

# Pathology of Renal Diseases Associated with Dysfunction of the Alternative Pathway of Complement: C3 Glomerulopathy and Atypical Hemolytic Uremic Syndrome (aHUS)

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## Abstract

Dysfunction of the alternative pathway of complement in the fluid phase results in deposition of complement factors in the renal glomeruli. This results in glomerular injury and an ensuing proliferative response. The term “C3 glomerulopathy” is used to define such an entity. It includes both C3 glomerulonephritis and dense deposit disease (DDD). Both C3 glomerulonephritis and DDD are characterized by a proliferative glomerulonephritis and bright glomerular C3 mesangial and capillary wall staining with the absence or scant staining for immunoglobulins (Ig). The two conditions are distinguished based on electron microscopy findings: mesangial and capillary wall deposits are noted in C3 glomerulonephritis, while ribbon-shaped dense osmiophilic intramembranous and mesangial deposits are noted in DDD. On the contrary, uncontrolled activation of the alternative pathway of complement on endothelial cell surface results in endothelial injury with an ensuing thrombotic microangiopathy, termed atypical hemolytic uremic syndrome (aHUS). Kidney biopsy in aHUS is often indistinguishable from other forms of thrombotic microangiopathy including enterohemorrhagic *Escherichia coli*-induced HUS and thrombotic thrombocytopenic purpura and shows thrombi in glomerular capillaries, mesangiolysis, and endothelial injury as evidenced by swelling and double contour formation along the glomerular capillary walls, with negative immunofluorescence studies for Ig and complement factors and no deposits on electron microscopy.

## Keywords

- ▶ glomerulonephritis
- ▶ classification
- ▶ membranoproliferative glomerulonephritis
- ▶ C3 glomerulonephritis
- ▶ complement

Dysregulation of the alternative pathway of complement can result in two most prominent disease states, involving the kidney, C3 glomerulopathy and atypical hemolytic uremic syndrome (aHUS). The classification, pathology, and kidney biopsy finding of these entities is reviewed.

Other forms of glomerulonephritis such as immunoglobulin A (IgA) nephropathy and antineutrophil cytoplasmic antibody-associated glomerulonephritis where the alternative pathway of complement may also be involved are not discussed in this review.

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## Classification of Glomerulonephritis

Proliferative glomerulonephritis results from deposition of Ig/immune complexes (IC) and/or complement factors in mesangium and/or along glomerular capillary walls.<sup>1</sup> The deposition of Ig and complement factors results in an inflammatory response from the following:

1. Proliferation of indigenous glomerular cells such as mesangial cells, endothelial cells, parietal epithelial cells and/or infiltration and proliferation of leukocytes, and
2. Synthesis of matrix material such as mesangial matrix material, basement membrane material, and fibrin.

Glomerular deposition of Ig/IC originates from three basic pathogenic mechanisms:

1. Deposition of monoclonal Ig as a result of a monoclonal gammopathy due to a plasma cell or B cell disorder,<sup>2-4</sup>
2. Deposition of antigen-antibody IC as a result of an infection,<sup>5</sup> and
3. Deposition of IC as a result of an autoimmune disease.<sup>6,7</sup>

Immunofluorescence studies can often confirm the underlying pathogenic mechanism of Ig/IC deposition based on the type of Ig detected. Complement factors are also noted along with the Ig/IC due to activation of the classical and terminal pathway by the Ig/IC. On the contrary, glomerular deposition of complement factors alone or in the presence of scant Ig results from dysregulation of the alternative pathway of complement. The term C3 glomerulopathy is used to define this entity. On the basis of these findings, proliferative glomerulonephritis has recently been classified into Ig/IC-mediated glomerulonephritis and complement-mediated glomerulonephritis.<sup>8</sup> Thus, immunofluorescence studies of the kidney biopsy are the key to the classification of proliferative glomerulonephritis into Ig/IC mediated or complement mediated.

## Pathology of C3 Glomerulopathy

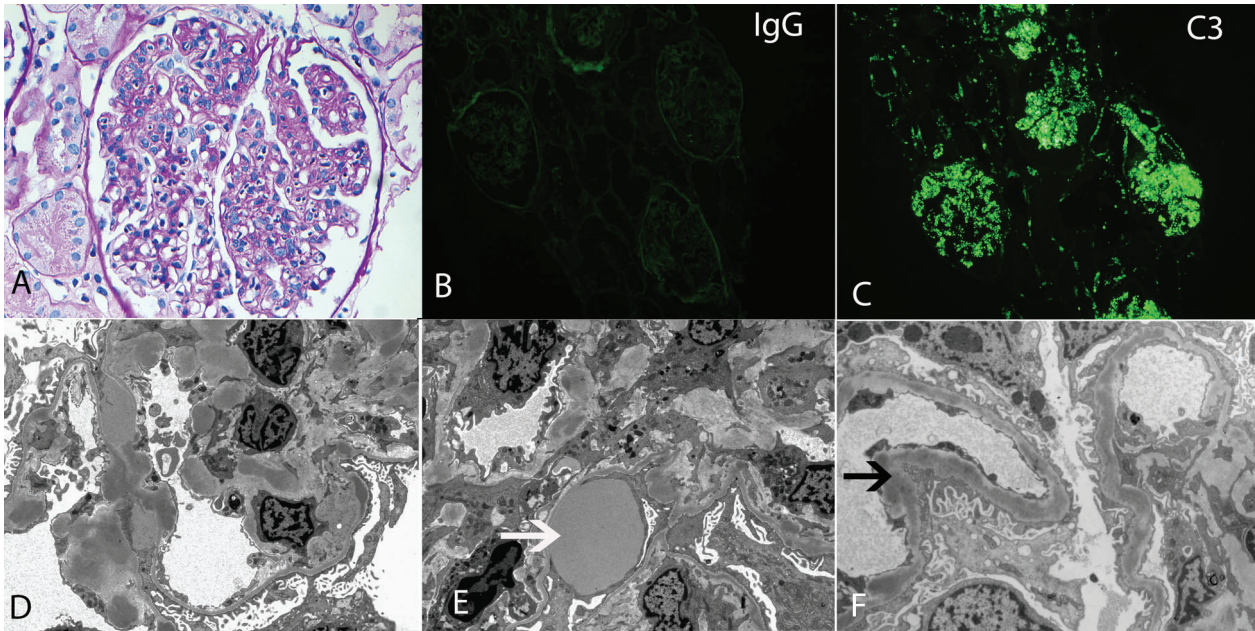
Deposition of complement factors in the mesangium and/or along the glomerular capillary walls results in a proliferative glomerulonephritis. The term "C3 glomerulopathy" is now used to define the entity of a glomerulonephritis characterized by C3 accumulation, with absent or scanty Ig deposition.<sup>9-12</sup> C3 glomerulopathy encompasses the entities of C3 glomerulonephritis and dense deposit disease (DDD).<sup>9,11,13</sup>

On kidney biopsy, C3 glomerulonephritis and DDD present as a proliferative glomerulonephritis. The most common pattern on light microscopy pattern for both C3 glomerulonephritis and DDD is that of a membranoproliferative glomerulonephritis. Other patterns of injury include diffuse proliferative glomerulonephritis, mesangial proliferative glomerulonephritis, or even a necrotizing and crescentic glomerulonephritis.<sup>14</sup> Two or more patterns of injury may be seen on the same biopsy. On immunofluorescence studies, both C3 glomerulonephritis and DDD are characterized by bright mesangial and capillary wall staining for C3. In DDD, C3 staining may also be seen along the tubular basement membranes. Tubular basement membrane staining for C3 is

uncommon in C3 glomerulonephritis. The main differentiating factor between C3 glomerulonephritis and DDD lies in the electron microscopy findings. In C3 glomerulonephritis, the complement deposits are discrete and are located in the mesangium and along the capillary walls in subendothelial region of the glomerular basement membrane. Subepithelial and few intramembranous deposits are also often present. The deposits often assume a lobular shape and have a waxy appearance with ill-defined margins. On the contrary, in DDD the deposits are intensely osmiophilic and are located in the mesangium and within the glomerular basement membranes (intramembranous deposits) often forming large dense ribbon-/sausage-shaped bands that can completely transform the glomerular basement membranes. On the basis of the pathology, it is not possible to differentiate between the acquired and hereditary causes of C3 glomerulonephritis or DDD. **Fig. 1** (A-E) shows a representative case of C3 glomerulonephritis. Electron microscopy of a case of DDD is also shown for comparison (panel F).

## Proteomics of C3 Glomerulonephritis and DDD

Both C3 glomerulonephritis and DDD are diseases resulting from dysregulation of the alternative pathway of complement. Why are the deposits discrete in C3 glomerulonephritis and intramembranous in DDD? Recent studies using the technique of laser microdissection of glomeruli followed by mass spectrometry showed accumulation of complement factors of the alternative pathway and terminal complement pathway in both the conditions. Large spectra numbers of C3 and C9 were noted in both C3 glomerulonephritis and DDD, while smaller spectra numbers of C5, C6, C7, and C8 were also present (**Fig. 2**).<sup>15,16</sup> Complement regulating proteins such as vitronectin and clusterin were also present in large spectra numbers. In addition, large spectra numbers of complement factor H-related protein (FHR)-1 and FHR-5 were present. There was little or no significant accumulation of complement factors of the classical complement pathway, such as C1, C2, or C4. In addition, there was little or no Ig present. There was also no factor B present, indicating absence of C3 and C5 convertase in the glomeruli, suggesting that activation of alternative and terminal pathway occurs in the fluid phase rather than resulting from local disturbance of the alternative pathway in both C3 glomerulonephritis and DDD. Thus, based on proteomic studies, it appears that the complement profile in both C3 glomerulonephritis and DDD is similar. As whole glomeruli are dissected, the proteomic studies are not absolutely quantitative, even though higher spectra numbers are indicative of greater abundance and typically yield greater amino acid sequence coverage. Thus, it is possible that the relative amounts of complement factors and their breakdown products might be responsible for the difference in appearance on electron microscopy studies. It should be pointed out, some cases do show crossover electron microscopy findings, with C3 glomerulonephritis showing few dense intramembranous deposits, and DDD showing few discrete subendothelial and mesangial deposits (Sethi, unpublished data, 2014).



**Fig. 1** C3 glomerulopathy (A–E). Representative kidney biopsy findings in C3 glomerulonephritis. (A) Light microscopy showing features of both membranoproliferative glomerulonephritis and diffuse proliferative glomerulonephritis (Periodic acid Schiff stain  $\times 40$ ), immunofluorescence microscopy showing (B) negative IgG staining and (C) bright mesangial and capillary wall staining for C3 (B and C  $\times 10$ ), electron microscopy showing (D) numerous mesangial and subendothelial electron dense deposits and (E) a subepithelial electron dense deposit (white arrow). (F) Electron microscopy showing numerous intramembranous deposits (black arrow) in a case of dense deposit disease as comparison with C3 glomerulonephritis shown in earlier panels. (D–F  $\times 10,900$ ). IgG, immunoglobulin G.

Postinfectious Glomerulonephritis and C3 Glomerulonephritis

Postinfectious glomerulonephritis is characterized by a proliferative glomerulonephritis on light microscopy, staining for granular IgG and C3 on immunofluorescence (IF) microscopy, and mesangial, subendothelial, and subepithelial “hump”-

like deposits on electron microscopy. However, in some cases while the electron microscopy shows the characteristic “hump”-like subepithelial deposits, IF studies show only dominant C3 with scant or no Ig. Thus, in this setting the IF findings are similar to C3 glomerulonephritis.

Many of these cases with the “hump”-like subepithelial deposits and bright C3 staining were deemed postinfectious

Probability Legend:							
over 95%							
80% to 94%							
50% to 79%							
20% to 49%							
0% to 19%							
Bio View:							
Identified Proteins (1541)							
	Accession Number	Molecular Weight	Protein Grouping Ambiguity	C3GN Case 1	C3GN Case 2	C3GN Case 3	DDD Case 1
Complement C3	CO3_HUMAN	187 kDa		80	45	80	48
Complement component C9	CO9_HUMAN	63 kDa		22	15	17	9
Complement factor H-related protein 1	FHR1_HUMAN	38 kDa	★	29	5	18	9
Complement C5	CO5_HUMAN	188 kDa		9	7	13	11
Complement component C8 alpha chain	CO8A_HUMAN	65 kDa		7	3	9	3
Complement factor H-related protein 5	FHR5_HUMAN	64 kDa	★	13	7	4	3
Complement component C7	CO7_HUMAN	94 kDa		6	2	5	7
Complement component C6	CO6_HUMAN	105 kDa		5	4	5	4
Complement component C8 beta chain	CO8B_HUMAN	67 kDa		2	3	5	2
Complement component C8 gamma	CO8G_HUMAN	22 kDa			2	4	2
							1
							2

**Fig. 2** Proteomics of C3 glomerulopathy. Representative mass spectrometry data of three cases of C3 glomerulonephritis and three cases of dense deposit disease. Mass spectrometry shows spectra of complement factors of the alternative pathway and terminal complement pathway, in particular C3 and C9 in all cases. The “spectra” value indicates the total number of mass spectra collected on the mass spectrometry that matched the protein in question utilizing the proteomics software. A higher number of mass spectra is indicative of greater abundance and will typically yield greater amino acid sequence coverage. A higher mass spectra value also indicates a higher confidence in the protein identification. (Reproduced with permission from Sethi S, Vrana JA, Theis JD, Dogan A. Mass spectrometry based proteomics in the diagnosis of kidney disease. *Current Opinion in Nephrology and Hypertension* 2013;22:273–280).<sup>15</sup>

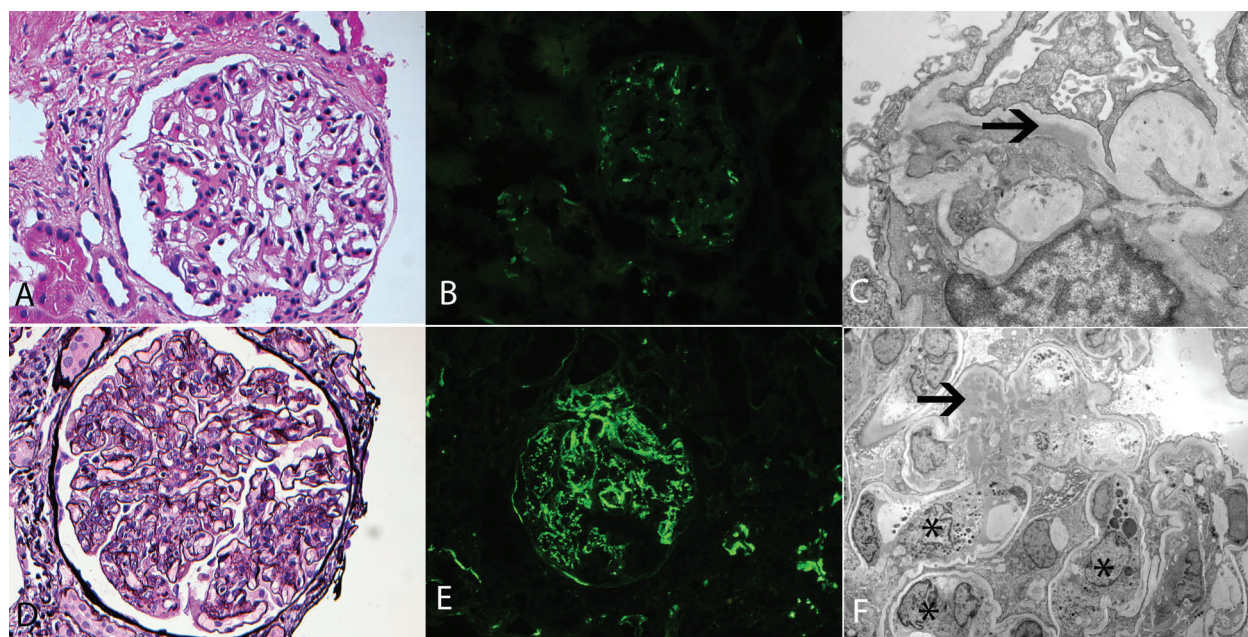


glomerulonephritis in the past. Terms such as “resolving” or “persistent” or “chronic” postinfectious glomerulonephritis were used when hematuria and proteinuria persisted or when there was deterioration of kidney function, as the postinfectious glomerulonephritis typically resolves within weeks. Recently, it was shown that such cases with “hump”-like subepithelial deposits and bright C3 staining and scant/no Ig and persistent hematuria/proteinuria, previously diagnosed as “resolving” postinfectious glomerulonephritis, were associated with abnormalities of the alternative pathway of complement. The term “atypical” postinfectious glomerulonephritis, similar to the terminology of aHUS was introduced to highlight the underlying alternative pathway abnormalities in these patients.<sup>17</sup> The key differentiating feature between postinfectious glomerulonephritis and “atypical” postinfectious glomerulonephritis is the presence of both Ig and C3 in postinfectious glomerulonephritis, while there is only C3 with scant or no Ig in “atypical” postinfectious glomerulonephritis, even though subepithelial humps are common to both entities. It is postulated that an infection activates the alternative pathway of complement in atypical postinfectious glomerulonephritis. However, due to an underlying defect in the regulatory mechanisms, there is persistent activation of the alternative pathway of complement with resultant deposition of complement factors and ensuing inflammation in the glomeruli. It should be pointed out that similar findings, that is, subepithelial “humps” are also seen in DDD.<sup>18</sup> Thus, it is conceivable that DDD and C3 glomerulonephritis may be triggered by an infection. It is

the underlying regulatory defect of the alternative pathway of complement that then drives the glomerular inflammation even after the infection is controlled. The term “atypical” DDD or C3 glomerulonephritis may thus be used to signify that the underlying pathophysiology is that of an alternative pathway abnormality, even though the triggering event may be an infection as evidenced by the presence of subepithelial “humps.”

### Recurrent C3 Glomerulopathy

There is a high recurrence rate of DDD and C3 glomerulonephritis in the transplant. With regard to DDD, there is a 60 to 85% rate of recurrence in the transplant, resulting in allograft failure in 45 to 50% within 5 years.<sup>19–21</sup> There is limited data with regard to recurrent C3 glomerulonephritis. In a recent study, there was recurrence of C3 glomerulonephritis in 66.7% of patients, with graft loss in 33% of patients within 5 years.<sup>22</sup> Kidney biopsy of early recurrent C3 glomerulonephritis, particularly those detected on routine protocol biopsies shows a mesangial proliferative glomerulonephritis on light microscopy, mesangial C3 deposition on IF studies, and mesangial electron dense deposits on electron microscopy. On the contrary, membranoproliferative glomerulonephritis is more common during the later stages or when the biopsy is done for clinical indications.<sup>22</sup> This is similar to the findings of recurrent membranoproliferative glomerulonephritis in general.<sup>23</sup> The kidney biopsy findings of recurrent C3 glomerulonephritis are shown in ►Fig. 3.



**Fig. 3** Recurrent C3 glomerulonephritis. Representative kidney biopsy findings in recurrent C3 glomerulonephritis. Top panel shows a case of early recurrent C3 glomerulonephritis. (A) Light microscopy showing a mild mesangial proliferative glomerulonephritis (hematoxylin and eosin,  $\times 40$ ), (B) immunofluorescence microscopy showing mild mesangial C3 staining ( $\times 20$ ), and (C) electron microscopy showing few mesangial electron dense deposits ( $\times 17,900$ ). Bottom panel shows a case of florid/late recurrent C3 glomerulonephritis. (D) Light microscopy showing a membranoproliferative and diffuse proliferative pattern of injury (silver methenamine,  $\times 40$ ), (E) immunofluorescence microscopy showing bright C3 staining in the mesangium and along capillary walls, and (F) electron microscopy showing numerous mesangial electron dense deposits and infiltrating leukocytes (asterisk) ( $\times 3,100$ ). Arrow points at deposits.

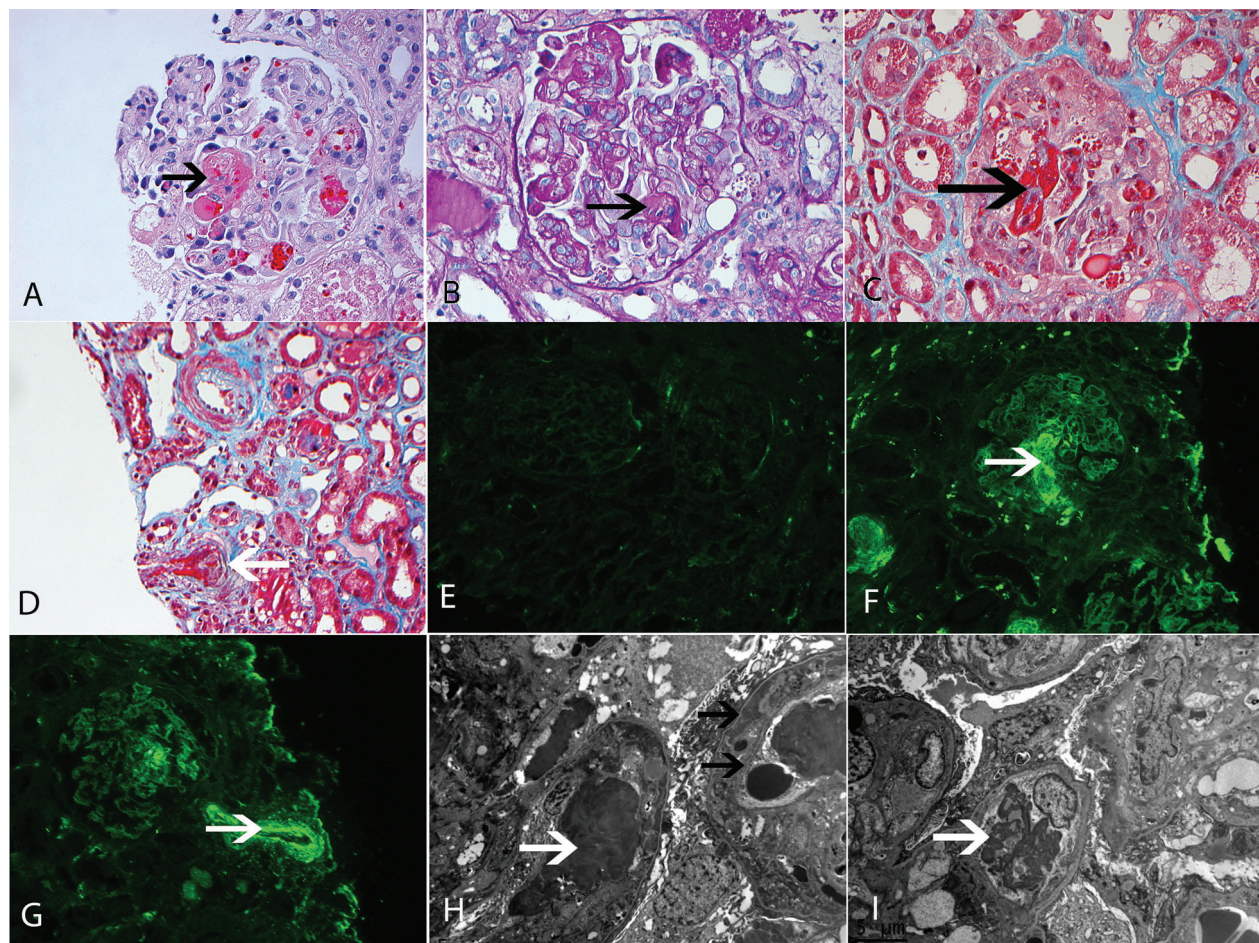


## Pathology of Atypical Hemolytic Uremic Syndrome (aHUS)

aHUS results from abnormalities in the alternative pathway of complement and is characterized by a thrombotic microangiopathy that results in a hemolytic anemia, thrombocytopenia, and multiorgan dysfunction.<sup>24,25</sup> aHUS belongs to a group of disorders in which the underlying characteristic finding is a thrombotic microangiopathy and includes diarrhea-associated hemolytic uremic syndrome, frequently resulting from infections with enterohemorrhagic *Escherichia coli* (EHEC)-HUS, and thrombotic microangiopathy purpura (TTP), due to deficiency of the enzyme ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), an enzyme that cleaves von Willebrand factor.<sup>24</sup>

Kidney biopsy findings in aHUS, EHEC-HUS, and TTP are often indistinguishable. Kidney biopsy shows a thrombotic microangiopathy in which the glomerular capillaries contain thrombi. However, in the setting of aHUS and EHEC-HUS, the thrombi typically are fibrin rich, whereas the thrombi in TTP

are platelet rich.<sup>26</sup> In addition, the glomeruli show mesangiolysis (fluffy mesangial expansion), endothelial swelling, thickening of the glomerular capillary walls, and schistocytes within the glomerular capillaries. Arterioles and small arteries may also be occluded by the microthrombi. As the lesion progresses and becomes chronic, capillary wall remodeling takes place with formation of new basement membrane material and entrapment of cellular elements. This results in double contour formation along glomerular capillary walls. The light microscopy findings at this time may mimic membranoproliferative glomerulonephritis. However, immunofluorescence studies are negative for Ig/IC and complement factors. Immunofluorescence studies of thrombotic microangiopathy show positive staining for fibrinogen with glomerular capillaries and arterioles and small arteries. Electron microscopy shows subendothelial expansion with fluffy material, endothelial swelling and loss of fenestrations, and fibrin material within the glomerular tufts but no deposits. This helps distinguish a thrombotic microangiopathy from a necrotizing glomerulonephritis in which there is rupture of the glomerular tufts, and fibrin is seen spilling out into the



**Fig. 4** Thrombotic microangiopathy. Representative kidney biopsy findings in aHUS: (A–C) Fibrin thrombi in the glomerular capillary lumen, (A) hematoxylin and eosin–stained section—note fragment red blood cells (black arrow), (B) periodic acid Schiff, (C) Masson trichrome (all  $\times 40$ , white arrows point at fibrin microthrombi), (D) Microthrombus in small artery (Trichrome,  $\times 20$ ), (E–G) immunofluorescence microscopy showing (E) no glomerular staining for C3, (F) fibrinogen staining with glomerular capillaries indicating fibrin thrombus, and (G) fibrinogen staining in small artery indicating fibrin thrombus, (H, I) electron microscopy showing fibrin microthrombus in glomerular capillary lumen (white arrow) and fibrin along the glomerular capillary walls (black arrow, E–G:  $\times 20$ , H, I:  $\times 4,200$ ).

Bowman space. Double contours are also a characteristic feature of thrombotic microangiopathy, particularly when the lesion has been present for a while. The kidney biopsy findings of aHUS are shown in ▶Fig. 4.

Thrombotic microangiopathy may also result from other causes such as connective tissue disorders, malignant hypertension, eclampsia, exposure to drugs, bone marrow transplantation, etc. These lesions may be difficult to distinguish from the thrombotic microangiopathy seen in aHUS/EHEC-HUS/TTP. However, vascular changes such as mucoid hyperplasia of the intima, hypertrophy of the media, and onion-skinning of the arterial walls is more likely to be seen in the setting of poorly controlled hypertension/connective tissue disorders/eclampsia, rather than in aHUS/EHEC-HUS/TTP.

## Concluding Remarks

In this review, we have summarized the kidney biopsy findings in disorders of the alternative pathway of complement, that is, C3 glomerulopathy and aHUS. C3 glomerulopathy is characterized by a proliferative glomerulonephritis, with bright C3 staining on IF studies, and mesangial and capillary wall deposits (C3 glomerulonephritis) or dense intramembranous deposits (DDD) on electron microscopy. On the contrary, aHUS is characterized by thrombotic microangiopathy as evidenced by thrombi in glomerular capillaries, mesangiolysis, and capillary wall changes such as endothelial swelling and double contour formation, with negative immunofluorescence and no deposits on electron microscopy.

### Financial Disclosure

Nothing to disclose.

### Conflict of Interest

None.

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