIG. 11. The associated stromal reaction usually accounts for much of the bulk of the tumor and typically has an edematous or myxoid appearance.

lymph nodes. It had extended to the adrenal in eight, to the perinodal retroperitoneal tissue in nine, to the peritoneum in two, and in six and seven patients, respectively, it had metastasized to the liver and lungs. An additional patient was found to have multiple lung densities 1 week after nephrectomy, following a negative preoperative chest film and, as already noted, the initial specimen from one patient was a positive cervical lymph node. In five cases, information pertaining to tumor spread was not available and, in Table 1, these are noted as showing only perinephric or local retroperitoneal disease.

Follow-up information was available on 19 patients, and all died of disease. Eight patients are considered lost, and the other six are more recent accessions. From the time of surgery, the 19 patients lived from 3 to 52 weeks. The mean duration of life was 15 weeks, and the median, 12 weeks. For nine cases, we know the duration of disease from initial symptoms to death. This ranged from 9 to 52 weeks, with a mean of 24 weeks and median of 21 weeks. A patient who survived for 52 weeks from onset of symptoms to death was, comparatively, exceptional. He lived for 32 weeks after surgery, and during this period, was said to show no response to two courses of adriamycin and cisplatinum or to methotrexate and vincristine. His tumor obviously was much more indolent than the others. Two patients receiving radiotherapy were said to show no response, and a third, given 3,000 rads for lung metastases, achieved transient improvement in breathing.

DISCUSSION

While accumulating this group of tumors, we classified and coded them as variants of renal pelvic carcinoma, because their glandular and squamoid features, together with prominent inflammatory and desmoplastic elements, were much more consistent with neoplasms originating from transitional epithelium than any other tumor found in the kidney. Thus our differential diagnosis was always pelvic carcinoma versus metastatic carcinoma. Many of these lesions had been referred to us as examples of collecting duct carcinoma, but, although some of these may originate from transitional epithelium of

FIG. 12. In one case, the stromal reaction had a dense, collagenous appearance, and in nine others, this was seen only focally.

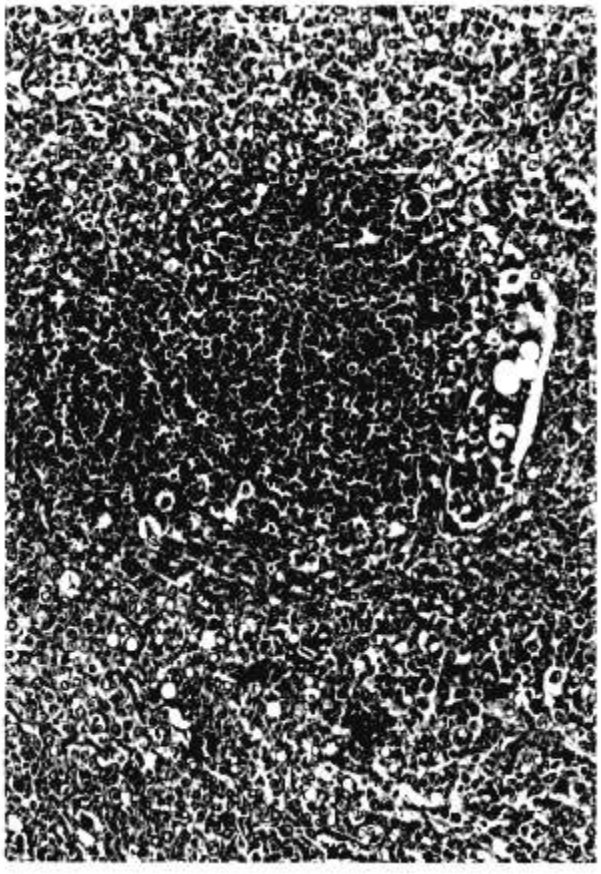

FIG. 13. Tumor necrosis often had the appearance of microabscesses.

the distal ducts, they do not resemble the lesions we and some other observers have classified as collecting duct carcinoma (7). The histological spectrum of the latter is more closely related to renal cell carcinoma than to renal pelvic carcinoma, except for their dominant medullary location. It has been our impression that a heterogeneous group of renal tumors is currently being classified as collecting duct carcinomas, but to avoid confusion with those lesions, we elected to designate these "renal medullary carcinomas."

The rapidly destructive nature of these tumors has made it difficult to identify an in situ point of origin. In some of the cases, the tumor appeared to arise from the calyceal epithelium (Figs. 16 and 17), but it was usually not possible to exclude epithelial invasion from the stroma.

That these tumors probably originate in and near the renal papillae is suggested by the accumulated experience with radiographic and pathologic findings in individuals with SCD and SCT. Eckert et al., in a prospective study of 200 black patients, found that 7.5% had SCT. Of the latter ~50% had a variety of abnormalities of renal papillae, which they regarded as representing the various stages of renal papillary necrosis (4). Marquis and Khazem (9) and Plunket et al. (11) found a high incidence of calyceal deformities ("sickle cell caliectiasis") in pediatric patients with SCD and SCT. In their pathologic study of 15 children with SCD, Bernstein and Whitten described changes in the renal papillae that correlated with the various radiographic studies (2). The occurrence of spontaneous, unilateral gross hematuria in patients with SCT is well known, and it is of interest that the age range of reported cases is essentially the same as that for the medullary carcinomas. The latter patients were 11 to 39 years. The patients with gross hematuria reported by Crone et al. were 15 to 39 years (3) and those of Mostofi et al. were 18 to 30 years (10). Curiously, most of the spontaneous bleeding is from the left kidney, and most of the carcinomas are on the right. In the study by Mostofi et al., the hematuria occurred chiefly on the left, by 19:3. The medullary carcinomas were chiefly on the right, by 23:8. The definitive pathological study of patients with unilateral hematuria in patients with SCT is that of Most-

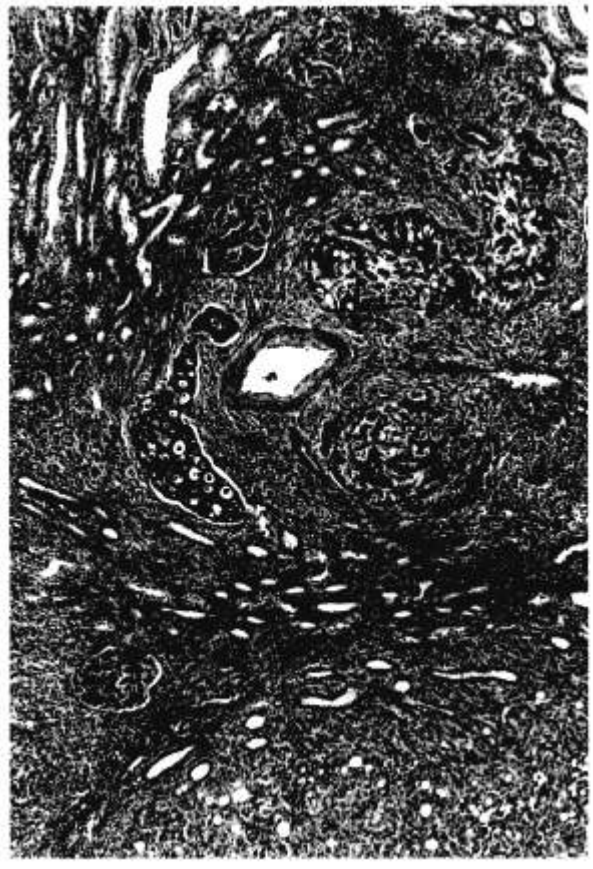

FIG. 14. Satellite tumor nodules peripheral to the main tumor, which is at the bottom. These often proved to represent venous or lymphatic invasion.

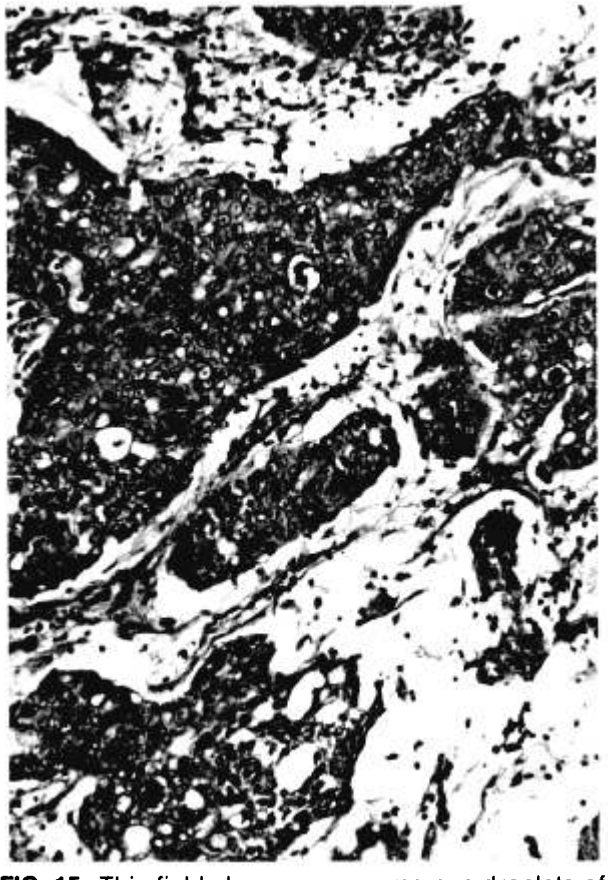

FIG. 15. This field shows more numerous droplets of cytoplasmic mucin than were seen in most of the other tumors. PAS-diastase.

ofi et al. (10). From their 22 patients, they had 21 nephrectomy specimens and one wedge biopsy available for evaluation. Of most relevance to this study is their observation of epithelial proliferation of the terminal collecting ducts in 12 cases and of the adjacent papillary mucosa in 14. It should be noted that transitional epithelium frequently lines the distal ducts, and their Figs. 7 and 10 are interpreted as a transitional cell proliferation, rather than one of columnar ductal cells. It seems plausible to believe that these carcinomas in patients with SCT likely originate in such areas of cellular activity.

With respect to the diagnosis of this tumor, the glandular and cellular features described, in addition to the unusually prominent stromal and inflammatory elements, present a picture unlike that of any other renal tumor. In renal carcinomas, a prominent inflammatory element and stromal proliferation are not usually present, although exceptions do occur. Moreover, these tumors should not contain epithelial mucin. Although carcinomas of the Bellini ducts may contain mucin and do involve chiefly the renal medulla, their histological features overlap with those of renal cell carcinoma, and they do not resemble lesions derived from transitional epithelium.

The demonstration of sickled erythrocytes in tissue sections has been detailed elsewhere (3,10). According to Hoffman, they can almost always be found at autopsy in patients with SCT (5). Briefly, unless there has been prolonged exposure of unfixed tissue to air, the red blood cells will be "frozen" in their original morphological configuration, and a clear distinction between the shrinkage and rounding artifacts of fixation and the elongated, double or multipointed, crescent or spindled erythrocytes of drepanocytosis can be made (Fig. 10). This distinction can be difficult, but, in our view, all of the 33 patients had sickled erythrocytes focally, and it usually required several minutes of searching. None of the cases exhibited the massive sickling characteristic of SCD, and none had the clinical features that would suggest that diagnosis. It is likely that the patients all had SCT, although one was known to have hemoglobin SC disease.

The sickle cell gene has been found in the Mediterranean basin and in Saudi Arabia and central In-

FIG. 16. An apparent example of calyceal carcinoma in situ, which was located lateral to the main tumor mass.

FIG. 17. Calyceal epithelium (arrows) appears to be the source of the carcinoma (arrowheads).

dia, but in the United States, it is seen almost exclusively in African Americans, with an incidence of ~7.5 to 9.5% (5,8). Considering the large population at risk, this obviously is a rare neoplasm. However, it is a very aggressive one, aptly described by one of the attending physicians as a tumor with "an astonishing rate of growth," and its recognition can be expected to make more difficult the management of patients with the much more common entity of unilateral hematuria (Berman's first sickle cell nephropathy). This is typically a self-limited process, which one would hope to manage conservatively, and it will be of little consolation in individual cases that most benign bleeding has been from the left kidney and most of the carcinomas were on the right side. A more vigorous initial evaluation with the most sophisticated imaging techniques will be indicated, and one might also consider careful cytological study of aliquots of ureteral blood for evidence of neoplasia or tissue necrosis. As already noted, many of these patients can be expected to show evidence of systemic disease at initial presentation. □

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