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Advances in Ultrastructural Pathology for Renal Biopsy Diagnosis

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Abstract

Renal biopsy remains the cornerstone of precise diagnosis and classification in nephrology. Ultrastructural pathology, centered on electron microscopy (EM), provides indispensable diagnostic value in immune-complex-mediated nephropathies, hereditary kidney diseases, and transplant-related injuries due to its nanometer-scale resolution. However, traditional transmission electron microscopy (TEM) is hindered by labor-intensive sample preparation, long turnaround times, limited field of view, and an inability to assess functional status, which limits its utility in the era of rapid, standardized, and quantitative precision medicine. Recently, emerging imaging technologies—including low-vacuum scanning electron microscopy (LVSEM), multiphoton microscopy (MPM), ultrasound localization microscopy (sULM), and structured illumination microscopy (SIM)—have expanded the scope of ultrastructural pathology from static two-dimensional morphological observation to three-dimensional structural reconstruction and real-time functional imaging. Concurrently, the integration of digital pathology and artificial intelligence (AI) has enabled automated recognition, quantitative analysis, and disease classification, significantly enhancing diagnostic efficiency and consistency. This article systematically reviews the traditional diagnostic value of ultrastructural pathology in renal biopsies, summarizes the breakthroughs and advantages of novel imaging techniques, discusses the progress of AI and digital pathology in ultrastructural analysis, and provides a forward-looking perspective on the development of multimodal, intelligent diagnostic systems to facilitate the modernization of renal pathology.

Keywords

Ultrastructural Pathology, Renal Biopsy, Electron Microscopy, Artificial Intelligence, Precision Diagnosis, Digital Pathology

1. Introduction

Kidney diseases are highly heterogeneous. While clinical manifestations may be similar, pathological mechanisms, treatment responses, and prognoses differ significantly. Renal biopsy pathological diagnosis has become the cornerstone for clinical classification, guiding treatment, and determining prognosis. Among the three major technical systems—light microscopy, immunofluorescence/immunohistochemistry, and electron microscopy—ultrastructural pathology, centered on electron microscopy, can reveal nanoscale fine structural changes in the glomerular basement membrane, foot processes, mesangial matrix, electron-dense deposits (EDD), and organelles. It serves as the "gold standard" for the definitive diagnosis of many kidney diseases. In certain diseases, the absence of electron microscopy examination can directly lead to misdiagnosis or missed diagnosis, resulting in severe clinical consequences [1].

Since the application of electron microscopy to renal pathology in the mid-20th century, it has continuously played a core role in identifying the location of electron-dense deposits, assessing basement membrane lesions, differentiating podocyte injury, and evaluating ultrastructural changes in transplant kidneys. However, with the development of precision medicine, the clinical demand for renal biopsy has expanded from purely morphological diagnosis to a comprehensive assessment encompassing disease activity, functional status, molecular mechanisms, and prognostic risk. Traditional transmission electron microscopy (TEM) suffers from complex procedures, long turnaround times, limited throughput, and heavy reliance on pathologist experience, presenting significant shortcomings in standardization, quantification, and rapid diagnosis.

In recent years, the rapid advancement of microscopic imaging technology, digital pathology, and artificial intelligence has brought revolutionary changes to ultrastructural pathology [2]. Low-vacuum scanning electron microscopy (LVSEM) simplifies sample preparation and shortens diagnostic cycles; multiphoton microscopy (MPM) and super-resolution ultrasound localization microscopy (sULM) enable structural and functional imaging of living kidneys; structured illumination microscopy (SIM) breaks the optical diffraction limit, allowing quantitative analysis of nanoscale ultrastructure; and deep learning models have demonstrated high accuracy in tasks such as identifying electron-dense deposits, assessing foot process effacement, and classifying nephropathies. Ultrastructural pathology is evolving from a traditional morphological tool into a multimodal, intelligent, and digital comprehensive diagnostic system. This article focuses on the evolution of ultrastructural pathology applications in renal biopsy, systematically reviewing its traditional value, technological innovations, integration with artificial intelligence, and future development trends.

2. Materials and Methods

Methods: A systematic search was conducted in the PubMed database using the following search strategy:

(ultrapatho*[Title/Abstract] OR microscopy[Title]) AND (kidne*[Title] OR nephrid*[Title] OR renal*[Title])

Database and Time Range: The search was performed in PubMed, covering the period from January 1, 2016, to January 1, 2026 (the past decade).

Inclusion and Exclusion Criteria:

Inclusion criteria: 1) Studies involving the application of ultrastructural pathology or microscopic imaging techniques in the diagnosis of kidney diseases; 2) Article types including original research, reviews, systematic reviews, or guidelines; 3) Articles written in English.

Exclusion criteria: 1) Conference abstracts, case reports, or dissertations; 2) Duplicate publications or articles for which full text was unavailable.

Study Screening Process:

A total of 162 articles were identified in the initial search. After abstract screening, 72 articles were excluded; after full-text screening, 61 articles were excluded. Ultimately, 29 articles were included. The screening was conducted independently by the researcher.

3. The Traditional Role and Core Value of Ultrastructural Pathology in Renal Biopsy Diagnosis

The core advantage of ultrastructural pathology lies in its nanoscale spatial resolution, enabling the detection of subtle structural changes invisible to light microscopy, thereby facilitating disease diagnosis, differential diagnosis, and prognostic assessment.

3.1. Key Diagnostic Basis for Immune-Mediated Glomerular Diseases

The core pathological feature of immune complex-mediated glomerular diseases is the abnormal deposition of electron-dense deposits (EDD) in different regions of the glomerulus, and their distribution pattern is a key marker for disease classification [3]. Electron microscopy can clearly distinguish deposition patterns in subepithelial, subendothelial, mesangial, and intramembranous locations, providing decisive evidence for disease diagnosis [4]. Acute post-streptococcal glomerulonephritis is characterized by pathognomonic subepithelial “hump-shaped” electron-dense deposits [5]. Active lupus nephritis often shows massive subendothelial electron-dense deposits, which may be accompanied by tubuloreticular inclusions, significant for assessing disease activity [6]. IgA nephropathy is diagnosed based on predominantly mesangial electron-dense deposits; electron microscopy can simultaneously assess the extent and degree of foot process effacement. Foot process effacement is clearly associated with the clinical prognosis of IgA nephropathy. Extensive foot process effacement (>50% of capillary loops) is independently associated with more severe proteinuria and faster decline in renal function [7]. Membranous nephropathy is characterized by typical subepithelial spike-like deposits; electron microscopy is an important supplement for distinguishing primary from secondary membranous lesions. By evaluating the ultrastructural distribution pattern of deposits and, in antigen-negative cases, assessing GBM structural changes and deposit morphology, electron microscopy can provide crucial clues for differential diagnosis [8], thereby avoiding the simplistic treatment of MN as a single disease and guiding the development of more targeted therapeutic strategies.

3.2. The "Gold Standard" for Hereditary Kidney Diseases

Hereditary nephropathies primarily involve structural abnormalities of the basement membrane or podocyte cytoskeleton. Light microscopy often lacks specific findings, making electron microscopy the only means to provide definitive diagnostic evidence. Alport syndrome is characterized by typical irregular thickening, lamellation, splitting, and basket-weave changes of the glomerular basement membrane [9] [10], with basement membrane thickness significantly deviating from the normal range, allowing precise differentiation from the diffuse thinning of the basement membrane seen in thin basement membrane nephropathy (TBMD). Such diseases are difficult to diagnose solely by light microscopy and immunofluorescence; ultrastructural changes are the most important morphological evidence prior to genetic testing.

3.3. Essential Tool for Transplant Renal Pathology

The causes of transplant kidney injury are complex and diverse, primarily including antibody-mediated rejection (ABMR), cellular rejection, recurrent glomerular disease, and drug toxicity. Recurrence of glomerulonephritis after transplantation is a significant clinical challenge leading to graft loss [11]. For example, the recurrence of focal segmental glomerulosclerosis (FSGS) is closely related to various circulating factors and molecular biomarkers. Membranous nephropathy (MN) can either recur or de novo occur after transplantation, and both conditions are often accompanied by a similar risk of antibody-mediated rejection. In such cases, electron microscopy (EM) can accurately determine the nature of the lesion by observing the degree of foot process effacement, the location of electron-dense deposits, and ultrastructural changes in the basement membrane [12]-[14], providing key evidence for adjusting clinical treatment strategies. Transplant glomerulopathy is primarily caused by chronic antibody-mediated rejection [15]. Electron microscopy can clearly reveal characteristic ultrastructural changes that are difficult to discern under light microscopy, such as double contours of the basement membrane, basement membrane duplication, and widening of the subendothelial space.

4. Technical Limitations of Traditional Ultrastructural Pathology

Despite its clear diagnostic value, traditional TEM faces multiple bottlenecks in modern clinical application. The maintenance cost of electron microscopy equipment is high [16], and it requires a specialized laboratory environment. Furthermore, traditional electron microscopy faces increasingly severe challenges in data management. Currently, the data volume generated from a single EM experiment has escalated from the gigabyte (GB) level to the terabyte (TB) or even petabyte (PB) level. Traditional local storage and manual management methods struggle to cope with the archiving, retrieval, and long-term preservation of such massive datasets [17]. The observation field of TEM is extremely small (typically only at the micrometer level). If the section happens to miss the lesional area, it can easily lead to missed diagnosis or misdiagnosis. TEM observes two-dimensional ultrathin sections and cannot fully represent the complex microvascular network within the glomerulus, the three-dimensional morphology of foot processes, or the spatial distribution of deposits, limiting the in-depth understanding of pathological mechanisms. These issues collectively constrain the widespread application of ultrastructural pathology in the era of precision medicine and have also driven a new wave of technological innovation.

5. Technological Innovations: From Morphological Observation to Functional Imaging

Ultrastructural pathology, centered on electron microscopy, studies nanoscale structural changes in cells, tissues, and the extracellular matrix. Its traditional scope was limited to two-dimensional static morphological observation of *ex vivo* biopsy tissue. In recent years, the emergence of various novel imaging technologies has expanded the boundaries of ultrastructural pathology research from *ex vivo* tissue to *in vivo* organs, from static structure to dynamic function, and from two-dimensional sections to three-dimensional space. Based on their application scenarios, these new technologies can be categorized into the following three groups.

5.1. Biopsy Tissue-Related Technologies: Enhancing Diagnostic Efficiency and Dimensionality of *Ex Vivo* Samples**

These technologies are directly applied to the ultrastructural analysis of *ex vivo* renal biopsy tissue, aiming to simplify sample preparation, shorten diagnostic turnaround time, or provide three-dimensional structural information unattainable by traditional TEM.

5.1.1. Low-Vacuum Scanning Electron Microscopy (LVSEM)

LVSEM allows direct observation of resin-embedded blocks under low-vacuum conditions [18], eliminating the need for ultrathin sectioning. This significantly simplifies sample preparation and markedly shortens diagnostic time, making it more suitable for rapid clinical diagnosis. Studies have shown that LVSEM can clearly visualize glomerular basement membrane duplication, lamellation, and mesangial changes. It demonstrates high sensitivity for detecting early ultrastructural changes associated with antibody-mediated rejection, offering the potential for rapid early warning of subclinical transplant injury [19] and showing good potential for clinical translation.

5.1.2. Structured Illumination Microscopy (SIM)

SIM, a super-resolution optical microscopy technique, overcomes the diffraction limit, enabling nanoscale structural observation. Its application in renal pathology has extended beyond single disease types. Liu *et al.* [20] applied dual-color fluorescence SIM to renal mass biopsies. By performing rapid, non-destructive optical sectioning imaging of fresh biopsy tissue while maintaining tissue integrity, they achieved high sensitivity and specificity in diagnosing renal tumors, providing a new clinical translation pathway for real-time pathological assessment of renal masses. Furthermore, SIM has demonstrated unique advantages in evaluating foot process effacement, measuring basement membrane thickness, and quantifying autophagosomes in non-neoplastic renal diseases [21] [22], indicating its potential as a versatile analytical tool for renal ultrastructural pathology.

5.2. *In Vivo** and Non-Invasive Adjunctive Technologies: Enabling Structural and Functional Imaging of Living Kidneys**

These technologies require minimal or no invasive procedures, allowing real-time observation of kidney structure and function *in vivo*, extending ultrastructural pathology from *ex vivo* diagnosis to *in vivo* functional assessment.

5.2.1. Multiphoton Microscopy (MPM)

MPM offers advantages such as deep tissue imaging, low phototoxicity, and the ability for long-term *in vivo* observation. It enables real-time visualization of tubular blood flow, organelle dynamics, immune cell migration, reactive oxygen species (ROS) generation, and mitochondrial functional changes in living kidneys. This provides novel tools for elucidating the pathophysiological processes of diabetic nephropathy, ischemia-reperfusion injury, hypertensive nephropathy, and renal inflammation [23]. Compared to traditional static electron microscopy, MPM truly achieves simultaneous assessment of structure and function, propelling renal pathology from "morphological diagnosis" towards "mechanistic analysis."

5.2.2. Super-Resolution Ultrasound Localization Microscopy (sULM)

sULM overcomes the resolution limitations of traditional ultrasound, enabling non-invasive visualization of microvasculature. It can precisely quantify renal microvascular hemodynamics, representing a breakthrough technology for early non-invasive diagnosis of kidney diseases. In early diabetic kidney disease (DKD), glomerular microvascular injury is the core initiating factor. Traditional ultrasound cannot detect subtle blood flow abnormalities, whereas sULM can clearly visualize glomerular microvascular distribution, blood flow velocity, and perfusion, capturing the characteristics of early DKD microvascular lesions and providing a new avenue for non-invasive, early, and precise diagnosis [24] [25]. Furthermore, sULM can directly visualize glomerular structures in both native and transplanted kidneys in humans without invasive procedures, holding broad application prospects for non-invasive monitoring of transplant kidneys and screening high-risk populations, extending ultrastructural pathology from invasive biopsy to non-invasive screening [26].

5.3. Virtual Digital Microscopy (VM): The Infrastructure for Digital Workflow

Virtual microscopy (VM) technology itself is not a novel microscopic imaging technique. Instead, it involves the whole-slide digital scanning of traditional pathology slides (including light microscopy, immunofluorescence, and electron microscopy slides) to generate high-resolution digital images that can be viewed, annotated, and shared on computers. The rationale for including it within the framework of ultrastructural pathology technological innovation is as follows: 1) **Technological Bridge: **VM serves as the bridge connecting ultrastructural pathology images with AI analysis, teleconsultation, and multi-center collaboration. Without the digital foundation provided by VM, AI models cannot obtain training data, and remote pathological evaluation cannot be realized. 2) **Process Restructuring: **VM transforms the workflow of ultrastructural pathology from a linear model of "sectioning → microscopy → reporting" to a parallel model of "sectioning → digitization → AI-assisted analysis → remote review → reporting," significantly improving diagnostic efficiency and accessibility. 3) **Prerequisite for Standardization: **VM enables the storage, retrieval, and quantitative analysis of ultrastructural pathology images, serving as the foundational infrastructure for advancing ultrastructural pathology from empirical interpretation towards standardized, quantitative, and traceable diagnosis.

Therefore, although VM does not directly enhance imaging resolution or functional imaging capabilities, as the core supporting technology of digital pathology, it is an indispensable component of the ultrastructural pathology technology system. Through digital slides, experts can perform remote pathological evaluation and achieve rapid sharing of donor kidney biopsy results, breaking down geographical barriers and significantly optimizing the efficiency of donor kidney assessment for transplantation, multi-center pathological review, and consultation for difficult cases [27], driving the transformation of the renal pathology workflow towards digitization and networking.

6. Deep Integration of Digital Pathology and Artificial Intelligence

AI and deep learning provide critical support for the standardization, quantification, and automation of ultrastructural pathology, reshaping diagnostic paradigms.

Automated Identification and Pattern Recognition: Deep learning models can automatically identify EDD in TEM images [28], determine their distribution, and assist in the rapid classification of immune-complex-mediated nephropathies, thereby reducing human error. Intelligent Disease Classification: Models such as MedKidneyEM-v1 have demonstrated high accuracy in automatically classifying amyloidosis, diabetic nephropathy, membranous nephropathy, and TBMD [29], serving as reliable diagnostic tools.

Despite these achievements, clinical translation faces challenges. AI model training is highly dependent on high-quality, expert-annotated datasets, which are currently scarce. Furthermore, data heterogeneity—arising from different equipment, staining protocols, and section thicknesses—limits model generalizability. Finally, the "black-box" nature of deep learning models limits clinical trust, necessitating the development of explainable AI.

7. Clinical Translation and Future Perspectives

Ultrastructural pathology remains indispensable, and technological innovation is revitalizing the field. Future trends include: 1) Multimodal Imaging Fusion: Integrating LVSEM, SIM, sULM, and MPM to achieve comprehensive "structure + function + molecular + non-invasive" assessment; 2) Full-Process Automation: Streamlining preparation, scanning, AI screening, and remote consultation to compress diagnostic cycles to within 24 hours; 3) Integrated Multi-omics: Correlating EM morphological data with genomic, transcriptomic, and proteomic data to build precise molecular classification systems.; 4) Intelligent Standardization: Using digital pathology and AI to unify quantitative metrics, reducing subjective variability.

Overall, ultrastructural pathology is gradually advancing from traditional electron microscopy-based morphological diagnosis toward a new era of multimodality, intelligence, digitalization, and functionalization, and will play an increasingly critical role in the precise diagnosis and treatment system of kidney diseases.

8. Conclusion

Ultrastructural pathology is a core technology in renal biopsy diagnosis, particularly for immune-complex-mediated, hereditary, and transplant-related diseases. While traditional TEM faces limitations, novel technologies like LVSEM, MPM, sULM, and SIM are driving the field toward rapid, three-dimensional, and functional imaging. The deep integration of digital pathology and AI is enabling automated recognition and intelligent classification. Moving forward, the synergy of multimodal imaging and AI will render ultrastructural pathology more efficient, precise, and standardized, providing robust support for early diagnosis, precise classification, and personalized treatment, thereby ushering renal pathology into a new era of precision medicine.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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