Glomerular disease in human malaria has long been recognized (Goldie, 1930; Laha, 1945). However, it was only in the last two decades that this subject has attracted considerable interest again. Two distinct groups of glomerulonephritis responsible for acute renal failure were reported to be specific for Plasmodium falciparum and P. malariae, respectively (Hartenbower et al., 1972) and their causation has to be regarded as species-specific interaction between host and parasite (Houba, 1979). The first group is characterized by a glomerular inflammation that develops during the clinical course of acute falciparum malaria, and a nephrotic syndrome may occur (Berger et al., 1967). Granular deposits of IgM and B1C- globulin with or without IgG accompanied by various types of inflammatory cells were detected in morphologically altered glomeruli, indicative of an immunopathological process (Bhamarapravati et al., 1973). Granular deposits of P. falciparum antigens were demonstrated in autopsy tissue. The second group is represented by the chronic progressive glomerulonephritis associated with P. malariae infection, and known as malarial nephropathy (Lancet, 1972; Hendrickse et al., 1972; White, 1973). Despite the several immunopathological investigations on the renal glomeruli in humans and experimental animals infected with the malaria parasite (Houba et al., 1971, 1976; Boonpucknavig et al., 1972, 1973, 1979; Bhamarapravati et al., 1973; Suzuki, 1974), studies on the ultrastructural pathological alterations of human glomeruli during acute infection with P. falciparum is still limited. This is the tenth paper in this series on human falciparum malaria (El-Shoura, 1993 a,b,c; El-Shoura, 1994 a,b; El-Shoura & Al-Amari, 1993 a,b; El-Shoura et al., 1993 a,b), and presents the result of our detailed

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MATERIALS AND METHODS

Nine patients aged 5 (2M + 1F), 10 (1F), 12 (1M + 1F), 25 (1M + 1F) and 56 (1M) years were admitted with a diagnosis of acute falciparum malarial infection. All patients had a history of fever with rigors of less than one week's duration before admission. Falciparum malaria parasites were seen in the peripheral blood films of all patients. Parasitaemia, i.e. the parasite count (PC) was expressed as the absolute number of parasitized erythrocytes per microliter (µL) blood. The mean PC was 63,720 PC/µL in all patients. Laboratory examination showed variable degrees of proteinuria with or without microscopic haematuria in all patients, in addition to aedema, the main diagnostic criteria of the nephrotic syndrome. All patients were treated with oral chloroquine alone and none showed the presence of malarial parasites at the time of kidney biopsy. Patient 4 had a glucose-6-phosphate dehydrogenase deficiency of the erythrocytes and developed acute renal failure that required peritoneal dialysis before she recovered.

For examination by transmission electron microscopy (TEM), percutaneous (needle) kidney biopsies were performed 10 days after the antimalarial treatment in all patients. Each biopsy was directly fixed in 2.5% glutaraldehyde in 0.1M sodium cacodylate buffer, pH 7.2, for 2 h at room temperature, postfixed in 1% osmium tetroxide, dehydrated in an ascending series of ethanol, and embedded in Spurr's resin through propylene oxide. Thin sections were stained with uranyl acetate and lead citrate, and examined in a Jeol 1200 EX TEM at 80 kV.

RESULTS

Except for a few differences, the detected glomerular ultrastructural alterations were similar in all cases. Glomeruli were generally large and hypercellular (Figs. 1, 2) due to an increase in endocapillary cells and an infiltration types of blood cells. The capillary lumen in the first four cases were characterized by the presence of erythrocytes and polymorphonuclear cells (Figs. 1-4), in addition to monocytes, lymphocytes and blood platelets in case 4 (Fig. 5). Leukocytic cytoplasmic processes extended to abut the endothelial cell surrounding the capillary lumen (Fig. 4). Many erythrocytes were also observed in the urinary space of case 5 glomeruli (Fig. 6). The capillary lumena were occasionally occluded either by swollen, hypertrophied, or by enlarged, projected endothelial cells (Figs. 1-3). The overlying epithelial cells, or podocytes, appeared normal in some glomeruli; their cytoplasm was rich in cell organelles including Golgi bodies, rough endoplasmic reticulum, mitochondria, submembranous pits and vesicles, and numerous free and polyribosomes (Fig. 7). Their foot processes were conspicuous and abuting the capillary basement membrane (Fig. 7). In altered glomeruli, the epithelial cells were hypertrophied, with a moderate to electron-dense cytoplasmic matrix (Fig. 4), or appeared aedematous filling the urinary space (Figs. 8, 9). These cells showed extensive diffused foot process fusion and numerous villous transformation (Figs. 1-4, 6, 8, 9). The glomerular capillary basement membranes were, in places, extremely thin, thick or completely missing (Fig. 8), or contained membranous structures. Three to five large mesangial cells with increase cytoplasmic matrices were apparently undergoing cell proliferation as indicated by the presence of centrioles in vicinity to the cell nuclei (Fig. 10). Increase of the marginal mesangial matrices obviously leads to the distortion of the surrounding capillaries (Fig. 1). Bowman's capsule was slightly thickened and showed poorly differentiated electron-dense deposits (Fig. 6). Characteristic subepithelial coarse granular deposits in the form of "hump-like" were seen in most cases (Figs. 4, 5). In addition, varying amounts of coarse and fine granular deposits were also detected in some mesangial matrices (Figs. 3, 10), and occasionally within the basement membrane. The largest amount of deposit was detected in cases 1-3 in which the patients were 5 years old (2M+1F) and their parasitaemia levels were the highest (Mean 165.230 PC/µL).

DISCUSSION

The present study showed that various glomerular histopathological alterations were developed during the acute infection with P. falciparum. Although these alterations were similar in all studied cases, the deposited material varied in amount and density from one case to another. With regard to glomerular histopathology, previous reports showed considerable variation. Proliferate glomerular lesions including minimal focal and lobular involvement in 29 of 31 cases with parasitaemia were found during studies of the malaria nephropathy in Uganda.
Fig. 1 et 2. - Hypercellular glomeruli (Cases 1 and 2, respectively). Note the enlarged endothelial cells (E) projected into (Fig. 1) or occluding (Fig. 2) the capillary lumen (C). Note also the numerous villous transformation (*) of the podocyte (P) foot processes. Fig. 3. - A part of a glomerulus (Case 3) showing capillary lumena occluded by endothelial cells (E). Note the mesangial deposit (D). R, lumenal erythrocytes. Fig. 4. - A blood capillary of a glomerulus (case 4) showing a polymorphonuclear cell (N) projecting cytoplasmic processes (thin arrow) abuting the endothelial cell (E). Note the subepithelial deposit (D) in the form of ‘hump-like’. Bend arrow points to fused foot processes. Asterisk represents villous transformation. Fig. 5. - A capillary lumen (C) enclosing blood platelets (case 4). D, subepithelial ‘hump’-like deposits. Fig. 6. - A part of a glomerulus (case 5) showing erythrocytes (R) in the urinary space (U). Short solid arrow points to fused foot processes. Long empty arrow represents poorly differentiated deposits in the Bowman’s capsule (B). Other letterings as in Figs. 1 and 2.
Fig. 7. - A normal looking podocyte (P) (case 6) with conspicuous foot processes beneath the regular capillary basement membrane (B). C, the capillary lumen. Fig. 8. - A part of altered glomerulus (case 7) showing oedematous epithelial cells (P). Note the extremely thin (straight solid arrow), missing (bend empty arrow) and thick (winged arrow) places of the capillary basement membrane (B). Other letterings as in Fig. 2. Fig. 9. - As in Fig. 8 but showing a rather regular capillary basement membrane (B) (case 8), but the endothelial cell (E) appears damaged. P, oedematous podocytes. Fig. 10. - Mesangial cells (m) (case 9) showing a centriole (thick arrow) indicating proliferation. Note also the mesangial deposits (thin arrows).
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While the present study has focused primarily on glomerular damage, one cannot exclude the possibility that tubular changes (hemoglobinuric nephrosis and hemosiderosis) and sequelae may be an additional feature of malarial nephropathy, as has been noted in many early studies of malaria.

CONCLUSION

This study showed that the glomerular pathological alterations during acute infection with falciparum malaria are as follows:

1. Hypercellular glomeruli with capillary blood cells.
2. Increase of endothelial cells in number and size.
3. Hypertrophied epithelial cells with fused podocytes and villous transformation.
4. Irregularly thickened BM.
5. Mesangial proliferation and increase in cell matrices.
7. The largest amount of deposits were detected in the youngest patients, in whom parasitaemia levels were the highest, indicating that the amount of immune deposits may correlate with both age of patients and the degree of parasitaemia. However, these pathological alterations correspond, for certain extents, to the membranoproliferative glomerulonephritis with abnormal deposits and seem to be specific morphological features during the course of acute infection with falciparum malaria.

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