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ORIGINAL ARTICLE

Histological characterization of liver involvement in systemic mastocytosis

Julien Rossignol[1] | Danielle Canioni[2] | Achille Aouba[3] | Cristina Bulai-Livideanu[4] | Stéphane Barete[5] | Charles Lancesseur[6] | Laura Polivka[1] | Marine Madrange[1] | Thomas Ballul[1] | Antoine Neuraz[7] | Celine Greco[1] | Julie Agopian[8,9] | Fabienne Brenet[8,9] | Patrice Dubreuil[8,9] | Richard Lemal[10] | Olivier Tournilhac[11] | Louis Terriou[12] | David Launay[12,13] | Laurence Bouillet[14] | Clément Gourguechon[15] | Laurent Frenzel[1] | Cécile Meni[1] | Caroline Gaudy-Marqueste[16] | Marie Gousseff[17] | Edwige Le Mouel[18] | Mohamed Hamidou[19] | Antoine Neel[19] | Dana Ranta[20] | Roland Jaussaud[21] | Philippe Guilpain[22] | Thierry J Molina[2] | Julie Bruneau[2] | Ludovic Lhermitte[23] | Nicolas Garcelon[24] | Rose-Marie Javier[25] | Fabien Pelletier[26] | Florence Castelain[26] | Frederique Retornaz[27] | Quentin Cabrera[28] | Patricia Zunic[28] | Marie Pierre Gourin[29] | Ewa Wierzbicka-Hainaut[30] | Jean François Viallard[31] | Christian Lavigne[32] | Cyrille Hoarau[33] | Isabelle Durieu[34] | Maël Heiblig[35] | Sophie Dimicoli-Salazar[36] | Jose M Torregrosa-Diaz[37] | Angèle Soria[38] | Michel Arock[39] | Olivier Lortholary[1,40] | Christine Bodemer[1] | Stanislas Pol[41] | Vincent Mallet[41] | Olivier Hermine[1] | Ghandi Damaj[6] | on behalf the CEREMAST Network

Correspondence
Ghandi Damaj, CEREMAST, Hematology Institute, Normandy University School of Medicine, Av. de la cote de Nacre, Caen, France.
Email: damaj-gl@chu-caen.fr

Olivier Hermine, CEREMAST, Necker Hospital, 149 rue de Sevres, Paris F-75015, France.
Email: ohermine@gmail.com

Abstract

Background and Aims: Systemic mastocytosis (SM) is characterized by the accumulation of atypical mast cells (MCs) in organs. Liver histology of SM has been marginally described and accurate histological classification is critical, given the consequences of aggressive SM diagnosis. We aimed to describe the histological features associated with liver SM using updated tools.

Methods: Using the database of the French Reference Centre for Mastocytosis, we retrospectively identified patients with a liver biopsy (LB) and a diagnosis of SM. All LB procedures were performed according to the local physician in charge and centrally reviewed by an expert pathologist.

Abbreviations: Adv-SM, advanced systemic mastocytosis; AFIRMM, Association for Research Initiatives on Mast Cells and Mastocytoses; ALP, alkaline phosphatase; ASM, aggressive systemic mastocytosis; BM, bone marrow; CEREMAST, *Centre de Reference des Mastocytoses* (French Mastocytosis Reference Center); CM, cutaneous mastocytosis; CRP, C-reactive protein; GI, gastro-intestinal; HPF, high-power field; ISM, indolent systemic mastocytosis; LB, liver biopsy; MCs, mast cells; NRH, nodular regenerative hyperplasia; NS, non-significant; OS, overall survival; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; SSM, smouldering systemic mastocytosis; TKI, Tyrosine kinase inhibitor; WBC, white blood cell; WHO, World Health Organization.

Julien Rossignol, Danielle Canioni Achille Aouba, Olivier Hermine and Ghandi Damaj are contributed equally.

For affiliations refer to page 1687.

Results: A total of 28 patients were included: 6 had indolent SM, 9 had aggressive SM, and 13 had SM with an associated hematologic neoplasm. Twenty-five (89%) patients presented hepatomegaly, and 19 (68%) had portal hypertension. The LB frequently showed slight sinusoid dilatation (82%). Fibrosis was observed in 3/6 indolent SM and in almost all advanced SM cases (21/22), but none of them showed cirrhosis. A high MC burden (>50 MCs/high-power field) was correlated with elevated blood alkaline phosphatase levels ($p = .030$). The presence of portal hypertension was associated with a higher mean fibrosis grade (1.6 vs. 0.8 in its absence; $p = .026$). In advanced SM, the presence of nodular regenerative hyperplasia (NRH) was associated with decreased overall survival (9.5 vs. 46.3 months, $p = .002$).

Conclusions: MC infiltration induced polymorphic hepatic lesions and the degree of fibrosis is associated with portal hypertension. NRH identifies a poor prognosis subgroup of patients with advanced SM. Assessing liver histology can aid in SM prognostic evaluation.

KEYWORDS

advanced systemic mastocytosis, fibrosis, liver, mast cells, nodular regenerative hyperplasia, portal hypertension

1 | INTRODUCTION

Mastocytosis corresponds to a heterogeneous spectrum of diseases characterized by the accumulation of neoplastic mast cells (MCs) in various organs.[1] The most commonly affected organs are the skin, the bone marrow (BM), and the gastrointestinal (GI) tract, whereas the liver is less commonly involved. The World Health Organization (WHO)'s mastocytosis classification distinguishes between cutaneous mastocytosis (CM), systemic mastocytosis (SM), and MC sarcoma.[2,3] Systemic mastocytosis is defined by the involvement of an organ other than the skin and can be classified as indolent (ISM), smouldering (SSM), aggressive (ASM), associated with other haematological neoplasms (SM-AHN), or MC leukaemia. The last three entities compose the advanced SM (Adv-SM) group. The diagnosis of SM subtypes is based on the degree of organ infiltration (B-findings) and dysfunction (C-findings). In the WHO classification, the so-called "B-findings" include a high MC burden, myeloproliferation, signs of dysplasia in a non–MC lineage (without meeting the criteria for haematological neoplasms), and organomegaly (including splenomegaly, hepatomegaly, and adenopathy) without organ impairment (when at least 2 B-findings and no C-findings are found, the final diagnosis is SSM). The so-called "C-findings" correspond to organ dysfunction; for the liver, they include hepatomegaly on palpation with the impairment of liver function, ascites, and/or portal hypertension (when at least one C-finding is found, the final diagnosis is ASM).

The histopathological features of mastocytosis in the skin and bone marrow have been extensively described and are included in the WHO classification of mastocytosis.[4–7]Although hepatic involvement can be a B-finding and/or a C-finding, depending on the presence or not of liver dysfunction, no histological data on mastocytosis-related hepatic lesions have been published recently.[8–12] Indeed, most histological studies were published before the introduction of the WHO classification and featured small numbers of patients (i.e. no more than 10 centrally reviewed patients with Adv-SM). A series reported by Mican et al. described the histopathological features of 10 Adv-SM (including 8 cases of SM-AHN), relative to those observed in 17 patients with ISM or CM. These authors found common MC infiltration, which was more severe in advanced diseases. In addition, they observed correlations between MC infiltration, the blood alkaline phosphatase (ALP) level, and liver fibrosis. However, they did not use immunohistochemistry to accurately study the infiltration by immune cells (including MCs) or MC CD25/CD30 expression and did not address the histological-clinical correlations with hepatic C-findings.

Key points

Mastocytosis is a rare disease of an immune cell called a mast cell. Some forms of mastocytosis can affect the liver and may considerably reduce life expectancy. Our study investigates the characteristics of liver biopsies from patients with hepatic mastocytosis. We report hepatic features associated with ascites and one particular abnormality (nodular regenerative hyperplasia) reduces dramatically patients' life expectancy. Liver biopsy may be a useful tool in deciding the management of a subset of mastocytosis patients.

Given that (i) SM is a rare cause of liver dysfunction and (ii) specific histological characterization should help the pathologist to distinguish between SM (especially its aggressive forms) and other more frequent diagnoses of hepatomegaly and cirrhosis, we decided to characterize the histological features of the hepatic lesions associated with SM. We also studied the consequences of MC infiltration on clinical and laboratory variables and evaluated the histopathological features associated with the WHO classification, liver C-findings, and outcomes.

2 | PATIENTS AND METHODS

We used the database curated by the French nationwide network of mastocytosis reference centers (CEREMAST) to identify adult patients with a confirmed diagnosis of SM (according to the WHO 2016 classification) and an available liver biopsy. The database was registered with French National Data Protection Commission (*Commission nationale de l'informatique et des libertés* (Paris, France)); reference: 1445939, dated 29 October 2010). All identified patients had participated in the "Association for Research Initiatives on Mast Cells and Mastocytoses" (AFIRMM) study, which had been approved by the local investigational review board (*Comité de Protection des Personnes Ile-de-France*, *Pitié-Salpétrière*, Paris, France; reference: 93–00) in accordance with the Declaration of Helsinki. The CEREMAST centers were contacted and asked to provide the patients' clinical data and outcomes. In a detailed review, we checked for all possible confounding factors for abnormal hepatic features, including alcohol abuse, hepatitis B or C, chronic heart failure, autoimmune, and/or granulomatosis diseases with a hepatitis component, storage/metabolic diseases (such as hemochromatosis, Wilson disease, amyloidosis, glycogenosis, lysosomal diseases, and obesity/metabolic syndrome), and hereditary or iatrogenic causes of liver disease. None of these conditions was considered to be a significant, a sole cause of liver function impairment. The diagnosis of portal hypertension was made by doppler ultrasonography.

Overall, 28 patients were included in this study, and all the liver biopsies (LBs) were reviewed centrally by the same CEREMAST pathologist (DC, Figure 1). The liver biopsies were performed between December 1999 and March 2016. Confounding factors for abnormal liver characteristics were investigated and are described in the online repository. Each formalin-fixed biopsy was stained

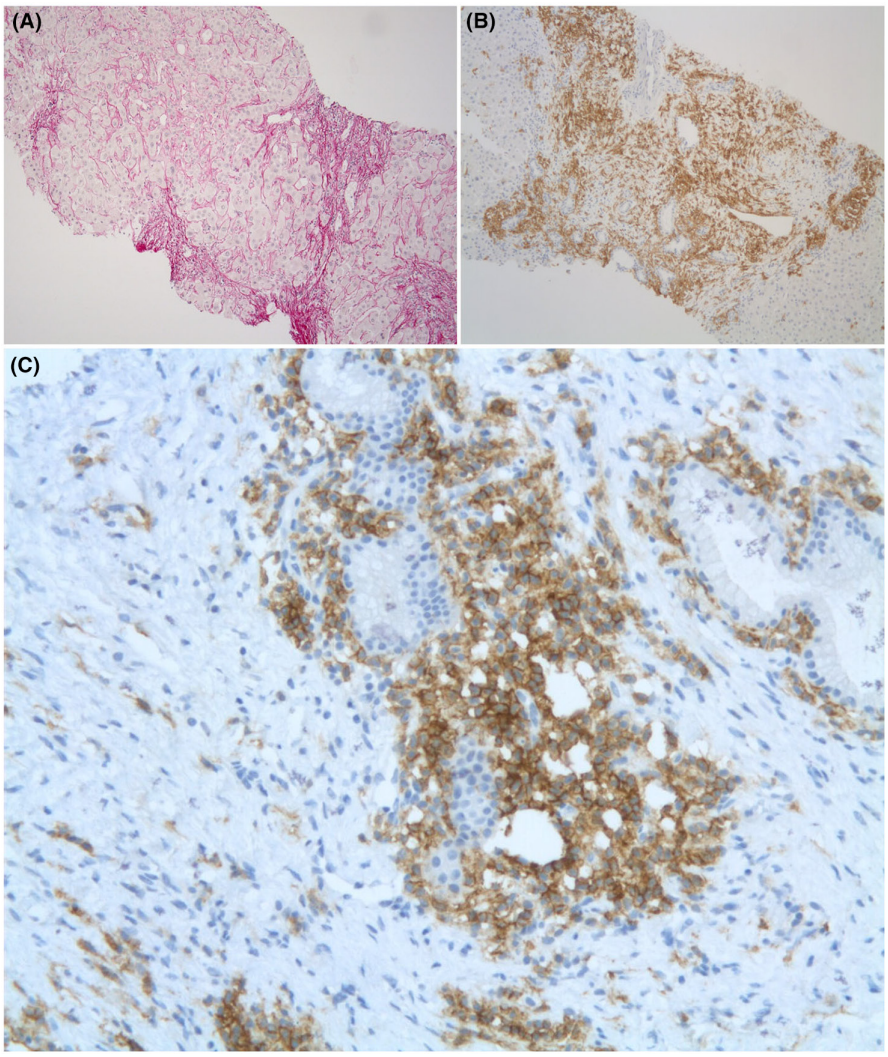

FIGURE 1 Hepatic histological features of systemic mastocytosis. (A) Grade 2 fibrosis (formalin-fixed biopsy was stained with Red Sirius, ×100 magnification). (B) High mast cell infiltration in the liver (formalin-fixed biopsy was stained anti-CD117 antibody, ×100 magnification). (C) CD30-positive mast cells (formalin-fixed biopsy was stained anti-CD30 antibody, ×200 magnification).

with haematoxylin–eosin, standard liver stains (Gordon-Sweet, Red Sirius, Masson trichrome, and Perls), and immunohistochemical reagents (anti-CD117 (c-kit), -tryptase, -CD25, and -CD30 antibodies).

For all LBs, we evaluated specific hepatic lesions: cirrhosis, fibrosis (according to the Metavir score),[13] portal or sinusoidal infiltration by lymphocytes or other cells, abnormal biliary ducts, hepatocyte necrosis, sinusoidal dilatation, cholestasis, or siderosis. The degree of MC infiltration was assessed with anti-c-kit or -tryptase antibodies and the number of MCs was counted on high-power field (HPF) (×40) for each LB. Overall survival (OS) analysis was considered from the date of liver biopsy to date of death or last visit. Statistical analyses were performed using the GraphPad Prism software (version 6.0; GraphPad Software, Inc, La Jolla, CA, USA). Groups were compared using Student's *t* test, a chi-squared test, or Fisher's exact test, as appropriate. Data were expressed as the mean, median [interquartile range], or median (range). OS probabilities were estimated using the Kaplan–Meier method and compared using the log-rank test. The threshold for statistical significance was set to $p < .05$.

3 | RESULTS

The median age at diagnosis was 65 years, and 82% of the patients were male. The median (range) time interval between the diagnosis of SM and the LB was 3 (0–15.5) months. At the time of the LB, 9 (32%) patients had ASM, 13 (46%) had SM-AHN, and 6 (21%) had ISM (Table 1). Patients with Adv-SM were older than those with ISM (median age: 67 vs. 42, respectively; $p = .002$). Twenty-seven patients (96%) had B-findings and 22 (79%) had C-findings. Twenty-five (89%) patients had hepatomegaly, 19 (68%) had splenomegaly, and 17 (61%) had both. Signs of portal hypertension (ascites and/or collateral venous circulation) and oesophageal varices were found in 19 (68%) and 4 (14%) patients, respectively.

At the time of the LB, 20 (71%) patients had abnormal serum liver function tests, including 5 (18%) with elevated transaminase levels (mean 1.7N [1.2–2.3]), 20 (71%) with elevated gamma-glutamyl transferase (median 3N [1.1–55]), 20 (71%) with an elevated ALP level (median 2.7N [1.1–19]), and 8 (29%) with an elevated total bilirubin level (median 1.6N [1.1–3.5]). Fourteen of 25 (56%) patients

TABLE 1 Clinical and laboratory data for the study cohort, overall, and as a function of the type of SM.

	Overall	ISM	ASM	SM-AHN
N	28	6	9	13
B-findings (*n* (%))	27 (96.4)	5 (83.3)	9 (100.0)	13 (100.0)
C-findings (*n* (%))	22 (78.6)	0 (0.0)	9 (100.0)	13 (100.0)
Portal hypertension (*n* (%))	19 (67.9)	1 (16.7)	8 (88.9)	10 (76.9)
Hepatomegaly (*n* (%))	25 (89.3)	3 (50.0)	9 (100.0)	13 (100.0)
Lymphadenopathy (*n* (%))	13 (46.4)	2 (33.3)	3 (33.3)	8 (61.5)
Weight loss >10% in the last 3 months (*n* (%))	23 (82.1)	1 (16.7)	9 (100.0)	13 (100.0)
Spider angioma (*n* (%))	2 (7.1)	0 (0.0)	0 (0.0)	2 (15.4)
Splenomegaly (*n* (%))	19 (67.9)	2 (33.3)	6 (66.7)	11 (84.6)
Albumin, g/L (mean (SD)) Normal values: 39.2–51.7	34.12 (7.35)	44.62 (3.90)	30.34 (6.46)	33.46 (5.57)
Albumin <34 g/dL (*n* (%))	14 (56.0)	0 (0.0)	7 (77.8)	7 (58.3)
Fibrinogen g/L (mean (SD)) Normal values: 2.0–4.0	3.28 (0.97)	2.98 (0.59)	3.00 (0.82)	3.50 (1.13)
CRP, mg/L (mean (SD)) Normal values: <6.0	25.85 (31.43)	50.58 (67.09)	21.50 (17.84)	19.00 (12.00)
Transaminase ×*N* (mean (SD))	1.13 (0.32)	1.04 (0.10)	1.32 (0.49)	1.04 (0.14)
Alkaline phosphatase level ×*N* (mean (SD))	3.42 (4.31)	0.93 (0.21)	4.85 (4.52)	3.58 (4.86)
Gamma-glutamyl transferase ×*N* (mean (SD))	6.50 (13.22)	1.42 (1.28)	11.60 (18.57)	5.32 (11.34)
Total bilirubin ×*N* (mean (SD))	1.22 (0.56)	1.07 (0.33)	1.14 (0.33)	1.36 (0.75)
Prothrombin ratio, % (mean (SD)) Normal values: 70–100	66.42 (15.46)	88.20 (16.16)	60.00 (6.11)	61.08 (10.57)
Serum tryptase, µg/L (mean (SD)) Normal values: <11.4	279.52 (249.24)	93.52 (70.06)	318.33 (174.90)	338.51 (308.44)
Haemoglobin, g/dL (mean (SD))	11.16 (2.02)	14.08 (1.17)	10.53 (0.98)	10.25 (1.57)
Platelet count, G/L (mean (SD))	176.75 (149.11)	221.67 (83.47)	188.67 (182.27)	147.77 (151.48)
WBC count, G/L (mean (SD))	12.19 (9.33)	7.37 (2.84)	10.76 (3.86)	15.40 (12.58)

Abbreviations: ASM, aggressive systemic mastocytosis; ISM, indolent systemic mastocytosis; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; WBC, white blood cell; ×*N*, times upper limit of normal value.

had low albuminemia (median 32.5 g/L [17–33]) and 16 (64%) had a low prothrombin ratio (median 65% [49%–69%]); all of these patients had ASM or SM-AHN.

In 5 of the 28 patients, the LB revealed a low degree of MC infiltration (1–5 MCs/HPF) (Table 2). The degree of MC infiltration was mild (>5 to ≤30 MCs/HPF) in 6 of the 28 patients, moderate (>30 to ≤80 MCs/HPF) in 11, and severe (>80 MCs/HPF) in 6. The mean MC infiltration was 17.5/HPF, 60.0/HPF and 64.1/HPF in patients with ISM, ASM, and SM-AHN, respectively. There was a non-significant trend towards a higher MC count in SM-AHN (64.1/HPF) than in ISM (17.5/HPF; $p = .053$). Twenty of the 23 infiltrated LBs (>5 MCs/HPF) contained both spindle-shaped MCs and monocytoid MCs. The MCs were usually found in portal tracts (19 out of 23) and were sometimes distributed around or in bile ducts ($n = 10$) or around vessels ($n = 4$). In all the samples, the MCs were positive for CD25, and CD30 expression by MCs was observed in 5 patients with Adv-SM (Figure 1). A high MC burden (≥50 MCs/ HPF) was significantly associated with an elevated ALP level ($p = .030$) and CD30 positivity ($p = .028$, Table 3). A slight infiltration by lymphocytes was common (22/26, 84.6%), while infiltration by eosinophils was only observed in 6/26 (23.1%) patients.

Although histological cholestasis was seen in only 3 LBs, sinusoidal dilatation was frequent (23 out of 28) but severe in only 5 cases. Nodular regenerative hyperplasia (NRH) was seen in 5 LBs, including in 4 patients with Adv-SM. The area of fibrosis did not have histological signs of cirrhosis. Overall, 24 of the 28 LBs showed fibrosis, including 9/24 (37.5%) perisinusoidal fibrosis and 4 with high-grade (stage 3) fibrosis. Cirrhosis was not observed in any of

TABLE 2 Histopathological findings in liver biopsies from patients with SM.

	Overall	ISM	ASM	SM-AHN
N	28	6	9	13
Number of MCs/HPF (mean (SD))	52.79 (51.00)	17.50 (15.36)	60.00 (56.73)	64.08 (53.00)
MC infiltration/HPF (*n* (%))				
<5	5 (17.9)	2 (33.3)	2 (22.2)	1 (7.7)
5–30	6 (21.4)	3 (50.0)	0 (0.0)	3 (23.1)
30–80	11 (39.3)	1 (16.7)	5 (55.6)	5 (38.5)
>80	6 (21.4)	0 (0.0)	2 (22.2)	4 (30.8)
Interstitial MCs (*n* (%))	24 (88.9)	5 (100.0)	8 (88.9)	11 (84.6)
MC morphology (*n* (%))				
Spindle-shaped > monocytoid	12 (44.4)	3 (60.0)	4 (44.4)	5 (38.5)
Spindle-shaped = monocytoid	8 (29.6)	1 (20.0)	3 (33.3)	4 (30.8)
Spindle-shaped < monocytoid	7 (25.9)	1 (20.0)	2 (22.2)	4 (30.8)
Periductal MC sites	13 (48.1)	2 (40.0)	4 (44.4)	7 (53.8)
Perivascular MC sites	6 (22.2)	2 (40.0)	1 (11.1)	3 (23.1)
CD30-positive MCs	5 (20.8)	0 (0.0)	2 (22.2)	3 (27.3)
CD25-positive MCs	28 (100)	6 (100)	9 (100)	13 (100)
Lymphocyte infiltration (*n* (%))	22 (84.6)	4 (66.7)	5 (71.4)	13 (100.0)
Eosinophil infiltration (*n* (%))	6 (23.1)	0 (0.0)	2 (28.6)	4 (30.8)
Abnormally high number of biliary ducts (*n* (%))	10 (37.0)	1 (20.0)	3 (33.3)	6 (46.2)
Abnormal biliary ducts (*n* (%))	12 (44.4)	2 (40.0)	4 (44.4)	6 (46.2)
Sinusoid dilatation (*n* (%))	23 (82.1)	5 (83.3)	6 (66.7)	12 (92.3)
Nodular regenerative hyperplasia (*n* (%))	5 (19.2)	1 (16.7)	2 (28.6)	2 (15.4)
Stained by Perls' reagent (*n* (%))	5 (33.3)	1 (50.0)	1 (16.7)	3 (42.9)
Cirrhosis (*n* (%))	0 (0)	0 (0)	0 (0)	0 (0)
Fibrosis (*n* (%))	24 (85.7)	3 (50.0)	8 (88.9)	13 (100.0)
Fibrosis stage (*n* (%))				
0	4 (7.1)	3 (50.0)	1 (11.1)	0 (0.0)
1	18 (64.3)	2 (33.3)	5 (55.5)	8 (61.5)
2	4 (14.3)	1 (16.7)	1 (11.1)	3 (23.1)
3	4 (14.3)	0 (0.0)	2 (22.2)	2 (15.4)

Abbreviations: ASM, aggressive systemic mastocytosis; HPF, high-power field; ISM, indolent systemic mastocytosis; MC, mast cell; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.

TABLE 3 Clinical, histologica,l and laboratory data as a function of hepatic MC infiltration.

	Overall	Low MC count (<50/HPF)	High MC counts (≥50/HPF)	*p*
N	28	19	9	
Advanced SM (%)	22 (78.6)	13 (68.4)	9 (100.0)	ns
Hepatomegaly (%)	25 (89.3)	16 (84.2)	9 (100.0)	ns
Hepatic C-findings (%)	19 (67.9)	12 (63.2)	7 (77.8)	ns
Albumin, g/L (mean) Normal values: 39.2–51.7	34.12	36.15	30.52	ns
Fibrinogen, g/L (mean) Normal values: 2.0–4.0	3.28	3.43	2.97	ns
CRP, mg/L (mean) Normal values: <6.0	25.85	30.52	18.5	ns
Transaminase ×*N* (mean)	1.13	1.10	1.18	ns
Alkaline phosphatase level ×*N* (mean)	3.42	2.22	5.95	.030
Gamma-glutamyl transferase ×*N* (mean)	6.50	4.88	9.92	ns
Total bilirubin ×*N* (mean)	1.22	1.19	1.3	ns
Prothrombin ratio, % (mean) Normal values: 70–100	66.42	65.44	68.38	ns
Serum tryptase, µg/L (mean) Normal values: <11.4	279.52	257.5	326.0	ns
CD30-positive MCs (%)	5 (20.8)	1 (6.25)	4 (50.0)	.028
Lymphocyte infiltration (%)	22 (84.6)	15 (83.3)	7 (87.5)	ns
Eosinophil infiltration (%)	6 (23.1)	2 (11.1)	4 (50.0)	ns
Abnormally high number of biliary ducts (%)	18 (66.7)	10 (55.6)	8 (88.9)	ns
Abnormal biliary ducts (%)	12 (44.4)	6 (33.3)	6 (66.7)	ns
Sinusoid dilatation (%)	23 (82.1)	15 (78.9)	8 (88.9)	ns
Nodular regenerative hyperplasia (%)	5 (17.9)	5 (26.3)	0 (0.0)	ns
Fibrosis stage (mean)	1.32	1.11	1.78	ns

Abbreviations: CRP, C-reactive protein; HPF, high-power field; MC, mast cell; ns, non-significant; SM, systemic mastocytosis; ×*N*, times upper limit of normal value.

the patients. When compared patients with vs. without C-findings, we observed a non-significant association between the presence of hepatic C-findings and the degree of mast cell infiltration ($p = .08$) (Table 4). The only marker significantly associated with the presence of hepatic C-findings was the severity of fibrosis (mean fibrosis stage: 1.6 vs. 0.8 in the absence of hepatic C-findings; $p = .026$). Finally, we have investigated hepatic histological features regarding OS in Adv-SM (Table 5). Abnormal biliary ducts were associated with better outcomes (83.1 vs. 20.2 months, $p = .018$) and the presence of NRH was associated with a poor prognosis, both at diagnosis (16.7 vs. 49.9 months, $p = .035$) and at liver biopsy (9.5 vs. 46.3 months, $p = .002$, Figure 2).

4 | DISCUSSION

Adv-SM is a rare cause of non-cirrhotic portal hypertension; hence, specific histological and immunohistochemical characterization is essential to distinguish between SM and other, more frequent etiologies of cirrhosis. This study is the first to have provided a detailed histological description of liver involvement in Adv-SM and to have assessed correlations between histological features on one hand and clinical and laboratory variables on the other hand. We observed correlations between CD30 expression by MCs, the blood ALP level, and the degree of MC infiltration. As blood ALP levels have already been linked to a poor outcome in SM, our observation suggests that the MC liver burden may be a prognostic marker.[14,15]

Previous studies have investigated the features of LBs from patients with SM.[8–12] As we observed, most of these studies reported a high MC infiltrate in the liver in general and in the portal tract in particular. In contrast to the frequently observed fibrosis, cirrhosis was rare or absent. Our result confirmed the high prevalence of liver fibrosis in SM but also highlighted a correlation between the severity of fibrosis and the presence of hepatic C-finding. The presence of this correlation suggests that fibrosis is pathophysiologically involved in portal hypertension.

Finally, we found a significant decrease in the OS of Adv-SM patients with NRH. Interestingly, NRH have been previously reported in LB from patients with mastocytosis. Indeed, Mican et al[11] have found NRH associated with fibrosis in 4/5 patients with mastocytosis

TABLE 4 Histological features, according to the presence or absence of hepatic C-findings.

	Hepatic – findings	No hepatic C-findings	*p*
N	19	9	
Number of MCs/HPF (mean (SD))	64,4	28,3	ns
Interstitial MCs (*n* (%))	16/19 (84)	8/8 (100)	ns
Periductal MC sites (*n* (%))	8/19 (42)	5/8 (63)	ns
Perivascular MC sites (*n* (%))	3/19 (16)	3/8 (38)	ns
CD30-positive MCs (*n* (%))	5/17 (29)	0/7 (0)	ns
Lymphocyte infiltration (*n* (%))	16/18 (89)	6/8 (75)	ns
Eosinophil infiltration (*n* (%))	5/18 (28)	1/8 (13)	ns
Abnormally high number of biliary ducts (*n* (%))	13/19 (68)	5/8 (63)	ns
Abnormal biliary ducts (*n* (%))	10/19 (53)	2/8 (25)	ns
Sinusoid dilatation (*n* (%))	15/19 (79)	8/9 (89)	ns
Nodular regenerative hyperplasia (*n* (%))	4/19 (21)	1/9 (11)	ns
Fibrosis stage (mean (SD))	1.6	0.8	.026

Abbreviations: HPF, high-power field; MC, mast cell; ns, non-significant.

TABLE 5 Overall survival according to hepatic histological features in advanced SM patients.

	N positive (%)	Median OS: positive versus negative (months)	*p* (log rank)
Number of MCs ≥ 50/HPF	9/22 (40.9%)	55.8 versus 25.4	ns
Abnormal biliary ducts	10/22 (45.5%)	83.1 versus 20.2	.018
CD30-positive MCs	5/20 (25.0%)	90.6 versus 25.4	ns
Nodular regenerative hyperplasia	4/22 (18.2%)	9.5 versus 46.3	.001
Fibrosis stage ≥2	8/22 (36.4%)	31.1 versus 27.8	ns

Note: OS analysis was considered from the date of liver biopsy to date of death or last visit. OS probabilities were compared using the log-rank test.
Abbreviations: HPF, high-power field; MC, mast cell; ns, non-significant; OS, overall survival.

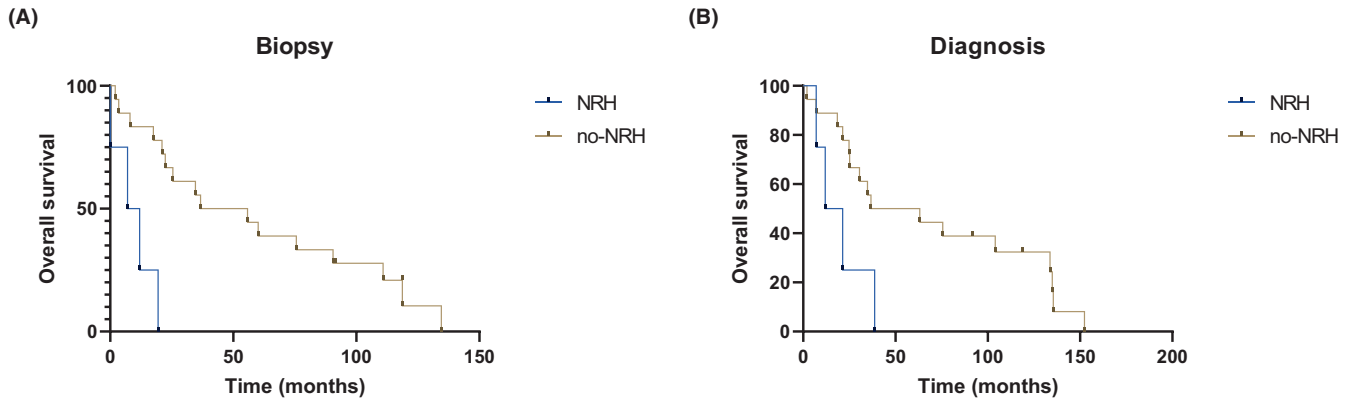

FIGURE 2 Overall survival according to the presence of nodular regenerative hyperplasia on LB in patients with Adv-SM. (A) Time from LB. Nodular regenerative hyperplasia was associated with decreased overall survival (9.5 vs. 46.3 months, $p = .002$). (B) Time from diagnosis. Nodular regenerative hyperplasia was associated with decreased overall survival (16.7 vs. 49.92 months, $p = .035$). OS probabilities were estimated using the Kaplan–Meier method and compared using the log-rank test. NRH: nodular regenerative hyperplasia.

and portal hypertension. Taking as the whole, NRH is associated with advanced SM and may be involved, together with fibrosis, in portal hypertension occurrence in Adv-SM patients. In addition, NRH identifies a specific poor prognosis subgroup of patients with Adv-SM; clinical studies, including allogenous haematopoietic stem cells transplantation, are critically needed to optimize the management of this specific population. Therefore, LB should be considered in Adv-SM patients with portal hypertension to assess the staging of liver involvement, including NRH presence. On the other hand, our

results suggest that SM should be assessed in patients with unexplained NRH, especially with signs of portal hypertension.

The management of advanced SM has been greatly improved with the approval of tyrosine kinase inhibitors (TKI) targeting the KIT D816V mutation (i.e. midostaurin and avapritinib). Phase II clinical trials highlighted that signs of liver dysfunction were responsive to treatment (including ascites and alkaline phosphatase levels).[16,17] In addition, a recent study has shown that the severity of liver fibrosis may decrease with TKI.[18] Interestingly, the authors analysed fibrosis in 2 patients using magnetic resonance elastography and repeated liver biopsies and the results appeared to be consistent between the two procedures. Magnetic resonance elastography may therefore be a tool for assessing liver stiffness and the degree of fibrosis in patients with advanced SM on therapy.

In conclusion, the hepatic lesions induced by MC infiltration are polymorphic and include abnormal biliary ducts, sinusoid dilatation, and fibrosis (the latter being associated with liver C-findings). The poor prognosis associated with NRH in advanced MS may argue for early intervention with dose-adapted kinase inhibitors and allogenous stem cell transplantation should be discussed if feasible in this context.

AUTHOR CONTRIBUTIONS

Julien Rossignol analysed the data and wrote the manuscript. D.C. reviewed all the liver biopsies, designed the study, supervised the overall project, analysed the data, edited, and approved the final version of the manuscript. Achille Aouba, Cristina Bulai-Livideanu, Stéphane Barete, Charles Lancesseur, Laura Polivka, Marine Madrange, Thomas Ballul, Antoine Neuraz, Celine Greco, Julie Agopian, Fabienne Brenet, Patrice Dubreuil, Richard Lemal, Olivier Tournilhac, Louis Terriou, David Launay, Laurence Bouillet, Clément Gourguechon, Laurent Frenzel, Cécile Meni, Caroline Gaudy-Marqueste, Marie Gousseff, Edwige Le Mouel, Mohamed Hamidou, Antoine Neel, Dana Ranta, Roland Jaussaud, Philippe Guilpain, Thierry J Molina, Julie Bruneau, Ludovic Lhermitte, Nicolas Garcelon, Rose-Marie Javier, Fabien Pelletier, Florence Castelain, Frederique Retornaz, Quentin Cabrera, Patricia Zunic, Marie Pierre Gourin, Ewa Wierzbicka–Hainaut, Jean François Viallard, Christian Lavigne, Cyrille Hoarau, Isabelle Durieu, Maël Heiblig, Sophie Dimicoli-Salazar, Jose M Torregrosa-Diaz, Angèle Soria, Michel Arock, Olivier Lortholary, Christine Bodemer, Stanislas Pol and Vincent Mallet helped to write the manuscript, to identify patients, and to collect clinical data. Olivier Hermine and Ghandi Damaj designed the study, supervised the overall project, analysed the data, edited, and approved the final version of the manuscript.

AFFILIATIONS

[1]CEREMAST, Imagine Institute, INSERM U1163, AP-HP, Necker Children's Hospital, Paris Centre University, Paris, France
[2]CEREMAST, Department of Pathology, Necker Children's Hospital, AP-HP, Paris Centre University, Paris, France
[3]Department of Internal Medicine, Normandy University School of Medicine, Caen, France
[4]CEREMAST, Department of Dermatology, Hôpital Larrey, CHU Toulouse, Toulouse, France
[5]CEREMAST, Dermatology Department, Pitié-Salpêtrière Hospital, AP-HP, Paris, France
[6]CEREMAST, Hematology Institute, Normandy University School of Medicine, Caen, France
[7]Department of Bioinformatics, Necker Children's Hospital, AP-HP, Paris Centre University, Imagine Institute, INSERM U1163, Paris, France
[8]Centre de Recherche en Cancérologie de Marseille, INSERM U1068, Marseille, France
[9]Association Française pour les Initiatives de Recherche sur le Mastocyte et les Mastocytoses (AFIRMM), Marseille, France
[10]Histocompatibility Laboratory, EA 7453—Université Clermont Auvergne, CHU de Clermont-Ferrand, Clermont-Ferrand, France
[11]CEREMAST, Adult Clinical Hematology, CHU Clermont-Ferrand, INSERM CIC501, EA 7453 – Clermont Auvergne University, Clermont-Ferrand, France
[12]CEREMAST, Department of Internal Medicine and Clinical Immunology, CHU Lille, Lille, France
[13]Lille University, INSERM U1286 INFINITE, CHU Lille, Lille, France
[14]CEREMAST, Clinical Immunology/Internal Medicine Department, National Reference Center for Angioedema, Grenoble University Hospital, Grenoble, France
[15]Department of Hematology, Amiens University Hospital, Amiens, France
[16]CEREMAST, Department of Dermatology, Aix-Marseille University, CHU Timone, Marseille, France
[17]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique, Vannes, France
[18]CEREMAST, Department of Internal Medicine and Clinical Immunology, Rennes University Hospital, Rennes, France
[19]CEREMAST, Department of Internal Medicine, Hôtel-Dieu University Hospital, Nantes, France
[20]Department of Hematology, Nancy University Hospital, Nancy, France
[21]Department of Internal Medicine and Clinical Immunology, Nancy University Hospital, Vandoeuvre-lès-Nancy, France
[22]CEREMAST, Department of Internal Medicine-Multi-organ Diseases, Saint-Eloi University Hospital, Montpellier University, Montpellier, France
[23]CEREMAST, Laboratory of Onco-Hematology, Necker Children's Hospital, APHP, Paris, France
[24]Paris Centre University, Imagine Institute, Data Science Platform, INSERM UMR 1163, Paris, France
[25]CEREMAST, Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France
[26]CEREMAST, Department of Dermatology, Allergology Unit, University Hospital of Besançon, Besançon, France
[27]Unité de soins et de recherche en médecine interne et maladies infectieuses, European Hospital, Marseille, France
[28]Department of Haematology, Sud Reunion University Hospital, Saint Pierre, La Réunion, France
[29]CEREMAST, Department of Hematology, CHU Dupuytren, Limoges, France
[30]CEREMAST, Department of Dermatology, CHU de Poitiers, Poitiers, France
[31]Department of Internal Medicine and Infectious Diseases, Haut-Lévêque Hospital, CHRU Bordeaux, Bordeaux University, Bordeaux, France
[32]CEREMAST, Department of Internal Medicine and Clinical Immunology, University Hospital, Angers, France
[33]CEREMAST, Service d'Immunologie Clinique et d'Allergologie, Centre Hospitalier Régional Universitaire, Tours, France
[34]CEREMAST, Department of Internal Medicine, Adult Cystic Fibrosis Care Center, Hospices Civils de Lyon, Lyon, France
[35]CEREMAST, Department of Hematology, Lyon-Sud Hospital, Hospices Civils de Lyon, Pierre-Bénite, France
[36]Department of Hematology, CHU de Bordeaux, Bordeaux, France
[37]Department of Hematology, CHU de Poitiers, Poitiers, France
[38]CEREMAST, Department of Dermatology and Allergy, Tenon Hospital, Sorbonne University, Paris, France
[39]CEREMAST, Laboratory of Hematology, Pitié-Salpêtrière Hospital, AP-HP, Paris, France
[40]Infectious and Tropical Diseases Department, Necker-Pasteur Infectiology Center, AP-HP, Necker Children's Hospital, Paris Centre University, Paris, France

[41]AP-HP.Centre Université Paris Centre, Groupe Hospitalier Cochin Port Royal, DMU Cancérologie et spécialités médico-chirurgicales, Service d'Hépatologie, Paris, France

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CONFLICT OF INTEREST STATEMENT

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All patients had participated in the "Association for Research Initiatives on Mast Cells and Mastocytoses" (AFIRMM) study, which had been approved by the local investigational review board (Comité de Protection des Personnes Ile-de-France, Pitié-Salpétrière, Paris, France; reference: 93–00) in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

All patients provided their written, informed consent.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No materials from other sources have been reported in this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon request.

ORCID

Julien Rossignol https://orcid.org/0000-0003-3052-1424
Richard Lemal https://orcid.org/0000-0002-5767-1628
Vincent Mallet https://orcid.org/0000-0003-2219-9201

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