Anatomy of Lymphatic system in Kidney — Poorly understood and important in future

Abstract
The cortex of a healthy kidney contains a significant number of renal lymphatics, though these have often been overlooked in discussions related to kidney diseases. These lymphatics originate within the renal lobule's core as capillaries that come to a closed end. They can either accompany alongside the primary arteries and veins toward the hilum, or they can penetrate the outer surface of the kidney to connect with capsular lymphatics. Valves are absent in the interlobular lymphatics, enabling lymph produced in the cortex to exit the kidney in either of the two directions. The medulla contains only a sparse number of lymphatics.

Lymph originates from the interstitial fluid in the cortex, consisting mainly of capillary filtrate, yet also containing fluid reabsorbed from the tubules. The formation of renal lymph depends mainly on two factors: the volume of interstitial fluid and the pressure within the veins inside the kidney.

The interaction between impaired renal lymphatic function and swelling in the renal interstitial area creates a reciprocal negative effect. These interactions are anticipated to diminish renal function as a result of changes in pressure within the enclosed kidney. This mechanism bears importance in various prevalent renal conditions.

Introduction

In the interstitial space everywhere over the body, closed-ended veins give rise to lymphatic capillaries. These capillaries combine over time to become more substantial collecting channels, which eventually join veins. This complex network transports big molecules and fluid from the interstitial space back to the systemic circulation, where they play a vital part in the body's functions, including those of the kidneys. This crucial process stops the accumulation of interstitial fluid, which can obstruct the transport of oxygen to tissues. The fact that the kidneys in particular have a sizable network of lymphatic vessels suggests that the renal lymphatic system plays a key role in healthy and demanding physiological conditions.[1] However, the architecture and physiology of renal lymphatics in general, as well as their function in illness, disregarded in recent times.

The failure of the lymphatic system to efficiently drain interstitial fluid has a variety of causes, including valve malfunction, lymphatic vessel obstruction, alteration of pressure gradients, and loss of smooth muscle contractility. When this illness affects a limb, it manifests as peripheral pitting edoema, but its effects on the kidney are less obvious. However, because the renal capsule is rigid, insufficient lymphatic drainage may result in elevated intra-renal pressure and compromise kidney function. In a number of clinical situations, including congestive heart failure (CHF), acute kidney injury (AKI) linked to systemic inflammatory response syndrome (SIRS), chronic renal failure, failure of renal transplant grafts, and others, we hypothesise that this frequently overlooked mechanism may be at work.

As a result, renal lymphatics may play a substantial role in a variety of clinical scenarios; nonetheless, the contemporary research on this crucial topic is surprisingly scarce. This in-depth analysis aims to fill this information gap about renal lymphatics. We start by comparing the anatomical makeup of these structures in humans and other animals. The physiology of the renal lymphatic system under regular conditions and under times of stress is then explored. Finally, we offer a succinct summary of how renal lymphatic insufficiency affects various disease states.

Renal Lymphatic Anatomy: Exploring the Structure

Approaches to Investigating Renal Lymphatic Anatomy

Paolo Mascagni is credited with discovering renal lymphatics in 1787 when he administered mercury to the kidneys of cadavers.[2] In order to examine renal microstructures under a microscope, the majority of research have used dyes such as tryptan blue, India ink, and Evans blue dye that have been injected intravenously or into the renal tissue. However, thanks to improvements in imaging techniques and the appearance of markers specific to Lymphatic Endothelial Cells (LECs), there has been a notable development in our understanding of renal lymphatic anatomy in recent years.

Distinctive Markers for Lymphatic Endothelial Cells

Despite not being restricted to LECs only, LEC markers do allow distinction between these cells and endothelial cells in blood vessels. Podoplanin, LYVE-1, vascular endothelial growth factor receptor 3 (VEGFR-3), and prospero-related homeo-box transcription factor 1 (Prox1) are the most often used indicators.[3] Among these, podoplanin, a transmembrane protein of the mucin type, is very effective for detecting human kidneys, and it can be precisely found in paraffin-embedded tissue using a podoplanin antibody.[4]

Live Imaging of the Renal Lymphatic System

Traditionally, kidneys had to be removed for microscopic or microradiographic analysis in research focusing on renal lymphatic architecture. Although modern methods (such as pedal lymphangiography, lymphangiography, and lymphoscintigraphy) have been developed to visualise bigger lymphatics while the organ is still in vivo, these techniques do not yet make it possible to see renal lymphatics. However, it is possible to scan the central lymphatic system by directly catheterizing the cisterna chyli via a trans-abdominal route or by injecting contrast agents into the inguinal lymph nodes (intranodal lymphangiography).5 Additionally, guidelines for minimally invasive techniques to examine lymphatics have been provided. When embolisation materials are injected into the lymph node interstitium, such as N-butyl cyanoacrylate (N-BCA) glue (TRUFILL, Codman Neuro, Rayhnam, MA, United States), this might result in downstream propagation and embolisation.[5] Imaging of the hepatic lymphatics can be done by injecting contrast materials into the peri-portal region.[6] These developments may eventually make it possible to image renal lymphatics by introducing contrast agents (or probes) into the renal interstitium.

Embryonic Structural Formation

Through recent lineage tracing investigations using LEC markers, Sabin's 1909 hypothesis that Lymphatic Endothelial Cells (LECs) arise from sprouts originating from embryonic veins has been confirmed.[7,8] Using LYVE-1 expression, Lee et al. carefully examined the early development of the renal lymphatics in mouse embryos.[9] Intra-renal lymphatics and extra-renal lymphatic plexuses were initially identified in embryos that were 13 days old. In the next days, these lymphatics developed painstakingly planned networks that paralleled the developing arcuate and interlobular arteries. Surprisingly, no similar lymphatics were found in the renal medulla at any point in its development.

LYVE-1+ cells were infrequently found in developing arcuate veins, notably in branching buds, according to Lee et al.[9] Up until the fourth postnatal day, lymphatic vessels were mostly concentrated around developing veins. Interestingly, LYVE-1+ lymphatic tubes did not develop until immature macrophages and dendritic cells did. These cells were discovered to be densely entwined or even integrated into the wall of the lymphatic vascular system. The inference made was that LYVE-1+ cells first emerge from veins, but that LYVE-1+ macrophages and dendritic cells play a crucial role in orchestrating a branching process that connects these cells with extra-renal lymphatic channels. VEGF-C appears to have a significant regulatory function in this branching mechanism, which is noteworthy.[9, 10] Tanabe et al. also discovered a similar pattern in rat kidneys, whereby renal lymphatic vessels develop from extra-renal lymphatic vessels already present and spread along the renal vascular framework in the direction of the cortex.[11] Around embryonic day 20, intra-renal lymphatic channels became visible for the first time. Despite these findings, it is still unclear whether the mammalian kidney contains intrinsic lymphatic precursors involved in the development of intra-renal lymphatic arteries.[10]

Renal Vascular Structure

The arrangement of the renal vascular system and the renal lymphatics are very similar.[12] Thus, a brief examination of the arterial supply to the kidneys is necessary. Each kidney typically receives its own renal artery. Within the renal sinus, this artery divides into the posterior, superior, anterosuperior, anteroinferior, and inferior segmental arteries.[13] Each segment of the kidney's structure includes a renal pyramid that is encased in a piece of renal cortex. These segments are further separated into renal lobules, each of which has a single medullary ray that empties into a single collecting duct and is surrounded by nephrons. This lobular pattern is followed by arteries that emerge from segmental arteries (Figure 1). Arcuate arteries are produced by an interlobar artery, which extends between the lobes and crosses the cortex-medulla junction. Interlobular arteries protrude from each arcuate artery and flow between lobules towards the outer capsule. The glomerulus is reached by afferent arterioles that are released by these interlobular arteries. The venous structure resembles

the arterial system, with the exception that veins from different segments join to one another, as opposed to segmental arteries, which finish in end arteries.

Comparing Renal Lymphatic Structure Across Species

Renal Lymphatic System in Non-Mammalian Vertebrates

It is believed that the development of the lymphatic system followed the transfer of aquatic creatures to terrestrial settings. Fish don't have a well-developed lymphatic system, but amphibians do.[14] Bird embryos, some amphibian embryos, and reptile embryos all have lymph "hearts," which facilitate lymph flow. These rhythmic chambers are located where veins and lymphatic vessels converge. Notably, these chambers have valves, have variable wall thickness, and pulse separately from the heart's rhythm.[15] In contrast to amniotes, fish and anuran amphibians rely less on the kidney for a supplementary lymphoid function.[16] Although renal lymphatics are frequently omitted from papers on reptile and bird renal anatomy.[17,18]

Mammalian Renal Lymphatic Structure

Research on renal lymphatic architecture has mostly focused on animals, particularly dogs. In a landmark study, Pierce et al used intravenous tryptan blue and India ink injections into the kidneys of dogs, rabbits, and guinea pigs to painstakingly map the renal lymphatics under a microscope.[19] Pierce noted that intralobular lymphatics—sparse, blind-ended tubules near renal tubules—are the origin of renal lymphatics within the cortex. These intralobular lymphatics pass through the renal corpuscles but do not penetrate them; they then combine to form interlobular lymphatics. These hilar lymphatics are subsequently drained into the larger interlobar and arcuate lymphatics that interact with these interlobular lymphatics (Figure 1). The dog normally has 4-6 lymphatic channels leaving the renal capsule and 6-8 hilar lymphatics. Following capsule ejection, renal sinus and hilum lymphatics seem to join with capsular lymphatics. Only 1% of the blood in the cortical peritubular capillaries in dogs' cortex is made up of cortical lymph, roughly speaking.

Despite a few exceptions, this renal lymphatic system is largely the same across animals. For instance, sheep kidneys lack a capsular system, while rabbit kidneys appear to lack intralobular lymphatics (Table 1). The ability to concentrate urine is correlated with the extent of intra-cortical lymphatics; the golden hamster has the most extensive system and is therefore more capable of concentrating pee than the rabbit. The kidney's defined lymphatic architecture in humans is very similar to that of other mammals (Figure 1). These findings were confirmed by autopsy microscopy and radiographic examinations, and LEC markers were then used to confirm them. As shown by Ishikawa et al. (2006) using podoplanin antibody application, the interstitial areas surrounding interlobular, arcuate, and interlobar arteries and veins host a profusion of lymphatic capillaries (Figure 2).

Lymphatic Communication and Pathways

When compared to the lymphatic vessels around interlobular arteries in humans, those around interlobular veins show more growth. While there are numerous lymphatics located around interlobar arteries in the interstitium, those that surround interlobar veins are dispersed within the vascular wall and cover the media and intima below the endothelium. Despite the close closeness of renal lymphatics and vasculature, concrete proof of intra-renal lymphatic-venous shunts is still difficult. However, lymphovenous linkages have not been found in human postmortem studies, only in rats and primates at the level of the renal vein.[20]

Summarizing Human Renal Lymphatic Anatomy

The basic anatomy of the human renal lymphatic system is similar to that of other mammals. Beginning close to the renal tubules, lymphatic capillaries travel close to the glomeruli before joining the renal arteries as interlobular, arcuate, and interlobar lymphatics. Notably, interlobular lymphatics lack valves in the cortex, allowing lymph to go in one of two directions: either towards the hilum or through the capsular lymphatic plexus and out the kidney. Although lymphatic capillaries are quite common in the cortex, they are uncommon in the medulla. These capillaries lack a basement membrane and include intercellular spaces between endothelial cells. They are attached to the surrounding interstitial tissue. Larger arcuate, interlobar, and hilar lymphatics have smooth muscle cells for lymph propulsion and valves to guarantee unidirectional flow.

Renal Lymphatic Function Under Physiological Conditions

Methods for Investigating Renal Lymphatic Physiology

Similar to studies on renal lymphatic anatomy, animal models have been the mainstay of studies on renal lymphatic physiology. While in vivo renal lymph collection has been accomplished in canines21 and rats22, comparable human studies have not been productively completed. Due to the kidney's distinctive lymphatic configuration, measuring renal lymphatic flow rates in animals has proven challenging. Despite this, significant progress has been made, as described in the following sections.

Generation of Renal Lymph

Drainage of fluid and macromolecules from the interstitial region between tubules and capillaries is carried out by lymphatic channels. The Starling equation, which governs the balance between hydrostatic and oncotic pressures, controls the admission of lymph into lymphatic capillaries.[23] Proteins are discharged into the interstitium of all blood capillaries; this process is made more obvious by the presence of endothelial fenestrations. Due to their close closeness, these fenestrations are more common on the side of capillary walls facing renal tubules of the kidney. Proteins that enter the interstitium are therefore more likely to build up between capillaries and tubules, lowering the critical oncotic pressure gradient. As a result, the movement of fluid and electrolytes from tubules to peri-tubular capillaries would be reduced. The kidney is the only organ with a significant extravascular albumin pool that is rapidly removed and replaced. This was demonstrated by Slotkoff and Lilienfield by giving dogs intravenously administered radioactively labelled red blood cells and albumin.[24] Following dextran perfusion, it was discovered that more labelled albumin than labelled red blood cells remained in the kidneys. As a result of fewer lymphatics to remove albumin in the medulla and a resultant substantial extravascular albumin pool, this showed the presence of extravascular albumin. Interstitial albumin is necessary for urine concentration in the medulla, but lymphatics are primarily responsible for removing it from the cortex, preserving the oncotic pressure gradients required for tubular reabsorption.
Hydrostatic and oncotic pressure gradients enable interstitial fluid and proteins to easily cross terminal lymphatics. In contrast to subcutaneous tissue or muscle, it is noteworthy that renal interstitial fluid pressure consistently remains positive, resulting in higher baseline lymph flow rates.[25] Lymphatic endothelial cells (LECs) interconnect to provide gaps that allow for entry into lymphatic channels. High endocytic activity in these endothelial cells enables transcellular fluid and macromolecule absorption.[3] Tethering filaments, which link LECs to the perivascular matrix and widen interendothelial gaps under edematous conditions, aid in entrance. Additionally, the lack of a basement membrane facilitates the admission of fluids and proteins. The composition of the lymph in terminal lymphatics closely approaches that of the progenitor, interstitial fluid.

Capsular Lymph vs. Hilar Lymph Formation and Flow

Depending on the cortical region, the renal lymph drainage varies. The outer cortex is largely drained by capsular lymphatics, while the medulla and inner cortex are primarily drained by hilar lymphatics. Despite the fact that the majority of renal lymph comes from the cortex, studies show that hilar lymph flow outpaces capsular lymph by a factor of 4–8, indicating that the majority of cortical lymph is removed via the hilar pathway. The electrolyte composition of hilar lymph, which reflects the similarity between cortical interstitium, from where the majority of hilar lymph originates, and plasma, supports this. The composition of renal hilar lymph, which mostly drains the cortex, does not mirror medullary conditions because the medullary interstitium has greater solute concentrations as a result of urine concentration mechanisms.

Composition of Renal Lymph Under Normal Conditions

Both capillary filtrate and tubule reabsorbate are the sources of renal lymph. Studies using chemicals that have been labelled have revealed the mixed origin of renal lymph. According to inulin lymph/plasma ratios, both filtrate and reabsorbate are involved.[26,27] Concentrations of sodium, chloride, and other solutes reveal independent solute reabsorption by the distal tubule, which combines with capillary filtrate to create renal lymph. In renal lymph, the relative percentage of proteins fluctuates greatly depending on flow rate and anaesthesia level. Due to its closeness to the juxtaglomerular system, renal lymph exhibits higher levels of

renin and angiotensin II. Similar albumin concentrations and high apolipoprotein levels highlight the importance of renal lymph in molecular transport.

Renal Lymph Flow Rates Under Normal Conditions

Since renal lymphatics do not converge before entering the periaortic chain, quantifying the total renal lymph flow rate presents difficulties. These complexity lead to different experimental measurements. Despite the fact that lymph flow makes only a small portion of renal fluid output, some research indicate that lymph and urine flows are comparable.[28] The range of the flow estimation is 2% of fluid reabsorption to 50% of urine flow.[29-31] Total renal lymph flow in fasted dogs averages 0.36 ml/min/100 g kidney, with each kidney accounting for 21% of thoracic duct flow.[31] The increased value in animals on fasts can be due to decreased cisterna chyla flows.[31]

Interstitial Fluid and Protein Drainage in the Medulla

Medullary fluid and proteins, in contrast to the cortex, are primarily eliminated by the vasa recta rather than the lymphatic system. Concentration gradients help medullary fluid migrate towards the vasa recta while convective flow directs proteins along with the fluid.[32,33] Due to the vasa recta's significant contribution to the reabsorption of interstitial fluid in the medulla, medullary lymph composition differs from that of cortical lymph.[32] As a result, comparable to the brain, cornea, and bone marrow, the medullary interstitial fluid drainage does not require lymphatics.[32]

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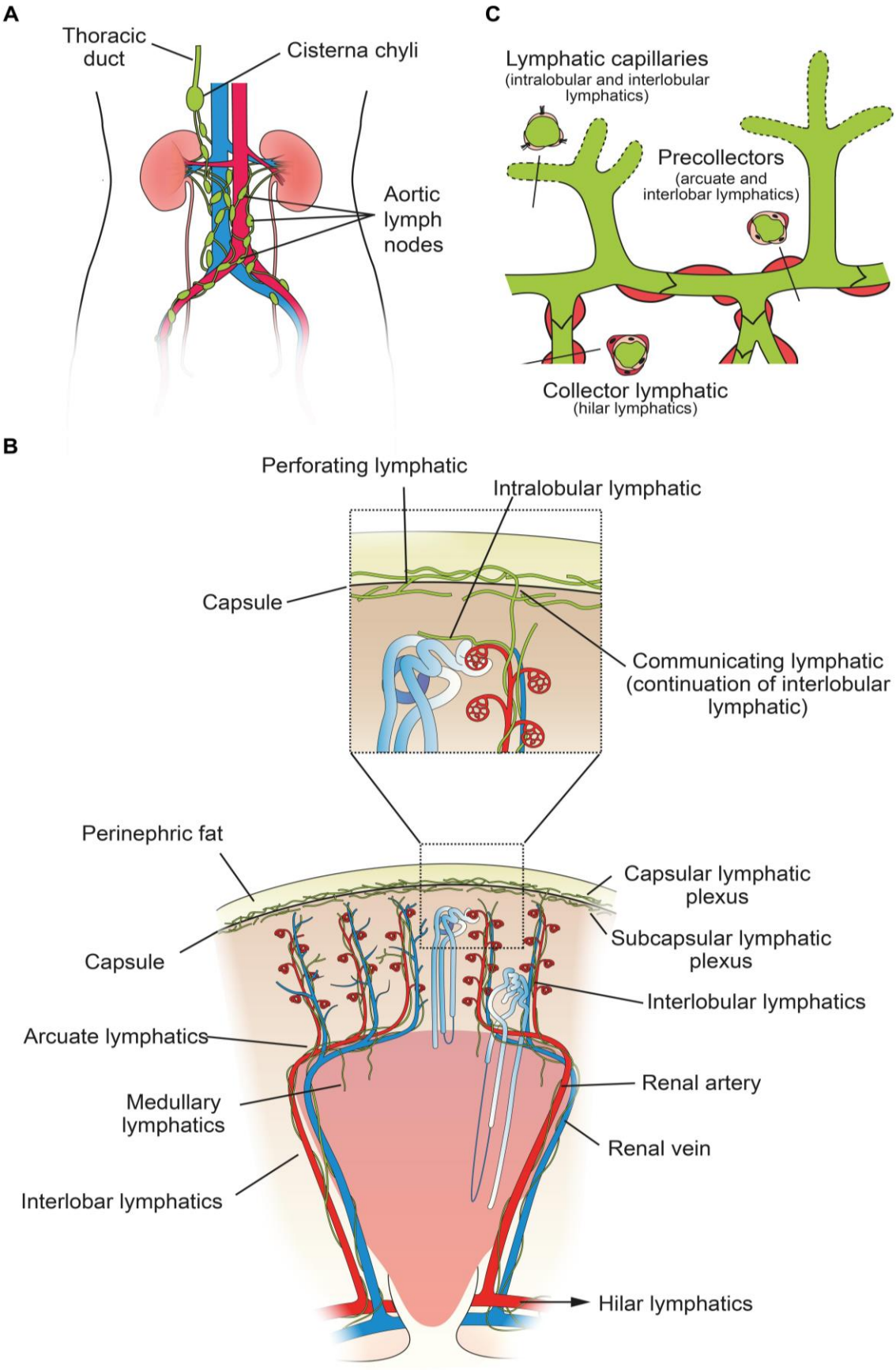

FIGURE 1. Structure of the human renal lymphatic system. **(A)** Lymph passes from 4–5 renal hilar lymphatics on each kidney to various groups of aortic lymph nodes. Most lymph draining from the kidney collects in the cisterna chyli and is drained via the thoracic duct into the central venous circulation in the neck. **(B)** Schematic diagram of a human renal lobe. **(C)** Schematic showing morphology of renal lymph vessels.

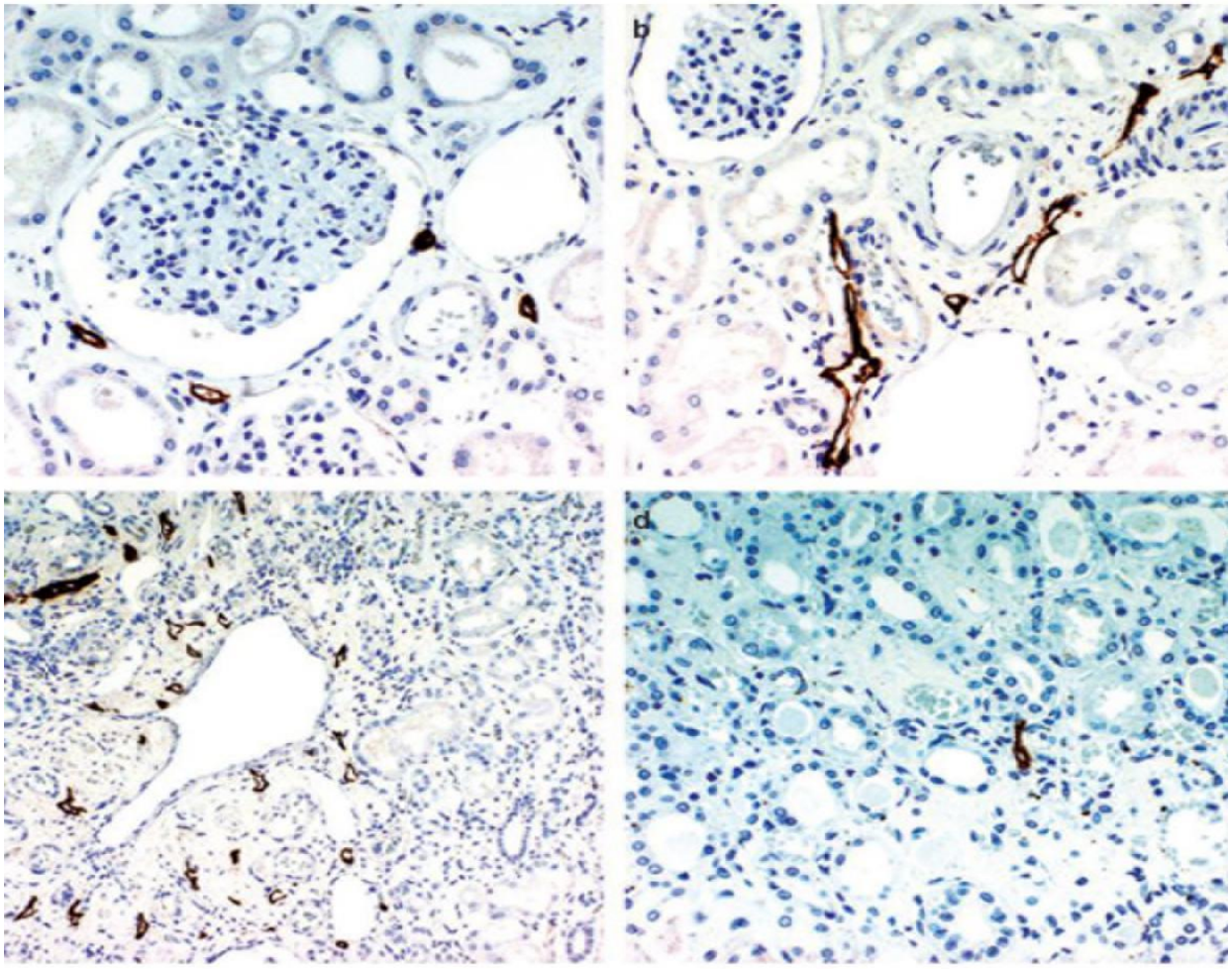

FIGURE 2. D2-40 immunostaining of lymphatics in the normal kidney. **(a)** Lymphatic capillaries in the interstitium around the glomerulus, **(b)** lymphatics exhibiting a slit-like structure are distributed around the interlobular artery and vein in the cortex, **(c)** multiple lymphatic capillaries in the interstitium around a dilated interlobular vein, a few lymphatic capillaries are present just beneath the venous endothelium, **(d)** a lymphatic capillary is recognizable in the center of the figure showing a normal medulla.

Table 1. Comparison of renal lymphatics between different species

Species	Intralobular Lymphatics	Medullary Lymphatics	Communication between renal and capsular lymphatics	Glomerular Lymphatics	Comments
Dog	Present	Present	Present	Partially surround Bowman's capsule	Species most extensively studied
Pig	Present	Present	Present		
Rat	Intermediate	Not found		Lymphatics lie close to glomerulus	Intrarenal lymphatic vessels appear at embryonic day 20
Mouse			Present		Intrarenal lymphatic vessels appear at embryonic day 20
Rabbit	Rare	Present	Not Found		Least extensive intralobular lymphatics and lowest urine concentrating ability
Guinea Pig	Extensive				Most extensive intralobular lymphatics and highest urine concentrating ability
Horse				Completely surround Bowman's capsule	
Sheep		Not found	Absent		
Human	Present	Rare and in outer medulla only or surrounding vasa recta	Present	Sporadically surround glomerulus	Medullary lymphatics seen in pathological specimen

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