Université Paris Cité

Actualités Néphrologiques Jean Hamburger

16 Mai 2023

Marie-Camille Lafargue
Interne DES Néphrologie

Kidney involvement in myelodysplastic syndromes and chronic myelomonocytic leukemia

Summary

The 2016 WHO classification has been revised in 2022 resulting in the International Consensus Classification of Myeloid Neoplasms

- **MDS = myeloid neoplasms**
  - Myelodysplasia, ineffective hematopoiesis
  - Cytopenias
  - Progression to **AML**
- **Diagnostic**
  - Dysplasia on bone marrow (≥10%)
  - Classification: dysplastic lineages, blasts, cytogenetics and mutations (UBA1 excluded)
- **Treatments**
  - Low risk: follow-up, ESA, lenalidomide
  - High risk : hypomethylating agents
  - Curative : **Allogeneic stem-cell transplantation**

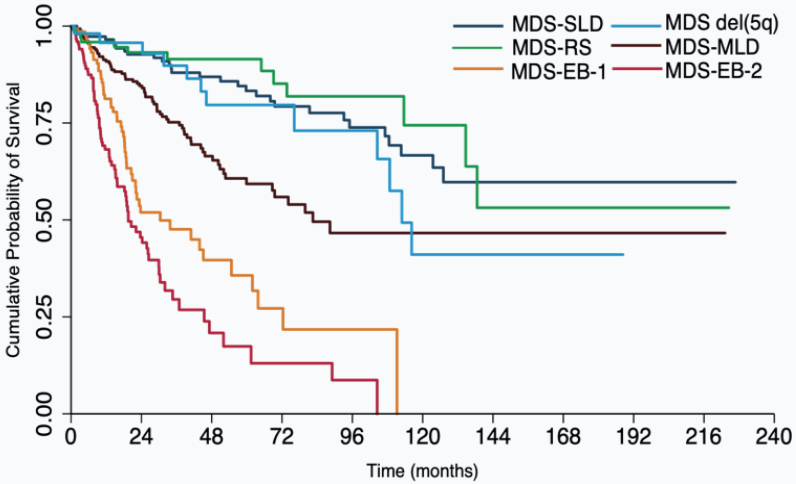


Figure : Kaplan Meier analyses of overall survival in 1110 patients diagnosed with MDS.
Cazzola et al. N Engl J Med. 2020.

Arber et al. Blood. 2016

Abbreviations : AML: acute myeloid leukemia; ESA: erythropoiesis-stimulating agents; MDS del(5q) : MDS with 5q deletioni; MDS-EB : MDS with excess of blasts; MDS-MLD : MDS with multilineage dysplasia; MDS-RS : MDS with ring sideroblasts; MDS-SLD : MDS with single lineage dysplasia; MDS : myelodysplastic syndromes; WHO: World Health Organization.

The WHO classification comprises the MDS/MPN category with chronic myelomonocytic leukemia

- **CMML = MDS/MPN**
  - Monocytosis ≥0.5G/L >and ≥10% of WBC
  - Cytopenia
  - Classification based on blasts %
  - Mutations >90% (*TET2*, *SRSF2*, *ASXL1*)
  - Progression to **AML**
- **Treatments**
  - Low risk : follow-up
  - High risk : hypomethylating agents
  - Myeloproliferative subtypes: hydroxyurea
  - Curative : **Allogeneic stem-cell transplantation**

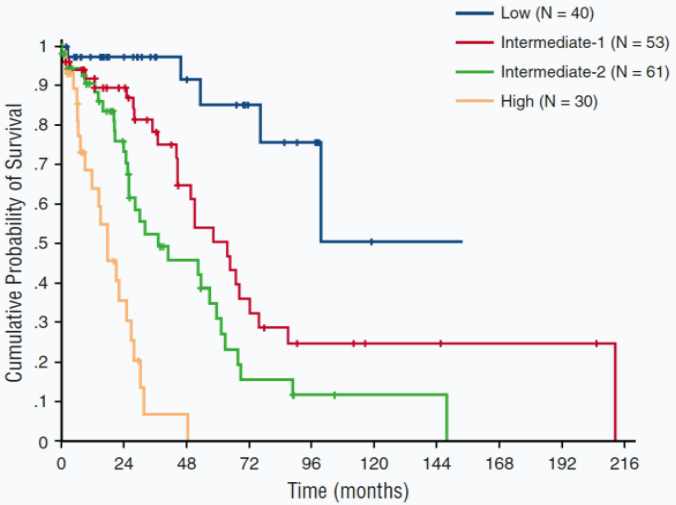


Figure : Kaplan Meier analysis of overall survival according to CPSS-Mol score.
Elena et al. Blood. 2016

Patnaik et al. Am J Hematol. 2020

Abbreviations : AML: acute myeloid leukemia; CMML: chronic myelomonocytic leukemia; CPSS-Mol : CMMLspecific progrostic scoring system including genetic analysis data; MDS: myelodysplastic syndromes; MPN : myeloproliferative neoplasms; WBC: white blood cells; WHO: world health organization.

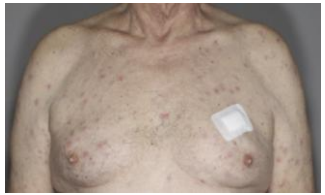
MDS/CMML are associated with systemic autoimmune and inflammatory disorders (SAID) in ~ 20% of cases

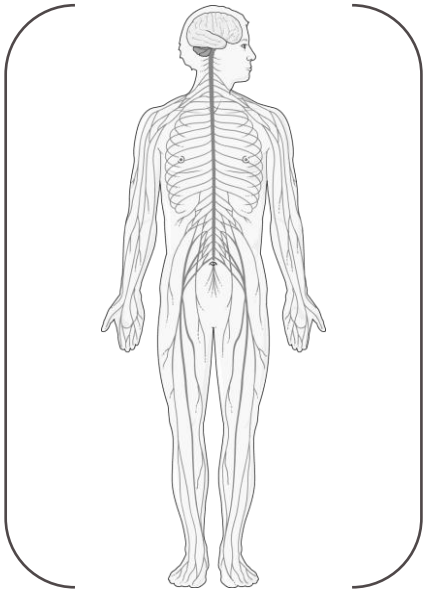
Examples of systemic inflammatory and autoimmune manifestations associated with MDS and/or CMML:

AIHA
Auto-immune thrombopenia

Behcet's like disease
Cronh's disease

Neutrophilic dermatosis
Myelodysplasia cutis





Relapsing polychondritis

Acute tubulo-interstitial nephritis
Extramedullary hematopoiesis

Systemic vasculitis

Inflammatory arthritis

Mekinian et al. Rheumatology. 2016; Fain et al. Rev Med Interne. 2011; Grignano et al. Leuk Res. 2016

Abbreviations : AIHA : autoimmune hemolytic anemia; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndromes.

Azacitidine may represent an interesting treatment for MDS/CMML patients with associated SAID

- **GFM AZA-SAID trial**
  - Prospective single arm multicenter phase II study
  - **Hematological indication** for AZA
  - **Steroid resistant / dependent** SAID
  - Therapeutic scheme: full dose AZA (6 cycles) + steroid 1mg/kg/j
- **Act on both hematological disease and systemic inflammation**
  - 19/29 (66%) of **SAID M6 response**
  - 17/29 (59%) of hematological M6 response
  - 15/29 (52%) SAID and hematological M6 response

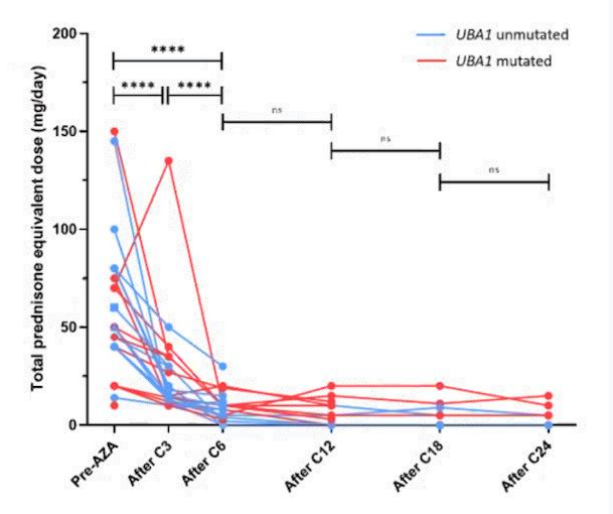


Figure: Important and sustained steroid-sparing effect of AZA, with a reduction to a median dose below 10 mg/day of prednisone equivalent after six cycles.
Mekinian et al. Leukemia. 2022

Mekinian et al. Leukemia. 2022

Abbreviations : AZA: azacitidine; CMML: chronic myelomonocytic leukemia; GFM: Groupe Francophone des Myélodysplasies; MDS: myelodysplastic syndromes; SAID: systemic autoimmune inflammatory disorders

In the literature, kidney manifestations associated with MDS are systemic vasculitis and acute tubulo-interstitial nephritis

Studies	Year	Number of patients	Kidney manifestations
Mekinian et al.	2016	123	19 cases : **PAN**, **GPA**
Roupie et al.	2020	54	5 cases : **PAN** (n=1), **C3 GN** (n=1), **IgA vasculitis** (n=1), **MPA** (n=1), **GPA** (n=1)
Schwotzer et al.	2021	19	**ATIN** (n=7), **ANCA-negative pauci-immune necrotizing and crescentic glomerulonephritis** (n=3), **membranous nephropathy** (n=2), **IgA nephropathy** (n=1), **IgA vasculitis** (n=1), **MPGN** (n=1), **C3 GN** (n=1), **fibrillary GN** (n=1), **MCD** (n=1)

Mekinian et al. Rheumatology. 2016; Roupie et al. Semin Arthritis Rheum. 2020; Schwotzer et al. Kidney Int Rep. 2021

Abbreviations : ANCA: antineutrophil cytoplasmic antibodies; ATIN: acute tubulo-interstitial nephritis; GN : glomerulonephritis; GPA : granulomatosis with polyangiitis; MCD: minimal change disease; MPA: microscopic polyangitiis; MPGN: membrano-proliferative glomerulonephritis; PAN: polyarteritis nodosa; MDS: myelodysplastic syndromes.

Kidney manifestations associated with CMML are mainly lysozyme-induced nephropathy and direct infiltration of myelomonocytic cells into tubules

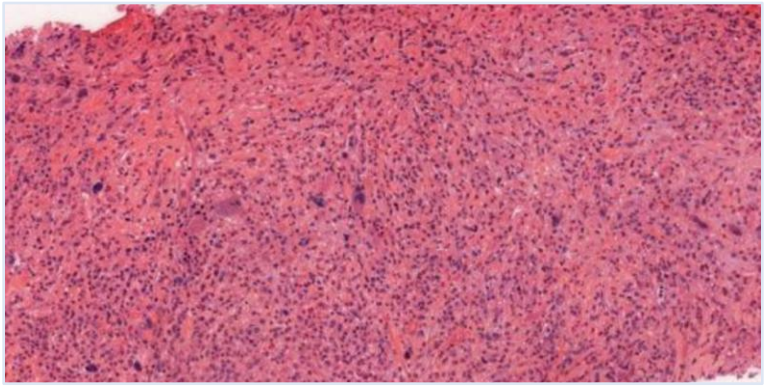


Figure : Massive infiltration of the kidneys in a patient with CMML. Erythropoietic, myelopoietic and megakaryopoietic cell aggregates.
Belliere et al. Kidney Int Rep. 2020.

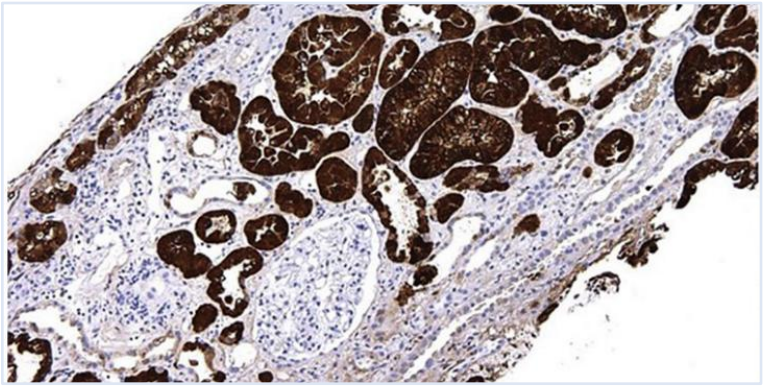


Figure : IHC staining with lysozyme showing intense granular reactivity in proximal tubular cells
Santoriello et al. Kidney Int Rep. 2016.

IHC
- **CD61+** : megakaryocytic component
- **MPO+ CD68+** : myelomonocytic component

Lysozyme = low-molecular weight (15 kDa), freely filtered protein that can accumulate in proximal tubular cells resulting in a proximal tubulopathy and kidney injury

Abbreviations : IHC : immunohistochemistry; CMML: chronic myelomonocytic leukemia.

Summary

This work seeks to improve our knowledge of the renal damages associated with MDS/CMML

- **Primary objectives:**
  - Describe the **demographic**, **hematological** and **renal** characteristics associated with MDS/CMML
  - Describe the **therapeutic management** and **evolution** of these manifestations
- **Secondary objectives:**
  - Compare our cohort with MDS/CMML patients **without renal involvement**
  - Comparing MDS-associated pauci-immune vasculitis with **control ANCA associated vasculitis**

Groupe Francophone des Myélodysplasies; Bhoudhabhay et al. J Am Soc Nephrol. 2021

Abbreviations : ANCA : anti-neutrophil cytoplasmic antibody; CMML: chronic myelomonocytic leukemia; MDS : myelodysplastic syndromes.

Summary

We conducted a retrospective descriptive study, and collected 33 cases, including 17 MDS patients and 16 CMML patients

Origin and selection of patients included in our retrospective descriptive study:

Patient pool	Inclusion and exclusion criteria	Nb. of selected patients
65 patients with a diagnosis of MDS/CMML and a kidney biopsy performed between 01/01/2000 and 09/31/2020 at **BWH/MGH, Boston**	Inclusion: ▪ MDS/CMML with bone marrow Exclusion: ▪ Kidney disease remaining stable after diagnosis of MDS ▪ Diabetic nephropathy ▪ Membranous nephropathy associated with GVHD	**4**
70 patients with a systemic vasculitis associated with MDS/CMML from a **multicentric French study** (Roupie et al. Semin Arthritis Rheum. 2020)	Exclusion: ▪ Vasculitis without kidney involvement	**6**
32 patients with kidney manifestations associated with MDS/CMML from **12 French universitary hospitals**	Exclusion: ▪ Kidney disease remaining stable after diagnosis of MDS ▪ Nephroangiosclerosis ▪ Acute tubular necrosis	**23**

Abbreviations : BWH : Brigham and Women's Hospital; CMML: chronic myelomonocytic leukemia; GVHD : graft versus host disease; MGH : Massachusetts General Hospital; MDS : myelodysplastic syndromes.

Summary

Characteristics of the MDS with kidney injury cohort (n=17)

General characteristics

- Age[1]: 76 years old (70 – 79)
- Gender: male (n=11, 65%)

Kidney presentation

- **RPGN: 11 (73%)**
- Nephrotic syndrome: 2 (13%)

Extra-renal manifestations[2]

- **General signs: 14 (82%)**
- **Skin lesions: 7 (50%)**
- Pulmonary lesions: 5 (36%)

Biological characteristics

- PU: 1.92 g/24h (0,8 – 3,3)
- Creatinine: 308 µmol/L (132 – 414)
- CRP: 71mg/L (20 – 103)
- **ANCA+: 9 (56%)**

Renal diagnosis

10 (59%) kidney biopsies

- **Delay: 3 months [0-14]**
- **MPA: 3/6 (35%)**
- **ANCA- PIGN: 2/4 (24%)**
- GPA: 1/2 (12%)
- C3GN: 2/2 (12%)
- Immune complex-mediated GN: 1/1 (6%)
- IgA vasculitis: 1/1 (6%)
- PAN : 1 (6%)

Treatments

- **Corticoids: 16 (94%)**
- Plasmatic exchanges: 3 (18%)
- Induction: **rituximab: 10 (59%)** / cyclophosphamide : 4 (24%)
- Azacitidine: 8 (44%)

1. Quantitative variables are expressed as median. 2. Each patient may have one or more of the following conditions. Abbreviations : C3GN: C3 glomerulonephritis; ANCA: antineutrophil cytoplasmic antibodies; GN : glomérulonéphritis; GPA : granulomatosis with polyangiitis; MDS: myelodysplastic syndromes; MPA : microscopic polyangiitis; PAN: polyarteritis nodosa; PIGN: pauci-immune glomerulonephritis; PU : proteinuria; RPGN: rapidly progressive glomerulonephritis.

The evolution of renal function is variable after hematological treatment

- **Heterogenous evolution**
  - **10 patients CKD 3 and 4**
  - **5 CKD 5 with 3 on hemodialysis**
  - **Worsened: 4 (23,5%)[1]**
  - **Improved: 8 (47%)[1]**
- **Treatments**
  - Corticoids: 16 (94%)
  - Plasmatic echanges: 3 (18%)
  - Induction:
    - Rituximab: 10 (59%)
    - Cyclophosphamide: 4 (24%)
  - Azacitidine: 8 (44%)

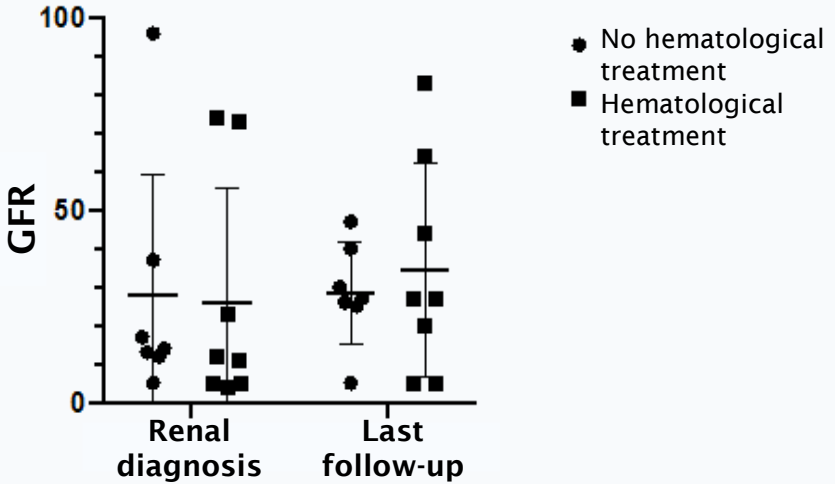


Figure: Evolution of GFR from renal diagnosis to last follow-up comparing patients treated (n=9) or not (n=8) with hematological treatment (azacitidine, allograft)

1. 2 missing data. Abbreviations : CKD: chronic kidney disease; GFR: glomerular filtration rate.

The main histological entity in our cohort is pauci-immune glomerulonephritis

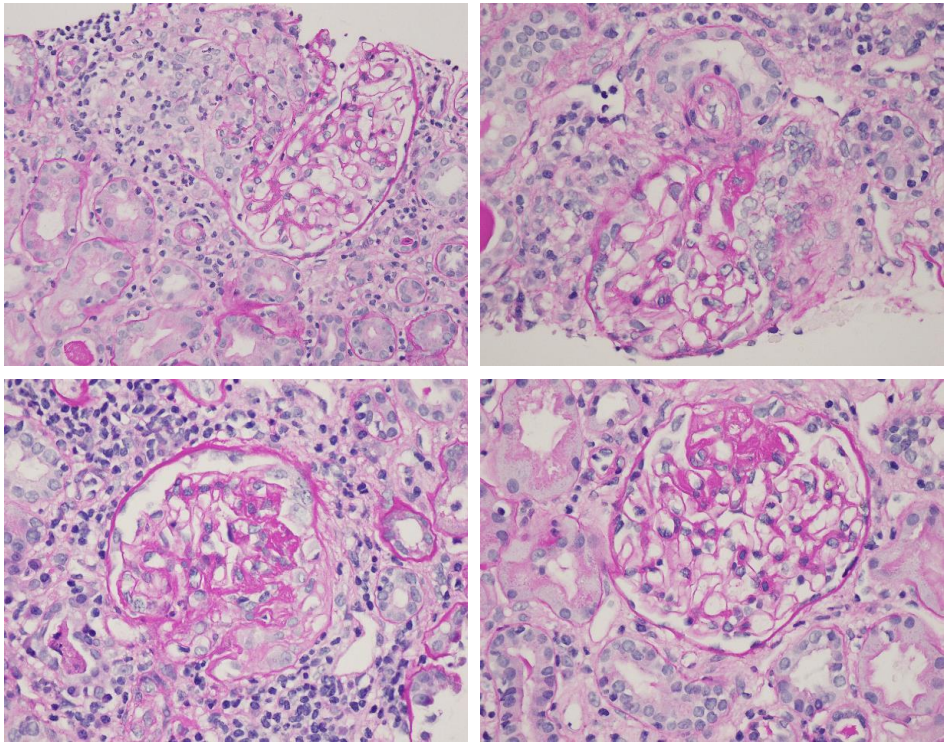


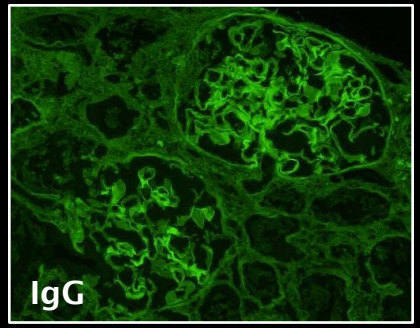
Figure: Haematoxylin-eosin. Proliferative focal glomerulonephritis: cellular crescents in 2/35 glomeruli (6%), and fibrocellular or fibrous in 4 glomeruli, with synechia.
Courtesy of Dr. Helmut G. Rennke

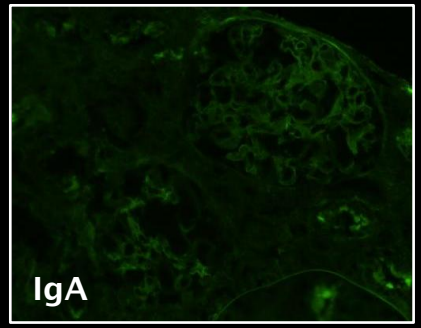
Case of a 28 years old male:

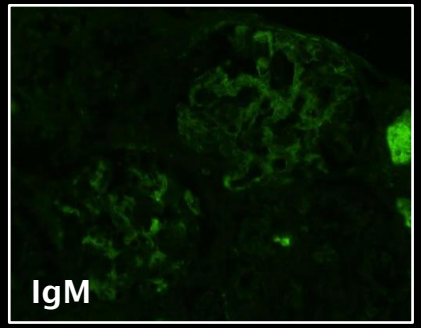
- **MonoMAC syndrome:** lymphedema, atypical mycobacterial infections, **MDS**
- **GATA2 mutation**
- PU/CU: 3.4g/g with 1.6g d'albuminurie
- Creatinine 98µmol/L
- **ANCA negativity**

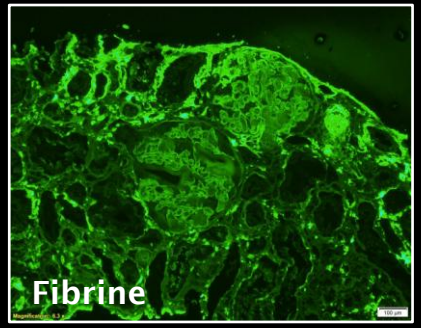
Abbreviations : ANCA: antineutrophil cytoplasmic antibodies; CU: creatininuria; MDS: myelodysplastic syndromes; PU: proteinuria.

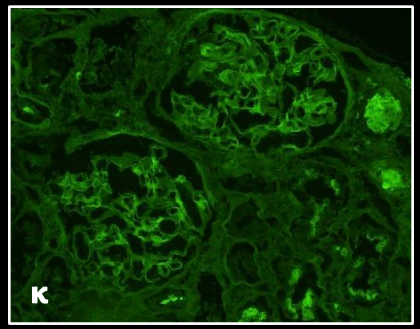
Pauci-immune glomeurlonephritis confirmed by IF

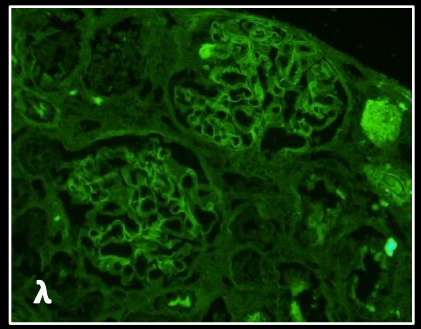












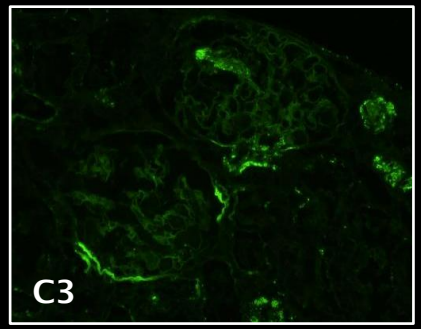


Figure: IF staining for IgG, IgA, IgM, fibrine κ, λ, C3

Abbreviations : ANCA: antineutrophil cytoplasmic antibodies; IF: immunofluoresence.

The diagnosis of AAV in an elderly subject, with cutaneous manifestations, without ANCA should lead to a search for MDS

ANCA associated vasculitis (AAV)	WITHOUT MDS n = 265	WITH MDS n = 11	Univariate analysis p
Age, median (IQR)	**63 (53 – 73)**	**76 (73 – 78)**	**0.019**
ANCA specificity, n (%)			
Proteinase 3	83 (31)	2 (22)	0.725
Myelopéroxydase	172 (65)	5 (56)	0.725
None/Negativity	**11 (4)**	**3 (27)**	**0.014**
Renal function			
Creatinine (µmol/L)	220 (123 – 396)	378 (176 – 431)	0.478
PU/CU (g/g)	1.5 (0.9 – 2.5)	2.6 (1.6 – 3.3)[1]	0.122
Hematuria	254 (96)	7 (86)[1]	0.305
Dialysis	42 (16)	2 (18)	0.690
ANCA Renal Risk Score Low, n (%)	**107 (40)**	**1 (16)[1]**	**0.1671**
Associated skin lesions, n (%)	**24 (9)**	**5 (46)**	**0.003**
Treatment for induction			
Cyclophosphamide	**198 (75)**	**3 (27)**	**0.002**
Rituximab	**59 (22)**	**6 (55)**	**0.023**
Plasmatic exhanges	47 (18)	3 (27)	0.425
Follow-up (months)	**46 (18-97)**	**8 (5-15)**	**<0.001**
Creatinine (at last follow-up)	114 (88 – 176)	141 (132 – 202)	0.285

1. Missing data. Abbreviations : AAV: ANCA associated vasculitis; CU: creatininuria; IQR : interquartile range; MDS: myelodysplastic syndromes; PU : proteinuria.

Does the renal involvement associated with MDS worsen the prognosis?

MDS	WITHOUT kidney injury n = 84	WITH kidney injury n = 17[1]	Univariate analysis p
Age, median (IQR)	**78 (74 – 84)**	**74 (68 – 79)**	**0.030**
MDS-MLD	32 (38)	9 (56)	0.267
3 dysplastic lineages	**2 (2)**	**4 (36)**	**0.001**
% Blasts Bone marrow, median (IQR)	3 (1 – 4)	8 (2 – 15)	0.080
Abnormal karyotype, n (%)	32 (38)	6 (60)	0.306
Neutrophils (G/L), median (IQR)	2.6 (1.4 – 4.4)	2.3 (1.8 – 3.2)	0.782
Monocytes, (/mm^3), median (IQR)	405 (223 – 623)	435 (280 – 563)	0.917
Hemoglobin (g/dL), median (IQR)	**10.1 (9.2 – 11.8)**	**9.5 (7.5 – 10)**	**0.017**
Platelets (G/L), median (IQR)	137 (99 – 235)	94 (57 – 192)	0.079
R-IPSS >3.5, n (%)	12 (14)	1 (14)	0.527
Hematological treatment, n (%)	**22 (26)**	**7 (64)**	**0.031**
Progression to AML, n (%)	**7 (8)**	**3 (27)**	**0.089**
Follow-up (months)	23 (12 – 35)	14 (4 – 34)	0.193

1. Missing data. Abbreviations : AML: acute myeloid leukemia; IQR : interquartile range; MDS: myelodysplastic syndromes; MLD : multilineage dysplasia; R-IPSS : revised-international prognostic scoring system;.

Comparison of overall survival between MDS+/- ANCA vasculitis and MDS with and without renal involvement

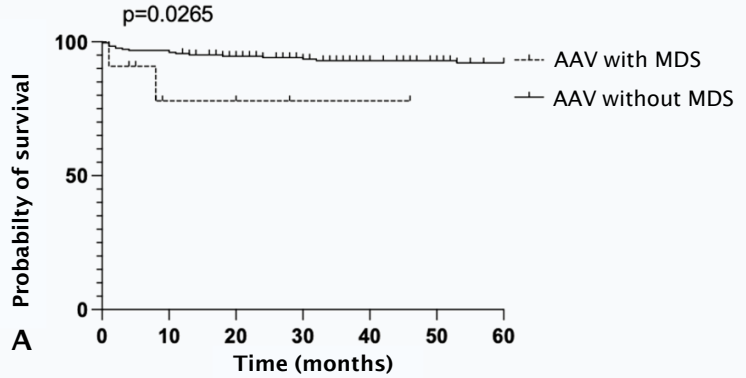


Figure A: Kaplan Meier analysis of overall survival comparing AAV with MDS (n=11) and AAV without MDS (n=265). Last follow-up represented at 5 years.
p = 0.0265. Log rank test

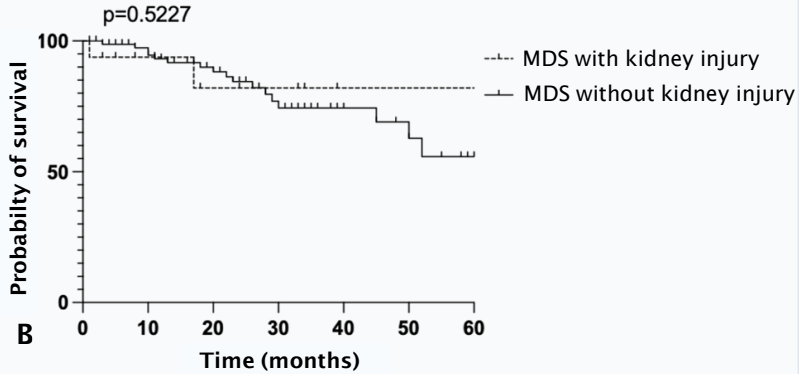


Figure B: Kaplan Meier analysis of overall survival comparing MDS with renal involvement (n=17) and control MDS (n=84). Last follow-up represented at 5 years.
p = 0.5227. Log rank test

Overall survival was significantly decreased in the MDS-associated AAV group compared with control AAV. There was no difference in overall survival between MDS with and without kidney injury (median survival 66 and 225 months, respectively).

Abbreviations: AAV: ANCA associated vasculitis; ANCA: antineutrophil cytoplasmic antibodies; MDS: myelodysplastic syndromes.

Summary

Characteristics of the CMML with kidney injury cohort (n=16)

General characteristics
- Age[1]: 76 years old (72 – 83)
- Gender: male (n=14, 87%)

Kidney presentation
- **AKI + tubular PU: 8 (53%)**
- Nephrotic syndrome: 3 (20%)
- RPGN: 2 (13%)

Extra-renal manifestations[2]
- **General signs: 4 (25%)**
- Purpura: 3 (19%)
- Intra-alveolar hemorrhage: 3 (19%)

Biological characteristics
- PU: 2 g/24h (1.25 – 3.4)
- Creatinine: 199 µmol/L (128 – 236)
- ANCA without specificity: 2/10

Renal diagnosis
- **Delay : 6 months [1.6-25.6]**
- **Lysozyme-induced nephropathy: 9 (56%)**
- **Myelomonocytic infiltrate: 6 (38%)**
- PAN: 1 (6%)
- Systemic vasculitis: 1 (6%)

Histology
- **14 (88%) kidney biopsies**
- **ATN: 4 (25%)**
- **Vacuoles within proximal tubules: 7 (44%)**
- **Lysozyme staining: 5/9**
- **Infiltrate: 9 (56%)**
  - MPO, CD68

Treatments
- Corticoids: 4 (25%)
- Azacitidine: 3 (19%)
- Hydroxyurea: 6 (38%)

1 Quantitative variables are expressed as median. 2. Each patient may have one or more of the following conditions. Abbreviations : AKI: acute kidney injury; ANCA: antineutrophil cytoplasmic antibodies; ATN: acute tubular necrosis; CMML: chronic myelomonocytic leukemia; PAN: polyarteritis nodosa; PU : proteinuria; RPGN: rapidly progressive glomerulonephritis.

Patients with CMML with renal injury have adverse prognostic markers

CMML	WITHOUT kidney injury n = 116	WITH kidney injury n = 16[1]	Univariate analysis p
Age, median (IQR)	77 (70 – 82)	75 (65 – 82)	0.359
CMML-0	**67 (58)**	**3 (25)**	**0.036**
0 dysplasia lineage	**63 (58)**	**0 (0)**	**0.001**
% Blasts bone marrow, median (IQR)	4 (2 – 7)	5 (3 – 10)	0.339
Abnormal karyotype, n (%)	31 (27)	2 (25)	1.000
Neutrophils (G/L), median (IQR)	5 (3 – 8.6)	5.9 (3.5 – 27)	0.297
Monocytes, (G/L), median (IQR)	**1.8 (1.3 – 2.8)**	**5 (3.6 – 10.8)**	**<0.001**
Hemoglobin (g/dL), median (IQR)	11.5 (9.9 – 13.3)	10 (9.2 – 11.6)	0.072
Platelets (G/L), median (IQR)	137 (77 – 218)	202 (149 – 267)	0.104
R-IPSS >3.5, n (%)	33 (28)	1 (20)	1.000
Hematological treatment, n (%)	**23 (20)**	**11 (85)**	**<0.001**
Progression to AML, n (%)	**8 (7)**	**4 (31)**	**0.020**
Follow-up (months)	21 (7 – 40)	35 (14 – 46)	0.174

1. Missing data. Abbreviations : AML: acute myeloid leukemia; CMML: chronic myelomonocytic leukemia; IQR : interquartile range; R-IPSS : revised-international prognostic scoring system.

Comparison of overall survival between CMML with and without kidney injury

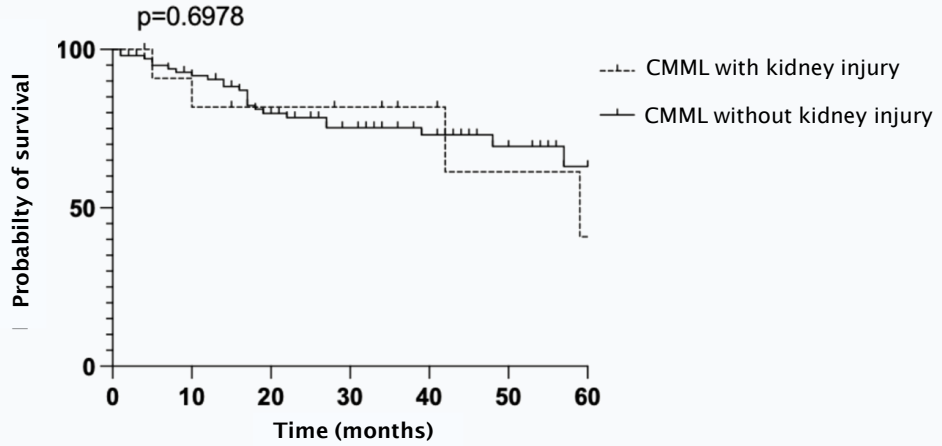


Figure : Kaplan Meier analysis of overall survival comparing CMML with kidney injury (n=16) and control CMML (n=116). Last follow-up represented at 5 years.
p = 0.6978.
Log rank test

There was no difference in overall survival between CMML patients with kidney injury and control CMML (median survival 59 months, and not reached, respectively).

Summary

Conclusion: MDS associated with kidney injury

- Kidney involvement associated with MDS is mainly **pauci-immune vasculitis ANCA±**
- Screening for MDS if AAV in **elderly**, with **skin lesions** or **ANCA negativity**
- In univariate analysis, **no overall survival difference between MDS with or without kidney injury**
- Limitations:
  - Retrospective study
  - Enrollment from a vasculitis cohort
- **Perspectives :**
  - **Re-reviewed kidney biopsies by an expert nephropathologist and compare them with control AAV**
  - **ANCA-: different local activation of neutrophils, potential role of the clone**

Conclusion: kidney involvement in CMML

- Kidney injuries associated with CMML are mainly:
  - **Lysozyme-induced nephropathy**
  - **Direct infiltration of myelomonocytic cells in the renal parenchyma**
- CMML with kidney injury have **adverse prognostic markers** (monocytes, CMML-0, dysplasia lineage number, progression to AML)
- Limitations :
  - Retrospective study
  - No reviewing of kidney biopsies by an expert nephropathologist
- **Perspectives :**
  - **NGS on kidney biopsies**
  - **Compare NGS with bone marrow/blood**

MDS/CMML: two related hematological diseases but with different kidney manifestations

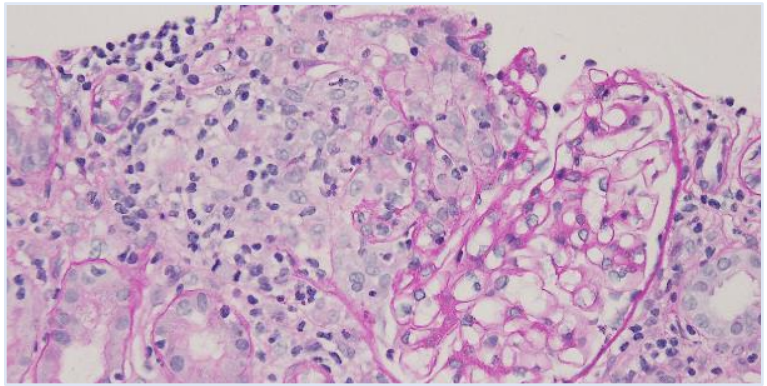


Figure : Haematoxylin-eosin. Proliferative focal glomerulonephritis
Courtesy of Dr. Helmut G. Rennke

Vasculitis: kidney as a target of autoimmunity
- **ANCA- , extra-renal manifestations**
- **MDS at high risk**

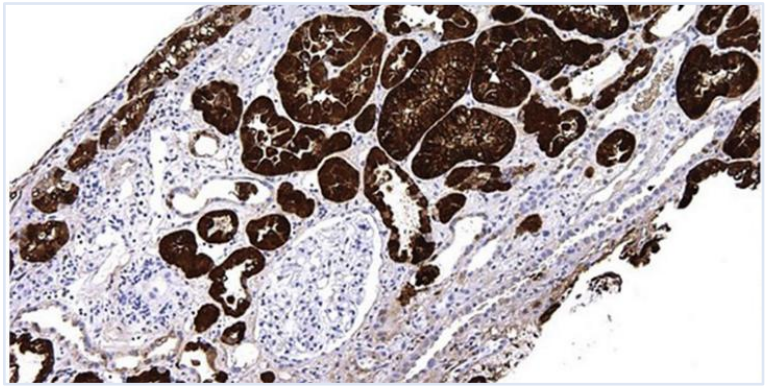


Figure : IHC staining with lysozyme showing intense granular reactivity in proximal tubular cells
Santoriello et al. Kidney Int Rep. 2016.

Storage disorders:
- **Lysozyme-induced nephropathy**: monocytosis risk factor
- **Direct infiltration of myelomonocytic cells** in the renal parenchyma

Abbreviations : IHC : immunohistochemistry; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndromes

Special thanks to

Groupe Francophone des Myélodysplasies, MINHEMON, French VEXAS group
CHU Saint-Antoine, Médecine interne: Pr Olivier Fain, Pr Arsène Mekinian
CHU Necker, Néphrologie, Anatomie pathologique: Dr Camille Cohen, Dr Hamza Sakhi, Dr Idris Boudhabhay, Pr Jean-Paul Duong Van Huyen, Dr Pierre Isnard
CHU Hôpital Européen Georges Pompidou: Pr Alexandre Karras
CHU Tenon, Néphrologie: Pr Jean-Jacques Boffa
CHU Grenoble-Alpes, Soins Intensifs: Dr Martin Carre
CHU Pitié Salpétrière, Néphrologie: Dr Lucile Mercadal
CHU Ambroise Paré, Néphrologie: Pr Marie Essig
CHU Angers, Hématologie: Dr Jonathan Farhi
AP-HM, Néphrologie: Dr Mickaël Bobot, Pr Noémie Jourde-Chiche, Pr Philippe Brunet
Oncopôle Toulouse, Médecine interne: Dr Thibault Comont
CHU Rennes, Néphrologie: Dr Hugoline Boulay, Dr Léonard Golbin, Dr Jonathan Chémouny, Dr Dorra Braham-Stambouli
CHU Clermont-Ferrand, Médecine interne, Néphrologie: Dr Vincent Grobost, Dr Carole Philipponnet
CHU Strasbourg, Médecine interne: Dr Juliette Jeannel
CH Valenciennes, Hématologie: Dr Nathalie Cambier
CH Le Mans, Hématologie: Dr Kamel Laribi
CHU Saint-Louis, Hématologie: Pr Lionel Adès, Pr Pierre Fenaux
Brigham and Women's Hospital, Massachusetts General Hospital: Dr Leonardo V. Riella, Dr Umut Selamet, Dr Helmut G. Rennke