

# Pathological aspects of membranoproliferative glomerulonephritis (MPGN) and haemolytic uraemic syndrome (HUS) / thrombocytic thrombopenic purpura (TTP)

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## Summary

In this paper, epidemiology, pathogenesis and typical morphological aspects of all three types of membranoproliferative glomerulonephritis (MPGN), of the haemolytic uraemic syndrome (HUS) as well as of thrombotic thrombopenic purpura (TTP) will be reviewed on the light microscopical, immunohistological or immunofluorescence and electron microscopical level. In particular, differences in the pathogenesis of these diseases are discussed. Important recent molecular and genetic insights into the pathogenesis of the three types of MPGN, of typical and

atypical HUS and of TTP, i.e. dysregulation of the complement system, distinct molecular defects in C3 and factor H, the major regulatory protein of the alternative pathway of complement activation, and deficiency of a von Willebrand factor (VWF)-cleaving protease, i.e. ADAMTS13, are highlighted. Finally, particular emphasis will be put on differences in glomerular and vascular morphology in the three types of MPGN and in thrombotic microangiopathy (TMA), which is the characteristic morphological alteration of the kidney in HUS and TTP, respectively.

## Keywords

Membranoproliferative GN (MPGN), dense deposit disease (DDD), thrombotic microangiopathy (TMA), haemolytic uraemic syndrome (HUS), thrombocytic thrombopenic purpura (TTP), pathology

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## Introduction

Membranoproliferative (MPGN or mesangiocapillary) glomerulonephritis (GN) represents an immunocomplex GN; it is an uncommon cause of renal disease morphologically characterized by diffusely thickened glomerular basement membranes (GBM) with double contours ('membrano') due to subendothelial /mesangial immune and/or intramembranous deposits and marked endothelial and mesangial cell proliferation ('proliferative') (Fig. 1A-C). On average in Western countries MPGN accounts for approximately 5% of primary renal causes of the nephrotic syndrome; it mostly affects young adults and children with 50% being primary (idiopathic) and the other half being secondary due to infections, cryoglobulinemia, systemic autoimmune disease, etc. (1).

MPGN is not a diagnostic label for one disease, but rather a description of a pattern of glomerular reactions to a variety of

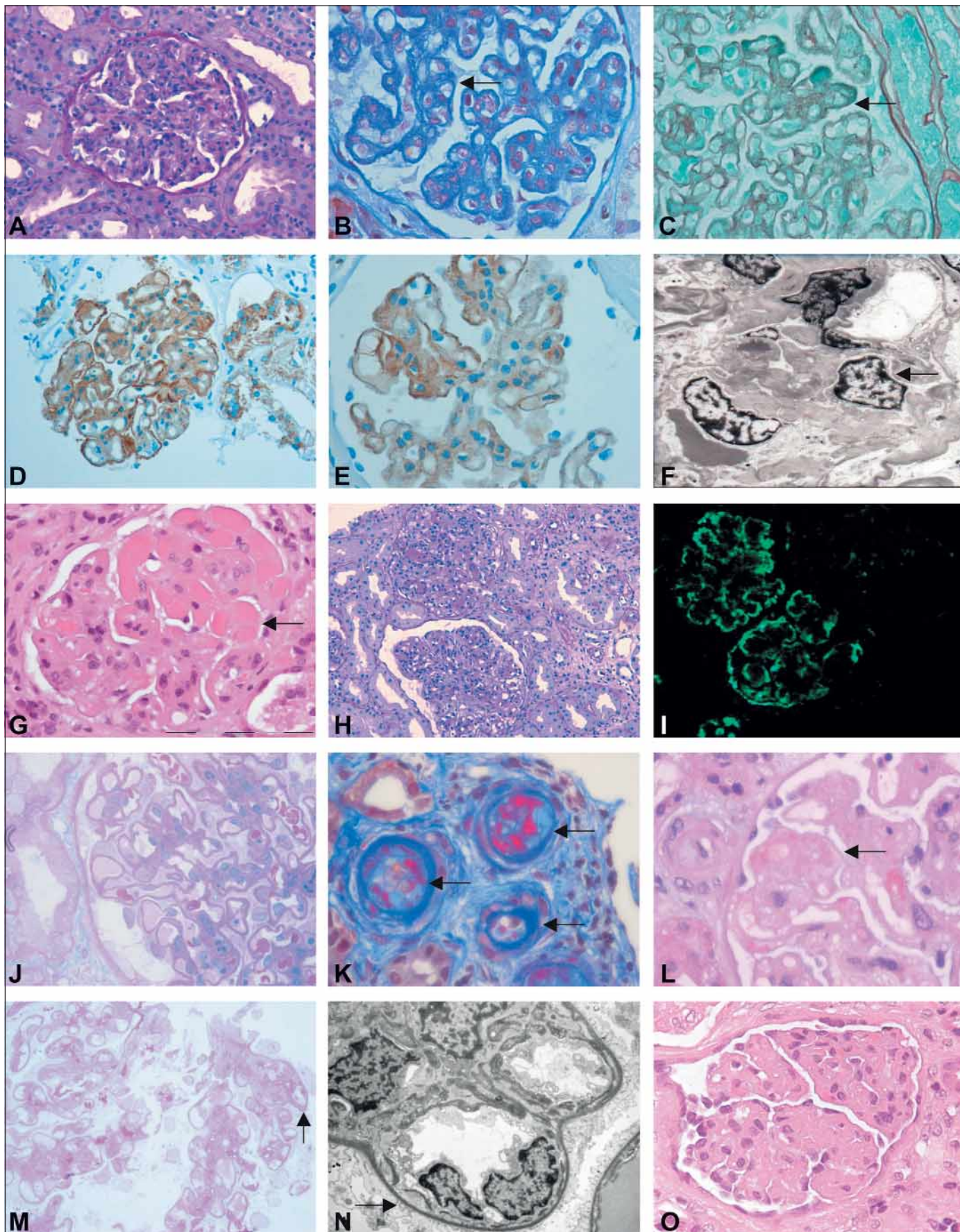
causes, i.e. infections, complement activation in systemic diseases, mutations of components of the complement system, etc. (2). Three distinct types of primary (idiopathic) MPGN have been described on the basis of immunofluorescence staining, ultrastructural appearance, complement profiles and recently also their genetic basis. MPGN was first described in 1965 as two main types with addition of a rare third variant over 10 years later. The light microscopy features and clinical presentation are similar among the three types. In recent years disturbances of the complement system and its regulatory factors were found to be important in the pathogenesis of MPGN (3). Clinically, hypocomplementaemia is a characteristic finding in all three types of MPGN, although different mechanisms of complement activation and dysregulation are operative (2–4). Types I (MPGN1) and III (MPGN3) are variants of an immunocomplex-mediated disease, whereas type II (MPGN2), now also known as dense-deposit disease (DDD), has no known association with immune

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complexes, but is caused by dysregulation of the alternative complement pathway either via the presence of the C3 convertase stabilizing antibody 3 nephritic factor (C3NeF) or via mutations/defects of regulatory proteins (2–4).

## Epidemiology, pathogenesis and morphological aspects of MPGN

Data from different kidney biopsy registers document that MPGN is the most common type of GN in Eastern Europe as well as in Africa and parts of Asia with a prevalence of up to 30% (5). In Western Europe, however, the prevalence of MPGN lies between 4.6% and 6.6% (6, 7) with a marked decrease in the prevalence over the last decade probably due to a better understanding of the pathogenesis and consecutively better therapeutically management of underlying diseases (6, 7). In the Italian registry Gesualdo et al. reported a frequency of 4.9–11.3% for MPGN depending on the underlying symptoms (8). In a recent retrospective US study in 4,504 kidney biopsies a percentage of 1.2% in adults and 0.2% in young adults (20–39 years) was found for MPGN (9). Another US study reported an age- and sex-adjusted incidence rate for MPGN of 0.1–0.6 per 100,000 residents between 1974–2003 (10).

The pathogenesis of MPGN is heterogenous and complex involving several aspects of dysregulation of the complement system. In particular dysfunction of factor H, the major regulatory protein of the alternative pathway of complement activation, and the presence of C3 nephritic factor (C3NeF), an IgG- or IgM-autoantibody directed against a neo-epitope on the alternative pathway convertase, that leads to uncontrolled alternative path-

**Figure 1: Morphological aspects of MPGN and TMA in HUS/TTP.** A-G) Typical histomorphological appearance of MPGN1 (A-G) and MPGN2/DDD (H-J): On light microscopy glomeruli present a lobular aspects with hypercellularity of the capillary (A) tuft together with thickening and double contours of the glomerular basement membrane (GBM, arrow) that can best be seen in fibrous tissue (B) and silver stains (C). Magnification  $\times 20$  (A) and  $\times 40$  (B, C). D, E) Characteristic immunohistology of MPGN1 with a granular pattern of IgG (D) and C3c (E) along the GBM and within the mesangium. Magnification  $\times 20$ . F) Characteristic electron microscopical appearance of MPGN1 with thickened and double contoured GBM and interposition of mesangial cells (arrow) between endothelium and GBM. G) Typical glomerular appearance in MPGN1 due to cryoglobulinemia. Lobulation of the capillary tuft with thickening of the GBM, endothelial and mesangial proliferation and intracapillary “thrombi” (arrow) that consist of immunoglobulins are seen. H) Characteristic lobular aspect of marked hypercellularity of the glomeruli is seen in MPGN2/DDD. I, J) The characteristic ribbon-like pattern of C3c staining in MPGN2/DDD can be seen on immunofluorescence (I) as well as on semithin sections (J). K-O) Vascular and glomerular changes in thrombotic microangiopathy (TMA). K) TMA with fibrinoid thrombi (arrow) in small arteries and arterioles is depicted in (K). L) Glomerular endothelial damage with endothelial and subendothelial swelling, formation of microthrombi (arrow) and subsequent endothelial cell proliferation. M, N) Thickening of the GBM with formation of double contours (arrow) and endothelial proliferation is also seen on semithin sections (M) and on ultrathin sections (N). In contrast, no immunodeposits are visible. O) Finally, in TMA so-called “bloodless glomeruli” that appear filled with fibrillary material may develop (O).

**Table 1: Typical histological features of MPGN.**

Endothelial and mesangial cell proliferation
Increase in mesangial matrix
Thickening and double contours of the GBM
Lobular aspect of the glomerular tuft
Variable infiltration of leucocytes

**Table 2: The three main types of MPGN.**

- <b>MPGN1:</b> diffuse immune-complex GN with subendothelial (and mesangial) immune deposits
- <b>MPGN2/DDD (dense deposit disease):</b> systemic disease with disordered complement regulation, no involvement of immune-complexes
- <b>MPGN3:</b> rare diffuse immune complex GN with subendothelial and subepithelial immune deposits and a familial predominance

way activation are found (3, 11). As shown in patients and experimental models with factor H deficiency uncontrolled activation of C3 either by factor H deficiency or factor H mutations is a major cause of MPGN. Of note, Pickering et al. (12) demonstrated that mice deficient in factor H develop MPGN spontaneously and are hypersensitive to renal injury caused by immune complexes.

Major clinical symptoms of MPGN are the nephrotic syndrome (35%) and rarely the nephritic syndrome (17%) or gross haematuria (5). Typical serological characteristics are low levels of complement factors (C1q, C3 and C4) and presence of the nephritic factor (C3NeF), i.e. an IgG- or IgM-autoantibody. The light morphological aspect of MPGN typically shows hypercellular glomeruli with proliferation of endothelial and mesangial cells leading to a lobular aspect of the capillary tuft (Table 1, Fig. 1A-C). The characteristic pattern in immunofluorescence / immunohistology or electron microscopy depends on the type of MPGN (Table 2, Fig. 1D-F).

## Characteristics of the three types of MPGN (Table 2, Fig. 1A-J):

### MPGN1

This type most likely occurs in the setting of chronic immune complex diseases (Table 3). It is characterized by a persistently low C3 serum level (i.e. hypocomplementemia) and in about 30% by the presence of C3NeF (3). Other disturbances of the complement system comprise factor H dysfunctions or deficiencies, dysfunctional C3 molecules and reduced factor B levels (13). The clinical course shows a progressive deterioration of renal function in 2/3 of cases over 10 or more years with the percentage of crescents being the most important prognostic factor (13). Other negative predictors for outcome are impaired renal function, hypertension and nephritic range proteinuria. MPGN1 may recur in the transplanted kidney in up to 50% with younger age at initial diagnosis and presence of crescents in the original biopsy being negative predictors (4, 14). On immunofluorescence / -histology a granular deposition of immunoglobulins

**Table 3: Conditions in which MPGN is likely to develop.**

<b>With mixed cryoglobulinemia</b>
Hepatitis C (70–90% of patients)
Other infections (i.e. bacterial endocarditis, hepatitis B)
Collagen vascular disease (i.e. SLE)
Malignancy
<b>Without cryoglobulinemia</b>
Bacterial infections (i.e. endocarditis, abscess, infected ventriculo shunt)
Viral infections (i.e. HBV, HCV, HGV, HIV, Hantavirus)
Collagen vascular disease (i.e. SLE, hypocomplementemic vasculitis)
Hereditary and acquired complement deficiencies
Malignancy

(IgG, IgM) and complement (C1q, C3) in the glomerular capillary loops and the mesangium ('mesangiocapillary pattern') is seen (Fig. 1D-F).

MPGN may also occur in the setting of cryoglobulinemia, i.e. immunoglobulins that precipitate in the cold. Here, all three types of MPGN may evolve. In general, mixed cryoglobulins (i.e. types II and III) that are present in various conditions (viral and bacterial infections, chronic lymphocytic leukaemia, lymphoma) are most commonly associated with MPGN. Morphologically, the presence of "thrombi", i.e. IgG and IgM deposition in arterial lumina and within the glomerular capillaries may help to distinguish MPGN in cryoglobulinemia from MPGN of other causes (Fig. 1G). These morphological aspects are very similar to that of proliferative Lupus GN (WHO IV, ISN/RPS IV); therefore, these diseases have to be distinguished by clinical data as well as by the characteristic immunohistological / immunofluorescence pattern.

### MPGN2 (dense deposit disease, DDD)

This is a rare, but devastating systemic disease that primarily affects children and is morphologically characterized by the presence of complement containing dense deposits within the GBM (15–17). Immunoglobulin (IgG) deposits are completely absent excluding a role for immune complexes in dense deposit formation. Since this is clearly different from the other two types of MPGNs the current literature moved from using the term "MPGN2" to "DDD (dense deposit disease)" in order to indicate both the unique pathomorphology as well as the specific pathogenetic background of this MPGN subtype. Dysregulation of the alternative complement pathway either via the presence of the C3 convertase stabilizing antibody 3 nephritic factor (C3NeF) or via mutations/defects of regulatory proteins are now accepted causes for MPGN2/DDD (16). Recent studies by Walker et al. (18, 19) document that DDD can occur with five different histological patterns of which MPGN2 is only present in about 25%. Other histological patterns that are described are mesangioproliferative GN and necrotizing GN. MPGN2/DDD is associated with complement abnormalities that lead to intense deposition of C3c in GBM deposits and persistent reduction of C3 serum levels. As already mentioned more than 80% of MPGN2/DDD cases are associated with the C3 nephritic factor, i.e. an IgG- or IgM-autoantibody that inhibits the inactivation of the alternative

C3 convertase C3bBb (20). Some of the remaining cases are associated with factor H deficiencies or mutations that lead to continuous activation of the alternative complement systems. Factor H deficiencies due to mutations in the *CFH* gene are common that impair secretion of factor H into the circulation (3, 21). In MPGN2/DDD it is assumed that the co-existence of a functionally inactive factor H or a factor H deficiency, with a complement activator such as C3NeF, probably exacerbates a situation of chronic complement activation and results in the complete consumption of C3 in plasma (21). The total number of reported cases in the literature with factor H deficiencies or defects, however, is very small. Evidence for a pathogenetic role of such a defect comes also from findings in factor H knockout animals, i.e. pigs (22). The available literature on factor H knockout mice, however, does not reveal typical MPGN2/DDD (11).

MPGN2/DDD may follow an infection (mostly viral, i.e. measles) and may be associated with retinal abnormalities and partial lipodystrophy (23). Characteristically, the disease progresses in up to 100% and the recurrence rate in kidney transplants is also nearly 100% (24, 25). The light microscopical appearance of MPGN2/DDD, however, is very similar to MPGN1 (Fig. 1H). The degree of hypercellularity may be more variable between glomeruli and double contours of GBM are generally less common than in MPGN1. On immunofluorescence / - histology a typical pseudolinear, often discontinuous, staining of the glomerular capillary loops for C3 and less frequent deposition of immunoglobulins is seen (Fig. 1I). On semithin plastic sections and in electron microscopy a characteristic ribbon-like zone of increased density is seen within the GBM and also in the tubular basement membrane, in basement membranes of peritubular capillaries and the elastic lamella of arterioles (Fig. 1J).

### MPGN3

Type III of MPGN is rare (approximately 15% of all MPGN); it is related to C3 and properdin and invariably also to immune complex and C1q depositions mostly due to secondary causes (i.e. hepatitis B and C) and or with / without presence of the terminal complement nephritic factor (26). Seldomly the disease is inherited in an apparently autosomal dominant fashion (27, 28). The light microscopy of MPGN3 is similar to MPGN1 and MPGN2/DDD. On immunofluorescence / immunohistology a similar pattern as in MPGN2 is seen with the exception that also subepithelial immune complex deposits occur. On electron microscopy, however, usually a more marked distortion of the GBM by massive amounts of electron-dense deposits on both sides of the GBM is seen; this aspect is clearly different from the findings in the other types of MPGN (29).

### Important differential diagnosis of MPGN

The spectrum of differential diagnoses of MPGN comprises glomerular involvement in systemic diseases such as paraproteinemias, thrombotic microangiopathy (TMA) in haemolytic uraemic syndrome (HUS) or thrombotic thrombocytopenia (TTP) (see below), scleroderma, radiation nephropathy or malignant hypertension. Also postinfectious GN and transplant glomerulopathy can morphologically sometimes be difficult to distinguish from MPGN since marked endothelial and to a lesser extent mesangial

cell proliferation as well as double contours of the GBM may occur. Moreover, rare kidney diseases such as collagen III nephropathy, C1q nephropathy, lipoprotein nephropathy also have to be taken into consideration. Morphologically, TMA with glomerular involvement is definitely the most important and most difficult differential diagnosis of MPGN with some overlapping aspects.

## Epidemiology, pathogenesis and morphological aspects of HUS and TTP

HUS and TTP are multi-system disorders with ischemic manifestations in the kidney and brain due to platelet aggregation in the arterial microcirculation. It is agreed that two main events may initiate this disorder, namely (i) abnormal platelet aggregation or (ii) endothelial cell injury (30). HUS refers to the triad of renal failure, thrombocytopenia and non-immune microangiopathic haemolytic anaemia demonstrated usually by red blood cell fragments (schistocytes) in peripheral blood smears. In contrast, TTP is characterized by thrombocytopenia, microangiopathic haemolytic anemia and neurologic dysfunction such as mental changes or focal deficits (31).

In the past, HUS and TTP were distinguished by clinical presentation with renal failure in HUS and neurological symptoms in TTP. Nowadays TTP and HUS are increasingly considered to be manifestations of the same disease process (32, 33). The discussion about overlap versus clear distinction between HUS and TTP is ongoing, however, and some authors stress that these diagnoses are to be differentiated by the underlying pathogenesis, i.e. distinct alterations of complement activation and von Willebrand factor (VWF) regulation ([31], Table 4).

Two forms of HUS are known, i.e. typical HUS related to infections with verocytotoxin-producing *Escherichia coli* or *Shigella* bacterial strains (so-called diarrhoea-associated HUS) and atypical HUS, i.e. non-diarrhoea-associated HUS. There is now evidence that atypical HUS is associated with defective regulation of complement activation, i.e. abnormal control of the complement alternative pathway by factor H, factor I, membrane cofactor protein deficiencies and factor C3 mutations (31, 33–37). As in MPGN2/DDD polymorphisms or mutations in the factor H gene leading to defective control of complement activation on renal endothelial cells are associated with atypical HUS (3, 10, 31).

In contrast, recent studies indicate that severe deficiencies of VWF cleavage protease, ADAMTS13, are the main cause of platelet thrombosis in TTP (31). TTP can also be divided into two forms, i.e. inherited and acquired TTP. Inherited TTP is usually associated with chronic renal failure whereas renal involvement in patients with acquired TTP due to inhibitory antibodies to ADAMTS13 is usually mild (31). Thus, it is now possible to distinguish the different forms of HUS and TTP on a molecular level (Table 4).

HUS and TTP are the classical diseases associated with the morphological finding of TMA, i.e. thrombosis of small arteries and arterioles that can also extend into glomerular capillaries. TMA in HUS/TTP is further characterised by vessel wall thickening with endothelial swelling, detachment of endothelial cells from the basement membrane triggering a cascade of events

that result in the formation of platelet-fibrin hyaline microthrombi that occlude arterioles and capillaries (Fig. 1K). By definition TMA is characterized by microvascular thrombosis coupled with thrombocytopenia, haemolytic anemia, and red blood cell fragmentation.

TMA also occurs in a wide range of diseases other than HUS/TTP (Table 4), i.e. autoimmune diseases, malignant hypertension, vascular rejection, endothelial damage due to drug toxicity, etc. The renal morphology, however, is always very similar.

In both typical and atypical HUS, TMA may affect glomeruli, renal arterioles and arteries. In addition, non-specific MPGN-like changes of the glomeruli may also be seen with detachment of the endothelium from the GBM due to endothelial damage, but without electron-dense deposits (38).

The diagnosis of TMA of the kidney is sometimes difficult, however, since TMA may occur either as primary symptom or as a complication of an underlying kidney disease with subsequent development of hypertension (39). TMA typically leads to thrombotic occlusion of small renal arteries and arterioles with more or less involvement of the vascular wall, i.e. inflammation and fibrinoid necrosis (Fig. 1K). In addition, in the glomeruli endothelial damage leads to formation of microthrombi within the

**Table 4: Pathophysiology and clinical presentation of diseases associated with TMA (adapted from [31]).**

Clinical entity	Cause	Etiology
<b>TTP</b>	ADAMTS 13	Ticlopidine, HIV, idiopathic
<b>Atypical HUS</b>	CFH mutations	hereditary (aut. dominant)
	CFH antibody	acquired
	MCP mutation	hereditary (aut. dominant)
	IF mutation	hereditary (aut. dominant)
	BF mutation	hereditary (aut. dominant)
	Unknown	unknown (50–70%)
<b>Typical (secondary HUS)</b>		
Shiga-toxin-HUS	bacterial infection	stx + <i>E. coli</i> , sh. Dysenteriae
TF-HUS	bacterial infection	bacterial neuraminidase
Others	unknown	Lupus erythematoses and related disorders*, bone marrow/stem cell transplantation, neoplasms
<b>Other TMA</b>		
PNH	somatic mutation	PIG-A
Tumor cell embolism	metastasizing malignancies	embolism of tumor cells
Hypertension	malignant hypertension	endothelial damage
Drugs	mitomycin, calcineurin inhibitors	endothelial damage
Vascular rejection	renal transplantation	endothelial damage

\* antiphospholipid syndrome (anti-phospholipid-antibodies: lupus anticoagulans and cardiolipin antibodies). BF: complement factor B, CFH: complement factor H, IF: complement factor, MCP: membrane cofactor protein, PNH: paroxysmal nocturnal hemoglobinuria, Stx: shiga toxins, TMA: thrombotic microangiopathy.

glomerular capillaries (Fig. 1L) and later on to endothelial cell proliferation, thickening of the GBM and also formation of double contours (Fig. 1L-N). Eventually, on light microscopy the characteristic morphological aspect of MPGN may evolve and then the differential diagnosis requires further analyses, i.e. immunohistology / immunofluorescence and electron microscopy (38). Longstanding TMA in HUS often leads to the development of so-called "bloodless glomeruli", i.e. glomeruli that appear filled with fibrillary material (Fig. 1M).

In routine diagnostics glomerular disease in TMA due to HUS/TTP and primary MPGN has to be differentiated on the basis of immunofluorescence or immunohistological findings. In TMA no or only minor deposition of IgG and C3c can be seen along the GBM whereas in MPGN there is the above mentioned typical pattern of IgG and C3 deposition in the glomeruli (Fig. 1D, E, I). On electron microscopy in TMA subendothelial swelling and deposition of fluffy material is visible (Fig. 1N) whereas subendothelial immunodeposits and interposition of mesangial cells as in MPGN1 is lacking (Fig. 1F).

In summary, MPGN is an uncommon cause of the nephrotic

or nephritic syndrome presenting with two distinct age distributions: (i) MPGN in childhood with all three types of MPGN is frequently idiopathic or associated with nephritic factor and (ii) MPGN in adults (> 18 years) with type I/III being common and mostly associated with HCV / cryoglobulinaemia. In general, MPGN is associated with an unfavourable prognosis that is influenced by the severity of crescents, tubulointerstitial lesions, interstitial fibrosis at initial presentation and a high recurrence rate in transplanted kidneys (up to 50% in MPGN1, 80–100% in MPGN2/DDD).

In HUS/TTP the kidney and the brain show characteristic vascular changes, i.e. TMA, due to endothelial damage that may also involve glomeruli and may lead to progressive renal failure. Of note, glomerular involvement in MPGN and HUS/TTP should be differentiated by clinical, morphological and in particular by additional immunohistology / immunofluorescence and electron microscopy. Moreover, recent genetic and molecular studies shed more light on the underlying pathogenesis, i.e. disturbances of various aspects of the complement system, which are also helpful in the differential diagnosis.

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