Glomerulonephritis in the Tropics: Who Are the Culprits?

Glomerular disease is common in tropical regions and may complicate many locally prevalent infections by a variety of mechanisms. In areas where HIV and malaria are common, these may be factors predisposing to renal disease. Primary glomerulonephritis also occurs in these regions, and the nature of the renal lesion can only reliably be determined if renal biopsy and expert histologic analysis are available. Assistance to the developing world in provision of these skills and resources is a major priority for the International Society of Nephrology. This article highlights some general principles regarding glomerular disease in the developing world, illustrated by the author's experience in rural Uganda. (*Ethn Dis*. 2006;16[suppl 2]:S2-52–S2-55)

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Introduction

Glomerular disease is an important cause of illness and death throughout the world. The predisposing/causative factors, clinical features, renal histology, treatment, and outcome have all been less extensively studied in the developing world, including many tropical regions, than in more affluent countries. Reviewing what is known about glomerular disease in the world's various geographic, climatic, and economic regions would be a huge task, but in this brief article I highlight some general principles and illustrate these with my experience in one tropical part of the developing world, rural Uganda.

Glomerulonephritis

The term glomerulonephritis (GN) covers a group of conditions in which the glomerulus is inflamed. Glomerulonephritis (GN) may occur as a primary disorder limited to the kidney, as part of various systemic illnesses (such as lupus or vasculitis), or as a complication of various infections, tumors or drugs; in these latter situations, GN is classified as "secondary" and the treatment and prognosis depend entirely upon the underlying cause. For example, most drug-induced GN will improve once the offending agent is withdrawn; the prognosis of tumor-associated GN generally relates to the prognosis of the tumor itself. In the developed world, GN is believed to be a complication of an underlying infection in few cases. Since communicable diseases are much more common in the developing world, infection is likely to be a much more important underlying factor in GN in these regions. Therefore, much GN in the developing world is secondary, and

opportunities exist for improved management if locally prevalent infections can be identified and treated or, ideally, prevented. Physicians seeing patients with GN in the developing world should actively seek underlying infections in their patients, which, if eradicated, might lead to improvement or even resolution of the glomerular injury.

Mechanisms Whereby GN May Complicate Infection

(a) Antigenic cross-reactivity. Classical post-infectious GN, of which the archetypal example is post-streptococcal GN, may result from antigenic cross-reactivity between the pathogen and intrinsic glomerular antigens.[1]

(b) Immune complex deposition. Any chronic sepsis, particularly pyogenic bacterial sepsis, can lead to generation of immune complexes: circulating complexes of antigen and antibody (immunoglobulin). These can deposit in tissues, and the glomerulus is particularly likely to be the site of such deposition. Inflammation ensues with complement fixation and/or engagement of leukocytes via their Fc receptors.

(c) Microangiopathic hemolytic anemia (MAHA). MAHA is a feature of hemolytic uremic syndrome (HUS), in which renal injury is predominantly in the glomerulus and consists of microthrombi in the glomerular capillaries. HUS most commonly complicates infection with particular serotypes of toxin-producing *Escherichia coli* but can also be a result of other infections. MAHA may occur as

a consequence of other infections, especially with gram-negative bacteria. Obstetric causes of MAHA include preeclampsia, placental abruption, intrauterine death, or retained products of conception.

(d) Cryoglobulinemia. This syndrome may include rash, arthritis and/or GN and results from the presence in the circulation of an immunoglobulin with physicochemical properties that favor precipitation at colder temperatures. It may be a complication of viral infection, especially with hepatitis C virus.

(e) Secondary amyloidosis. Any chronic infection may lead to the deposition in the tissues of amyloid, and the glomerulus (and indeed other blood vessels in the kidney) is typically affected.

(f) Specific infections, eg, HIV and malaria. Several specific infections may have glomerular manifestations: two that are particularly relevant to the tropics are HIV and malaria.

Glomerular Injury in HIV

As prophylaxis and management of opportunistic infections in HIV-infected individuals improves, and access to antiretroviral drugs for the developing world is widened, longer-term complications of HIV infection can be expected to be seen increasingly frequently. In the developed world, kidney involvement is one such manifestation, and the glomerular manifestations can take several forms:[2,3]

(1) HIV-associated nephropathy (HIVAN) can cause nephrotic syndrome and rapidly progressive loss of excretory kidney function. The typical glomerular changes are focal segmental glomerulosclerosis and proliferation of glomerular epithelial cells (podocytes) in Bowman's space, which may compress the glomerulus (so-called collapsing glomerulopa-thy). There is evidence that HIV can directly infect podocytes, causing dedifferentiation and proliferation of these cells.[4] Other typical histologic features reported include interstitial inflammation/fibrosis and tubular dilatation: the latter may be marked and cause microcystic change.

(2) HUS may complicate HIV infection.

(3) "Conventional" infection-related GN is more frequent because of the predisposition of immunocompromised individuals to acute and chronic bacterial and other infections.

(4) "Primary" GN has been reported to be more common in HIV-infected individuals, especially IgA nephropathy.

(5) There may be complications of co-infections, for example, with hepatitis B or C viruses, which have their own typical glomerular manifestations (membranous GN with chronic hepatitis B, cryoglobulinemia with hepatitis C).

(6) Opportunistic infections themselves can directly involve the glomerulus (Figure 1).

Malaria and the Kidney

The classical renal syndrome associated with malaria is "blackwater fever," the passage of dark urine containing blood pigments as a result of intravascular hemolysis. This typically occurs in acute malaria due to *Plasmodium falciparum* and is more common in individuals with inherited erythrocyte enzyme defects such as deficiency of glucose-6-phosphate dehydrogenase. Fever, hypotension, and intravascular volume depletion together with severe anemia may cause pre-renal acute renal failure, which is probably common in malarious areas. More controversial are the glomerular syndromes putatively associated with malaria. Old literature from Africa describes an association between proteinuric renal disease, espe-cially in children, and quartan malaria caused by *P. malariae*.[5–7] Our observations from Uganda did not support this association,[8] and GN is also common in areas where *P. malariae* is rare. Another issue on which little definitive information is available is the question of whether repeated episodes of acute renal failure due to malaria can culminate in chronic renal impairment: the author is among those who think this is likely to be the case.

MBARARA, SOUTHWESTERN UGANDA

The author has been privileged to visit Mbarara University Medical School on several occasions in recent years as part of a teaching link with Bristol University. Mbarara is located close to the equator in tropical Uganda, close to the borders with Congo to the east and Rwanda and Tanzania to the south. It is a rural area where many of the population live in remote areas. Traditional healers are often consulted first because of geographic proximity and prevalent local beliefs. Malaria is common, mostly due to *P. falciparum*, and chloroquine resistance is widespread. HIV seroprevalence in the local population has not been precisely defined but is believed to be around 10%, with the seroprevalence among hospital in-patients being much higher, maybe 40%–50% in adults. The incidence of proteinuric renal disease in Mbarara is high, particularly in children. A retrospective review of admissions to the children's ward at Mbarara showed that GN was at least 10 times more common than in the United Kingdom, that nephritic presentations with hypertension, active urinary sediment, and acute renal failure were most frequent and carried the worst prognosis, that the death rate was high (at least 17% of children died).[8] We found no evidence to implicate HIV as a causative factor in this age group, and we also found that *P. malariae* was rare and unlikely to be implicated. More
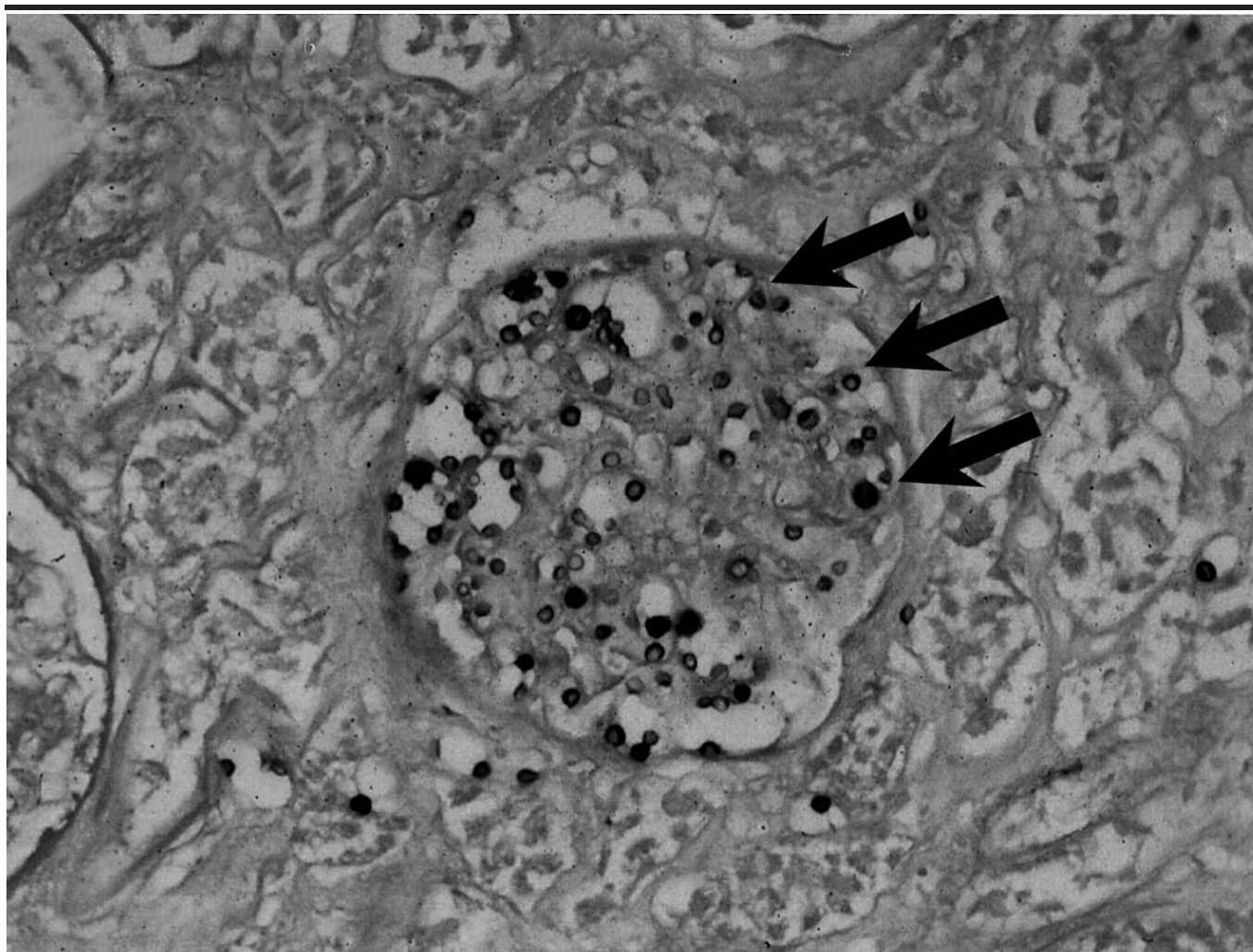
Fig 1. Glomerular involvement in disseminated cryptococcosis in an HIV-infected individual. Numerous blue ring-staining infectious particles are seen in glomerular capillaries (arrow) (hematoxylin and eosin stain)

recently we conducted a prospective study in Mbarara, including renal biopsy in selected cases (unpublished observations). Most renal biopsies have shown a characteristic proliferative GN in which eosinophil infiltration is a prominent feature (Figure 2).

GN IN MBARARA: WHO ARE THE CULPRITS?

This is the subject of ongoing investigation. HIV and malaria are locally prevalent but are not obviously implicated. Evidence of recent streptococcal infection is common in Mbarara (positive tests for anti-streptolysin O and anti-

DNAse B were common in our series) but did not correlate with the renal lesion. Low serum complement (C3 and/or C4) was also common but again did not correlate with GN. The eosinophilic infiltrate suggests the involvement of parasitic infection: filariasis is locally prevalent and has previously been implicated in the causation of a similar glomerular lesion.[9] Dietary components may cause eosinophilic reactions,[10] and this is another possibility, as is some component of local traditional medicines.

As socioeconomic conditions in rural Africa improve, infection and its consequences, including GN, should become less prevalent. Meanwhile, the search goes on for preventable and/or

treatable causes of renal injury. In resource-poor settings, renal failure is a death sentence: prevention must be the key for the future.

CONCLUSIONS

In the developing world, GN is more commonly a complication of infection than in the developed world: a search for treatable and/or preventable infections is worthwhile. Any locally prevalent infection can be implicated, and numerous mechanisms exist whereby infection can predispose to glomerular disease. Renal biopsy is essential for accurate characterization of the renal lesion but is often not
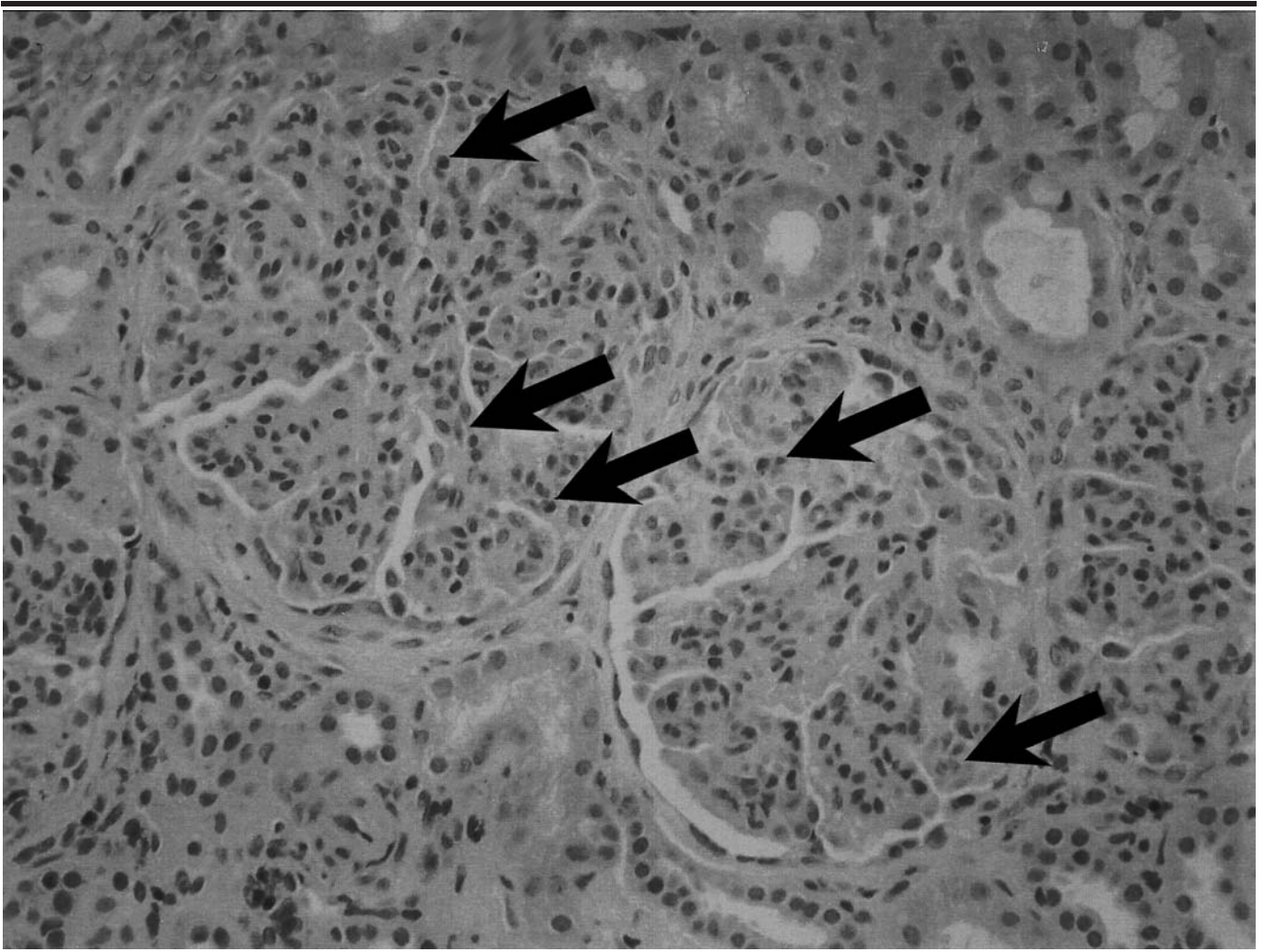
Fig 2. Renal biopsy from a child with acute nephritis in Mbarara, southwest Uganda. The figure shows a diffuse proliferative glomerulonephritis in which eosinophils are prominent (arrow) (hematoxylin and eosin stain)

easily available. The International Society of Nephrology is helping to tackle this problem by providing training and education to physicians and pathologists via teaching visits and link programs to centers in the developed world.

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