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# A clinicopathological study of 24 children with hemolytic uremic syndrome

## A report of the Southwest Pediatric Nephrology Study Group*

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**Abstract.** This study reports the pattern of renal injury in 24 North American children with hemolytic uremic syndrome (HUS), and the extent of extrarenal involvement in 9 of these children examined at autopsy. Fifteen of the 24 children were studied during the first 16 days of hospitalization; their renal specimens demonstrated glomerular thrombotic microangiopathy (TMA) in 8 children, cortical necrosis in 1, and varying degrees of glomerular TMA and cortical necrosis in 6 children. Nine of the children were studied after 16 or more days of hospitalization; these patients had prominent renal arterial lesions. Of 9 children examined at autopsy, extrarenal microthrombi were identified in 8. In 4 children who died during the acute phase of the disease, hemorrhagic colonic necrosis (3 children) and pancreatic islet cell necrosis (2 children) were the principal extrarenal lesions encountered. Rare microthrombi were present in the brains of the 3 children who manifested seizures.

**Key words:** Hemolytic uremic syndrome – Renal failure – Thrombotic microangiopathies

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## Introduction

The hemolytic uremic syndrome (HUS) is a clinical syndrome that is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure [1–3]. Since renal biopsies are usually not required for diagnosis and since most pediatric patients with HUS recover, renal tissue is rarely obtained from North American children with idiopathic HUS. Histopathological studies of HUS from individual pediatric nephrology centers in North America have, therefore, been limited. Much of the information pertaining to the re-

nal lesions associated with childhood HUS comes from studies in France [4]. These studies have revealed three major morphologicae patterns of renal injury in such patients: (1) glomerular thrombotic microangiopathy (TMA); (2) arterial TMA, and (3) cortical necrosis (CN) [4]. Similar morphological patterns have been described by others using slightly different nomenclature [5]. It has been reported that the lesions of CN and glomerular TMA are usually associated with patient recovery, whereas patients with arterial TMA often develop hypertension and chronic renal failure.

Although HUS was originally distinguished from thrombotic thrombocytopenic purpura by the clinical absence of extrarenal involvement, more recent reports of extrarenal involvement in HUS have blurred the distinction between these two syndromes [6]. However, the mortality in young children with HUS is low; hence, morphological evidence of extrarenal involvement in North American children has not been extensively reported.

The present study reports the spectrum of renal lesions observed in 24 children with HUS by members of the Southwest Pediatric Nephrology Study Group (SPNSG). These observations were made in approximately 10% of all patients with idiopathic HUS treated in our centers during the period of study [7]. The extent of extrarenal involvement is reported in 9 children who were autopsied [8, 9].

## Patients and methods

Clinical data and histological materials were reviewed in 24 of 243 children with HUS presenting to the SPNSG centers. The 24 patients included 17 with primary, non-familial HUS,2 with recurrent HUS, 3 with familial HUS, and 2 patients with HUS superimposed on pre-existing conditions. In the familial cases, the onset of symptoms in the siblings began within days of one another. Of the 243 children, 13 died, including 3 children in whom the HUS was familial.

### *Renal studies*

Twenty-six renal specimens were studied; i.e., a follow-up renal specimen (repeat biopsy or autopsy) was available for 2 children. Glass slides of renal specimens were prepared using standard methods from 12 renal biopsies (mean 3.3 slides per specimen, range 2–4), five bilateral nephrectomies (mean 9 slides per specimen, range 4–18), and nine autopsies (mean 33 slides per patient, range 21–49). These slides and the original pathology reports were examined by two SPNSG pathologists (JCA, TJP), using a prepared checklist that considered 40 different light microscopic variables.

Renal lesions were graded on a scale of 0–4+, according to the approach described by Pirani et al. [10] and utilized in previous SPNSG studies [11]. The patterns of renal injury described by Habib et al. [4] were also determined for each specimen. These were defined as follows.

*Glomerular TMA.* These were specimens in which swelling and detachment of the endothelial cells resulted in thickening of the glomerular capillary walls and narrowing of the capillary lumina. Fibrillary material in areas of swelling, as shown by electron microscopy, and thrombosis of capillary lumina, were often present in these specimens. The number of affected glomeruli varied considerably and additional glomerular lesions were present, including so-called paralytic glomeruli with extremely dilated and congested capillary lumina and ischemic glomeruli with wrinkled glomerular basement membranes [4]. The renal arteries, with the exception of an occasional thrombus in a glomerular arteriole, were uninvolved in specimens classified as glomerular TMA.

*Arterial TMA.* Specimens classified as arterial TMA showed renal tissue in which the arterioles and interlobular arteries were narrowed or obstructed by swelling of the endothelium and/or thrombi. Fibrinoid mural necrosis and intimal swelling and proliferation were regarded as "early" arterial TMA. Arteries showing fibrous replacement of the thickened intima and laminar intimal fibroplasia (so-called "onion-skinning") were regarded as "late" arterial TMA. The glomeruli in arterial TMA sometimes showed changes similar to those seen in a glomerular TMA, but shrinkage of the tuft and wrinkling of the basement membrane were commonly observed. Segmental or global glomerular sclerosis and tubular atrophy were regarded as late changes [4].

*Cortical necrosis.* This lesion was characterized by recent or old infarction of all cortical structures in a portion of the renal tissue, sometimes accompanied by dystrophic calcification of infarcted tissues.

**Table 1.** Summary of selected clinical and laboratory findings from 24 children with hemolytic uremic syndrome (HUS)

| | |
|---|---|
| Number of patients | 24 |
| Male/female ratio | 12/12 |
| Age at presentation: | |
| Mean | 48 months |
| Range | 6 months – 12 years |
| Type of prodrome: | |
| Gastrointestinal symptoms | 17 (70%) |
| Upper respiratory tract infection | 4 (17%) |
| Central nervous system symptoms | 3 (13%) |
| Anemia[a] (hematocrit less than 25%) | 22 (92%) |
| Thrombocytopenia[a] (platelets less than 100,000/mm$^3$) | 22 (92%) |
| Acute renal failure (serum creatinine more than 3.5 mg/dl)[a] | 23 (96%) |
| Anuria (greater than 1 day) | 22 (92%) |
| Severe systemic hypertension[a] (diastolic greater than 90 mmHg) | 21 (87%) |
| Outcome | |
| Died | 10 (42%) |
| Required transplantation | 6 (24%) |
| Chronic renal insufficiency (2-to 5-year follow-up) | 5 (21%) |
| Complete recovery of renal function | 3 (13%) |

[a] The values are the most extreme recorded

When more than one of the three patterns were present, the specimen was classified as having a combination of patterns. In addition to the light microscopy studies, electron photomicrographs and results of immunofluorescence studies performed on eight renal biopsies were reviewed.

*Extrarenal studies*

Nine patients, including one familial case, were also examined at autopsy for extrarenal thrombi, hemorrhage, necrosis, and any other vascular disease process. The severity of the extrarenal lesions was semi-quantified on a 0–3+ scale.

## Results

### *Clinical findings*

By definition, a microangiopathic hemolytic anemia was present in the peripheral blood smear of all 24 children included in this study. No specific infection was identified in any patient. In the 17 children with primary, non-familial HUS, 12 had a typical presentation characterized by a 3- to 6-day diarrheal prodrome and 2 had a preceding upper respiratory tract infection. Central nervous system symptoms (seizures, headaches, hemiparesis) predominated in 3 patients, including 1 whose renal failure was mild. In 2 children, the HUS was recurrent. Depressed serum C3 concentrations were documented in one girl who had recurrent HUS. The details of this case have been reported previously [12]. In 3 children, the siblings had concurrent HUS. Mortality was high (3 of 8 children overall) in the pairs of siblings who had concurrent HUS. In one case, the HUS was superimposed upon what was considered a recessive form of polycystic kidney disease and another had a previous diagnosis of focal segmental glomerulosclerosis. With respect to histological findings, children with idiopathic HUS and those with unusual clinical features were similar. The outcome of the 24 patients in this study was generally very poor; 10 of the patients died (autopsy not performed in 1), and 5 of them progressed to end-stage-renal disease (ESRD) and underwent renal transplantation. In only 3 of the 24 patients has renal function returned to normal after 2–7 years of follow-up (Table 1).

### *Early patterns of renal injury*

Glomerular TMA was noted in 8 of 15 specimens obtained during the first 16 days of hospitalization; 70%–100% (mean 86%) of glomeruli demonstrated segmentally or globally the thickening of the capillary walls and narrowing of the glomerular capillary lumens which characterizes the predominantly glomerular TMA pattern. Glomerular thrombi were seen in 5 of 8 specimens, but were numerous (3+) in only 2. Focal mural necrosis of afferent arterioles was present in three of eight kidneys, but larger arteries were morphologically uninvolved. Diffuse cortical necrosis was seen in 1 biopsy specimen and a combination of CN and glomerular TMA was seen in the remaining 6 specimens obtained during the first 16 days of hospitalization. In 3 of 6 specimens in which necrosis was subtotal (5%–10%; mean 59%), arterial and glomerular thrombosis was present at the edges of the cortical infarcts. Arterial thrombosis in this context was not regarded in our study as evidence of arterial TMA. In specimens with subtotal CN, glomerular TMA predominated in the

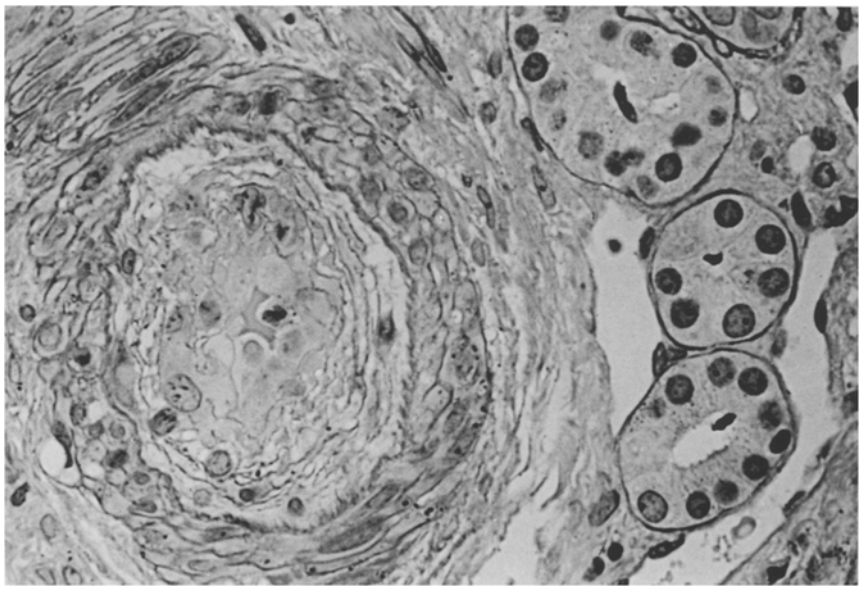

**Fig. 1.** Interlobular artery from a hypertensive patient nephrectomized 18 days after hospitalization. There is marked intimal fibroplasia characteristic of an arterial thrombotic microangiopathy. Periodic acid-Schiff, ×400

**Table 2.** Summary of autopsy findings from nine children with HUS

| Patient no. | Age at onset | Clinical presentation | Days in hospital | Morphological findings | | | Cause of death |
|---|---|---|---|---|---|---|---|
| | | | | Pattern of renal injury | Necrosis | Thrombi | |
| 1 | 1 year | Vomiting, bloody diarrhea | 2 | G, CN (5%)[a] | Kidney (1+)[b] | Kidney (2+) | Catheter-induced cardiac tamponade |
| 2 | 2 years | Bloody diarrhea, DIC | 3 | G | Colon (3+) | Kidney (3+)<br>Colon (2+)<br>Lungs (1+)<br>Adrenals (1+) | Shock (tissue necrosis versus sepsis) |
| 3 | 14 months | Vomiting, diarrhea, respiratory arrest, coma | 3 | G, CN (90%) | Kidney (3+)<br>Colon (3+) | Kidney (1+)<br>Colon (2+) | Shock (tissue necrosis versus sepsis) |
| 4 | 11 years | Headache, purpura, DIC | 4 | G | Pancreas (2+) | Kidney (1+)<br>Pancreas (3+)<br>Heart (3+) | Hemopericardium |
| 5 | 3 years | Familial, vomiting, bloody diarrhea, hyperglycemic coma | 6 | G, CN (10%) | Kidney (1+)<br>Colon (3+)<br>Pancreatic islets (3+) | Pancreas (1+) | Hyperosmolar coma |
| 6 | 12 years | Vomiting, bloody diarrhea, seizures, coma | 21 | G, CN (35%) | Kidney (3+)<br>Colon (1+) | Brain (2+) | Intracerebral hemorrhage |
| 7 | 32 months | Bloody diarrhea, seizures, DIC | 31 | G, A | Colon (1+)<br>Pancreas (1+) | Kidney (1+)<br>Colon (1+)<br>Pancreas (1+)<br>Brain (1+) | Pulmonary hemorrhage |
| 8 | 6 months | Upper respiratory infection, hyperglycemia | 49 | G, A | Colon (1+) | Kidney (2+)<br>Colon (1+)<br>Brain (1+)<br>Lung (1+) | Sepsis complicating dialysis |
| 9 | 4 years | Hemiparesis, seizures | 78 | A | None | Brain (1+)<br>Heart (1+) | Intracerebral hemorrhage |

DIC = Disseminated intravascular coagulopathy; G = glomerular TMA; A = arterial TMA; CN = cortical necrosis

[a] Percent tissue necrosis

[b] relative severity of lesion on a 0-3+ scale (see text)

non-infarcted portions of the cortex. CN was observed only in patients who had diarrheal prodromes (8 of 17). Arterial TMA, characterized by interlobular arterial endothelial swelling or intimal thickening, was not seen in any of the 15 renal specimens obtained within the first 16 days of hospitalization.

*Late patterns of renal injury*

Renal arterial lesions were present in specimens from 9 patients with chronic renal failure that were obtained after more than 16 days of hospitalization (17–60 days in 3 patients and greater than 60 days in 6 patients). An early, predominantly arterial TMA (Fig. 1) was observed in the bilateral nephrectomy specimen obtained after 18 days of hospitalization from a 10-year-old boy who, after presenting with a gastrointestinal prodrome, developed uncontrollable hypertension (mean 174/120 mmHg). A combination of glomerular TMA and arterial TMA was found at necropsy in 2 hypertensive patients who died at 31 days and 49 days, respectively (Table 2; patients 7 and 8). Extensive endarteritis obliterans with "onion-skinning" of renal arterioles and interlobular arteries was seen in two biopsies, one autopsy, and four bilateral nephrectomies obtained from patients who had sustained renal failure and hypertension for more than 2 months. For only one patient was renal tissue obtained both early and late in the course of the disease. The late pattern of arterial TMA was observed in a bilateral nephrectomy specimen obtained at 3 months, while a glomerular TMA had been present in the renal biopsy examined at 2 weeks.

*Relationship of age and outcome to pattern of renal injury*

Of 9 children less than 28 months of age, 2 patients had an arterial TMA and another had a combination of glomerular and arterial TMA patterns. Of these, 1 required renal transplantation and 1 died. Six patients had glomerular TMA and/or CN. Three patients under 28 months of age died during the fulminant phase of the disease.

Of 15 children over 28 months of age, 5 had an arterial TMA and 1 had a combination of glomerular and arterial TMA patterns. Of these, 3 required renal transplantation and 2 died. Of the 9 patients who had a glomerular TMA and/or CN, 4 died of the extrarenal complications of HUS and another was transplanted after progressing to ESRD.

*Renal immunofluorescence/ultrastructure*

Immunofluorescence studies were performed on eight renal biopsies (five with a combination of CN and glomerular TMA, and three with glomerular TMA). Staining for fibrinogen-related antigen was detected in the glomeruli of six patients. Diffuse, granular glomerular basement membrane deposits of C3 were reported in two biopsies showing a glomerular TMA and two showing a combination of CN and glomerular TMA. Widening of the subendothelial space and deposition of electron-lucent "fluffy" material were present in the seven biopsies examined by electron microscopy, including four with a combination of CN and glomerular TMA, and three with glomerular TMA.

*Extra-renal autopsy findings*

Recent hyaline thrombi were identified in extrarenal arterioles in eight of the nine autopsied patients (Table 2). They were found in the large bowel of six patients who had hemorrhagic colitis and in the pancreatic islets of three patients in association with hemorrhagic necrosis of the islets of Langerhans. Thrombi were also noted in kidney (six patients), brain (three patients), heart (two patients), adrenals (one patient), and lung (one patient). In three patients, including two children in whom coagulation studies documented a disseminated intravascular coagulopathy (DIC), thrombi were found in three or more extrarenal sites (Table 2; patients 2, 7, 8). Extrarenal thrombi were generally limited in number, but were numerous in the viscera of an 11-year-old boy (patient 4) in whom headaches, delirium, and DIC were prominent (Fig. 2). This fatality was the only one in our study in whom anuria was absent and creatinine remained below 3.5 g/dl. Only one child (patient 8) had prominent thrombi both in the renal glomeruli and extrarenal tissues, and that was noted in an infant who died on the 49th day of hospitalization following dialysis. Interestingly, cerebral thrombi were found in the three children who had seizures (patients 6, 9; Table 2). These hyaline thrombi were confined to cerebral arterioles. Since they were not recanalized or in-

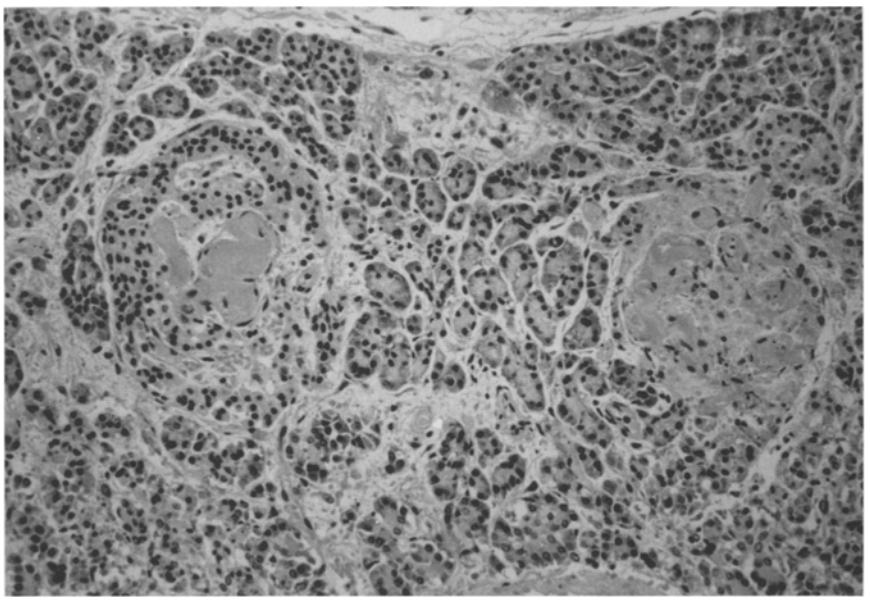

**Fig. 2.** Thrombosis and necrosis of the pancreatic islets with sparing of the acini (×250)

corporated into the arterial walls, the thrombi were likely of recent origin.

## Discussion

The present clinicopathological study was undertaken to complement the recent SPNSG retrospective review of its experience with idiopathic HUS [7]. Since children in our population rarely undergo renal biopsy (12 of 243 children, 5%), specimens derived from autopsy studies and bilateral nephrectomies were included to increase the amount of material for study. With this approach, renal tissue was available from approximately 10% of the patient population (24 of 243). However, it should be noted that the specimens were obtained almost exclusively from patients with severe illnesses and/or poor outcomes, a process which would, of course, be expected to select patients with more severe histopathological lesions.

The most extensive information on the renal injury in childhood HUS has come from Habib et al. [4] who described renal biopsy findings in 52 of 70 consecutive patients. Of 38 children less than 28 months old in the French study, 3 patients had an arterial TMA; all 3 died within several weeks. Thirty-five patients less than 28 months of age had either CN or glomerular TMA; 3 of these patients progressed to chronic renal failure. In contrast, of the 14 older children, 10 had an arterial TMA; 9 of these progressed to renal failure. The authors suggested that the difference in prognosis between early and late childhood HUS was related to the increased prevalence of an arterial TMA in the older patients.

In the patients reported in this study, no arterial TMA was identified in renal tissue obtained during the first 16 days of hospitalization. This may indicate that the frequency of arterial TMA in the SPNSG population is low, or that the arterial lesion evolves over time and may not be recognizable at the light microscopic level early in the course of the disease.

In our SPNSG series, extensive mural necrosis and thrombosis of the interlobular arteries was identified in some specimens in the histologically semi-viable tissue near edges of infarcts, but glomerular TMA was observed in viable renal cortex. The presence of multiple patterns within the same specimen limits the usefulness of small renal biopsies.

Our observations on extrarenal lesions in pediatric patients dying in the acute phase of HUS are similar to those reported previously [6, 13]. Gianantonio et al. [6] performed autopsies on 47 Argentinian patients with HUS and found extrarenal microthrombi in 20 of 26 patients who died during the first 2 weeks of the illness, but no thrombi in 20 patients who died more than 1 month after onset. The thromboses involved multiple organs, including the myocardium and brain. Similar lesions were reported by Upadhaya et al. [13] in 3 North American children who died within 8 days of hospitalization. We found extrarenal thrombi in 4 of 5 children who died in the first 2 weeks of illness (patients 1–5; Table 2). However, we also observed such lesions in all 4 children who died 3–11 weeks after the onset of their disease (patients 6–9). As reported previously, the individual sites for the thrombi included the colon (4 patients), brain (4), pancreas (3), heart (2), lung (2), and adrenals (1).

A few microthrombi were found in the brains of all 4 children who died 3 or more weeks after the onset of HUS (patients 6–9; Table 2). Three of these patients exhibited recurrent seizures (patients 6, 7, 9), and 2 of them died from intracerebral hemorrhage. It should be noted, however, that extensive thrombosis of cerebral vessels, as may be seen in patients with TTP, was not observed in any of our patients.

Pancreatic islet cell destruction is a recognized complication of HUS [14]. Some patients develop severe hyperglycemia, and survivors may become insulin-dependent diabetics. Hyperglycemia was responsible for the death of 1 child in this series (patient 5). At autopsy, complete hemorrhagic necrosis of the islet tissue was found. In two additional autopsies, pancreatic small vessel thrombosis and focal necrosis were identified.

An important caveat should be incorporated into the interpretation of these results. Although the microthrombi encountered at autopsy in HUS patients may have been produced by the same mechanisms which produce renal microthrombi in the acute phase of the illness, additional thrombogenic processes, such as shock, sepsis, and tissue necrosis, are usually present in patients who die. Extrarenal microthrombi resulting from HUS are not readily distinguishable from microthrombi produced by other mechanisms. As shown in Table 2, extrarenal thrombi were as prominent and as diffusely distributed in the 4 patients who died 3 or more weeks after hospitalization as they were in the 5 patients who died during the acute phase of their illness. Bowel and pancreatic necrosis were characteristic of HUS in the early stages, but were not encountered in patients who died after more than 3 weeks of hospitalization.

In summary, we have studied renal tissue in 24 patients and extrarenal tissues in 9 patients with HUS. We have confirmed the presence of the three patterns of renal injury described by Habib et al. [4]. However, since in many of our renal specimens a combination of patterns was observed, we believe that sampling error could be a significant factor in the interpretation of a small renal biopsy. An arterial TMA was recognized only in specimens obtained from patients with chronic renal failure and sustained hypertension, and was not recognized in specimens obtained from 15 patients with severe disease during their first 16 days of hospitalization. Because the incidence of an arterial TMA was low, we believe that the usefulness of an early renal biopsy in patients with HUS may be limited. Microthrombosis of extrarenal arterioles was present at autopsy in most of our fatal cases of HUS, but the pathogenesis of the thrombosis remains uncertain. The most frequent sites of extrarenal involvement were the large intestine, brain, and pancreas. These extrarenal lesions appeared to have contributed significantly to the mortality of children with HUS in our series.

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