Retinal Manifestations of Renal Diseases

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Abstract

Various diseases affecting the renal excretory system can be associated by or secondary cause of pathological changes in the retina and choroid. Some of these entities such as tubulointerstitial nephritis and uveitis (TINU) are well recognized for their characteristic clinical manifestations. Similarly, patients with systemic lupus erythematosus may present with protean clinical manifestations. Recently, it has been recognized that fundus examination among patients with renal diseases may provide insights into the disease pathogenesis, severity, and progression. Thus, careful correlation between renal and retinal diseases may enable the clinician scientist to understand the pathophysiology of the disease and its natural history. In the index chapter, retinal findings of various diseases affecting the renal system have been elucidated. In addition, the features on imaging evaluation have also been provided. A brief note on their management has been discussed.

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5.1 Introduction

Patients with renal diseases especially autoimmune conditions may present with various pathological alterations involving the ocular tissues. Although several ocular tissues may be involved, the most commonly affected tissue is the retinochoroid. A host of autoimmune, metabolic, and biochemical processes affect the chorioretinal milieu resulting in characteristic tissue abnormalities and/or ocular inflammation. If the ocular symptoms precede diagnosis of systemic involvement, there may be a clinical challenge in determining the exact etiology and planning appropriate treatment. Thus, recognition of the disease phenotype and comprehensive systemic evaluation form the cornerstone of the management.

With numerous advances in the techniques of noninvasive imaging and recognition of disease patterns, our understanding of renal disease pathogenesis has been greatly enhanced. A number of asymptomatic and symptomatic changes have been described among patients with renal conditions such as tubulointerstitial nephritis and uveitis (TINU), systemic lupus erythematosus (SLE), and end-stage renal disease, among others. A thorough review of these ocular associations may aid in our knowledge of the complex mechanisms involved in the pathogenesis of these diseases. Establishing correlation between ocular signs and systemic disease severity may help in clinical decision-making and altering the line of management.

In the subsequent sections, clinically relevant and common renal diseases with chorioretinal involvement have been described. A brief summary of SLE has also been provided (described in details in a separate chapter). The relevance of retinal imaging in these conditions has been highlighted.

5.2 Glomerulonephritides

5.2.1 Membranoproliferative Glomerulonephritis

5.2.1.1 Introduction and Types

Membranoproliferative glomerulonephritis (MPGN) is characterized by proliferation of cellular elements in the glomerular tissue and basement membrane changes [1]. Histological studies show increased mesangial matrix deposition (electron dense material) and hypercellularity [2]. MPGN is associated with features of chronic glomerulonephritis, secondary hypertension, and systemic features due to immune complex deposition. The most common age of diagnosis is 5–15 years, and within a period of 10 years, approximately 50% of patients may progress to end-stage renal disease (ESRD) [3].

Type 1 MPGN is characterized by subendothelial glomerular electron dense deposits; type 2 MPGN is characterized by deposition of electron dense material of unknown origin in the lamina densa of the glomerular basement membrane; and type 3 MPGN is characterized by the presence of both type I and type II lesions [4]. Recently, a consensus conference on MPGN has reclassified the disease into two types: immune complex mediated and complement mediated [5].

5.2.1.2 Ocular Manifestations

Classically, pathological manifestations of the posterior segment of the eye have been observed in patients with type 2 MPGN (dense deposit disease). These pathological alterations commonly affect the outer retina and retinal pigment epithelium (RPE)-Bruch's membrane complex [4]. Due to RPE and outer retinal involvement, these patients may have altered visual fields and color perception, prolonged dark adaptation, and electroretinogram changes. The pathogenesis of these RPE changes has been attributed to the dense deposits at the RPE-Bruch's membrane complex. In a study by Michielsen et al., 11 out of 12 patients with type 2 MPGN were diagnosed with diffuse RPE alterations [6]. Various manifestations of the condition include RPE-Bruch's deposits similar to basal laminar deposits, exudative drusen, and pigment epithelial detachments [7]. This condition may also be complicated by development of subretinal/choroidal neovascularization (CNV) [6, 8, 9]. Development of CNV may be higher among patients with bilateral widespread RPE alterations and outer retinal changes. Fluorescein angiography (FA) and spectral-domain optical coherence tomography (SD-OCT) greatly aid in the detection of subretinal fluid, pigment epithelial detachments, and atypical central serous retinopathy [10].

Due to the decompensation of the RPE, patients may also develop central serous retinopathy-like picture with subretinal fluid and drusen-like deposits (DLDs) at the RPE-Bruch's membrane complex (Fig. 5.1) [7, 11]. DLDs may be common finding among patients with type 2 MPGN [12]. Presence of DLDs in patients of type 2 MPGN was first reported in 1989. Usually, the DLDs are located in the posterior pole and the mid-periphery. However, the presence of peripheral drusen has also been described in the literature [13]. SD-OCT imaging of DLDs in type 2 MPGN gives an appearance of subretinal RPE-Bruch's membrane elevations and hyper-reflectivity due to the deposition of matrix material [14]. Using high-speed ultra-high-resolution OCT, irregular thickening of the Bruch's membrane has been observed in patients with MPGN [15].

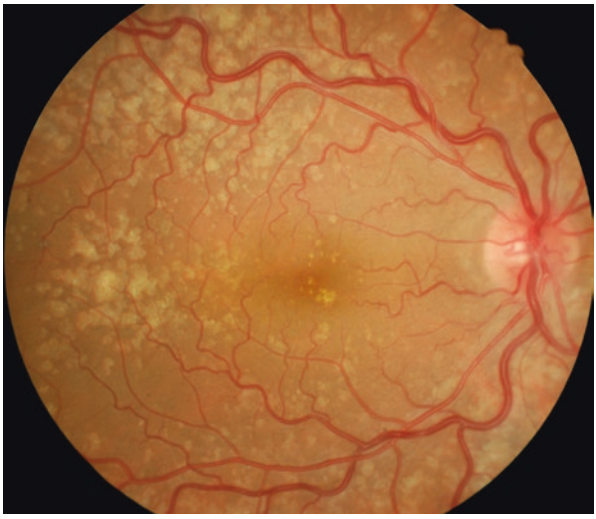

Fig. 5.1 Fundus photograph of a patient with biopsy-proven membranoproliferative glomerulonephritis with subretinal drusen-like deposits

Fundus autofluorescence (FAF) imaging shows multifocal hyper-autofluorescence in the areas with DLDs. Similarly, FA and indocyanine green angiography show multifocal hyperfluorescence associated with the subretinal deposits [16].

In the past, presence of DLDs and other outer retinal/RPE abnormalities were noted only in patients with type 2 MPGN. However, recent literature has shown that such changes may be observed even in patients with type 1 and 3 MPGN. Recently, Han et al. have described presence of extensive DLDs in a patient with type 1 MPGN [17]. These recent investigations have shed the light on the importance of the newer classification of MPGN which is based on molecular methods rather than anatomical location of the dense deposits. In a report by Dalvin et al., DLDs were observed in two patients with type 1 and 3 MPGN (based on anatomical classification). Thus, the authors proposed that ophthalmologists must recognize the importance of recognizing the newer classification of MPGN based on complement activation or immune complex-mediated disease [18]. Such an approach may aid in the better understanding of the pathophysiological mechanisms behind these complex diseases.

5.2.2 IgA Nephropathy

5.2.2.1 Introduction and Pathogenesis

IgA nephropathy (also known as Berger's disease) is a complement-mediated condition characterized by glomerulonephritis and progression to ESRD in approximately 40% individuals [19]. This condition was first described by Berger and Hingais in 1968 [20]. The disease is characterized by complement activation and deposition of IgA (as well as IgG) immune complexes in the mesangium of the glomeruli leading to a chronic disease. The deposition of polymeric IgA1, IgG, and complement C3 occurs in a diffuse granular manner. Recent progress in the diagnostic techniques has improved our understanding of the glycosylation pathways of IgA1 glycans and binding galactose-deficient IgA1 complexes to mesangial cells responsible for development of IgA nephropathy. While the trigger of inflammation is suggested to be autoimmune in nature, various antigenic stimuli due to bacteria, viruses, and fungi have been implicated in the pathogenesis [21]. The diagnosis of IgA Nephropathy requires renal biopsy and examination of mesangial matrices with periodic acid-Schiff staining.

5.2.2.2 Ocular Manifestations

The major clinical findings of IgA nephropathy include secondary hypertension (more than 40% patients at presentation) and chronic kidney disease [22]. Thus patients with IgA nephropathy may develop features of hypertensive retinopathy including arteriolar narrowing, changes in the arteriovenous crossings, and ischemia of retinal nerve fiber layer (cotton-wool spots) [23]. Patients may also develop serous retinal detachments which may be bilateral. These can be confirmed on SD-OCT. [23, 24] The findings of cotton-wool spots and serous retinal detachments are reversible on therapy with hemodialysis, peritoneal dialysis, or plasmapheresis.

In a case report by Taban et al., imaging evaluation using FA demonstrated presence of choroidal infarction secondary to possible immune complex deposition [23]. Other manifestations of IgA nephropathy include presence of bilateral

subretinal drusenoid deposits (SDDs). In a case report by Lally et al., a 42-year-old Asian woman with renal biopsy-proven IgA nephropathy showed presence of well-defined yellow clusters of SDDs in the macula. These were well appreciated using SD-OCT imaging. On SD-OCT, SDDs appeared as perifoveal hyper-reflective convex deposits internal to the retinal pigment epithelium (RPE)-Bruch's membrane complex. There was elevation of the ellipsoid zone and granular reflectivity between the ellipsoid and interdigitation bands adjacent to the deposits. In the report, the authors postulate that SDDs are histopathological correlate of reticular pseudodrusen and occur due to deposition of circulating serum IgA1 complexes [25].

Figure 5.2 shows a patient with subretinal hyper-reflective deposits at the fovea due to possible subretinal complement deposition.

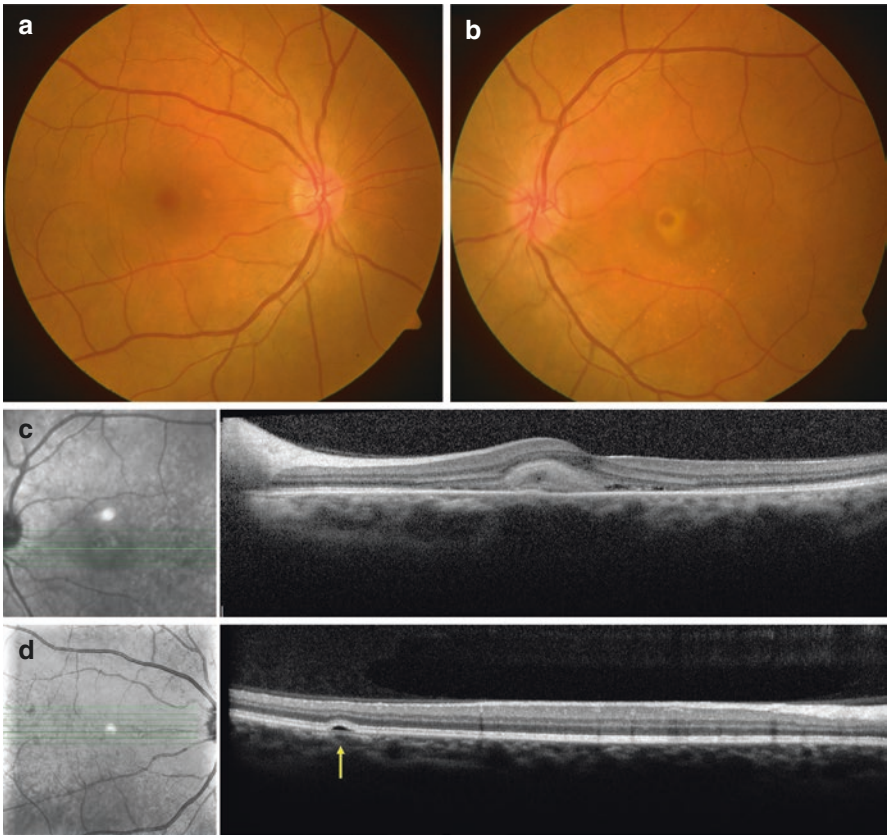

Fig. 5.2 A 33-year-old male with proteinuria was diagnosed with stage III renal disease associated with biopsy-proven IgA nephropathy. Fundus examination revealed the presence of yellow-white ring-shaped deposit in the macula of OS and discrete, small, subretinal deposits in the macula OU (**a** and **b**). Spectral-domain optical coherence tomography (OCT) showed the presence of subretinal hyper-reflective deposits at the fovea of OS suggestive of complement and/or IgA complex deposition (**c**). OCT scan through the small discrete lesions (**d**) revealed hyper-reflective drusenoid deposits at the level of the retinal pigment epithelial (RPE)-Bruch's membrane complex and elevation of the RPE

5.3 Tubulointerstitial Nephritis and Uveitis (TINU)

5.3.1 Introduction and Etiopathogenesis

Tubulointerstitial nephritis and uveitis (TINU) is an autoimmune oculorenal syndrome common in younger aged population (mean age 15 years) with female predominance (3:1). TINU is characterized by the acute interstitial nephritis (AIN) and uveitis with no known etiology [26]. TINU was first described in 1975 by Dobrin et al. and has a reported prevalence of 1–2%. Although the exact pathogenesis of TINU is unknown, it is thought to have an autoimmune basis triggered by infections, antibiotics, or NSAIDs. TINU has an established association with HLA-DRB1*01 and HLADQA1*01 and a particularly strong association (RR = 167) with HLA-DRB1*0102 [27]. Clinically the patients with TINU present nonspecific systemic symptoms of fever, malaise, myalgia, and fatigue. About one third of patients present with signs and symptoms of AIN characterized by flank pain, hematuria, sterile pyuria (eosinophiluria), and mild proteinuria [28, 29].

5.3.2 Ocular Manifestations

Approximately 21% cases of TINU present with ocular manifestations preceding systemic symptoms. Ocular symptoms in TINU predominantly present as bilateral, non-granulomatous anterior uveitis (80% cases) [29–31]. The anterior uveitis is sudden in onset and is characterized by pain, redness, and photophobia. On slit-lamp examination, fine keratic precipitates, anterior chamber cells, occasionally a high flare, and rarely a hypopyon can be seen. Posterior synechiae can also be visualized in certain cases. Figure 5.3 illustrates anterior segment inflammation in a patient with TINU.

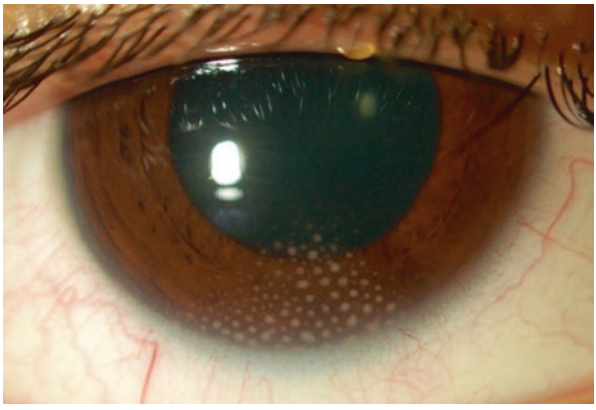

Fig. 5.3 Figure shows anterior segment photograph of a patient with tubulointerstitial nephritis and uveitis (TINU). There is presence of anterior chamber cells and flare and granulomatous keratic precipitates *(Image courtesy: Peter McCluskey, MD, Australia)*

Posterior segment involvement in TINU is usually limited to occasional mild vitreous cells and rare complications of disk and macular edema. Other associations include development of cataract and glaucoma. It is imperative to note that while diagnosing TINU may be challenging especially in cases with unexplained chronic or recurrent uveitis, the prognosis is generally good. Timely diagnosis and management with corticosteroids and/or immunosuppression improve the long-term outcomes in these patients [28, 32].

5.4 Metabolic Renal Diseases: Hyperoxaluria

5.4.1 Incidence and Pathogenesis

Although rare, primary hyperoxaluria is a clinical entity of considerable importance due to its association with nephrolithiasis, nephrocalcinosis, and renal failure [33]. Primary hyperoxaluria is inherited in an autosomal recessive manner and is caused by a deficiency of a liver enzyme alanine-glyoxylate aminotransferase (AGT). AGT catalyzes the conversion of glyoxylate to glycine. Absence of AGT results in formation of oxalate crystals which deposit in the kidneys and other organ systems [34].

5.4.2 Ocular Manifestations

Retinal involvement in patients with hyperoxaluria has been recognized as early as 1974 [35]. Hyperoxaluria manifests as deposition of crystals in the macula (*crystalline retinopathy*) [36, 37]. Ocular involvement in hyperoxaluria may be bilateral and symmetrical. The pathological changes are usually confined to the posterior pole and mid-periphery. Fundus lesions are usually small (100–200 microns) and appear dark due to deposition of calcium oxalate crystals. Sometimes, the fundus lesions may be large (*retinal oxalosis*) and appear geographic in nature [38]. Hyperoxaluria may also be associated with retinal flecks [39]. *Oxalate maculopathy* may also be associated with diffuse optic disk pallor [36].

The subretinal deposits in hyperoxaluria may also be visualized using SD-OCT imaging [40]. Due to outer retinal/RPE damage, there may be development of secondary choroidal neovascular membranes [41]. These can be confirmed using FA. Choroidal neovascularization usually occurs adjacent to the site of macular scarring. Recently, Derveaux et al. proposed phenotypic classification of oxalate maculopathy in type 1 primary hyperoxaluria. The authors described four distinct retinal phenotypes: bilateral perifoveal retinal pigment epithelium hyperplasia, subretinal crystals, confluent macular RPE hyperplasia, and subretinal fibrosis. Thus, retinopathy in hyperoxaluria may show considerable phenotypic variations [42]. A thorough understanding of this phenotypic manifestation may aid the clinician in predicting visual outcome in these patients.

5.5 Systemic Lupus Erythematosus

5.5.1 Introduction and Pathogenesis

Systemic lupus erythematosus (SLE) is a multi-organ disease with a characteristic relapsing/remitting course due to activation of autoimmune mechanisms leading to production of polyclonal antibodies, development of immune tolerance against nuclear antigens, and deposition of immune complexes in tissues [43–45]. Due to widespread organ-tissue damage, SLE has protean clinical manifestations. Diagnosis of SLE is based on the presence of clinical criteria defined by the American Rheumatology Association (ARA). These criteria include the presence of nephritis, skin rash, arthritis, and other organ dysfunction due to serositis. The presence of 4 out of 11 criteria is necessary for establishing a diagnosis of SLE [46].

SLE is most commonly seen in women of child-bearing age. In pregnancy, SLE may result in severe comorbidities and complicate the course of the pregnancy. In the following section, ocular findings of SLE have been highlighted. Details of ocular involvement in SLE have also been listed elsewhere in this book.

5.5.2 Ocular Findings

Approximately 2–30% patients with SLE present with ocular manifestations [47]. Retinal manifestations of SLE may be asymptomatic, such as the presence of isolated cotton-wool spots, DLDs, or few retinal hemorrhages, or may be severe sight threatening such as near-complete vaso-occlusion [47–50]. While various ocular tissues may be involved in SLE, retinal vessels are predominantly affected in SLE. Involvement of retinal vasculature in SLE is termed as *lupus vasculitis*. Lupus vasculitis is typically a *vasculopathy* due to fibrinoid necrosis rather than true vessel wall inflammation [51]. On FA, lupus vasculopathy may present with mild late perivascular hyperfluorescence unlike typical inflammatory retinal vasculitis. The spectrum of findings in lupus vasculitis include cotton-wool spots, intra-retinal hemorrhages, vascular occlusion (especially arteriolar in severe cases), and secondary neovascularization that may lead to vitreous hemorrhage or tractional retinal detachment [50].

Patients with SLE may present with *Purtscher-like retinopathy* due to widespread complement activation leading to large cotton-wool spots, optic disk edema, retinal hemorrhages and edema, and arteriolar occlusion on FA [52]. Due to the hypercoagulable state in patients with SLE and the presence of antiphospholipid antibodies (APLA) that predispose to a prothrombotic state [53], patients with SLE may present with a *central retinal vein occlusion (CRVO)-like picture*. This condition may mimic typical CRVO with widespread hemorrhages, cotton-wool spots, and optic disk edema.

Lupus choroidopathy is characterized by multifocal serous retinal elevations and RPE detachments [54, 55]. This condition is relatively rare and occurs in severe conditions. On the other hand, DLDs may be a more common outer retinal/RPE/

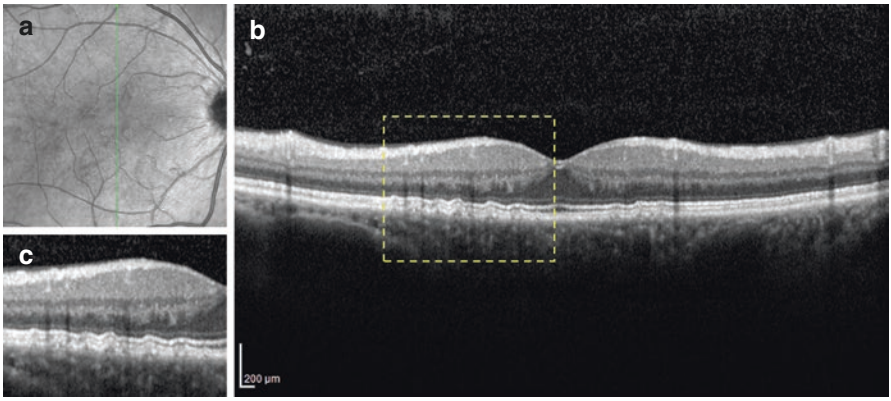

Fig. 5.4 Optical coherence tomography (OCT) using the enhanced depth imaging (EDI) mode shows the presence of drusen-like deposits (DLDs) temporal to the fovea. These DLDs can be well appreciated on the reflectance image (**a**). The vertical line scan through the fovea shows presence of DLDs as irregular elevations of the retinal pigment epithelium (**b**). Magnified view (**c**) shows the detailed structure of these drusen

inner choroidal manifestation of SLE [56]. Classically, DLDs were thought to be present in retinae of patients with SLE-associated nephritis but not in those with SLE and no renal involvement. However, it has been recently recognized that DLDs may be present in patients with SLE without kidney involvement. Recognition of DLDs in patients with SLE may therefore have prognostic significance and may serve as a useful biomarker in assessing the natural history of the disease.

Figure 5.4 shows a patient with typical DLDs as observed on EDI-OCT.

5.6 Conclusions and Summary

A number of pathologies involving renal system result from complex autoimmune pathological processes that may be associated with ocular findings. *Investigations into these processes demonstrate the anatomical similarities between the renal glomeruli and the choriocapillaris/RPE-Bruch's membrane complex*. Certain ocular findings may not be sight threatening, such as presence of few cotton-wool spots or DLDs away from the fovea. However, recognition of these pathological changes especially sight-threatening conditions that sometimes precede the development of renal manifestations may lead to diagnostic challenges. Clinicians may face difficulty in deciphering the etiology of the ocular manifestations and determine its clinical relevance. In addition, due to the wealth of information in the recent literature on certain manifestations such as DLDs may lead to confusion on the prognostic significance of these lesions.

Advanced imaging modalities such as SD-OCT and EDI-OCT and improved fluorescein angiography techniques have improved our understanding of the distinct and remarkable changes that occur in various chorioretinal layers in diseases of the

kidney. For instance, due to newer technologies such as near-infrared reflectance imaging, autofluorescence, and EDI-OCT, the morphology and significance of DLDs in conditions such as MPGN and SLE have been recently recognized. Updated and newer classification of entities such as MPGN have changed our understanding and highlighted the importance of ocular examination in type 1 and 3 MPGN. Similarly, modalities such as laser flare photometry have advanced our abilities of monitoring patients with inflammatory conditions such as TINU.

In summary, comprehensive analyses of various ocular conditions and their clinical presentations using advanced retinal imaging techniques are relevant in a number of diseases affecting the kidneys. As the wealth of information in literature continues to expand, it is likely that the pathogenetic mechanisms of these conditions will be more clearly elucidated in the near future.

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