

Rejection of Renal Transplants Immunopathologic Study

Thesis

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of the **Master Degree of Pathology**

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LIST OF ABBREVIATIONS

CAPD	: Continuous ambulatory peritoneal dialysis
CTL	: Cytotoxic T-lymphocyte
CyA	: Cyclosporine A
DST	: Donor-specific transfusion
ESRD	: End-stage renal disease
FNAB	: Fine-needle aspiration biopsy
HLA	: Human-leucocyte antigen
HTL	: Helper T-lymphocyte
I.N.	: Interstitial nephritis
I.R.	: Interstitial rejection
LD	: Lymphocyte-defined
MHC	: Major histocompatibility complex
MLC	: Mixed leucocyte culture
NK cells	: Natural killer cells
SD	: Serologically defined
TCIS	: Total <i>corrected</i> incremental score
HX & E	: Haematoxylin and Eosin stain
M.T.	: Masson-trichrome stain
P.A.S.	: Periodic-acid-schiff stain.

Introduction & Aim of the work

INTRODUCTION AND AIM OF THE WORK

In the past 25 years, kidney transplantation and long-term dialysis both have proved successful in extending the lives of patients who otherwise would have died of chronic renal failure. Only transplantation, however, offers the hope of recovery of normal renal function, cure of the uraemic syndrome and full rehabilitation from renal disease. In addition, patients with successful transplants have been considered to have a quality of life superior to that of patients on chronic dialysis (*Levey, 1984*).

However, transplantation has had only limited use, principally because of the risks of graft rejection and immuno-suppression. So finding a painless, safe and specific method which can diagnose kidney transplant rejection early is of great interest to those working in the field of organ transplantation. It is believed that a transplant tru-cut biopsy specimen is probably the most commonly accepted method for diagnosing rejection, differentiating it from other causes of renal allograft dysfunction (*Harry and Von Willebrand, 1984*).

Fortunately the last ten years have witnessed striking improvements in the survival of patients and grafts resulting from advances in immunologic management, including restricted use of immunosuppression, better histocompatibility testing, human leucocytic antigen (HLA) matching, blood transfusions and new drugs for prevention and reversal of transplantation rejection. (*Donnelly, 1987*).

Aim of the work

The progressively increased number of renal transplants performed in Egypt, encouraged the performance of this study about the different immunologic and pathologic aspects of renal transplant and its rejection. Aiming at

differentiating between the various types of rejection through histopathological findings.

Meantime, trying to throw some lights on the newly developed factors that have helped in improving the prognosis of renal transplantation in the recent years.

Review of Literature

EMBRYOLOGY AND MICROANATOMY OF THE KIDNEY

Embryology of human kidney

During development in the embryo, 3 successive bilateral excretory systems can be recognized including the pronephros, the mesonephros and the metanephros. All three kidneys are formed from the nephrogenic cord which is of mesodermal derivation. The metanephros represents the final developmental stage of the mammalian and has its beginnings in the second month of gestation. It has a dual origin i.e. formed jointly from two different mesodermal structures. The renal corpuscles and tubules arise from the mesenchyme of the nephrogenic ridge. The excretory portion including the collecting ducts, calyces, pelvis and ureter takes origin from a specialized structure of the mesonephric duct; the ureteric bud. (*Hamilton et al. 1962*).

In early development, the ureteric bud grows dorsally and cephalad to form several branches that come into contact with the nephrogenic ridge. Nephron formation begins about the eighth week from small foci of condensed mesenchyme located adjacent to the ampullae of the ureteric bud. The condensed mass becomes S-shaped tubular structure, the lower portion of the S-shaped structure differentiates into the renal corpuscle, the remaining portion forms the proximal and distal tubules and the loop of Henle. The renal pelvis and calyceal system form by repeated divisions of the ampullary portion of the ureteric bud. Nephrons in the developing metanephros may begin functioning as early as the 11th or 12th week after conception (*Osathanondh and Potter, 1963*).

Micro-anatomy of human kidney

Each kidney has the general shape of a lima bean, with an extensive convex surface and a smaller concave border. In the concavity of the kidney, which is

known as its hilum, a variable amount of adipose tissue is present. The drainage tube of the kidney, called its ureter, together with the renal artery, vein and lymphatics and their surrounding nerve plexus reach the kidney through the hilar fat tissue.

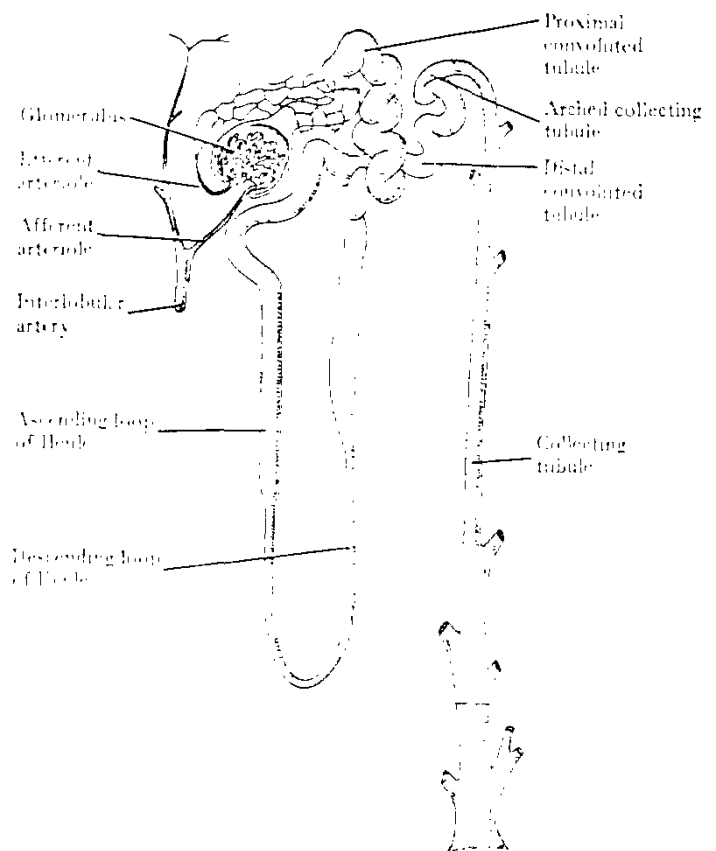
The kidney is enclosed by a tough capsule of dense ordinary connective tissue. The outer region of the kidney is known as its cortex and its inner region as its medulla. In contrast to the cortex, the medulla has a striated appearance caused by striations that fan out from the hilum. The unit of gross kidney structure is the lobe made up of a conical medullary pyramid and a cap of cortical tissue. The apex of each medullary pyramid forms a rounded papilla that projects into the renal pelvis. Each lobe of the kidney consists of a number of lobules demarcated from each other by interlobular arteries and their central cores are known as medullary rays, each lobule consists of parts of the organ in which all the nephrons drain in the same collecting tubule. Each nephron consists of renal corpuscle from which emerges a thick-walled proximal convoluted tubule that pursues a tortuous course in the cortical tissue, then extends straight down into the medulla as the descending limb of the loop of Henle, the proximal portion of which is thick-walled while its distal portion is thin walled, then it loops back into the cortex as straight ascending limb of the loop of Henle where it leads into the tortuous thick-walled distal convoluted tubule. (*Ham and Cornmack, 1987*).

The renal corpuscle (glomerulus) consists of a number of groups of capillary loops or lobules each arranged around a mesangial matrix which merges with the media of the afferent arteriole at the hilum or vascular pole. The capillary loops comprise three cell types:

1. A reflection of the visceral epithelium of Bowman's capsule covers the urinary surface of the loop

Diagram (1):

Diagrammatic representation of a typical nephron, with its glomerulus at its blind end, and connecting at its distal end with a collecting tubule. The normal anatomical relation between the distal convoluted tubule and the root of the glomerulus is not shown. Actually, the tubule returns closer to the glomerulus, fitting into the space between the afferent and efferent arterioles. (Ham and Cornmack 1987)



2. A fenestrated endothelium which lines the vascular space and
3. Mesangial cells seen in the axial area where several capillaries are conjoined (*Bennington and Beckwith, 1975*).

The juxtaglomerular apparatus consists of:

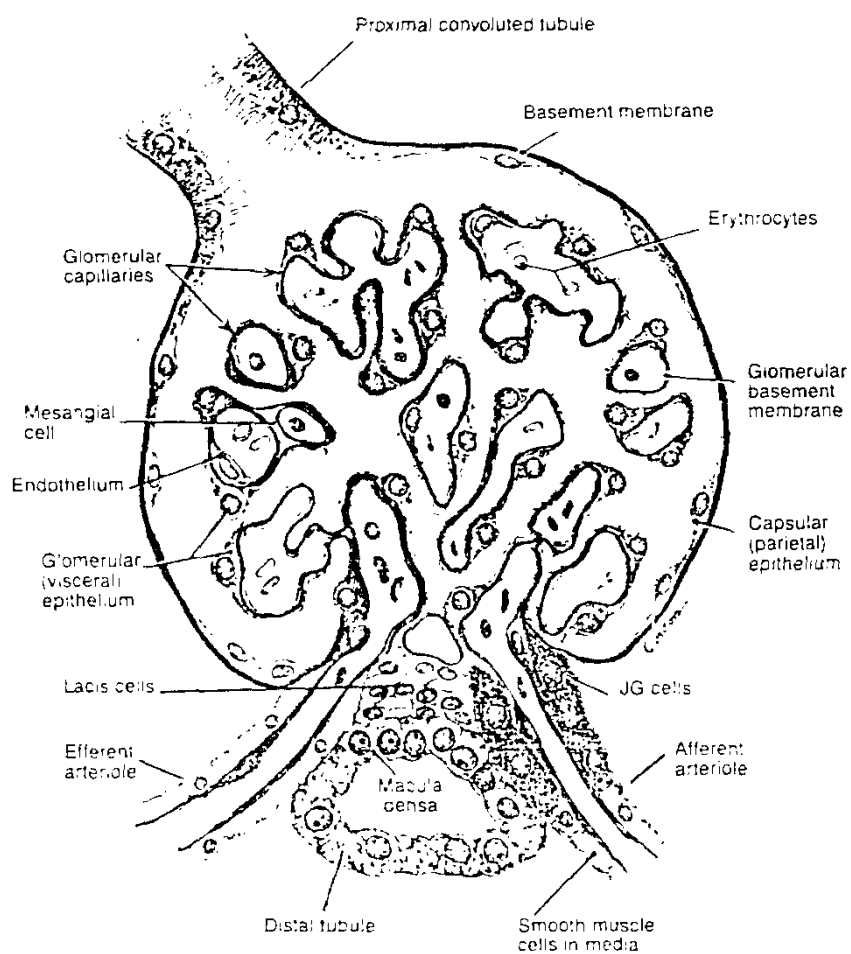
1. A vascular component comprising a specialized secretory smooth muscle (the granular epithelioid cells) intercalated in the media of the afferent arterioles,
2. Extraglomerular mesangium (laci cells) occupying the triangular space between the afferent and efferent arterioles and the macula densa.
3. Tubular component (macula densa) which is a specialized segment of the distal convoluted tubule (*Barajas, 1970*).

The proximal convoluted tubule is lined by a single layer of long, truncated pyramidal cells containing numerous mitochondria and abundant amounts of cytoplasm. The free surfaces form the brush border. The epithelial cells of Henle's loop are squamoid in the descending portion and somewhat cuboidal in the ascending limb. The cells lining the distal convoluted tubules lack the brush borders. The cells lining the collecting tubules have sharp outlines with distinct hyperchromatic nuclei and clear pale cytoplasm (*Bennington and Beckwith, 1975*).

Each kidney is supplied by a large renal artery that arises from the abdominal aorta. Close to the hilum of the kidney, the renal artery divides into two large branches. From these branches, five end arteries called "segmental arteries" originate. They give off branches that ascend toward the cortex as interlobar arteries. They branch at the corticomedullary border forming arches known as "arcuate arteries". There are no anastomoses between interlobar arteries or between their arcuate arteries so occlusion of an interlobar artery leads to death of a pyramid-shaped zone of kidney tissue described as "kidney infarct". The arcuate arteries give off branches that run between cortical lobules "interlobular arteries".

Diagram (2):

Diagrammatic representation of a renal corpuscle, showing its juxtaglomerular apparatus (stained by the PAS technique). Its tubular pole is at the top, and its vascular pole is at the bottom. See text for details (*Ham and Cornmak 1987*)



which give off branches on all sides entering the lobules and known as "intralobular arteries". They give rise to the afferent arterioles of glomeruli. The efferent arterioles empty their blood into the capillary beds that surround the proximal and distal convoluted tubules and loops of Henle known as arterial vasa recta. (Kriz *et al*, 1976).

Diagram (3):

Schematic representation of the basic arrangement of nephrons and collecting tubules in a lobule of the kidney (Ham and Cornmack (1987)

