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HEMOLYTIC-UREMIC SYNDROME (HUS): A CLINICOPATHOLOGICAL STUDY OF 15 CASES*

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SUMMARY: Tınaztepe K, Akkök N, Tınaztepe B. (Nephropathology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Hemolytic-uremic syndrome (HUS): A clinicopathological study of 15 cases. Turk J Pediatr 35: 23-36, 1993.

Although hemolytic-uremic syndrome (HUS) is a clinico-pathological entity, renal biopsies are usually not indicated for diagnosis, and therefore, studies concerning the histological aspects of the syndrome are few. This study mainly describes the morphological characteristics of 15 tissue-diagnosed sporadic cases of HUS. The ages of the patients ranged between 10 mos. to 15 yrs., with five being under two. The male/female ratio was 2:3. The prodromal phase was present in 10 patients (67%) with gastrointestinal symptoms in four patients (27%) with neurological symptoms, and in three patients (20%) with upper respiratory infections. Five patients had HUS associated with diarrhea (D+) (three infants and two children), while the remaining ten patients (two infants and eight children) had no diarrhea (D−). *E.coli* was identified in the stool of four of the D+ cases, one of which was also associated with Shigella. The shortest clinical course was 14 days and the longest 55 days in 13 patients. The disease recurred after three months in one patient, and on three occasions in 15 months after onset of HUS in the other.

Fourteen patients died and one biopsy-diagnosed case recovered after the acute phase. All patients had anemia (Hb 3.4-10 g/dl) and acute renal failure. Seven cases demonstrated Burr cells, eight cases had thrombocytopenia and six cases oliguria/anuria. Microscopic hematuria was detected in four cases and gross hematuria in two cases. All patients revealed proteinuria and azotemia (40-200 mg/dl).

Five/five (100%) cases had decreased creatinine clearance, 12/14 (86%) cases had increased uric acid levels, 9/14 (64%) cases had an electrolyte imbalance.

Light microscopy revealed microangiopathic type involvement of the glomeruli in all cases. According to additional findings, the cases were classed into three histological groups: type 1 showing cortical necrosis (3 cases), type 2 predominant glomerular and arteriolar involvement (11 cases) and type 3 predominant arterial involvement (1 case). All cases were considered primary HUS except for one which was associated with membranous glomerulonephritis. (D+) HUS cases were predominantly of the microangiopathic type, similar to the (D−) group; the latter being contrary to the literature. Hypertension was present in 67% of cases and there was no correlation found between the clinical duration of HUS and the histological type. All five patients studied immunohistologically revealed a nonspecific type fibrinogen deposition. Extra-renal microangiopathy was demonstrated in the adrenals, stomach, pancreas, liver and skin in two necropsies studied. *Key words: hemolytic-uremic syndrome, thrombotic microangiopathy, acute renal failure.*

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The hemolytic-uremic syndrome (HUS) represents one of the major causes of acute renal failure in childhood, especially in infancy. The syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure has a characteristic renal vascular pathology[1-3]. The etiology varies, and in the majority of cases, the cause remains unknown. Whatever the cause, the end result is extensive injury of the renal microvasculature[4]. For practical purposes, cases can be divided into two main clinical types: those associated with prodromal diarrhea (D+) and the others without diarrhea (D−). D+ HUS has an acute presentation with bloody diarrhea which carries a better prognosis[5,6]. An association between D+ HUS and Verocytotoxin producing *Escherichia coli* (VTEC) was first demonstrated by Karmali et al[7,8]. Serotype 0157:H7 is now recognized as the most important cause of HUS in this group[9], but other serotypes can also be found[6,7]. A wide spectrum of other organisms including *Shigella, Salmonella,* enteroviruses and other infectious agents have been hitherto reported to be associated with D+ HUS[10]. The rare D− (atypical) form may be familial, sporadic or relapsing and carries a poor prognosis[6].

A great deal of information concerning the histopathological findings of HUS in children is reported in the studies conducted by Levy et al[11] and by Habib et al[12] in France. These studies have revealed three major morphological patterns of renal injury in such patients:

1. Thrombotic microangiopathy (TMA) with predominant glomerular involvement,
2. Thrombotic microangiopathy (TMA) with predominant arterial involvement,
3. Cortical necrosis (CN).

Similar morphological patterns have also been described by some other authors using slightly different nomenclature[13,14].

Since a diagnostic renal biopsy is rarely indicated, there are few studies in the literature describing the histopathological aspects of HUS. The present study reports the spectrum of clinical and renal pathological findings of 15 children with tissue-diagnosed HUS. The extent of extrarenal involvement is also reported in two of these cases.

Material and Methods

Fifteen cases with a tissue diagnosis of HUS and whose ages varied from 10 mos to 15 yrs were studied retrospectively for a clinicopathological evaluation over a twelve-year period from 1978 to 1990. Of these, five cases (33%) were in the 0-2 year-old age group, three cases (20%) were in the 3-5 year-old age groups, four cases were in the 6-12 year-old age group and three cases were in the 13-15 year-old age group. Fourteen of these patients died and one survived. A light microscopical study of the renal tissue was carried out in all cases, while

additional fluorescence microscopical studies were available in five of them. The samples of renal specimens were needle biopsy in one case, postmortem material in six cases (one incisional, five needle samples), a unilateral nephrectomy in six cases and an autopsy in two cases.

The renal tissues were fixed both in formalin and in Duboscq-Brasil solution. The sections were stained with hemotoxylin-eosin, periodic acid-Schiff (PAS), trichrome and Jones silver stains.

Immunofluorescence microscopical studies were carried out on fresh frozen tissues. The monospecific fluoresceinated antisera used were: anti-IgA, anti-IgG, anti-IgM, anti-C3 and anti-fibrinogen.

The patterns of renal injury described by Habib et al[12] were determined for each specimen, which were defined as follows (Figs. 1-7):

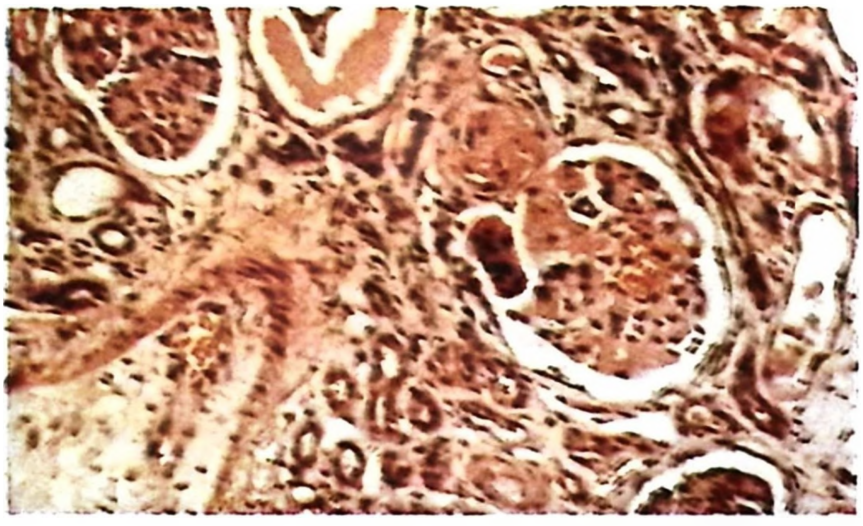

Fig. 1: Thrombosis of an arcuate artery with subintimal edema and a glomerulus with thrombotic microangiopathy (HE × 200).

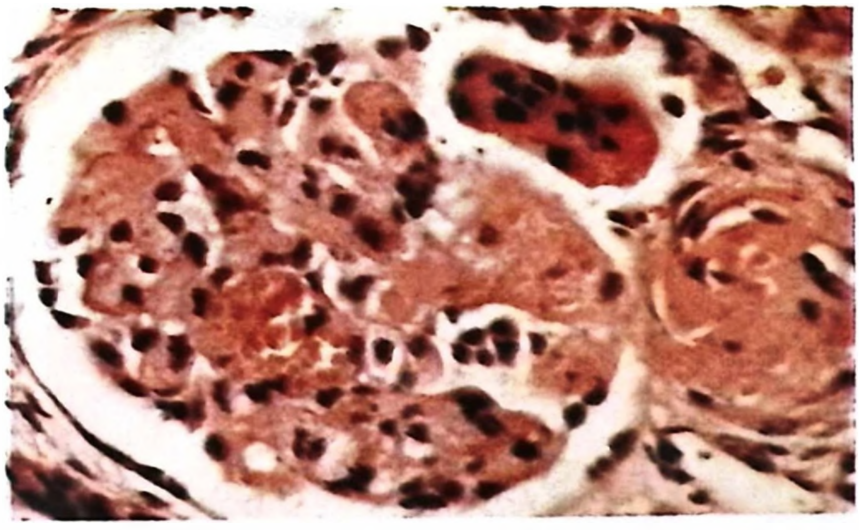

Fig. 2: Glomerulus showing widespread thickening of the capillary walls; there is no increase in cellularity. The afferent arteriole is occluded by fibrin-like material (HE × 350).

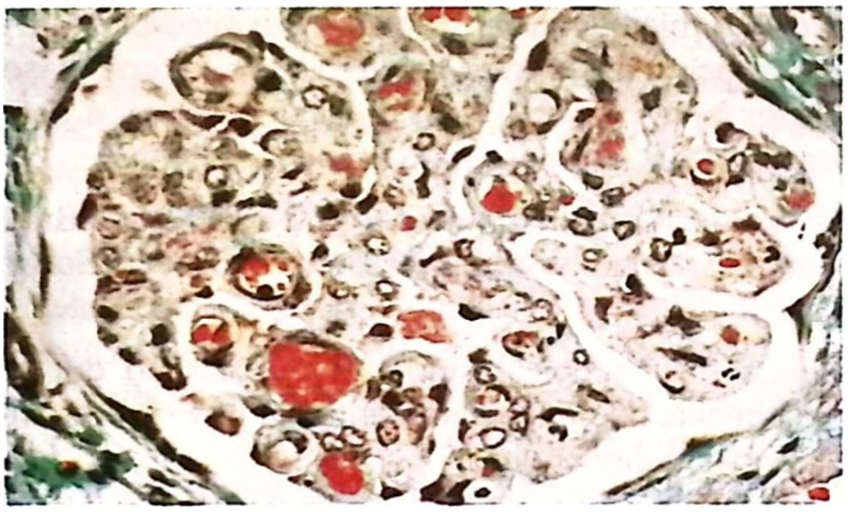

Fig. 3: Glomerulus showing narrowing of the lumina of the glomerular capillaries with thrombi, subendothelial and intraluminal fibrin deposition and widened subendothelial space (Trichrome light-green × 350).

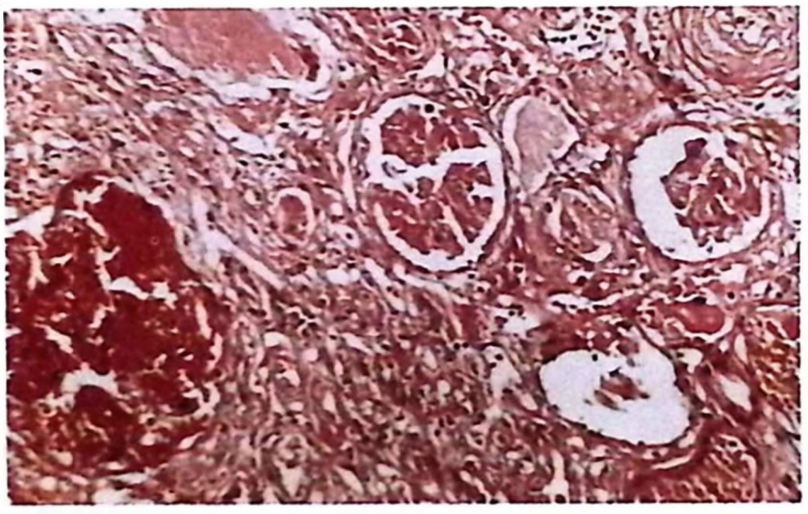

Fig. 4: Four heterogenously involved glomeruli. The one at the bottom shows fibrinoid necrosis, while the others are segmentally involved. The lumen of the artery in the corner is narrowed, showing an "onion-skin" pattern (HE × 150).

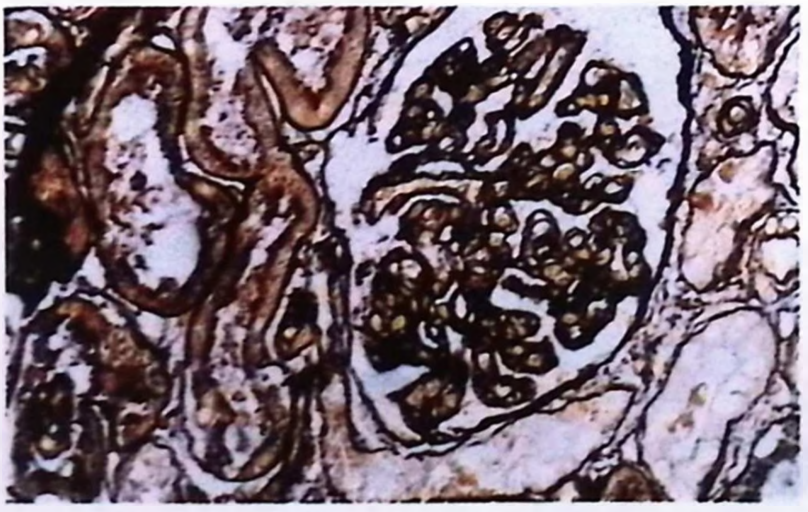

Fig. 5: Thickening and "double-contour" appearance of the glomerular tuft. Similar changes are also seen in the tubular basal membranes (John's Silver × 250).

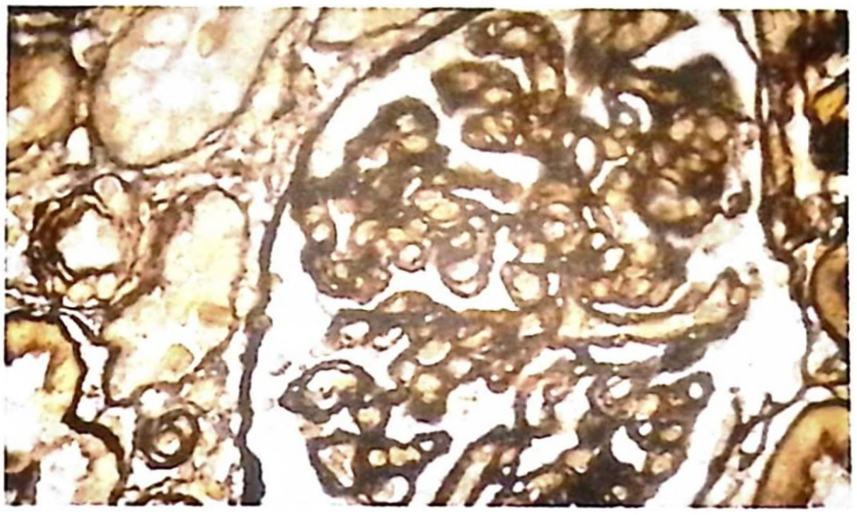

Fig. 6: Double contours are clearly visible in the glomerular tuft (John's Silver × 350).

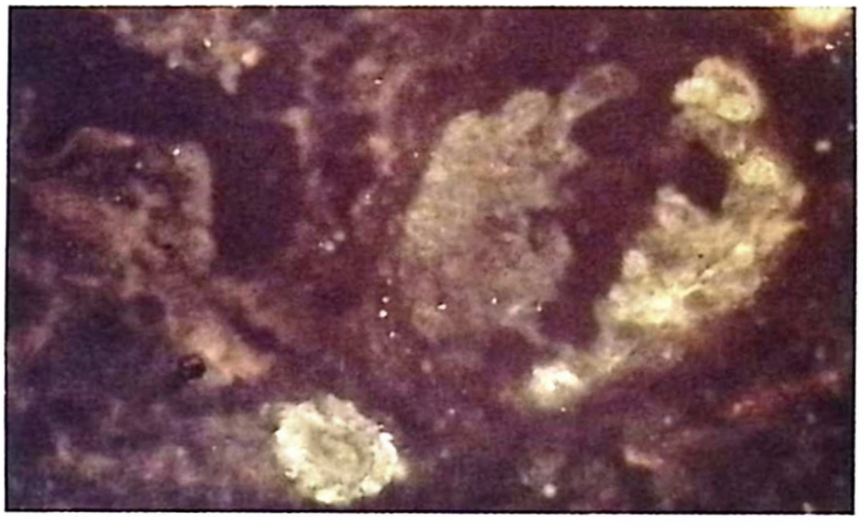

Fig. 7: Immunofluorescent appearance of HUS. Deposits of IgM in the pre-glomerular arteriole wall in the basal membrane zone of the glomerular capillary walls showing segmental distribution and a partial granular pattern.

TMA with predominant glomerular involvement: These specimens showed swelling and detachment of the endothelial cells which resulted in thickening of the glomerular capillary walls and narrowing of the capillary lumina. 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 "double-contours" due to widening of the subendothelial space. The renal arteries, with the exception of an occasional thrombus in the glomerular arterioles, were not involved in the specimens classified as glomerular TMA.

TMA with predominant arterial involvement: These specimens showed renal tissue in which the arterioles and interlobular and arcuate arteries were narrowed or obstructed by swelling of the endothelium and/or thrombi. Fibrinoid necrosis,

intimal swelling and proliferation, "onion-skinning" due to fibrous replacement of the thickened intima and laminar intimal fibroplasia were found.

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

Extrarc al studies: Two cases were examined at autopsy (one complete and one partial). Liver tissue was examined in ten cases, muscle in two cases and the gastrointestinal tract in one case (Fig. 8).

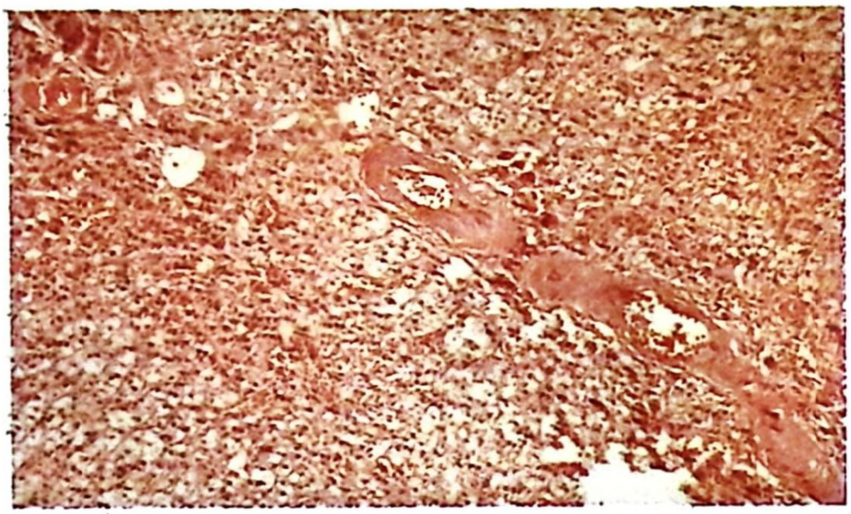

Fig. 8: Adrenal microangiopathy with deposition of fibrinoid material in the capillary wall and occlusion of the lumen is seen (HE × 200).

Results

Clinical Findings

Of 919 pediatric renal biopsies evaluated at the Hacettepe Children's Hospital between the years 1978 and 1990, one case was diagnosed by biopsy as having HUS. Among the intra vitam tissue-diagnosed pediatric nephrologic diseases in our center, the rate of HUS was found to be 0.1 percent, while the rate of HUS among postmortem pediatric material was 10 percent (14/147).

The ages of the patients at the onset of disease ranged from 10 months to 15 years in our study. Five were infants and seven were young children. The male/female ratio was 2/3. Five children had prodromal diarrhea (D+ HUS) and the remaining ten were (D−) cases. Five of the (D−) cases had gastrointestinal symptoms other than diarrhea (abdominal pain, vomiting), three cases presented with upper respiratory tract infection (20%) and two cases showed no distinct prodromal symptoms (14%). The (D+) group consisted of three infants and two children, while there were two infants and eight children in the (D−) group. E.coli infection was identified in the stool specimens of four of the (D+) cases, and the

fifth (D+) case, had both *E.coli* and *Shigella* infections. No specific infection was identified in any of the (D−) cases. Two children had recurrent HUS, one of whom had a previous diagnosis of membranous glomerulonephritis. This case was classified as having the secondary type of HUS.

Anemia was present in all cases. Thrombocytopenia was present in eight cases (53%) and Burr cells were demonstrable in seven cases (47%). All 15 children had acute renal failure and proteinuria. Five of them had hematuria (33%) and six showed oligoanuria (40%). All cases had microangiopathic hemolytic anemia and azotemia (100%), but thrombocytopenia was present in only eight of them (53%). Complications of acute renal failure, a high level of uric acid, electrolyte imbalance and congestive heart failure were present in 12/14, 9/14 and 8/15 cases, respectively.

Hypertension developed in ten patients (67%) and there was no response to therapy in seven. Eighty percent of the (D−) and forty percent of the (D+) cases had hypertension. It developed in two TMA cases with predominant arterial involvement (one associated with cortical necrosis), in seven of the 11 cases with predominant glomerular involvement and in one of two cases with cortical necrosis. Symptoms of central nervous system (CNS) involvement were observed in ten cases, such as alterations in the level of consciousness (four cases), focal or generalized convulsions (four cases) and decerebrate rigidity (two cases). Gastrointestinal hemorrhages were observed in three cases.

Fourteen of the patients died, twelve during the stage of acute renal failure and two after progressing to end-stage renal failure. Only one patient survived and was followed for four years (Table I).

Histopathological Findings:

Thrombotic microangiopathy (TMA) which is essential in the diagnosis of HUS was noted in all cases. Cortical necrosis was associated with TMA in three cases and arterial involvement was associated with TMA in two cases.

Histopathological Classification:

1. TMA with predominant glomerular involvement was noted in 11 patients (73%) and arteriolar involvement was also present in four of them. The percentage of glomeruli presenting the typical pattern of TMA varied in our study (< 25% in one case, between 25 and 50% in four cases, between 50 and 75% in five cases and > 75% in one case). Other glomeruli appeared normal. Paralytic glomeruli were also observed.
2. TMA with predominant arterial involvement was noted in two patients. In one of these cases, it was seen in combination with cortical necrosis. Interlobular and arcuate arteries showed almost complete occlusion of the lumina due to

Table I: Summary of Selected Clinical and Laboratory Findings of 15 Children With Hemolytic-Uremic Syndrome

Number of patients	15
Male / Female ratio	6/9
Age at presentation:	
Mean	60 months
Range	10 months-15 years
Type of prodrome:	
Diarrhea	5 (33%)
Other gastrointestinal symptoms	5 (33%)
Convulsions and unconsciousness	4 (27%)
Upper respiratory tract infection	3 (20%)
Anemia (Hb less than 11 g/dl)	15 (100%)
Thrombocytopenia (less than 100,000/mm^3)	8 (53%)
Burr cells	7 (47%)
Proteinuria	15 (100%)
Anuria-oliguria	6 (40%)
Hypertension (more than 95 percentile)	10 (67%)
Outcome:	
Chronic renal insufficiency	1 (7%)
Mortality	14 (93%)

thrombosis, intimal edema, intimal proliferation and thickening of the muscular walls.

3. Cortical necrosis was noted in three nephrectomy cases. It was widespread in all cases

In four cases, renal tissue was examined during the first three weeks of the disease and early patterns of renal injury were found. In contrast, in the nine cases in whom renal tissue was examined after the first three weeks of the disease, late patterns of renal injury were noted, with arterial involvement being present in two of these cases.

In the recurrent HUS cases, renal tissue was examined three and fifteen months after the onset of disease. Both early and late patterns of renal injury were noted in these cases and one of them also had cortical necrosis.

Table II: Histopathologic Groups and Age Distribution of 15 HUS Cases

Histopathologic Groups	Age Groups	
	Infancy (0-2 Years)	Childhood (3-16 Years)
TMA with predominant glomerular involvement	4	7
TMA with predominant arterial involvement	–	2 (one case with cortical necrosis)
Cortical necrosis	1	1
Total	5	10

Relationship between age, prodrome and pattern of renal injury (Fig. 9):

Of five children under 24 months of age, four had TMA with predominant glomerular involvement and one had cortical necrosis. Of ten children over 24 months of age, seven had TMA with arterial involvement, one had cortical necrosis and two had TMA with predominant glomerular involvement (one case revealed a combination of cortical necrosis and TMA with predominant arterial involvement).

Of five children with prodromal diarrhea (D+), four had TMA with predominant glomerular involvement and one had cortical necrosis. Of ten children without

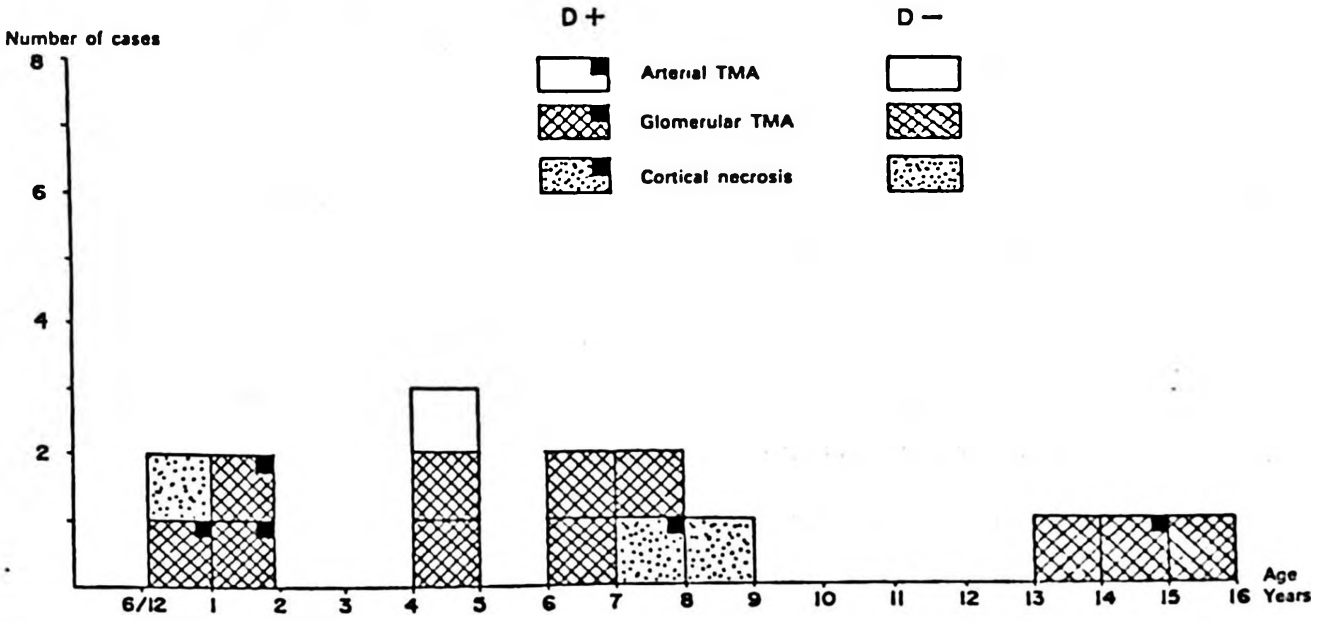

Fig. 9: Distribution of three histopathologic patterns of HUS according to age and prodromal presence (D +) or absence (D –) of diarrhea.

prodromal diarrhea (D−), seven had TMA with predominant glomerular involvement, two had TMA with predominant arterial involvement and two had cortical necrosis (in one patient it was associated with arterial involvement).

Only one patient with glomerular TMA survived, and in this case, 25 percent of the glomeruli were involved in which thrombotic microangiopathic changes were minimal.

Renal Immunofluorescence Findings:

Immunofluorescence studies were performed on one biopsy with TMA and predominant glomerular involvement and on four necropsies (two with cortical necrosis, one with TMA and predominant arterial involvement and one with TMA and glomerular involvement). Staining for fibrinogen-related antigen was detected in the glomeruli of all five cases. No specific pattern of staining was observed. Diffuse, broken, linear and/or granular glomerular basement membrane deposits were noted. CD23 deposition was found in three cases and IgM in two. Of the cases with HUS secondary to membraneous glomerulonephritis, immunofluorescence findings revealed the diagnostic pattern of membraneous glomerulonephritis (Table III).

Table III: Immunohistological Findings in Five HUS Patients

Case No.	Histopathological Groups	Immunofluorescence Findings Immunoreactant	Localization
1	TMA with predominant arterial involvement	Fibrinogen IgM	GBM* zone
2	Cortical necrosis	Fibrinogen IgM C_3	Glomeruli and arterioles
7	Cortical necrosis (Secondary to membraneous glomerulonephritis)	Fibrinogen IgM IgG granular IgA	GBM zone
8	TMA with predominant glomerular involvement	Fibrinogen C_3	GBM zone
13	TMA with predominant glomerular involvement	Fibrinogen C_3	Glomeruli and capillaries of interstitium

* GBM: Glomerular basement membrane.

Extrarenal Findings:

Extrarenal microthrombi were identified in two necropsy cases. They were present in the adrenals, gastrointestinal tract and pancreas of one case and in the liver and skin of the other. Diffuse brain edema was observed in one patient whose CNS was examined.

Discussion

Since the hemolytic-uremic syndrome is a syndromic condition, its clinical and pathological findings are heterogeneous. It occurs in infancy and early childhood[1,2,13,15,16]. In our study, we also found it to occur in these age groups. Most of the patients in our series were in the 0-2 year-old age group (33%), the mean age at onset being 60 months. HUS is usually associated with diarrhea, and the majority of patients in large series have (D+) type HUS[11,15-17]. In our series, 33 percent constituted (D+) cases and 67 percent (D−) cases. The (D+) HUS type occurs principally in infants, while the (D−) type is seen mostly at a later age[18]. In our series, 60 percent of the (D+) group were infants, while only 20 percent of the (D−) group were infants.

On clinical examination, microangiopathic hemolytic anemia and azotemia were found in all our patients, whereas, thrombocytopenia was present in only 53 percent, which may be due to the fact that thrombocytopenia varies according to the stage of the syndromic condition. Since the duration of thrombocytopenia may be short, it can be easily overlooked and thrombocytosis may therefore be seen as a rebound phenomenon following the thrombocytopenic period[3]. In our series, disseminated intravascular coagulation (DIC) was detected in four patients with thrombocytopenia because of the presence of elevated fibrin degradation products in the blood and prolonged PT/PTT values. Fibrin thrombi were noted in the glomerular capillaries of the glomeruli of two cases with a clinical diagnosis of DIC.

Hypertension develops in HUS and can be severe. Uncontrollable hypertension carries a poor prognosis[19]. Severe hypertension occurs in older patients with (D−) type HUS[12,20]. Our findings were consistent with these reports. Hypertension was present in 80 percent of (D−) cases and 40 percent of (D+) cases studied. Although hypertension is known to develop more frequently in older patients than in infants, we found it to occur almost equally in infants (60%) and older children (70%).

Thoenes and John[21] reported a strong correlation between the arterial form of TMA and hypertension. Severe hypertension developed in two of our cases with arterial TMA. This result is in accordance with the study done by the above-mentioned authors. In our study, hypertension was prominent in both the cortical necrosis group and the TMA with predominant glomerular involvement

group. Therefore, hypertension is one of the major clinical findings in all histopathological groups.

Central nervous system (CNS) involvement, which is a serious complication of HUS, carries a poor prognosis. CNS involvement is reported in 25-90 percent of cases in various series studied[1,2,19]. In our series, it was noted in 10 cases (67%) having a severe clinical course and fatal outcome. A CNS examination was performed only in one patient in which microthrombi were not detected, but diffuse brain edema was present.

Upadhyaya et al[22] reported microthrombi in a wide distribution of organs including the brain and myocardium. Extrarenal thrombi were present in two cases examined in our series involving the adrenal glands, gastrointestinal tract and pancreas in one case and the liver and skin in the other. These sites are similar to those reported in large series[14,22]. Evidence of ischemia and focal areas of infarction with surrounding edema are frequently noted in the extrarenal organs[22]. We demonstrated similar findings in liver tissue of five of the 12 cases we examined.

Immunofluorescence microscopical studies revealed varying amounts of fibrinogen in all five cases studied (Table III). Stainings with antisera against fibrinogen, C_3 and IgM were observed mainly along the glomerular basement membranes and were also occasionally present in the arteriolar walls, as reported in the literature[2,14].

Since the cases we studied had mostly fatal outcomes, a correlation between histopathological groups and prognosis could not be made. Habib et al[12] has suggested that prognosis is poor in cases in which more than 50 percent of the glomeruli are involved and that sequelae have been observed in these patients if they survive. Less than 25 percent of the glomeruli were involved in only one patient that survived in our study, but late sequelae developed such as hypertension and a decrease in the creatinine clearance level.

Summary

This retrospective clinicopathological study consists of 15 cases of tissue diagnosed hemolytic-uremic syndrome (HUS) observed over a twelve-year period of experience. HUS constituted 0.1 percent (1/919) of renal biopsies and 10 percent (14/147) of renal necropsies in a Hacettepe University series. The age distribution varied from 10 months to 15 years, with a mean age of 60 months.

Of 15 HUS cases (33%), five had (D+) type with prodromal diarrhea and two had a recurrent clinical course, in one of whom it was secondary to membranous glomerulonephritis. All patients had anemia and acute renal failure. Burr cells were detected in seven cases (47%), thrombocytopenia was seen in eight cases (53%),

oliguria/anuria was present in six cases (40%) and hematuria was observed in five cases (33%).

Light microscopy revealed microangiopathic type involvement of the glomeruli in all cases. Classification based on light microscopic studies showed:

1. Thrombotic microangiopathy with predominant glomerular involvement (11 cases),
2. Thrombotic microangiopathy with predominant arterial involvement (two cases),
3. Cortical necrosis in three cases (one case in combination with arterial TMA).

All five patients studied immunohistologically revealed a non-specific type of fibrinogen deposit and few other immunoreactants. Extrarenal microangiopathy was demonstrated in the adrenals, stomach, pancreas, liver and skin in two necropsies studied.

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