SUMMARY

Adult Paris R-III mice with localized mammary tumors were found to have subendothelial glomerular immune complex deposits by electron microscopy and immunofluorescence. In addition to IgG and B-I-C, the glomeruli contained antigenic material that reacted with an antiserum to mouse mammary tumor virus. These findings support the hypothesis that many animals with congenitally or neonatally induced virus-related tumors are not immunologically tolerant to the oncogenic virus.

INTRODUCTION

The absence of classical immunological tolerance in animals with neoplastic disease associated with congenitally acquired virus has been demonstrated (11, 12). Overt as well as subclinical glomerulonephritis in AKR mice with spontaneous leukemia is related to the presence of C-type particles and immune complex deposits situated in the subendothelial region of the glomerular capillary wall and in the mesangium (1, 13). Viral particles, budding from mesangial cells, may have been a source of antigen for the in situ production of immune complex deposits. The additional factor of the deposition of circulating complexes could not be excluded, because antibody to leukemic cell surface antigen has been demonstrated in AKR mouse kidneys (11).

Among humans with malignant diseases, nephrotic syndrome associated with glomerular immune complexes has been reported, and most of the cases occurred with lymphoreticular neoplasms (3-6, 9, 14, 15). In a preliminary study of patients with a variety of neoplasms, but without clinically apparent nephrotic syndrome, subendothelial glomerular basement membrane deposits are seen with a significant frequency (R. R. Pascal, F. M. Rollwagen, T. A. Harding, and P. M. Iannaccone, Glomerular Immune Complex Deposits Associated with Human Malignancies, in preparation). Many animal models are available to study this phenomenon. The MMT<sup>2</sup> model used in the present study represents a virus-induced, localized, solid neoplasm with no involvement of the kidney by malignant cells. In the past, strains of mice with a high incidence of mammary tumors were believed to be immunologically tolerant to the MTV (7).

MATERIALS AND METHODS

Twelve adult, female Paris R-III/Haag (Columbia University) mice, obtained from the Department of Surgery, College of Physicians and Surgeons, were sacrificed by cervical dislocation. Portions of kidney were immediately fixed in cold 2% buffered glutaraldehyde and prepared for electron microscopy as previously described (13). One-half kidney was snap-frozen and sectioned for immunofluorescence staining as described elsewhere (13).

Goat antiserum to mouse IgG was obtained from Hyland Laboratories, Los Angeles, Calif. Goat antisera to mouse IgM, IgA, B-I-C, and fibrinogen were obtained from Cappel Laboratories, Downingtown, Pa. Rabbit antiserum to goat IgG (Cappel Laboratories) was fluoresceinated by standard methods (10). The indirect immunofluorescence staining method was used (10). Rabbit antiserum to mouse MTV, prepared and purified as described elsewhere (2, 8), was kindly supplied by Dr. Sidney Bennett of the Department of Surgery, College of Physicians and Surgeons. Fluoresceinated sheep anti-rabbit IgG was obtained from SYCCO Sylvana, Milburn, N. J.

Controls for immunofluorescence consisted of parallel incubation of the kidney sections with nonimmune goat and rabbit serum and parallel staining of kidney sections from healthy CBA female mice with the anti-MTV serum.

RESULTS

The glomeruli of all animals contained electron-dense deposits situated between the capillary endothelium and the lamina densa of the basement membrane (Fig. 1). The deposits were of varying sizes but, in general, were rather large. Deposits were also seen in the mesangial regions (Fig. 2). No subepithelial deposits were seen. No viral particles were encountered in any of the sections. Foot process fusion was variable. An occasional polymorphonuclear leukocyte was encountered near some of the deposits, but no structural damage to the basement membrane was observed. Humps of basement membrane material were frequently observed over the deposits (Fig. 1).

Immunofluorescence studies showed the presence of...
Immune Deposits in MMT

Fig. 1. Capillary loop of glomerulus from a tumor-bearing R-III mouse. A large dense deposit is situated between the endothelium (e) and the basement membrane (b). Some smaller deposits are seen in I of the humps of basement membrane (arrow). Lead citrate and uranyl acetate, × 9600.

Fig. 2. Electron-dense deposits (arrows) within the mesangial matrix of a glomerulus. m, mesangial cell; b, basement membrane. Lead citrate and uranyl acetate, × 9600.

Fig. 3. Glomerulus of R-III mouse stained with rabbit anti-MTV and fluoresceinated sheep anti-rabbit IgG. There is strong fluorescence in the capillary loops and mesangium. × 1200.

DISCUSSION

Adult female Paris R-III mice bearing mammary tumors are capable of forming humoral antibodies against the mouse MTV. Although the virus was introduced during suckling, these mice are not immunologically tolerant to the virus. Lack of classical immunological tolerance to onco-genic viruses introduced in utero has previously been demonstrated in AKR leukemic mice (11–13). The glomerular immune complex deposits in AKR mice contain leukemic cell surface antigen and Gross virus antigen (11) as well as formed viral particles (1, 13). The PR-III mouse glomeruli contain immune complex deposits, but, as yet, no viral particles have been found in association with the deposits. By immunofluorescence, these deposits contain IgG, B-1-C, and antigenic material related to the mouse MTV. Antigenic material from mammary tumor cell membranes may also be involved in these immune complexes. Others (1) have noted that cell membrane material may be present in purified virus preparations. Preliminary studies of an eluate of kidneys from MMT-bearing PR-III mice have shown reactivity between the eluted antibody fraction and MMT cells. (S. J. Bennett, M. N. Koss, S. F. Slovin, and R. R. Pascal, Demonstration of a Tumor Cell-Reactive Antibody in Kidneys of Mice Bearing Mammary Tumors, in preparation).

The glomerular deposits in the AKR mice (13) and the PR-III mice occur in the subendothelial region and in the mesangium. This would suggest that the antigenic material is of relatively large size and that the complex is unable to cross the basement membrane.

In the absence of viral particles in the glomeruli of the PR-III mice studied, we believe that the renal lesions are the result of the deposition of circulating immune complexes consisting of antigens related to the MTV and to mammary tumor cells plus their corresponding antibodies. The rela-
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...relationships, if any, of this humoral antibody response to the suppression or enhancement of tumor growth in the host are unknown.

REFERENCES

Glomerular Immune Complex Deposits Associated with Mouse Mammary Tumor


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