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Renal disease associated with myeloproliferative neoplasms and myelodysplastic syndrome/myeloproliferative neoplasms

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Aims: Renal changes in patients with myeloproliferative neoplasms (MPNs) or myelodysplastic syndrome (MDS)/MPNs have been addressed by few, respectively no, reports. The aim of this study was to focus on a systematic evaluation of renal biopsies in patients with MPNs or MDS/MPNs.

Methods and results: The cohort comprised 29 patients (23 men) aged 67 ± 11 years (mean ± standard deviation), diagnosed with chronic myeloid leukaemia (n = 5), polycythaemia vera (n = 9), primary myelofibrosis (n = 5), essential thrombocythaemia (n = 2), or chronic myelomonocytic leukaemia (n = 4), as well as MPNs or MDS/MPNs not otherwise specified (n = 4). Patients manifested with proteinuria (93%), partially in the nephrotic range (46%), haematuria (72%), and impaired kidney function (93%). The most prominent histological findings included double-contoured glomerular basement membranes (71%), acute endothelial damage (68%), intracapillary platelet aggregation (62%), mesangiolysis (21%), thrombotic microangiopathy (24%), segmental glomerulosclerosis (66%), mesangial hypercellularity and sclerosis, extramedullary haematopoiesis (17%), and also IgA nephropathy (21%) and glomerulonephritis (GN) with features of infection-related GN (21%). MPN and MDS/MPN patients showed significantly more chronic changes than age-matched and sex-matched controls, including global and segmental glomerulosclerosis, mesangial sclerosis, and hypercellularity, whereas the extent of arteriosclerosis was comparable.

Conclusions: MPN and MDS/MPN patients show glomerular scarring that exceeds age-related phenomena. Ongoing endothelial damage, growth factors released by platelets and deposition of immune complexes are probably the causative mechanisms. Early recognition of renal failure heralded by proteinuria and haematuria, and consequent control of risk factors for kidney failure, should be recommended for MPN and MDS/MPN patients.

Keywords: endothelium, glomerulopathy, myelodysplastic syndrome/myeloproliferative neoplasms, myeloproliferative neoplasms, thrombotic microangiopathy

Introduction

Myeloproliferative neoplasms (MPNs) encompass clonal hematopoietic stem cell disorders characterised by proliferation of one or more myeloid lineages with overproduction of mature cells, including chronic myeloid leukaemia (CML), polycythaemia vera (PV), primary myelofibrosis (PMF), and essential

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thrombocythaemia (ET).[1] Myelodysplastic syndrome (MDS)/MPN patients simultaneously show aspects of MDS and MPNs, with partially ineffective haematopoiesis and dysplastic changes including chronic myelomonocytic leukaemia (CMML) and several less frequent disorders.[1]

Until now, renal diseases have not been recognised as a prominent complication of MPNs or MDS/MPNs. However, at the time of diagnosis, 11–29% of patients show stage 3 or 4 chronic kidney disease, and ~20% show a rapid annual decrease in the estimated glomerular filtration rate that negatively correlates with monocyte/neutrophil counts, indicating that not only age-related nephrosclerosis but also MPN-associated or MDS/MPN-associated mechanisms probably play a causative role in the development of renal disease.[2,3]

The spectrum of glomerular alterations associated with MPN has been investigated in only a few studies. The initial descriptions revealed glomerular intracapillary hematopoietic cells[4] as well as focal segmental glomerulosclerosis (FSGS) and mesangial sclerosis.[5,6] The two largest cohorts published so far showed features of chronic thrombotic microangiopathy (TMA), glomerulosclerosis, and intracapillary haematopoiesis.[7,8] Some of these features were also described in subsequent reports.[9–14] However, owing to the selection bias of case reports focusing on particularly interesting cases, the morphological spectrum and frequency of renal biopsy findings are difficult to estimate. For MDS/MPN patients, no such data are available.

In this study, we systematically evaluated non-preselected kidney biopsies obtained from patients with a history of MPNs or MDS/MPNs. In order to control for age-related phenomena, we compared the findings with those of age-matched and sex-matched zero-time graft biopsies.

Materials and methods

PATIENTS

Twenty-nine renal biopsies from MPN or MDS/MPN patients were retrieved from the archives of (nephro-)pathology departments in Erlangen (25), Hamburg (two), and Mannheim (two), Germany. Digital pathology reports were screened for kidney biopsies with pre-existing diagnoses of MPNs or MPN/MDSs. Biopsies were submitted between 2013 and 2019. Age-matched and sex-matched zero-time donor biopsies of renal transplants served as controls.

HISTOLOGY

Haematoxylin and eosin and periodic acid–Schiff stains applied to 1-μm sections were reassessed by two experienced nephropathologists (M.B.-H. and S.P.). Total, globally and segmentally sclerosed glomeruli were quantified. Extramedullary haematopoiesis (EMH) and mesangiolysis were evaluated as present or absent. Mesangial cell counts were assessed as the maximum number of mesangial cells in one mesangial area. Mesangial sclerosis was scored semiquantitatively as (0 = no, 1 = mild, 2 = moderate, and 3 = strong). Interstitial fibrosis and tubular atrophy were estimated in 5% steps, and arteriosclerosis and arteriolohyalinosis were scored according to the Banff classification.[15]

IMMUNOHISTOCHEMISTRY

Immunohistochemistry was performed with polyclonal antibodies (Dako, Glostrup, Denmark), on a Ventana Benchmark stainer (Ventana, Basel, Switzerland) on formalin-fixed paraffin-embedded material (1-μm sections) after digestion with protease from *Streptomyces griseus* (Sigma-Aldrich, Munich, Germany; product number P5147) in Erlangen. The antibodies used were as follows: A0262 (1:150 000) for IgA; A04231 (100 000) for IgG; A04251 (75 000) for IgM; A01361 (75 000) for C1q; and A0062 (1:75 000) for C3c. CD61 staining was performed for the detection of platelet aggregates and megakaryocytes (1:100, clone 2f2, product number 161M-15; Medac, Wedel, Germany).

ULTRASTRUCTURAL ANALYSES

Ultrathin sections of 25 cases were semiquantitatively evaluated (M.B.-H.) for signs of endothelial damage (loss of fenestration and swelling: 0, absent; 1, <25%; 2, 25–75%; 3, ≥75%), podocyte injury (foot process effacement: 0, absent; 1, <25%; 2, 25–75%; 3, ≥75%), and double-contoured glomerular basement membranes (GBM) (0, absent; 1, segmental, 2, global double contours).

STATISTICAL ANALYSES

For statistical analyses, SPSS for Windows (version 24; SPSS, IBM, Munich, Germany) was used. For comparison of two groups, the Mann–Whitney test was used. For comparison of five groups, the Kruskal–Wallis test and post-hoc testing were used. Nominal parameters were assessed with cross-tabulation (chi-square), and, when expected values in 2 × 2 cross-tabulation were <5,

Table 1. Clinical data from the current and previous series

Publication	Cases	Diagnosis (no. of cases)	Age (years), mean (range)	Sex	Creatinine (mg/dl), mean (range)	Haematuria (%)	Proteinuria (%)	Nephrotic proteinuria (%)
Current	29	All (29)	67 (37–83)	23 M, 6 F	2.4 (0.8–7.9)	72	93	46
		CML (5)	65 (43–78)	4 M, 1 F	1.9 (1.4–3.0)	60	80	40
		PV (9)	64 (48–83)	6 M, 3 F	2.6 (0.8–7.9)	75	88	63
		PMF (5)	66 (37–81)	4 M, 1 F	2.1 (1.7–2.7)	100	100	100
		ET (2)	69 (63–75)	2 M	1.6 (1.3–1.9)	50	100	0
		CMML (4)	70 (59–77)	3 M, 1 F	2.4 (1.7–3.6)	50	100	0
		NOS (4)	71 (66–74)	4 M	3.3 (1.5–6.0)	100	100	0
Alexander *et al*. (2015)[7]	12*	PV (1)	79	F	1.2	NR	100	100
		PMF (9)	71 (56–87)	6 M, 3 F	2.8 (1.2–7.3)		100	67
		ET (1)	67	M	2.5		100	100
		NOS (1)	72	M	3.4		100	100
Bardy *et al*. (2014)[9]	8	CML (2)	65 (49-80)	2 F	56 (21–91)†	0	100	100
		PV (4)	69 (45–84)	4 M	78 (33–174)†	25	100	100
		PMF (1)	65	M	70†	0	100	100
		ET (1)	40	M	34†	100	100	100
Fujita and Hatta (2013)[14]	3	PV (1)	51	M	1.4	NR	100	0
		ET (2)	69 (62–76)	2 F	1.0 (0.7–1.2)		100	0
Said *et al*. (2011)[8]	11	CML (1)	78	F	2.5	NR	100	100
		PV (1)	68	M	2.2		100	100
		PMF (8)	73 (60–87)	7 M, 1 F	2.8 (1.3–5.6)		100	100
		ET (1)	74	F	1.0		100	100

CML, Chronic myeloid leukaemia; CMML, Chronic myelomonocytic leukaemia; ET, Essential thrombocythaemia; F, Female; M, Male; NOS, Myeloproliferative neoplasm or myelodysplastic syndrome/myeloproliferative neoplasm not otherwise specified, owing to lack of information; NR, Not reported; PMF, Primary myelofibrosis; PV, Polycythaemia vera.
All publications with more than one case are listed.
*Patients with plasma cell myeloma are not included.
†Creatinine clearance was reported in ml/min.

Fisher's exact test was used. For the comparison between patients and age-matched and sex-matched controls, the Wilcoxon signed-rank test was used. *P*-values of <0.05 were considered to be statistically significant.

Results

CLINICAL PRESENTATION

The cohort comprised non-preselected patients ($n = 29$) for whom a renal biopsy had been submitted between 2013 and 2019 and who had a history of MPNs or MDS/MPNs: five CML, nine PV, five PMF, two ET, four CMML, and four MPN or MDS/MPN not otherwise specified (NOS) because of lack of information (Table 1). The age was 67 ± 11 years [mean $\pm$ standard deviation (SD)]. Twenty-three patients were men (79%), giving a male/female ratio of 3.8:1. Twenty-one of 25 (84%) patients with available information had a history of arterial hypertension, and four of 22 (18%) had known diabetes mellitus. Data on creatinine levels available for 27

Table 2. Distribution of morphological findings and diagnoses

Morphological findings	All*	CML	PV	PMF	ET	CMML	*P*-value†
Endothelial damage (score 0–3), mean (range)	2 (0–3), *N* = 25	2 (1–2), *N* = 4	1.5 (0–3), *N* = 8	3 (1–3), *N* = 4	2 (1–3), *N* = 2	2 (1–3), *N* = 4	0.641
Mesangiolysis, *n* (%)	6/29 (21)	2/5	0/9	1/5	0/2	2/4	0.181
Double contours (score 0–2), mean (range)	1 (0–2), *N* = 24	0.5 (0–1), *N* = 4	0.5 (0–2), *N* = 8	1 (1–1), *N* = 2	1.5 (1–2), *N* = 2	1.5 (1–2), *N* = 4	0.135
Podocytopathy ≥75%, *n* (%)	8/25 (32)	1/4	3/8	3/4	0/2	1/4	0.383
TMA, *n* (%)	7/29 (24)	1/5	3/9	0/5	1/2	1/4	0.593
IgAN, *n* (%)	6/29 (21)	2/5	2/9	0/5	1/2	0/4	0.325
IR-like GN, *n* (%)	6/29 (21)	0/5	2/9	1/5	0/2	1/4	0.755
AML infiltration, *n* (%)	1/29 (3)	0/5	1/9	0/5	0/2	0/4	0.763
EMH, *n* (%)	5/29 (17)	0/5	2/9	3/5	0/2	0/4	0.100

AML, Acute myeloid leukaemia; CML, Chronic myeloid leukaemia; CMML, Chronic myelomonocytic leukaemia; EMH, Extramedullary haematopoiesis; ET, Essential thrombocythaemia; IgAN, IgA nephropathy; IR-like GN, Infection-related-like glomerulonephritis; PMF, Primary myelofibrosis; PV, Polycythaemia vera; TMA, Thrombotic microangiopathy.
*Including the four cases with myeloproliferative neoplasm (MPN) or myelodysplastic syndrome (MDS)/MPN not otherwise specified.
†Comparison of CML, PV, PMF, ET, and CMML.

patients showed impaired kidney function in 25 of them (93%). The creatinine values averaged 2.4 ± 1.5 mg/dl. Proteinuria was present in 26 of 28 patients (93%), and reached nephrotic levels (i.e. >3 g/day or g/g creatinine or g/l) in 12 of 26 (46%). Haematuria was reported in 18 of 25 patients (72%; Table 1). The time span between haematological diagnosis and renal biopsy was 0–20 years (mean ± SD, 7.4 ± 6.7 years, $n = 16$). The available data on MPN-specific therapies included: hydroxyurea ($n = 4$), imatinib ($n = 2$), anagrelide ($n = 1$), dasatinib ($n = 1$), interferon-α ($n = 1$), ruxolitinib ($n = 2$), bloodletting ($n = 1$), and no therapy ($n = 5$). Kidney function deteriorated in four patients, remained impaired without substantial alteration in three, and partially improved in two (Table S1).

HISTOLOGICAL FINDINGS

Ultrastructural signs of acute glomerular endothelial damage (swelling or loss of fenestration involving at least 25% of the endothelial lining) were prevalent findings in 17 of 25 (68%) biopsies. Mesangiolysis was seen in six of 29 patients (21%; Table 2; Figure 1). Double-contoured GBM was seen in 17 of 24 (71%) cases, indicating chronic endothelial damage. Light and electron microscopic findings were sufficient for the diagnosis of TMA in seven (24%) patients (Table 2; Figure 1).

Podocytopathy, defined as substantial (>75%) foot process effacement, was seen in eight of 25 patients (32%), six of whom (75%) had associated FSGS of the NOS type. In total, FSGS was seen in 19 patients (66%) (Table S2; Figure 2).

IgA nephropathy (IgAN) was seen in six (21%) patients. According to the criteria of the Oxford classification, three of them had mesangial hypercellularity, one had endocapillary hypercellularity, five had segmental scleroses, and four had crescents. The rate of interstitial fibrosis and tubular atrophy (IFTA) averaged 17.9%, and did not significantly differ from that in the non-IgA cases (27.5%, $P > 0.05$). No information on pre-existing liver disease was available (in one patient, normal liver parameters were reported). Six patients (21%) showed glomerular immune deposits reminiscent of an infection-related origin [infection-related-like glomerulonephritis (GN) (IR-like GN)] (Table 2; Figure 3). Specifically, two patients showed mild granular, in part coarse, mesangial C3 deposits [Figure 3b; no humps shown by electron microscopy (EM), and one with cutaneous herpes zoster virus infection]. In two patients, strong C3 deposits and mild IgG and subepithelial deposits were shown by EM; one patient had

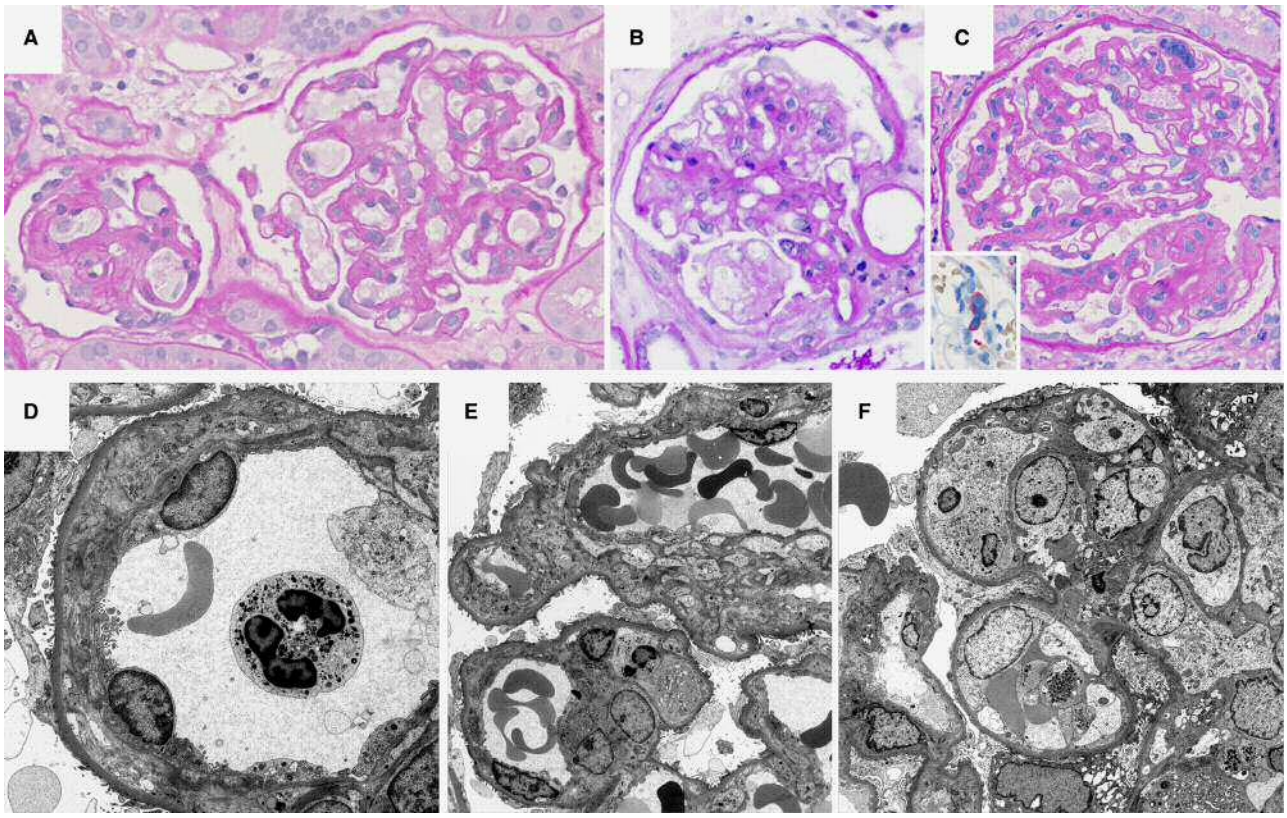

Figure 1. Acute and chronic endothelial damage. **A**,**B**, Glomeruli showed endothelial and subendothelial oedema (**A**) progressing to mesangiolysis in some cases (**B**). **C**, In other patients, double-contoured glomerular basement membranes (GBMs) and/or marginating megakaryocytes visualised by the use of CD61 (inset) could be seen. **D**–**F**, Ultrastructural signs of ongoing endothelial damage such as loss of endothelial fenestrations, oedema, production of extracellular matrix in the subendothelial space, and double-contoured GBMs. Endocapillary hypercellularity is visible in some cases, despite the absence of osmiophilic depositions (**F**). **A**–**C**, Periodic acid–Schiff stain. Inset in (**C**): immunohistochemistry for CD61.

serological signs of streptococcal group A infection and findings of IgA-dominant IR-GN with subepithelial deposits, and one had strong C3 positivity accompanied by moderate IgM and C1q deposits (no humps). Dense deposits as a specific finding for C3 glomerulopathy were not present in those biopsies. In two biopsies, interstitial nephritis was diagnosed. Interstitial infiltration by acute myeloid leukaemia (AML) and EMH were seen in one and five patients, respectively (Table 2; Figure 3).

Some patients showed partially overlapping histological changes (Figure 4). TMA and/or IR-like GN coincided with EMH in three cases. The patient with AML infiltration additionally showed IR-like GN. No overlap between IgAN and other diagnoses was observed. Podocytopathic changes were strongly associated with the diagnosis of EMH (4/5), but also with TMA (3/7), and IR-like GN (3/5), whereas no IgAN cases showed this high extent of podocyte damage (0/5). Endothelial damage was seen in most cases of EMH (4/5), IR-like GN (4/5), and TMA (7/7) but also in three of five IgAN cases (Table S2).

COMPARISON OF THE UNDERLYING HAEMATOLOGICAL NEOPLASMS

When the underlying haematological diseases were compared with regard to serum creatinine, proteinuria, or haematuria, no significant differences were seen (all $P > 0.05$). Similarly, the haematological diseases did not show significant differences in histological changes (i.e. endothelial, mesangial or podocyte alterations) or renal diagnoses (all $P > 0.05$; Table 2).

COMPARISON WITH AGE-MATCHED AND SEX-MATCHED ZERO-TIME BIOPSIES

Age-matched and sex-matched zero-time transplant biopsies served as controls for non-specific age-related

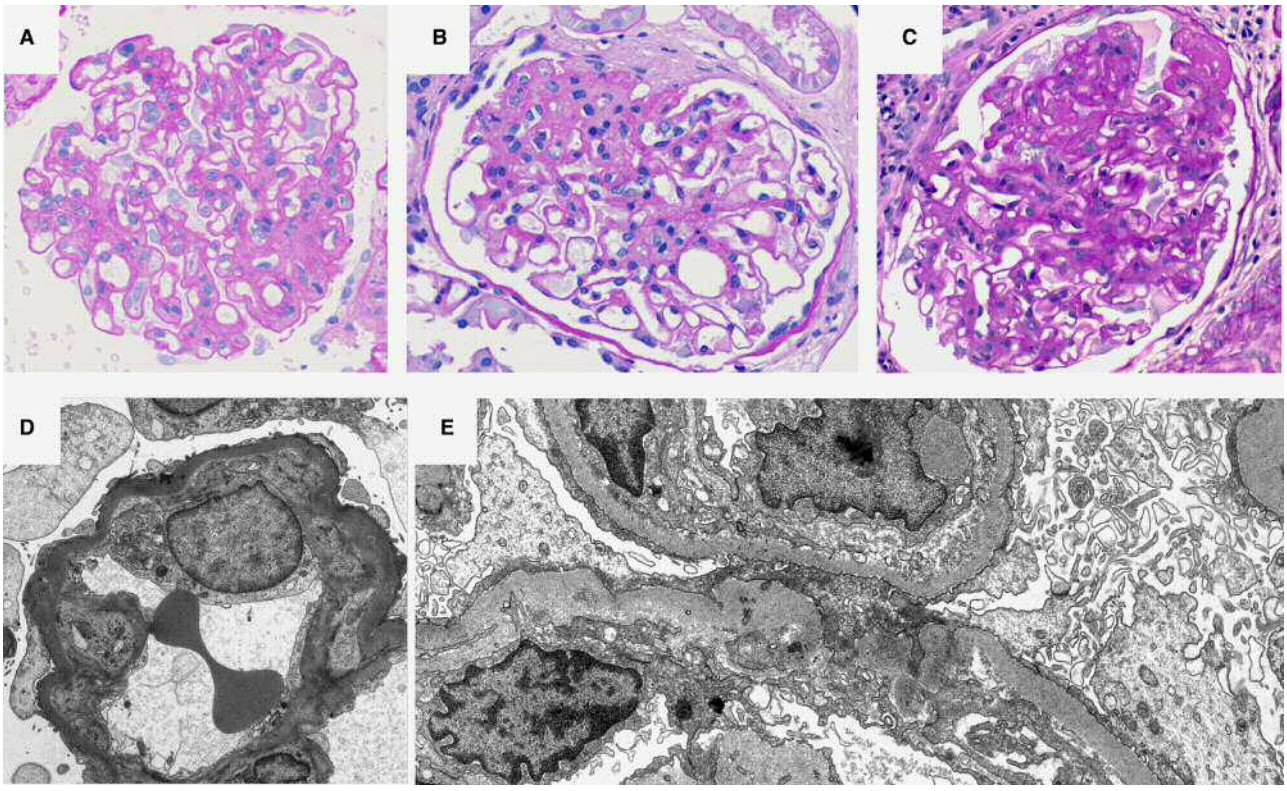

Figure 2. Progression to segmental sclerosis. **A–C**, Glomeruli frequently showed sclerosis of the mesangium and of the glomerular tuft that developed as a continuation of the chronic endothelial damage (**A**, lower right). Other cases showed mesangial hypercellularity (**B**) or no additional changes (**C**). **D**,**E**, Ultrastructural podocyte damage visible as a loss of foot processes. Note also the chronic endothelial damage. **A–C**, Periodic acid–Schiff stain.

degenerative changes, and showed significantly lower global and segmental glomerulosclerosis, mesangial sclerosis, mesangial cell counts, and IFTA (all $P < 0.05$; Table 3). Although arteriolohyalinosis was also less prominent in the controls ($P = 0.009$), the degree of arteriosclerosis did not show a significant difference ($P = 0.134$; Table 3). Also, when patients with GN or known diabetes were excluded, the differences in mesangial matrix expansion, cell count, global and segmental glomerulosclerosis and IFTA remained significant (all $P < 0.05$), whereas arteriosclerosis and arteriolohyalinosis did not differ (all $P > 0.05$, data not shown).

INTRACAPILLARY PLATELET AGGREGATES

CD61-positive intracapillary platelet aggregates were significantly more frequent in the patient cohort (18/29, 62%) than in the controls (5/17, 29%, $P = 0.032$; Table 3). Within the group of MPN and MDS/MPN patients, the presence of platelet aggregates did not show a significant association with the degree of mesangial sclerosis or cellularity, TMA, mesangiolysis, EMH, IgAN, global or segmental glomerulosclerosis, podocyte damage, or endothelial damage (all $P > 0.05$; Table S3).

Discussion

Kidney failure and proteinuria have been reported previously in MPN patients[7–9,14] (Table 1). Our cohort represents a systematic, and so far the largest, collection of patients with a history of MPNs or MDS/MPNs in whom a renal biopsy was performed. As in the aforementioned reports, the principal symptoms in our patients were reduced kidney function (93%) and proteinuria (93%). Similar symptoms occurred in MDS/MPN patients, for whom no data have been published so far. Interestingly, the rate of proteinuria (especially in the nephrotic range) was lower in our cohort than in the previous reports (Table 1). This may have been because 72% of our patients suffered from haematuria, which may have prompted the biopsy. A direct comparison with the previous studies listed in Table 1 is, however, difficult, because we

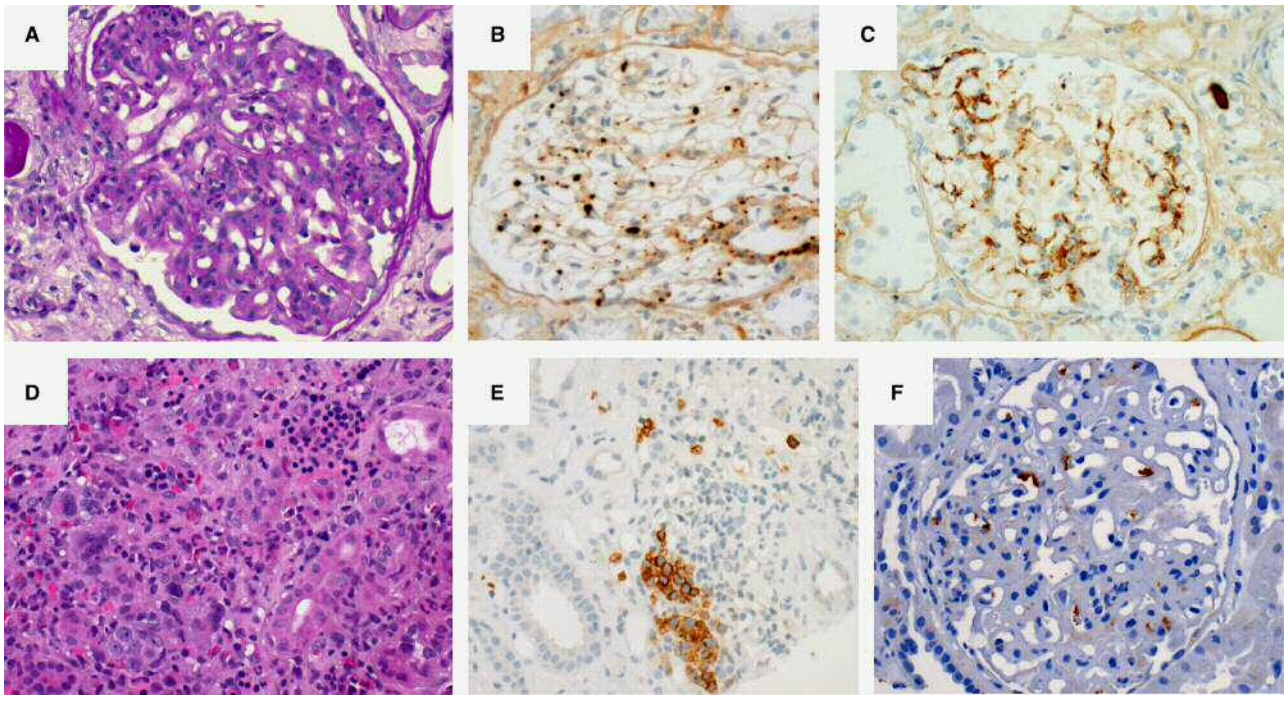

Figure 3. Other glomerular and interstitial changes. **A**–**C**, Cases showing several other disease patterns, such as glomerulonephritis in line with an infection-related origin with an increased endocapillary content of mononuclear cells and granulocytes plus signs of thrombotic microangiopathy with double-contoured glomerular basement membranes (**A**), hump-like C3 deposits (**B**), or IgA nephropathy (C). **D**,**E**, Extramedullary haematopoiesis in the interstitium with islands of erythropoiesis detectable by immunohistochemistry for glycophorin A (**E**). **F**, Immunohistochemistry for CD61 revealing endocapillary platelet aggregates in the absence of endocapillary megakaryopoiesis. Note also the mesangial sclerosis. **A**, Periodic acid–Schiff stain. **B**, Immunohistochemistry for C3. **C**, Immunohistochemistry for IgA. D, haematoxylin and eosin. **E**, Immunohistochemistry for glycophorin A. **F**, Immunohistochemistry for CD61. [Colour figure can be viewed at wileyonlinelibrary.com]

have chosen a systematic and unselective approach, in contrast to the focus on clinically and/or histologically interesting cases in the preceding reports.

In terms of histology, segmental and global glomerulosclerosis, mesangial sclerosis and hypercellularity were the leading chronic changes, in line with earlier reports.[5,8,9] The comparison with controls suggests that mere age-related and sex-related or hypertensive phenomena are unlikely to be the central contributors to the chronic glomerular alterations in MPN and MDS/MPN patients; instead, mechanisms elicited by MPNs and MDS/MPNs themselves are more likely to be responsible. Our data indicate that ongoing podocyte damage and endothelial damage are probably important mechanisms responsible for glomerular scarring. Numerous cytokines and growth factors [e.g. interferon-γ, interleukin-6, platelet-derived growth factor, transforming growth factor (TGF)-β, and fibroblast growth factor] documented in patients with MPNs and other haematological diseases (such as POEMS syndrome or haemophagocytic lymphohistiocytosis) are capable of directly eliciting endothelial damage.[8,16–20] In addition, growth factors can directly contribute to mesangial cell proliferation and mesangial and subendothelial matrix production in a manner similar to the induction of myelofibrosis in some MPN and MDS/MPN patients.[21–25] Marginating platelets and cells of extramedullary haematopoiesis can produce growth factors locally and, together with hyperviscosity, aggravate the endothelial damage.[26,27] Indeed, we demonstrated an increased frequency of intracapillary platelet aggregates in MPN and MDS/MPN patients in comparison with controls. However, their local presence was not significantly associated with glomerular scarring, endothelial damage, or podocyte damage, thus supporting a systemic rather than a paracrine pathogenesis.

It cannot be excluded that modern therapies with tyrosine kinase inhibitors contribute to the chronic endothelial damage in MPN and MDS/MPN patients. Such effects have been suggested for Jak2 inhibitors.[11,28] However, several of the archived cases (in our study and the previous studies) were not exposed to these drugs, thus making a sole manifestation of adverse drug effects unlikely.

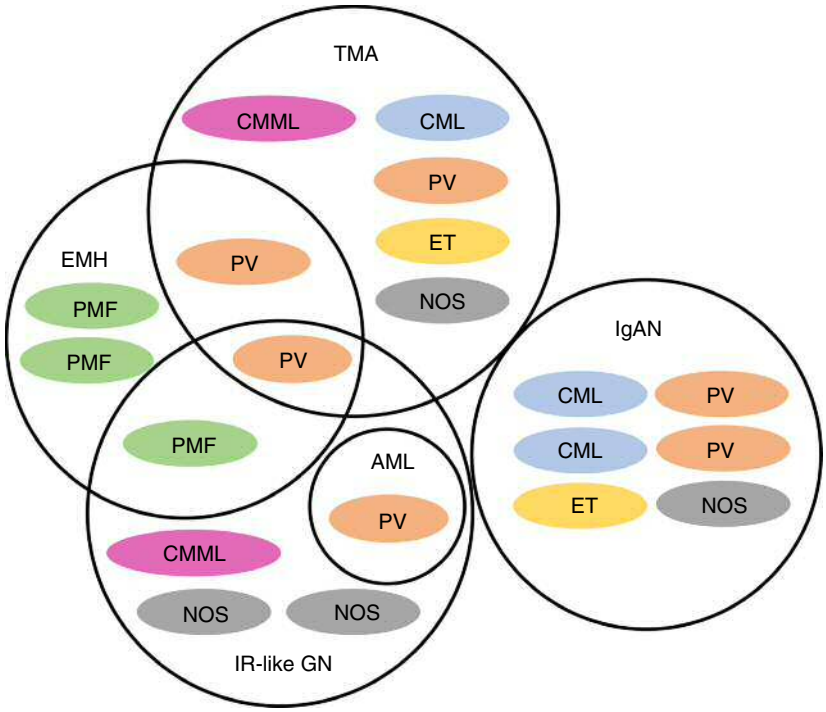

Figure 4. Venn diagram showing the relationships between the haematological and the—mutually not exclusive—renal diseases. Patients localised in the overlaps showed more than one renal disease; for example, one polycythaemia vera (PV) patient showed thrombotic microangiopathy (TMA) and extramedullary haematopoiesis (EMH), another showed acute myeloid leukaemia (AML) and infection-related-like glomerulonephritis (IR-like GN), and a third showed three renal diseases in parallel, namely TMA, EMH, and IR-like GN. Note that the IgA nephropathy (IgAN) group did not overlap with any other group. CML, Chronic myeloid leukaemia; CMML, Chronic myelomonocytic leukaemia; ET, Essential thrombocythaemia; NOS, Myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative neoplasm not otherwise specified; PMF, Primary myelofibrosis. [Colour figure can be viewed at wileyonlinelibrary.com]

Pronounced podocyte damage was seen in 32% of patients. Podocyte damage and FSGS in the context of MPNs and MDS/MPNs might be secondary to hyperviscosity, vascular thrombosis, or hyperperfusion.[29–31] Interestingly, no patient showed collapsing FSGS with podocyte hypertrophy as observed by Boub *et al.* in the setting of other TMAs.[32] Therefore, in MPN and MDS/MPN patients, primary podocyte damage could directly result from secreted factors such as TGF-β that have proapoptotic effects on podocytes.[33]

Remarkably, many patients (41%) showed IgAN or IR-like GN (Table 2). Although some IgAN cases have been reported previously,[9,14] our data indicate, for the first time, that there might be a link between MPN-associated or MDS/MPN-associated renal disease and GN with C3 deposition, reminiscent of infection-related GN. This observation could possibly point to activation of the complement system due to secreted soluble factors, or possibly a subtype of C3 GN developing in the context of myeloid disease. MPN-associated or MDS/MPN-associated immunodeficiency might be involved in the pathogenesis of IgAN or IR-like GN, which are related to infectious disease. Conversely, the presence of IR-like GN and IgAN as the most common types of GN[34] might be coincidental in some cases.

In summary, nephropathy associated with MPNs and MDS/MPNs is characterised by kidney failure, proteinuria, and haematuria. The histological picture is dominated by ongoing endothelial and podocyte damage, mesangial sclerosis and hypercellularity, and segmental and global glomerulosclerosis. The chronic changes are unlikely to be mere age-related or hypertension-related phenomena, but might rather be the consequences of hyperviscosity, aberrant function and/or activation of excessive neoplastic blood cells, and the production of growth factors. Early recognition of renal failure heralded by proteinuria and haematuria should be recommended during the follow-up of MPN and MDS/MPN patients, and subsequent control of risk factors for kidney injury should be warranted.

Acknowledgements

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Table 3. Comparison of MPN and MDS/MPN patients with age-matched and sex-matched controls

	All*	CML	PV	PMF	ET	CMML
N	29	5	9	5	2	4
Global glomerulosclerosis (%), mean ± SD						
Patients	26.8 ± 22.6[†]	31.4 ± 17.5	21.4 ± 17.6	42 ± 29	19.4 ± 7.9	10 ± 3
Controls	10.5 ± 14.8	8.9 ± 14.5	9.7 ± 14.3	9.6 ± 13.2	6.25 ± 8.8	4.2 ± 5
Segmental glomerulosclerosis (%), mean ± SD						
Patients	7.3 ± 8.4[‡]	6.9 ± 9.7	9.4 ± 8.7	13.4 ± 10.0	9.0 ± 3.0	1.1 ± 2.3
Controls	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Mesangial sclerosis (score 0–3), mean (range)						
Patients	1.5 (0–2.5)[‡]	1.5 (0.5–2)	1 (0–2.5)	2 (1–2)	1.5 (1–2)	1.5 (0.5–2)
Controls	0.5 (0–1)	0 (0–0.5)	0 (0–0.5)	0 (0–0.5)	0.3 (0–0.5)	0.5 (0–0.5)
Mesangial cell count, mean ± SD						
Patients	3.9 ± 1.1[‡]	3.5 ± 0.5	4 ± 1.1	3.9 ± 0.5	3.5 ± 2.1	3.75 ± 1
Controls	2.4 ± 0.7	2.3 ± 0.7	2.3 ± 0.5	2.8 ± 1.25	2 ± 0	2.25 ± 0.3
Intracapillary CD61 aggregates, *n* (%)						
Patients	18/29 (62.1)[§]	3/5	6/9	4/5	2/2	1/4
Controls	5/17 (29.4)	1/1	1/5	5/5	2/2	1/2
Arteriosclerosis (score 0–3), mean (range)						
Patients	1.5 (0–2.5)	2 (1–2)	1 (0.5–2)	2 (1–2.5)	0 (0–0)	0.8 (0–2)
Controls	1 (0–2.5)	0 (0–1)	1.5 (1–2.5)	1.3 (0–2)	0.8 (0.5–1)	1 (0–2)
Arteriolohyalinosis (score 0–3), mean (range)						
Patients	1 (0–2)[†]	2 (0.5–2)	1 (0–0.5)	1 (0.5–1)	0.8 (0.5–1)	1 (0–1)
Controls	0.5 (0–1.5)	0.5 (0–1)	1 (0–1)	0 (0–0.5)	0 (0–0)	0.8 (0–1.5)
IFTA (%), mean ± SD						
Patients	25.5 ± 18.5[‡]	24.5 ± 15.9	19.4 ± 19.0	38.0 ± 22.0	15.0 ± 14.1	23.8 ± 16.9
Controls	6.8 ± 8.0	6.5 ± 10.6	9.2 ± 9.4	5.0 ± 5.3	3.8 ± 1.8	3.1 ± 3.8

CML, Chronic myeloid leukaemia; CMML, Chronic myelomonocytic leukaemia; ET, Essential thrombocythaemia; IFTA, Interstitial fibrosis and tubular atrophy; PMF, Primary myelofibrosis; PV, Polycythaemia vera; SD, Standard deviation.
*Including the four cases with myeloproliferative neoplasm (MPN) or myelodysplastic syndrome (MDS)/MPN not otherwise specified.
[†]$P < 0.01$ for differences between patients and the corresponding controls.
[‡]$P < 0.001$ for differences between patients and the corresponding controls.
[§]$P < 0.05$ for differences between patients and the corresponding controls.

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Conflict of interest

All authors declare that they do not have any conflicts of interest.

Author contributions

S. Porubsky initiated the study. M. Büttner-Herold and S. Porubsky collected and analysed the data, and wrote the manuscript. T. Wiech analysed the data. M. Büttner-Herold, C. Sticht and S. Porubsky performed the statistics. All authors approved the final version.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Follow-up data on kidney function.

Table S2. Podocyte and endothelial cell damage.

Table S3. Association of CD61-positive intracapillary glomerular aggregates with renal findings.

