Subclinical Immune Complex Nephritis in Patients with Hodgkin’s Disease

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Summary

Kidneys from 55 patients with Hodgkin’s disease were examined by immunofluorescence for the presence of glomerular immune complex deposition. Two of 23 postmortem kidneys and 5 of 22 biopsied during staging laparotomies stained positively for γ-globulin and complement. None of the patients exhibited clinical evidence of glomerulonephritis and all kidneys were essentially normal histologically. Previous studies analyzing subclinical glomerular immune complex deposition in 2 patients with acute leukemia have identified a mammalian oncornaviral related antigen. The nature of the antigen or antigens being observed within the present study have not yet been defined.

Introduction

During the last few years, some chronic viral infections in animals have been studied in which no circulating antibodies to the etiological agent could be detected by ordinary serological methods. Because of these negative findings, mice with lymphocytic choriomeningitis (2) and mice with spontaneous leukemia (9) were considered immunologically tolerant to the etiological agent. In mice with lymphocytic choriomeningitis, however, antibody to virus complexed to viral antigen has been found deposited on glomerular basement membranes (11). Similarly, immune complexes were found in kidneys of AKR mice which contained G (Gross) antigen (10) and antigens of the internal nucleoid (7).

Although the deposition of such complexes has generally been associated with light microscopic changes consistent with nephritis, recent studies have suggested that immune complex deposition may occur in the absence of overt nephritis. Markham et al. (8) have studied the incidence of immune complex deposition in the glomerulus of the normal laboratory mouse and have found that such deposition occurs in roughly 80% of normal laboratory mice. In addition, Banks and Henson (1) have demonstrated that normal horses have immune complexes deposited in glomeruli in the absence of overt nephritis.

The ability to elute both antibody and antigen from kidneys having immune complex deposition makes the kidney a focal point in the study of host immune responsiveness in situations in which such responsiveness cannot be detected utilizing standard immune assays. We recently have reported the occurrence of subclinical immune complex nephritis in 9 of 94 postmortem kidneys obtained from patients with lymphoma or leukemia (14). Two of these patients, having acute myelogenous leukemia, were found to have an antigen in these complexes identical to or related to the gs-3 antigen of the mammalian oncornaviruses. This report details our preliminary findings concerning the incidence of subclinical immune complex nephritis in Hodgkin’s disease. An analysis of our present results which include the study of 23 kidneys obtained at autopsy and 22 surgical biopsies obtained at staging laparotomy is made.

Although the nephrotic syndrome has occurred in association with Hodgkin’s disease (5, 6, 13), none of the patients reported in the study had glomerular changes as determined by either clinical or light microscopic criteria.

Materials and Methods

Whole kidneys were obtained at autopsy from 23 patients, 7 women and 16 men. Their ages ranged from 17 to 67 with an average of 41. The original diagnostic lymph nodes were classified as nodular sclerosing (10 patients), mixed cellularity (8 patients), lymphocyte predominant (3 patients), and lymphocyte depleted (1 patient). One was unknown to us. Twenty-two biopsies were taken from kidneys during staging laparotomies. Eleven of these patients were classified as being in Stage III of the disease and the rest as being in Stages I or II. The histological classification was nodular sclerosing Hodgkin’s disease in 20 and mixed cellularity in 2.

Our methods for evaluating the presence of glomerular immune complexes have been previously described (14). In brief, cryostat cut sections of cortex were fixed in acetone and stained with the following fluoresceinated antisera: goat anti-human γ-globulin (IgG, IgM, and IgA), rabbit anti-human βc-globulin (C13), rabbit anti-human fibrinogen, and rabbit anti-human albumin. Slides were evaluated with a Leitz microscope utilizing an Osram HB-200 light source and UG-1 excitor filter in combination with a K460 barrier filter. For purposes of photography, either a BG12 or a KP490 excitor filter was used in combination with a K530...
Barrier filter. Kidneys were considered putatively positive for immune complexes if γ-and βc-globulins were found deposited in an irregular or segmental pattern on glomerular basement membrane. Absolute documentation of immune complex deposition can be made only if antigen is also defined, thus the use of the word putative in the preceding sentence.

The results of staining are summarized in Table 1. Immune complexes were found in 9% (2 of 23) of kidneys taken at autopsy and 23% (5 of 22) of kidneys sampled during laparotomy. The distribution of globulin was capillary in 3 kidneys and capillary and mesangial in 3, and in 1 it was capillary when stained for γ-globulin and capillary and mesangial when stained for βc-globulin. The extent of the positivities ranged from involvement of all loops in all glomeruli to an average of 10% of the loops in only 10% of the glomeruli. Fluorescence in the postmortem kidneys tended to be more extensive when assessed on this basis than in those sampled during staging laparotomy.

Four of the 23 patients from whom kidneys were taken postmortem had clinically or histologically evident terminal viral infections. One had an acute hepatitis of possible viral origin, another had herpes zoster, and 2 others had cytomegaloviral pneumonia. Immune complexes were not found in the kidneys of these patients. There was no evidence of a clinically or histologically evident terminal viral infection in the 2 patients whose kidneys contained immune complexes.

Discussion

This preliminary screening study has demonstrated that a significant percentage of kidneys tested either early in the course of Hodgkin’s disease (23%) or postmortem (9%) had subclinical immune complex nephritis. The criteria for concluding putative immune complex deposition consisted of finding both γ- and βc-globulins in the same locus on basement membrane in a segmental or irregular pattern. A more detailed outline of these criteria has previously been published (3, 4). We have not as yet defined the antigens present in these complexes. If they are viral antigens, the most likely candidates would be viruses whose infectious course would be characterized by chronicity and minimal host responsiveness (12).

The analysis of immune complex nephritis in NZB X W mice indicates that multiple complexes may be present (15). In these mice, 45% of the antibody eluted from kidney represented antinuclear antibodies, 21% was anti-Gross antibodies, while the specificity of the remaining molecules was unaccounted for. The demonstration by Markham et al. (7) of the ubiquitous occurrence of immune complex deposition in normal mice and the analogous demonstration of immune complex deposition in normal horses by Banks and Henson (1) suggest that the clearance by fixation to glomerular basement membrane may be a common route for the catabolism of select populations of antigen-antibody complexes during the natural history of all or a majority of antibody complexes. It has been our observation that acute infections terminating in death in patients with neoplasia are not necessarily associated with detectable immune complexes.

The analysis of subclinical immune nephritis in patients with neoplasia may allow the demonstration of minimal host responsiveness to antigens in situations in which such responsiveness cannot now be determined and should provide a mechanism to search more thoroughly for antigens and the response to antigens associated with agents now putatively considered to play a role in human neoplasia.

References

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