Clinico-Pathological Study of Hemolytic Uremic Syndrome In Ain Shams University Hospitals

Thesis

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List of Abbreviations

Abb.	Meaning
ADAMTS13	Von Willebrand Factor Cleaving Protease
aHUS	Atypical hemolytic uremic syndrome
AIDS	Acquired immunodeficiency syndrome
ARF	Acute renal failure
C3bBb	C3 convertase
CFB	Complement factor B
CFH	Complement factor H
CFI	Complement factor I
CMV	Cytomegalovirus
CNS	Central nervous sytem
D-	Diarrhea-negative
D+	Diarrhea-positive
E-coli	Escherichia coli
EHEC	Enterohemorrhagic Escherichia coli
ESRD	End stage renal disease
Gb3	globotriaosylceramide cell surface receptor
GBM	Glomerular basement membrane
H&E	Haematoxylin and Eosin
HELLP syndrome	Hemolysis, elevated liver enzymes and low platelets syndrome
HIV	Human immunodeficiency virus
HUS	Hemolytic uremic syndrome
JGA	Juxtaglomerular apparatus

List of Abbreviations (Cont…)

Abb.	Meaning
MAC	Membrane attack complex
MCP	Membrane cofactor protein
MD	macula densa
NO	Nitric oxide
Non-Stx	Non Shiga toxin
PAS	Periodic acid-schiff
PE	Plasma exchange
SLE	Systemic lupus erythematosus
STEC	Shiga toxin producing Escherichia coli
Stx	Shiga toxin
THBD	Thrombomodulin
TMA	Thrombotic microangiopathy
TNF	Tumour necrosis factor
TTP	Thrombotic thrombocytopenic purpura
TXA2	Thromboxane A2
VEGF	Vascular endothelial growth factor
VTEC	Verotoxin producing Escherichia coli
VWF	Von Willebrand factor

INTRODUCTION

Hemolytic uremic syndrome (HUS) is defined by the characteristic triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. It is a common cause of acute renal failure in patients younger than three years who require acute dialysis. The renal histological lesion is glomerular thrombotic microangiopathy and in more severe cases, arteriolar thrombotic microangiopathy. Thrombotic microangiopathy may affect other organ systems, including the central nervous system ***(Boyer & Niaudet, 2011).***

HUS can be divided into two forms, typical and atypical HUS. Typical (diarrhea positive) or shiga-toxin associated HUS is the most common form of HUS in children accounting for 90 percent of all cases. It usually occurs after a prodromal episode of diarrhea that is frequently bloody. In the majority of cases, HUS is associated Shiga toxin-producing enterohemorrhagic Escherichia coli (EHEC) especially O157:H7 or Shigella and generally carries a good prognosis. Approximately 5-10 % children only will eventually develop end-stage renal disease requiring renal transplantation. The posttransplant course is favourable with almost no increased risk of disease recurrence ***(Boyer & Niaudet, 2011, Chaturvedi & Licht, 2011 & Kumar & Bagga, 2011).***

Atypical HUS (aHUS) or non diarrhea associated HUS may manifest at any age but is more frequent in adults and is

responsible for only 10 percent of cases in children. aHUS comprises a heterogenous group with diverse etiology including infections(other than those due to shiga toxin producing EHEC) drugs, pre-eclampsia, genetic causes and autoimmune diseases like SLE. This group is characterized by an insidious onset and a progressive course with remissions and relapses. It has a worse prognosis with approximately 50% risk of ESRD and high risk of post kidney transplant reccurence ***(Chaturvedi & Licht, 2011).***

There is a relationship between Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura. Although the morphologic lesions of these two conditions are thought by many to be virtually identical, certain clinical differences have been enumerated. Chief among them are that TTP (a) occurs among older patients, (b) affects the CNS more commonly, (c) exhibits less frequent and less severe involvement of the kidney, and (d) involves multiple organs and has a poorer prognosis ***(Zoltan & Fred, 2007).***

AIM OF THE WORK

This work aims to study the light microscopic and electron microscopic features of renal biopsies of cases of hemolytic uremic syndrome and correlate them with clinical data.

HISTOLOGY OF KIDNEY

Glomerulus:

In 1666, Malpighi first described the glomeruli and demonstrated their continuity with the renal vasculature ***(Hayman, 1925).*** About 175 years later, Bowman elucidated in detail the capillary architecture of the glomerulus and the continuity between its surrounding capsule and the proximal tubule ***(Fine, 1985).***

The renal corpuscle consists of a tuft of interconnected capillaries and an enclosing capsule named Bowman. The term glomerulus is commonly used to refer to the glomerular capillary tuft and Bowman's capsule. The glomerulus does not simply represent a ball of capillaries. Providing structural support for the capillary tuft is a central region termed the mesangium, which contains cells and their surrounding matrix material ***(Geneser, 1986)*** .

The capillaries are lined by a thin layer of endothelial cells, contain a basement membrane, and are covered by epithelial cells (also called podocytes) that form the visceral layer of Bowman's capsule. The parietal epithelium is continuous with the visceral epithelium at the vascular pole where the afferent arteriole enters the glomerulus and the efferent arteriole exits. The cavity situated between the two

epithelial layers of Bowman's capsule is called Bowman's space, or the urinary space ***(Geneser, 1986)*** **(Fig. 1)**.

The glomerulus is responsible for the ultrafiltration of plasma. The glomerular filtration barrier consists of the fenestrated endothelium, the peripheral glomerular basement membrane (GBM), and the slit diaphragms between the podocyte foot processes ***(Madsen & Tisher, 2004).***

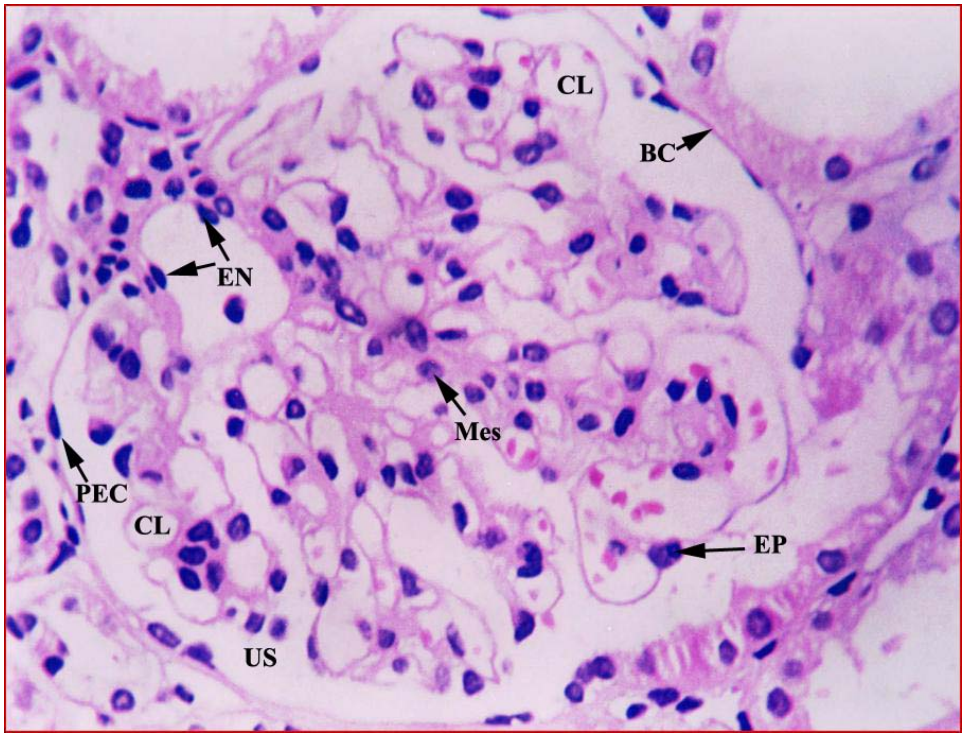

Figure (1): H&E of normal glomerulus. CL: Capillary lumen, EN: Endothelial cell, EP: Visceral epithelial cell, US: Urinary space, BC: Bowman's capsule, Mes: Mesangial cell, PEC: Parietal epithelial cell.

Endothelial Cells:

A thin fenestrated endothelium lines the glomerular capillaries. By light microscopy, the endothelial cells have light eosinophilic cytoplasm and slightly oval nuclei. Their nuclei are present within the capillary lumina **(Fig. 1)**. Ultrastructurally, the cytoplasm contains microtubules, microfilaments, and intermediate filaments ***(Vasmant et al., 1984).***

The attenuated portion of endothelial cytoplasm is perforated by fenestrae 70 to 100 nm in diameter ***(Jorgensen, 1966).*** Results from recent studies have suggested that glomerular endothelial cells have a glycocalyx surface layer about 60 nm thick, and this surface coat fills the fenestrae forming cohesive plugs ***(Hjalmarsson et al., 2004).*** There is emerging evidence that the glomerular endothelial glycocalyx may be an important component of the glomerular filtration barrier ***(Jeansson & Haraldsson, 2006).***

Vascular endothelial growth factor (VEGF), produced by podocytes, is an important regulator of glomerular endothelial cell function; VEGF induces fenestrae and increases permeability of endothelial cells ***(Esser et al., 1998).***

Mesangial Cells:

The mesangium, composed of mesangial cells and their surrounding matrix, is observed as a periodic acid-Schiff (PAS) and methenamine silver-positive structural support for the

glomerular capillary loops. By light microscopy, the mesangial cells usually can be distinguished by their mesangial location and dark-staining nuclei ***(Drenckhahn et al., 1990)*** **(Fig. 1).**

Ultrastructurally, they are irregular in shape and have elongated cytoplasmic processes that may extend between the endothelium and the glomerular basement membrane. The mesangial cell processes have microfilaments that contain actin, myosin and actinin. With smooth muscle contractile properties, the mesangial cell has been proposed to be a specialized pericyte that likely modulates glomerular filtration ***(Drenckhahn et al., 1990)***.

The mesangial matrix is similar but not identical to the GBM and contains several types of collagen, as well as fibronectin and small proteoglycans ***(Schaefer et al., 2004)***. The presence of microfibril-mediated attachments between mesangial cell processes and the GBM suggests that the mesangial cell and the GBM represent a biomechanical functional unit ***(Kriz et al., 1990).***

It has been proposed that the contractile apparatus of the mesangium appears to maintain the structure of the capillary walls by counteracting the distention caused by the intracapillary hydraulic pressure ***(Kriz et al., 1995).***

The mesangial cell also has phagocytic capability and plays a role in the clearance of macromolecules and debris from