Natural History of Papillary Lesions of the Urinary Bladder in Schistosomiasis

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ABSTRACT

Variable epithelial hyperplasia was observed in urinary bladder of nine capuchin monkeys (Cebus apella) when examined at cystotomy 94 to 164 weeks after infection with Schistosoma haematobium. These hosts were followed for 24 to 136 weeks postcystotomy to determine the status of bladder lesions in relation to duration of infection and to ascertain whether lesion samples removed at cystotomy reestablished themselves in autologous and heterologous transfers. There was involution of urothelial hyperplasia in eight of nine animals and no evidence for establishment of transplanted bladder lesions.

INTRODUCTION

Observations on severe bladder pathology associated with schistosome infection were made by several investigators in the latter part of the 19th century. These suggested a causal relationship between schistosome parasites and their eggs and bladder carcinoma. Ferguson (5) is credited with the priority for making a more convincing case for the association of Schistosoma haematobium and bladder cancer.

Attempts to evaluate the carcinogenic potential of S. haematobium under experimental conditions were forestalled, since this schistosome could not be satisfactorily managed in mammals (rats, mice, guinea pigs, etc.) ordinarily used in biomedical research. This problem has been alleviated by the use of nonhuman primates in which schistosomiasis haematobia has presented a clinical and pathological picture more comparable to that in humans. Bladder lesions in experimentally infected nonhuman primates have varied in frequency, extent, duration, and histological character (8, 13, 15). We demonstrated noninvasive papillary transitional-cell lesions in several S. haematobium-infected primates (9, 10), and have designated these bladder lesions in experimentally infected nonhuman pri-

MATERIALS AND METHODS

Young adult capuchin monkeys obtained from Primate Imports, Port Washington, N. Y., were quarantined 1 month for microbiological monitoring and laboratory acclimatization prior to infection. Hosts were lightly anesthetized with Ketaset (ketamine hydrochloride), and the abdominal hair was clipped. The skin was cleansed with water prior to exposure to 1,000 or 2,000 cercariae of S. haematobium (Iran) counted in drops of water on glass coverslips. Monkeys were individually caged and fed Purina Monkey Chow.

Fifteen S. haematobium-infected capuchin monkeys, anesthetized by intravenous injection of Ketaset and mask inhalation of Florothane, were examined by laparotomy and cystotomy 109 to 113 weeks postinfection to determine the nature and extent of bladder lesions. Six, 2 exposed to 1,000 cercariae and 4 to 2,000 cercariae, were chosen for autologous transplant studies. Samples, generally 2 x 5 mm in size, were taken from one lesion in each host. A part of biopsy material was fixed for histopathological evaluation; the remaining epithelium was placed in 0.9% NaCl solution, cut into 1-mm pieces with a razor blade, and immediately transferred to other sites of each host. Injections s.c., i.m., and s.p. were made with a 12-gauge trocar. These transplant sites were examined grossly but not microscopically at the time of necropsy.

A second group of 3 capuchins was selected for transfer studies on the basis of urine cytology (J. A. Moore and R. E. Kuntz, unpublished observations). At cystotomy, bladder biopsies were placed in Hanks' balanced salt solution and injected within 30 to 45 min after removal. Some material was well macerated with tissue scissors and forceps and some was ground in a glass tissue grinder and trypsinized (2.5% trypsin for 30 min). Injections were made into the urinary bladder wall (macerated), inguinal lymph node (trypsinized), s.c. near the umbilicus (macerated), or into a femoral vein (trypsinized).

Both groups were examined at regular intervals, and sites at which sample bladder lesions had been introduced were palpated. At necropsy, hosts were processed by conventional techniques to establish basic parasitological parameters, i.e., the number and location of schistosomes, numbers of eggs in organs, and distribution of lesions (9). Samples were removed from the injection sites, except as noted above. Tissues for histological evaluations were fixed in

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buffered formalin, sectioned at approximately 5 μm, and stained with hematoxylin and eosin.

RESULTS

At cystotomy, lesions were scattered diffusely over the surface of the bladder (Fig. 1). The sectioned portions of the biopsies removed at cystotomy showed papillary hyperplasia, with or without nodular hyperplasia, in 6 of the 9 animals (Figs. 3 to 5; Table 1). In 2 animals, only focal nodular hyperplasia was seen and, in one, the epithelium was normal. Marked active S. haematobium infection was evidenced in all biopsy specimens by the presence of numerous embryonated schistosome eggs and acute diffuse and granulomatous tissue response to the eggs.

At necropsy, 23 to 114 weeks after cystotomy, marked active schistosome infection was found in the bladder of only 1 monkey (Ca-67) which died 36 weeks after cystotomy. This was the only monkey in which the epithelial hyperplasia persisted (Figs. 2 and 6; Table 1). One other monkey (Ca-23) had occasional embryonated schistosome eggs in the bladder at necropsy. In other animals, most notably, Ca-62, dead eggs persisted in the bladder, but there was minimal tissue reaction to these eggs and the urothelium was normal.

No growth of transplanted epithelium was evident by palpation, gross examination or microscopic examination. The site of transplantation was unequivocally identified microscopically in only one animal in which the schistosome eggs present in the transplanted bladder tissue were sectioned.

DISCUSSION

We have previously designated the papillary lesions in the bladder of S. haematobium-infected capuchin monkeys as low-grade papillary transitional-cell carcinomas, recognizing that this interpretation rested entirely on morphological grounds, since the lesions were noninvasive and had not metastasized. The lesions showed clear papillary growth, often with fusion of papillae, and marked thickening of the bladder epithelium. There were few mitoses and only slight atypia was present. Nodules of hyperplastic urothelium often appeared to lie beneath the epithelium, but clearcut invasion was not seen (2, 3).

The most striking finding in our study was the involution of urothelial hyperplasia in 8 of the 9 animals in which hyperplasia was detected at the time of biopsy. In all these animals the schistosome infection was no longer active in the bladder. Observations in a number of primates subjected to variable conditions of parasitism, e.g., intensity and duration of infection, have demonstrated that there is a close association of parasite residence and egg deposition to bladder involvement. We have been unable, however, to determine whether continued egg deposition in the bladder would affect the evolution of the lesions because the chronically infected monkeys were resistant to reinfection with S. haematobium (R. E. Kuntz, J. A. Moore, T. C. Huang, and A. W. Cheever, unpublished observations). The present investigation, based upon a small number of hosts selected for this particular aspect of schistosomiasis haematobia, indicates that the proliferative transitional-cell lesions have restricted growth potential. Because of their similar morphology, we would expect the lesions in schistosome-infected talapoin monkeys (9), gibbons (10), and opossums (12) to behave in a like fashion.

Friedell (6), concerned with the biology of early lesions in the urogenital system of humans, noted the difficulty in attaching a definitive diagnosis to various urothelial lesions, i.e., whether they should be classed as "precancer," "noninvasive carcinoma," or "carcinoma in situ." In this context, the production of papillary bladder lesions which later

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**Table 1**

*Cumulative data from S. haematobium-infected capuchin monkeys (C. apella) with epithelial hyperplasia in urinary bladder*

Nine monkeys with different durations of infection showed variable bladder involvement when examined by cystotomy. These hosts were followed for 24 to 136 weeks postcystotomy to determine the status of bladder lesions in relation to prolonged infection and to ascertain whether bladder lesion samples removed at cystotomy established themselves in autologous and heterologous transfers.

<table>
<thead>
<tr>
<th>Host</th>
<th>Duration (wks) of infection</th>
<th>Gross mucosal lesions</th>
<th>Activity of infection</th>
<th>Epithelial hyperplasia in bladder</th>
<th>Eggs/g bladder, in thousands, (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca 64</td>
<td>M</td>
<td>114</td>
<td>227</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Ca 70</td>
<td>M</td>
<td>94</td>
<td>172</td>
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<td>0</td>
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<tr>
<td>Ca 23</td>
<td>M</td>
<td>109</td>
<td>215</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>228</td>
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<tr>
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<td>M</td>
<td>109</td>
<td>145</td>
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<tr>
<td>Ca 111</td>
<td>F</td>
<td>135</td>
<td>159</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

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*a Abbreviations: C, examination at cystotomy; N, examination at necropsy.

*b Based on scale of + to ++++: + = slight lesions, ++++ = extensive lesions.

*c Hosts died, but death was not attributable to schistosomiasis.
regress is of unusual interest, especially since the regression of lesions associated with cancer represents a basic consideration in the understanding of carcinogenesis. As indicated by Cole (4), lesion regression may depend upon a multiplicity of factors including elimination of the carcinogen. The effect of S. haematobium infection in combination with chemical carcinogens is being examined in hamsters and baboons by Hicks et al. (7) and deserves further attention. We remain interested in the possible effects of tryptophan loading (1), vitamin A deficiency (3), and bacterial cystitis or other contributing factors in S. haematobium-infected monkeys.

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