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Invited Review

Spindle cell lesions of the urinary bladder

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Summary. Spindle cell proliferations of diverse types which vary greatly in their behavior may occur in the urinary bladder. Some of them such as the inflammatory pseudotumor and the postoperative spindle cell nodule are reactive and clinically benign although they may be responsible for significant symptoms. On the other hand, certain other lesions such as sarcomatoid carcinomas are typically highly malignant tumours. The features of the inflammatory pseudotumor and postoperative spindle cell nodule have only recently been defined. The tendency of the former to occur in young patients and the association of the latter with a recent operative procedure are important pieces of clinical information which may prevent their mis-diagnosis. The diagnosis of sarcomatoid carcinoma should always be considered when a malignant spindle cell proliferation is encountered in the urinary bladder. Careful search for minor foci of obvious epithelial differentiation is important in establishing the diagnosis which may also be aided by immunohistochemical staining for epithelial markers. Sarcomatoid carcinoma should be distinguished from the rare transitional cell carcinoma with pseudosarcomatous stroma and from carcinosarcoma. The final lesions briefly reviewed here are mesenchymal tumors both benign and malignant, which generally do not pose the same degree of diagnostic difficulty as non-neoplastic mesenchymal proliferations and sarcomatoid carcinomas.

Key words: Urinary bladder, Atypical stromal cells, Postoperative spindle cell nodule, Inflammatory pseudotumor, Benign mesenchymal tumors, Malignant mesenchymal tumors, Sarcomatoid carcinoma, Transitional cell carcinoma with pseudosarcomatous stroma.

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Introduction

Although the majority of problematic lesions of the urinary bladder have an epithelial appearance, spindle-cell lesions account for a small but frequently challenging subset of cases. A number of the entities in this categories have only been delineated recently and knowledge of their clinical and pathologic features is still incomplete. Other lesions in this group have been recognized for a relatively long time but because of their rarity still provide considerable diagnostic difficulty when encountered. Some of the problems these lesions engender are still not widely appreciated and there is new information concerning many of them. The differential diagnosis in many of these cases is between lesions with a markedly different behaviour and their correct recognition, which may be difficult, is, therefore, of great clinical importance. The lesions to be discussed fall in four general categories each of which will be discussed in turn: 1) non-neoplastic mesenchymal proliferations; 2) benign mesenchymal tumors; 3) malignant mesenchymal tumors; 4) carcinomas with a spindle cell component.

Non-neoplastic mesenchymal proliferations

Atypical stromal cells

These atypical mononucleated or multinucleated spindle cells that are often present in the lamina propria are the most common atypical, mesenchymal cells found in the bladder (Fig. 1). These cells were described by Putschar (1934) over 50 years ago, and subsequently were encountered in one third of cases of cystitis in an autopsy study. The term «giant cell cystitis» was applied to such cases (Wells, 1938), but in our experience these cells are relatively common in the absence of obvious evidence of cystitis. They are rarely troublesome diagnostically but may be confusing when they occur in the stroma of a polyp (Young, 1986) or carcinoma

Fig. 1. Atypical mesenchymal cells in inflammed lamina propria of urinary bladder.

(Young and Wick, 1988; Mahadevia et al., 1989; Paulson et al., 1990). In the former instance they may suggest the diagnosis of a rhabdomyosarcoma and in the latter they may suggest the diagnosis of a sarcomatoid carcinoma or carcinosarcoma. Their degenerative appearance and lack of mitotic activity are important clues to their benign nature. These cells may also be seen in patients with a history of chemotherapy or radiation therapy but usually there is no such association (Young, 1989).

Postoperative spindle cell nodule

This recently described exuberant, but benign, mesenchymal proliferation of the bladder is readily confused with a sarcoma when the history of a recent procedure, usually a transurethral resection, is not provided. Proppe et al. 1984 described eight examples of this lesion that developed from 5 weeks to 3 months after an operation had been performed on the lower genital tract of four women and the bladder or prostate of four men. The majority of the lesions of this type which we have seen since the initial paper describing this lesion have occurred in the bladder after a similar procedure and two similar additional cases have been reported (Guillou and Costa, 1989).

These lesions may mimic a bladder tumor grossly and have a variety of appearances ranging from friable to nodular and firm. Microscopic examination shows intersecting fascicles of spindle cells (Fig. 2) with eosinophilic cytoplasm, the appearance closely resembling that of a leiomyosarcoma. Confusion with the latter may be compounded when the spindle cell nodule involves the muscularis propria of the bladder as it sometimes does. There is often a delicate network of small blood vessels and overlying ulceration with a superficial acute inflammatory cell infiltrate; chronic inflammatory cells are often seen in the deeper portions of the lesion. Foci of hemorrhage and mild to moderate edema are common (Fig. 3). In some cases the stroma is myxoid. Mitotic figures are generally numerous but the cells do not exhibit significant cytologic atypia. Surprisingly, the postoperative spindle cell nodule has stained immunohistochemically for cytokeratin as well as desmin (Wick et al., 1988). The differential diagnosis of this lesion is similar to that of the inflammatory pseudotumor and will be discussed under the latter lesion.

Inflammatory pseudotumor

Benign proliferative mesenchymal lesions of the bladder which microscopically may resemble a sarcoma, but are unrelated to a prior operation have now been well documented. The first reported case in this category was described by Roth in 1980. He reported the case of a

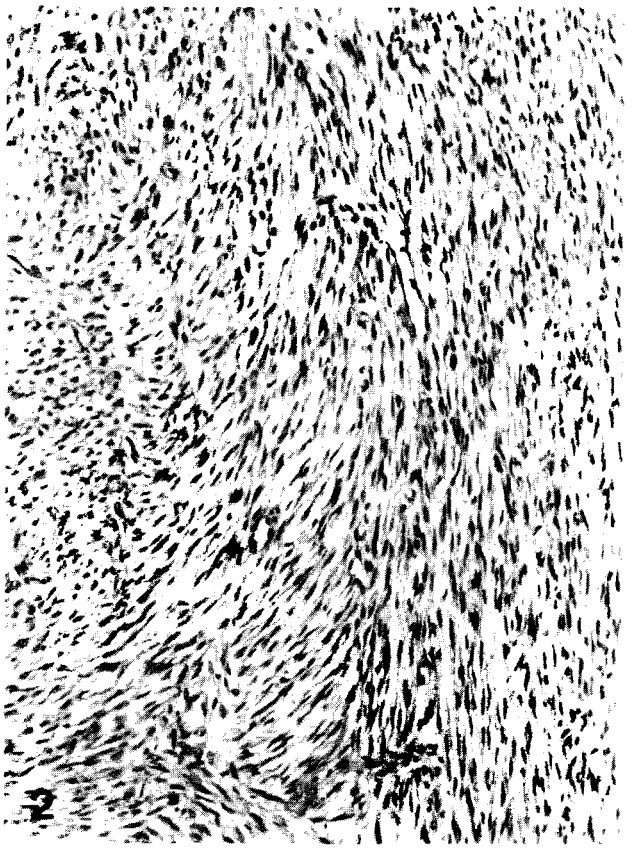

Fig. 2. Postoperative spindle cell nodule. Fascicles of spindle cells imparting a resemblance to a leiomyosarcoma are present.

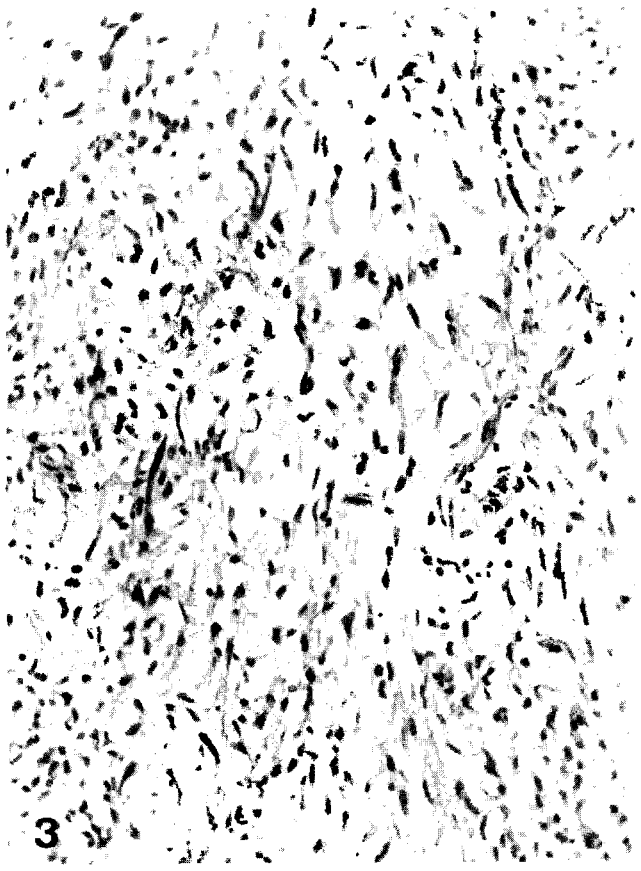

Fig. 3. Postoperative spindle cell nodule. The cells are separated by an edematous stroma.

32-year-old woman with recurrent cystitis and hematuria who had an ulcerated bladder lesion. A segmental resection was performed, and a follow-up of approximately one year was uneventful. Microscopic examination revealed spindle-shaped cells exhibiting mitotic activity within a myxoid stroma containing scattered chronic inflammatory cells. The process infiltrated between bundles of superficial muscle but did not extend to the margins of resection. Subsequently, Olsen (1984) illustrated the case of a 24-year-old woman with symptoms of acute cystitis associated with a 1-cm ulcer in the bladder dome. Biopsy revealed a spindle-cell lesion that contained many leukocytes and eosinophils and resembled a myosarcoma. The lesion, which was resected with negative margins, was interpreted as reactive, and follow-up of almost three years was uneventful. Nochomovitz and Orenstein (1985) reported the first bladder lesions given the specific designation of inflammatory pseudotumor. One of their patients was a 22-year-old man, the other a 73-year-old woman. Both of them complained of hematuria and had pedunculated masses that protruded into the bladder lumen. The lesions were gelatinous or mucoid on gross inspection and were composed on microscopic examination of widely separated spindle cells with elongated eosinophilic cytoplasmic processes set in a background which was described as loose and edematous, or myxoid, and contained inflammatory cells and slender blood vessels. The nuclei of the cells were large, but not hyperchromatic, and mitotic figures were rare.

Eighteen additional examples of lesions similar to those described by Nochomovitz and Orenstein (1985) have been described subsequently, sometimes under somewhat different designations (Ro et al., 1986; Young and Scully, 1987; Forrest et al., 1988; Goussot et al., 1989; Stark et al., 1989; Coyne et al., 1990; Saavedra et al., 1990). The follow-up in all these cases has been uneventful. It is of note that 12 of the 22 documented cases of inflammatory pseudotumor of the bladder have occurred in patients under the age of 20 years. Furthermore, most of the remainder have occurred in young adults with only four patients over 50 years of age. Hematuria is the usual presenting symptom. The majority of the lesions appear to have been polypoid and they are frequently soft and gelatinous or myxoid on gross examination. The appearances on microscopic examination (Figs. 4-7) appear to have been similar to those described in the initial reports. The cells often resemble the plump spindle cells seen in nodular or proliferative fasciitis and occasional cells exhibit mitotic figures. Extravasated red blood cells that may form large

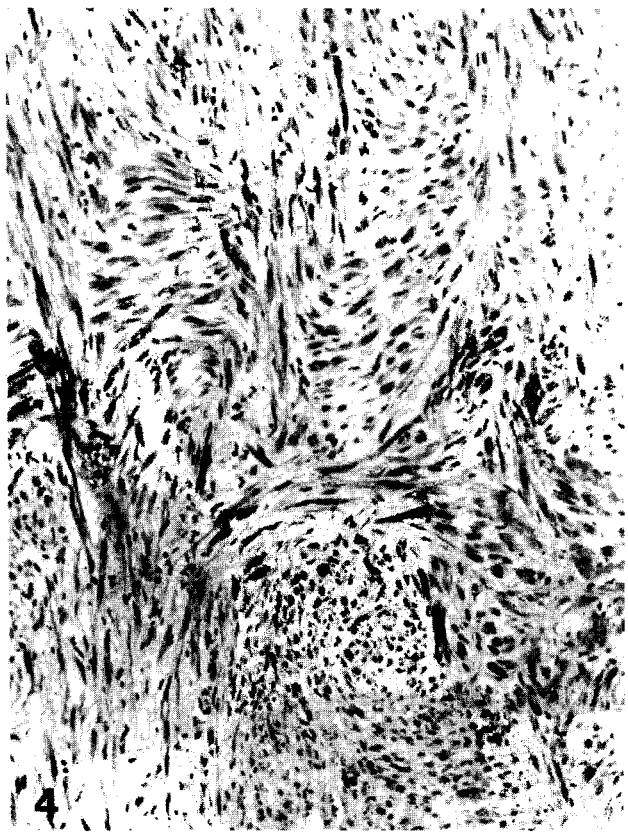

Fig. 4. Inflammatory pseudotumor. The cells are arranged in a storiform pattern.

Fig. 5. Inflammatory pseudotumor. Mesenchymal cells are relatively widely separated and lie in an edematous stroma.

aggregates are sometimes conspicuous. It is of note that in the largest series of 10 cases, infiltration into the muscularis propria was described in six of them (Fig. 6) (Saavedra et al., 1990). In the same series, six cases studied immunohistochemically expressed vimentin and muscle specific actin and two additionally expressed desmin and cytokeratin. Electron microscopic examination characteristically shows features of myofibroblasts.

The major differential diagnosis of both the postoperative spindle cell nodule (PSCN) and the inflammatory pseudotumor (IF) is with a leiomyosarcoma particularly the myxoid variant, because of the myxoid appearance that may characterize the stroma of the PSCN and IF. Myxoid change within leiomyosarcomas of the bladder is quite common, being seen in approximately 60 per cent of them (Young et al., 1987; Mills et al., 1989). In our experience the cellularity of the PSCN and IF is more variable than that of a leiomyosarcoma which tends to be uniform throughout. Inflammatory cells are more pronounced in the PSCN and IF than in most leiomyosarcomas. Both non-neoplastic lesions also tend to have a more prominent network of small blood vessels than generally seen in leiomyosarcomas. Identification of an aggressive infiltrative margin of the lesion with destruction of smooth muscle is not a diagnostic feature as both non-neoplastic lesions may also involve and destroy muscle. Immunohistochemical or ultrastructural evidence of the typical features of smooth muscle cells favors leiomyosarcoma over PSCN or IF in which the cells typically have the characteristics of myofibroblasts (Dehner, 1986). If any doubt exists as to whether a lesion is reactive or a leiomyosarcoma close follow-up is mandatory and if there is significant doubt about the diagnosis, it may be advisable to excise the lesion widely so that it can be thoroughly evaluated.

Benign mesenchymal tumors

Almost every form of benign mesenchymal tumor has been described in the bladder but even the most common of them, the leiomyoma, is rare (Walker et al., 1989). The tumors may be large exophytic masses protruding into the bladder lumen, intramural, or on the serosal surface. Their typical morphologic features on light microscopic examination should not provide any diagnostic difficulty although superficial biopsies of lesions with surface ulceration may sometimes cause difficulty primarily due to the inadequate nature of the sample. Criteria for the distinction of a leiomyoma from a leiomyosarcoma of the bladder are less well defined than in other sites. Any significant degree of mitotic activity should be viewed with suspicion and should

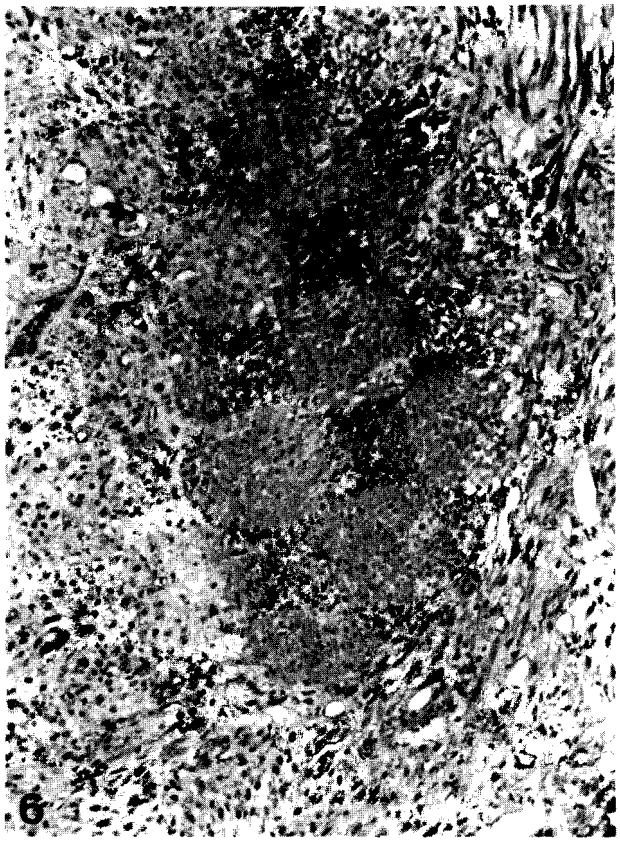

Fig. 6. Inflammatory pseudotumor involving muscularis propria of urinary bladder.

Fig. 7. Inflammatory pseudotumor. Plump spindle cells with abundant cytoplasm are present.

probably lead to a wide excision of the lesion so that its overall morphologic features including its margin can be adequately evaluated. Epithelioid smooth muscle tumors of the bladder appear to occur less commonly than in other locations but this possible diagnosis should be kept in mind when examining a bladder tumor with an unusual appearance that is difficult to classify.

Malignant mesenchymal tumors

As pertains to benign mesenchymal tumors, myogenic neoplasms account for the vast majority of malignant mesenchymal tumors of the bladder. In children and young adults rhabdomyosarcomas account for the majority of the cases (Dehner, 1989) whereas in older patients the great majority of tumors are leiomyosarcomas (Mills et al., 1989). The latter are exceedingly rare in the first decade, occasionally occur in the teenage years and occur with increasing frequency from then on. Approximately 80 per cent of the patients present with hematuria. The tumors are typically large and exophytic with a variable underlying component that is invasive of the bladder wall. The surface is often focally ulcerated and the sectioned surface shows an appearance which may vary from relatively firm to quite soft. Hemorrhage may be present and extensive, particularly in poorly differentiated neoplasms. Occasional tumors that have a prominent myxoid component may be gelatinous on gross inspection. Microscopic examination shows a similar range of appearances to that seen elsewhere in the body. The majority of the tumors are well or moderately differentiated. Mitotic counts are often low but in the context of a cellular tumor with some mitotic activity and an infiltrative margin a diagnosis of low grade leiomyosarcoma is appropriate. A major differential diagnosis of leiomyosarcoma is with sarcomatoid carcinoma (Young et al., 1988), something which is discussed under the latter neoplasm. A similar differential diagnosis arises with the other less common sarcomas of the bladder occurring in adults, such as malignant fibrous histiocytoma and rhabdomyosarcoma. The latter diagnosis should be made with great circumspection in adults because of the rarity of these tumors beyond the age of 20 and because of the propensity for them to be mimicked by sarcomatoid carcinomas.

Rhabdomyosarcoma accounts for the vast majority of malignant mesenchymal tumors of the bladder in children (Dehner, 1989). The bladder is one of the commoner sites of this neoplasm in the pediatric age

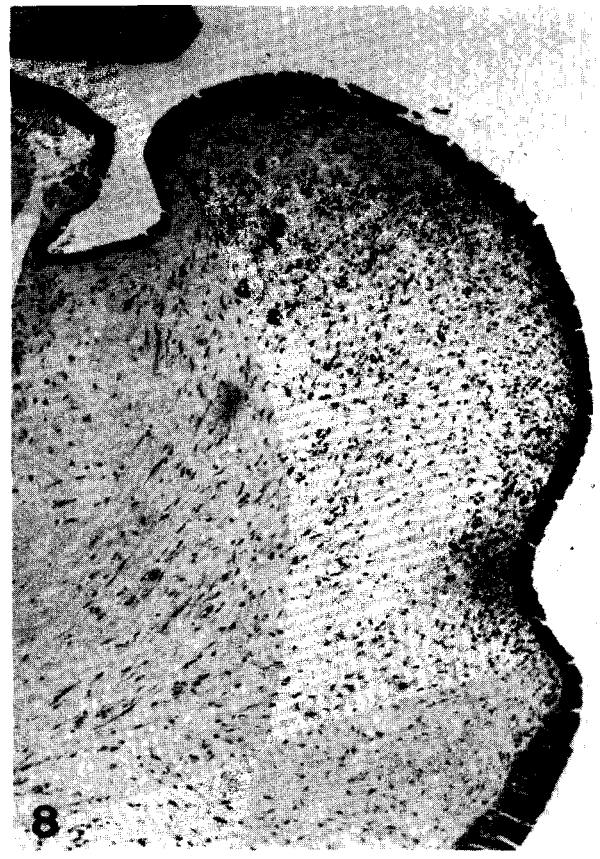

Fig. 8. Embryonal rhabdomyosarcoma of urinary bladder. A polypoid tumor is edematous and contains widely scattered cells which appear relatively innocuous.

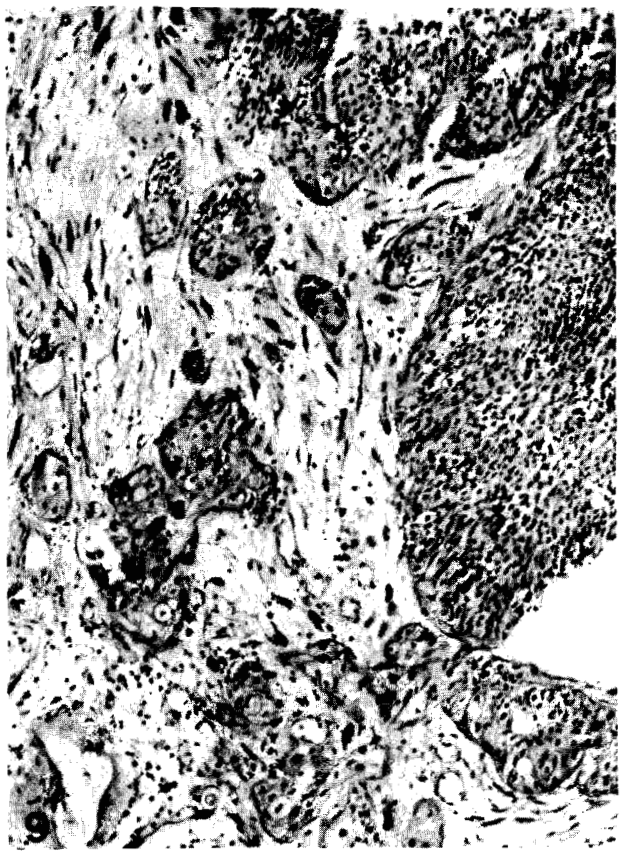

Fig. 9. Transitional cell carcinoma with pseudosarcomatous stroma. The stroma between nests of superficially invasive transitional cell carcinoma contains numerous atypical mesenchymal cells. Note the lack of mitotic figures in these cells.

group, accounting for approximately 20 per cent of the cases. The tumors classically take the form of the typical «sarcoma botryoides» a polypoid, sometimes lobulated mass that often protrudes into the bladder lumen but other less characteristic appearances may be encountered. Microscopic examination usually shows the typical features of this tumor with in most cases a cambium layer underlain by a tumor which varies from densely cellular to relatively paucicellular, with a superficially innocuous loose edematous appearance (Fig. 8). Some tumors are composed predominantly of relatively mature appearing skeletal muscle cells. Because of these various innocuous looking foci it is possible to underdiagnose one of these tumors in a biopsy specimen, and there should be a high index of suspicion for this diagnosis when evaluating a polypoid bladder tumor from a young person. The differential diagnosis of rhabdomyosarcoma of the bladder in children involves the same differential diagnosis as pertains when this tumor is seen elsewhere in this age group with the exception than in the bladder other diagnostic considerations are much less common and a malignant small round cell or spindle cell tumor of the bladder in a child will turn out to be a rhabdomyosarcoma with only very rare exceptions.

Carcinomas with a spindle cell component

Tumors in this category fall into two groups: 1) carcinomas with atypical, but non-neoplastic, spindle cells of mesenchymal derivation in their stroma and 2) carcinomas in which many of the malignant cells are spindle shaped.

Carcinoma with pseudosarcomatous stroma

Tumors in this category are uncommon, only two completely convincing examples having been reported in detail (Young and Wick, 1988; Mahedevia et al., 1989). As alluded to at the outset of this review, cases of this type are explainable on the basis of the presence within the stroma of a carcinoma of atypical stromal cells of the type seen in cases of so-called giant cell cystitis. When adjacent to nests of carcinoma (Fig. 9), they may be misconstrued as spindle-cell forms of the carcinoma cells. Their degenerative appearance and lack of mitotic activity are a clue to their nature as is the lack of any transition between them and obvious epithelial cells. It may be helpful in these cases

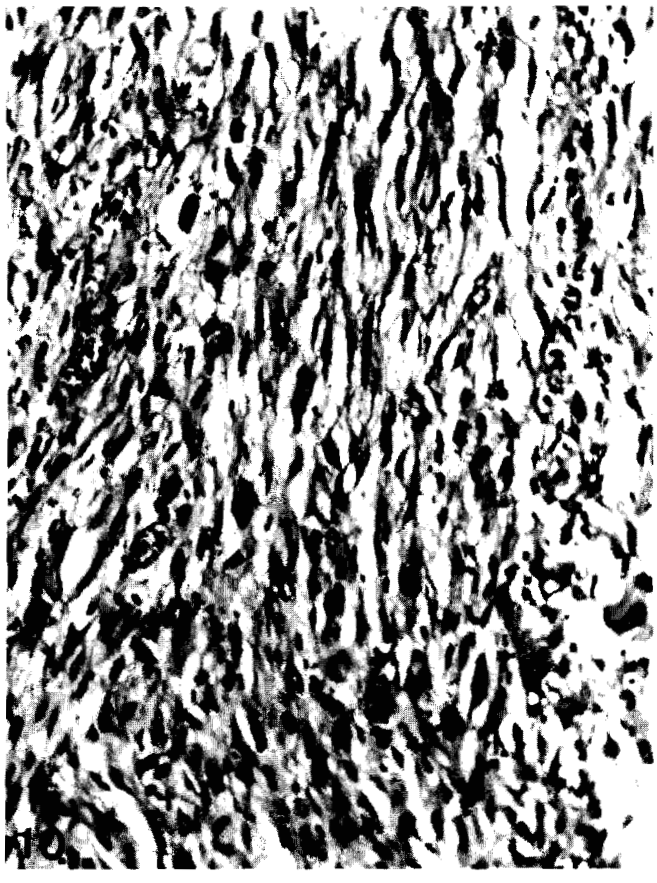

Fig. 10. Sarcomatoid carcinoma. Spindle-shaped cells with conspicuous nuclear atypia are present.

to perform immunohistochemistry as these cells, in contrast to the cells of sarcomatoid carcinoma, will be negative for cytokeratin (Young et al., 1988; Wick et al., 1988).

Sarcomatoid carcinoma

It is not rare to find a minor spindle cell component in a transitional cell carcinoma of the urinary bladder and in occasional cases the spindle cell component is sufficiently prominent that a designation of sarcomatoid carcinoma is appropriate (Ro et al., 1988; Young et al., 1988). In many of these cases the differential diagnosis with a sarcoma or carcinosarcoma (Young, 1987) is difficult, and with regard to the latter, to an extent arbitrary. Sarcomatoid carcinomas occur in the same age group as typical transitional cell carcinomas. The only difference on gross inspection is a greater tendency for sarcomatoid carcinomas to be polypoid. On microscopic examination the spindle cells in these tumors may have a variety of patterns. Most frequently there are interlacing fascicles of cells which may closely resemble leiomyosarcoma. In other cases a storiform pattern stimulating the appearance of a malignant fibrous histiocytoma is encountered (Young et al., 1988; Pearson et al., 1989) and in still others the appearance of a rhabdomyosarcoma, fibrosarcoma or a nonspecific sarcoma may be simulated (Fig. 10). The major clue to the diagnosis in these cases is the presence of associated foci of conventional invasive transitional cell carcinoma or transitional cell carcinoma-in-situ. Because sarcomatoid carcinomas are probably more common than sarcomas of the bladder, a high index of suspicion for sarcomatoid carcinoma should always pertain when a malignant spindle cell tumor of the bladder is encountered. In the absence on routine examination of the available material of obvious foci of carcinoma, it is important to obtain immunohistochemical stains to help delineate the neoplasm as a carcinoma will be expected to stain for markers of epithelial differentiation whereas the converse will be true in cases of sarcoma and the latter will on the other hand be expected to stain, in some cases at least, for myogenic markers.

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