CARCINOSARCOMA OF BLADDER

Evaluation by Electron Microscopy and Immunohistochemistry

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ABSTRACT—A case of carcinosarcoma of the urinary bladder characterized by electron microscopy and immunohistochemistry is described. The use of these studies in poorly differentiated bladder neoplasms and in suspected cases of carcinosarcoma is encouraged. Increased accuracy in characterizing these tumors will permit a better understanding of their natural history and response to therapy.

Carcinosarcoma of the urinary bladder is a rare neoplasm with simultaneous malignancy of both the epithelial and stromal components of the bladder wall. The mesenchymal component may express a variety of histologic types including chondrosarcoma, leiomyosarcoma, osteogenic sarcoma, and rhabdomyosarcoma.[1] This diagnosis is particularly difficult in the evaluation of poorly differentiated urothelial tumors where conventional light microscopy is often confusing resulting in such terminology as pseudosarcomatous stroma. Despite this difficulty in diagnosis, more than 40 cases of carcinosarcoma of the urinary bladder have been described in the world literature.[1-7] This report describes a patient whose diagnosis of carcinosarcoma was confirmed with electron microscopy and immunohistochemistry.

Case Report

A thirty-nine-year-old Caucasian female had a history of frequency, urgency, and nocturia beginning in September, 1981. She was initially treated with medical management without symptomatic relief. In August, 1982, gross hematuria developed. Cystoscopy and biopsy were performed which revealed a poorly differentiated transitional cell carcinoma invasive into muscle. Some of the neoplastic cells in the stroma had a spindle shape and were interpreted as a spindle variant of urothelial carcinoma. She was referred to the University of Michigan Medical Center where her outside slides were reviewed and the diagnosis was confirmed. A metastatic evaluation was negative. She was treated with 2,000 rad preoperative irradiation followed by cystectomy and ileal loop diversion in September, 1982. She had an uneventful postoperative course and is currently asymptomatic.

Electron microscopy

Specimens were fixed in 2% phosphate buffered glutaraldehyde and post fixed in 2% osmium tetroxide. After staining with 2% urinyl acetate, sections were embedded in Polybed/Araldite. Ultrathin sections were cut on a Reichert ultramicrotome, stained with lead citrate, and examined with a Zeiss 109 electron microscope.

Immunohistochemistry

Sections for immunohistochemistry were prepared from paraffin-embedded blocks. The avidin-biotin peroxidase method of Hsu, Raine, and Farzer[8] as previously reported by Lloyd, Gikas, Chandler[9] was used. Briefly, after inhibition of endogenous peroxidase with methanol-hydrogen peroxide, tissues were incubated overnight with anti-myoglobin antiserum produced in rabbit (Dako, Santa Barbara, California) used at 1:1000 dilution. The sections

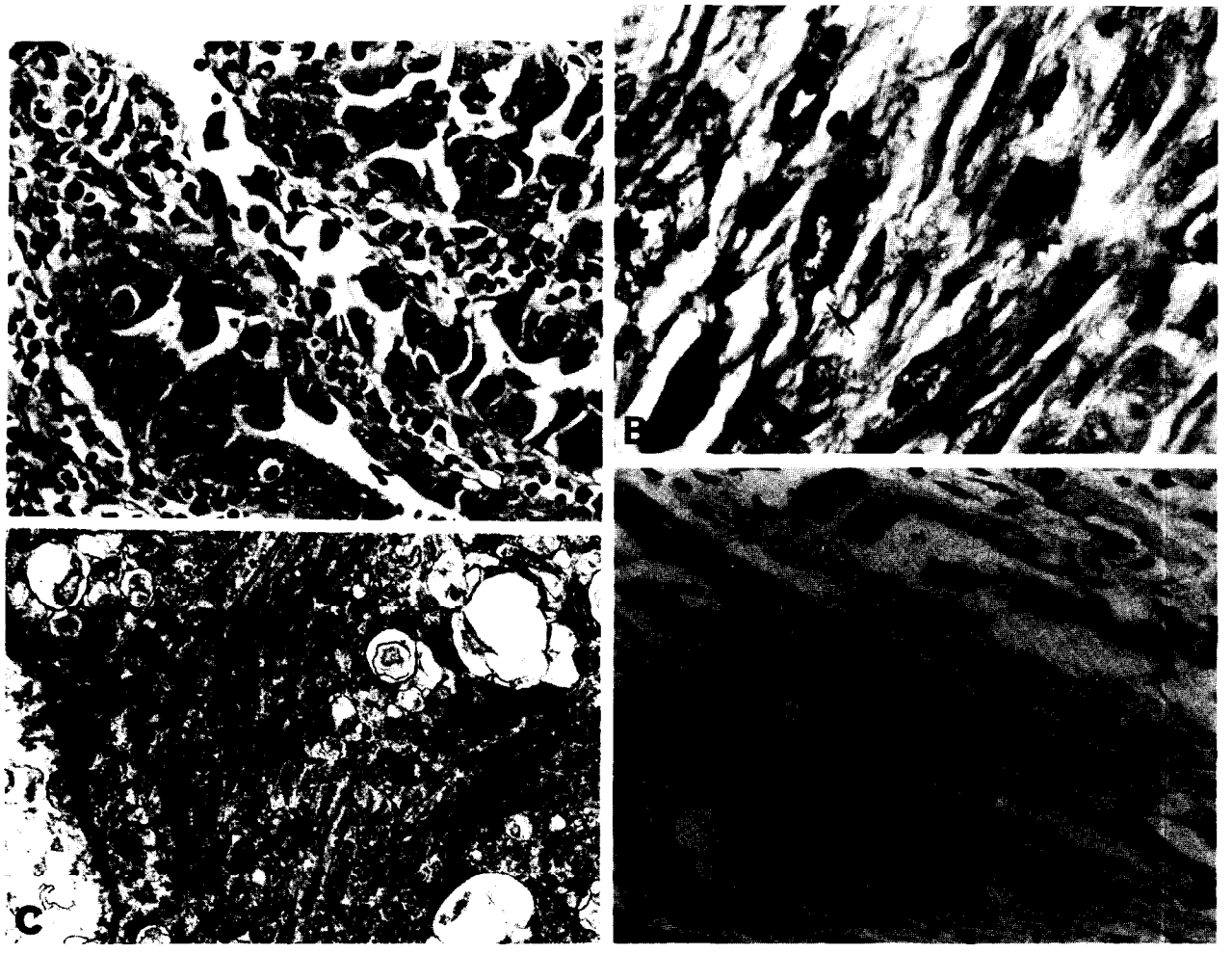

FIGURE 1. *(A) Area from carcinosarcoma showing poorly differentiated transitional cell carcinoma showing clusters of epithelial cells with enlarged pleomorphic nuclei (hematoxylin and eosin, original magnification, × 330). (B) Spindle cell component of carcinosarcoma showing rhabdomyosarcomatous differentiation; a rhabdomyoblast with distinct cross striation is present (arrow) (hematoxylin and eosin, original magnification, × 570). (C) Electron micrograph of carcinosarcoma showing cells with abundant parallel bundles of fibrils with abortive sarcomere formation; numerous thick and thin filaments and abortive Z-disk formation are present (electron micrograph, original magnification, × 25,000). (D) Immunoperoxidase staining of rhabdomyosarcomatous elements of tumor; several elongated tumor cells (arrows) stain positively for myoglobin (original magnification, × 330).*

were washed in phosphate buffered saline (PBS), then incubated with a 1:200 dilution of biotin-labeled goat immunoglobulin for thirty minutes followed by washing in PBS, and then incubated with avidin-biotin-peroxidase complex for thirty minutes (Vector, Burlingame, California). After washing, the sections were developed in diaminobenzidine and counterstained with hematoxylin.

Results

Light microscopy of the cystectomy specimen revealed focal grade I transitional cell carcinoma along with infiltrative poorly differentiated carcinoma (Fig. 1A). The high grade neoplasm exhibited both large pleomorphic cells and spindle cells, some of which exhibited cross striations (Fig. 1B). Electron microscopy demonstrated parallel bundles of fibrils in the cytoplasm of neoplastic cells attempting to form sarcomeres. Ribosomes were seen associated with some of the parallel bundles of fibrils. An occasional Z-disk was recognized in the sarcomeres. Mitochondria, lysosomes, and rough endoplasmic reticulum were also present in the cytoplasm in the neoplastic cells (Fig. 1C). Staining for myoglobin was positive in some of the spindle-shaped tumor cells (Fig. 1D). The diagnosis of carcinosarcoma was suggested by light microscopy but was confirmed using electron microscopy and immunohistochemistry.

Comment

The etiology of carcinosarcoma of the urinary bladder appears to be similar to that of the more usual urothelial tumor. Carcinogens

which produce transitional cell carcinomas in rats are also capable of producing carcinosarcoma.[10] Just as is seen clinically, the incidence of urothelial neoplasia alone in carcinogen-induced animal tumors is much higher than that of the combined malignancy of both epithelial and stromal components.

The presence of poorly differentiated carcinoma and rhabdomyosarcoma differentiation in this tumor fulfills the rigorous criteria of Willis[11] for a carcinosarcoma. He considered carcinosarcomas as tumors in which there was a simultaneous malignant neoplasm of an epithelial tissue and of its nonepithelial component or a subsequent sarcomatous change in the stroma of the carcinoma. These lesions should be distinguished from a collision tumor which usually occurs when separate unrelated neoplasms meet in contiguous areas. These neoplasms are usually unrelated to each other except in the area where they collide.[12] Examples of collision tumors would include a urothelial bladder carcinoma and a pure leiomyosarcoma of the bladder. Various examples of such tumors, including 2 cases of Holtz, Fox, and Abell[1] have been reported. In the present case a malignant change probably occurred simultaneously in the epithelium which showed in situ and invasive transitional cell carcinoma and in the contiguous substantia propria which showed rhabdomyosarcomatous differentiation. It is generally assumed that the tumors are not related but may arise through a common or interrelated pathogenesis.

Carcinosarcomas must be distinguished from anaplastic spindle cell carcinomas of the bladder. The finding of rhabdomyosarcoma as demonstrated by immunohistochemistry and electron microscopy excludes this diagnosis in the present case. Some other possible pathologic diagnoses also have been excluded by these findings. These include the rare cases of carcinomas with a severely reactive stroma, which may appear malignant, and the rare occurrence of metaplastic benign bone in the stroma of a poorly differentiated carcinoma.

The diagnosis of carcinosarcoma by light microscopy alone can be difficult. In this case, the use of electron microscopy and immunohistochemistry both easily confirmed the diagnosis. Myoglobin has been demonstrated to be a tumor marker for rhabdomyosarcoma.[13] Its usefulness in this instance was confirmed. The incidence of carcinosarcoma may, in fact, be higher than is reported because some patients with poorly differentiated neoplasms may go unrecognized as having this unusual tumor combination. At least some cases thought to represent pseudosarcoma may have sarcomatous changes when studied ultrastructurally or immunologically. In addition, electron microscopic and immunohistochemical evaluation of presumed cases of carcinosarcoma should be encouraged. Increased accuracy in characterizing these tumors will permit a better understanding of their natural history and response to therapy.

Because of the few cases in the literature little can be said definitively about optimal therapy. However, because of the aggressive nature of this neoplasm and tendency for local recurrence, radical cystectomy appears to offer the best chance for control of this tumor. After surgical attempts at local control have failed, the prognosis is poor. Perhaps with more aggressive chemotherapy, such as is used in children with rhabdomyosarcoma, some of these patients can yet be salvaged.[14]

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