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Coincidence or Connection? Revisiting the Relationship Between Mastocytosis and Lymphoma

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To the editor.

Mastocytosis is a clonal hematologic neoplasm characterised by the proliferation and accumulation of neoplastic mast cells in one or more organs.[1] Approximately 20-30% of patients with SM present with an associated hematologic neoplasm (SM-AHN).[2] The vast majority of these associations involve myeloid malignancies, including myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML), and acute myeloid leukaemia (AML).[1,2] The prognosis of SM associated with myeloid neoplasms (SM-AMN) is significantly worse than indolent forms of SM (ISM), with a median overall survival of 2 years compared to 24 years for ISM.[3] In stark contrast to the well-documented association with myeloid neoplasms, the concurrent occurrence of SM with lymphoproliferative disorders is exceedingly rare. The published literature consists primarily of isolated case reports describing SM associated with various lymphoma subtypes, including chronic lymphocytic leukaemia (CLL) and marginal zone lymphoma (MZL).[4–10] Given the paucity of reported cases, the clinical characteristics, biological behaviour, therapeutic strategies, and prognostic implications of SM associated with lymphoproliferative disorders remain poorly defined. We conducted a retrospective analysis of patients diagnosed with both SM and lymphoma at our institutions to describe their clinical and laboratory characteristics, evaluate the distribution of lymphoma subtypes, analyse the temporal relationship between diagnoses, assess treatment approaches and outcomes, and compare our findings with the limited available literature.

Results

Overall Cohort Characteristics. Between 2015 and 2025, we identified 9 patients in our centres who met the diagnostic criteria for both mastocytosis and lymphoma according to the WHO 2022 classification (**Table 1**). The cohort consisted of 6 males (66.7%) and 3 females (33.3%), with a median age at diagnosis of 56 years (range: 53-79).

Most patients (n=8) presented with ISM, while only one patient had ASM. Cutaneous involvement with urticaria pigmentosa was documented in 3 patients (33.3%). The KIT D816V mutation status was available for 9 patients, of whom 88.9% tested positive. Median baseline serum tryptase was 79 ng/mL (range: 9.77–247) across all patients. Regarding mast cell-related symptoms and complications, 1 patient reported a history of severe allergic reactions, including anaphylactic shock requiring emergency intervention. Skeletal involvement was common, with 4 patients (44.4%) diagnosed with osteoporosis based on DEXA scan findings. Only one patient required specific treatment for mastocytosis due to the presence of C-findings (osteolytic vertebral lesion with risk of pathological fracture). This patient received Midostaurin, achieving stable disease without complete remission of the mast cell component. The remaining patients with ISM were managed conservatively with antihistamines and observation. The lymphoproliferative disorders identified in our cohort were predominantly B-cell (88.9%), with only 1 case of T-cell lymphoma. The specific subtypes included: CLL in 2 patients, MCL in 1 patient, MZL in 2 patients, DLBCL in 1 patient, WM in 1 patient, and Mycosis Fungoides in 1 patient. Bone marrow involvement by lymphoma was documented in 6 patients (66.7%) at the time of diagnosis. Constitutional B symptoms likely attributable to lymphoma were present in 4 patients (44.4%) at diagnosis or during follow-up.

The temporal relationship between mastocytosis and lymphoma diagnosis varied across the cohort. In most cases (66.7%), both diagnoses were established concomitantly, defined as diagnoses made within 3 months of each other. In the remaining 3 patients (33.3%), the diagnosis of lymphoma preceded the

Table 1 - Clinical, molecular, and outcome characteristics of patients with mastocytosis and associated lymphoid neoplasms.

Patient	Age	Sex	Mastocytosis Type	KIT D816V	Tryptase (ng/mL)	Lymphoma	Timing of Lymphoma Diagnosis	Treatment	Lymphoma Outcome	Mastocytosis Outcome
1	53	Male	BMM	Present	69	MZL	Concomitant	Watchful waiting	Stable disease	Stable disease
2	56	Female	BMM	Present	55	MCL	Concomitant	Watchful waiting	Stable disease	Stable disease
3	56	Male	BMM	Present	9	DLBCL	Prior to mastocytosis	R-CHOP	Complete response	Stable disease
4	61	Male	BMM	Present	64	WM	Concomitant	Rituximab + Bendamustine	Complete response	Stable disease
5	64	Female	ISM	Present	28	CLL	Concomitant	Watchful waiting	Stable disease	Stable disease
6	55	Female	ISM	Absent	61	CLL	Concomitant	Watchful waiting	Stable disease	Stable disease
7	40	Male	ISM	Present	31	Mycosis fungoides	Prior to mastocytosis	Watchful waiting	Stable disease	Stable disease
8	57	Male	BMM	Present	66	FL	Prior to mastocytosis	Rituximab + Bendamustine, then Mosunetuzumab	Complete response	Stable disease
9	79	Male	AM	Present	247	MZL	Concomitant	Midostaurin	Stable disease	Stable Disease

Abbreviations: BMM, bone marrow mastocytosis; ISM, indolent systemic mastocytosis; AM, aggressive mastocytosis; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; MW, Waldenström macroglobulinemia; CLL, chronic lymphocytic leukaemia; FL, follicular lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

identification of mastocytosis by a median of 96 months (range: 12-240 months). No patient in our cohort had mastocytosis diagnosed prior to lymphoma.

Management strategies were individualised based on the characteristics of both disease components. For the lymphoma component, 3 patients (33.3%) required systemic treatment and achieved complete remission. The specific regimens used were: Rituximab plus CHOP, Rituximab plus Bendamustin, and, in second line for one patient, Mosunetuzumab. The remaining 6 patients (66.7%) were managed with only active surveillance. The median follow-up for the entire cohort was 44 months (range: 5-158months), and at the last follow-up, all patients were alive with disease. In brief, during follow-up, 77,7% of patients demonstrated stable disease in both mastocytosis and lymphoma components; disease progression was observed in only 2 patients: 1 progressed only in the lymphoma component, while 1 progressed only in mastocytosis.

Characteristics of Patients with Concomitant Diagnosis. Among the six patients (66.7% of the total cohort) with concomitant diagnoses of mastocytosis and lymphoma, there was an equal sex distribution (50% males), with a median age of 58 years (range, 53–79). In our cohort, in 4 of 6 cases, the bone biopsy was performed due to suspicion of mastocytosis, and the lymphoma was an incidental finding; conversely, in 2 patients, the biopsy was performed for suspected lymphoma, with mastocytosis identified incidentally. Only 1 patient in this subgroup had aggressive systemic mastocytosis, while the remaining 5 had indolent systemic mastocytosis. Molecular testing for the KIT D816V mutation was performed in 6 patients, of whom 5 (83.3%) tested positive.

Cutaneous manifestations with urticaria pigmentosa were documented in only 2 patients. The median baseline serum tryptase level in this subgroup was 54 ng/mL (range: 28.3-247). Skeletal complications were notably frequent, with osteoporosis documented in 3 patients (60%). All 6 patients in the concomitant diagnosis subgroup had B-cell lymphoproliferative disorders with an indolent biological behaviour at presentation. The specific subtypes were: CLL in 2 patients, MZL in 2 patients, WM in 1 patient, and MCL in 1 patient. Given the indolent nature of both disease components in all patients at diagnosis, the entire concomitant diagnosis subgroup was initially managed with active surveillance without immediate therapeutic intervention. During the observation period (median duration: 13 months, range: 12-158), close monitoring was performed in accordance with clinical practice, including semiannual clinical assessments, laboratory evaluations, and imaging studies as indicated. Lymphoma progression requiring treatment intervention occurred in 1 patient (16.7%) after 12 months of observation. This patient, affected by WM syndrome, was treated with Rituximab plus Bendamustine. The treatment resulted in complete remission of the lymphoma component (confirmed by PET-CT and bone marrow biopsy) while the mastocytosis remained stable and asymptomatic. Therapy was well tolerated, with no treatment-related adverse events reported. One patient required specific therapy directed at the mastocytosis component due to C-finding (symptomatic osteolytic lesion). This patient was treated with midostaurin, achieving stable disease for both mastocytosis and lymphoma components. The lymphoma did not progress

during mastocytosis treatment. The remaining 4 patients (66.7%) continued under active surveillance at last follow-up, maintaining stable disease in both components without requiring therapeutic intervention for lymphoma.

Discussion. We report a series of 9 patients diagnosed with systemic mastocytosis and lymphoproliferative disorders. Unlike the well-established association between mastocytosis and myeloid neoplasms, which accounts for approximately 90% of SM-AHN cases, the concurrent occurrence of SM with lymphomas is exceedingly rare and poorly characterised.[1,11]

In our cohort, most patients (88.9%) presented with indolent systemic mastocytosis, and all lymphomas were of B-cell origin except for one case of mycosis fungoides. Notably, among patients with a concomitant diagnosis (66.7% of the cohort), all lymphomas demonstrated indolent biological behaviour at presentation and were initially managed with active surveillance, without requiring immediate treatment. During follow-up, both disease components exhibited a chronic, indolent course in most patients. Importantly, treatment of one disease component did not appear to influence the natural history of the other: patients achieving complete remission of lymphoma maintained stable mastocytosis, and conversely, treatment directed at mastocytosis did not impact lymphoma behaviour. This pattern may suggest that these represent two independent disease processes rather than clonally related malignancies.

A comprehensive literature review identified only isolated case reports of SM associated with lymphomas. To our knowledge, approximately 13 individual cases have been reported in the literature to date.[4–10,12–16]

Previous case reports have predominantly described SM-CLL associations. The first report by Sanz et al. described systemic mast cell disease in association with B-CLL, establishing recognition of this rare association.[14] Subsequent reports by Iqbal et al., Hauswirth et al., Du et al., Horny et al., Ault et al., and Zagaria et al. have documented similar associations, with treatment outcomes generally demonstrating independent disease behaviour.[4–8] Beyond CLL, isolated cases of SM with MZL, WM, DLBCL, and cutaneous lymphomas have been reported.[9,10,12,13,17] To our knowledge, our series represents the largest cohort published to date.

A fundamental distinction between SM associated with myeloid versus lymphoid neoplasms lies in the clonal relationship between the SM and the neoplasm. In SM-AMN, the KIT D816V mutation is frequently detected not only in mast cells but also in myeloid lineage cells, suggesting a common clonal origin at the level of the hematopoietic stem cell.[18,19] Sotlar et al. demonstrated variable presence of KITD816V in clonal hematopoietic non-mast cell lineage diseases associated with SM, with the mutation commonly found in myeloid but not lymphoid neoplasms.[20] Wang et al. (2013) used combined immunofluorescence and fluorescence in situ hybridization (FISH) imaging to analyze chromosomal abnormalities in four SM-AHN patients; they demonstrated that in cases of SM associated with CMML and MDS, the same chromosomal alterations (trisomy 8 and del(20q)) were present in both mast cells and myeloid cells, indicating a common clonal origin.[21]

In contrast, molecular studies in SM-lymphoma cases have consistently demonstrated distinct clonal origins. Kim et al. (2007) performed comprehensive clonality studies demonstrating that the KIT D816V mutation was present in mast cells but completely absent in neoplastic lymphocytes, suggesting these represent two separate, independent neoplastic processes.[22] Similarly, in the work by Wang et al. cited previously, in SM associated with CLL, the ATM deletion identified in leukemic cells was not detected in mast cells, further supporting distinct clonal origins.[21] This biological independence is corroborated by our clinical observations: treatment directed at one disease component had no impact on the other.

The co-occurrence of SM and lymphoma may reflect coincidental detection rather than a pathogenic link. Chronic lymphocytic leukaemia has a relatively high incidence in the general population, with an annual incidence of 4.7 per 100,000 and a prevalence of approximately 97-100 per 100,000.[23] Similarly, MZL represents approximately 5-17% of non-Hodgkin lymphomas, with an incidence of approximately 1.5 per 100,000 person-years.[24] Given that bone marrow examination is a routine diagnostic component in the evaluation of systemic mastocytosis, lymphoproliferative disorders, particularly indolent B-cell lymphomas that commonly involve the bone marrow, may be detected as incidental findings during mastocytosis workup. Consistently, in our cohort, bone marrow biopsy was most often performed for suspected systemic mastocytosis rather than lymphoma, with lymphoproliferative disorders being identified as incidental findings. However, the possibility of a shared genetic predisposition to hematologic neoplasms cannot be entirely excluded and warrants further investigation.

The co-occurrence of these conditions has important clinical implications. Both mastocytosis and lymphoproliferative disorders are now highly treatable with expanding therapeutic options, including KIT inhibitors for mastocytosis and BTK inhibitors, BCL-2 inhibitors, and chemoimmunotherapy for lymphomas.[3,23] BTK inhibitors are currently under investigation as potential therapeutic agents also in mastocytosis, given their role in modulating mast cell activation pathways.[25] Therapeutic agents used for one condition may have toxicities that are particularly relevant in patients with the other disease. In our cohort, however, no clinically meaningful therapeutic

interference between treatments for the two conditions was observed, although this observation is limited by the small sample size. Accurate characterisation of both disease components is important for prognostication, as the indolent nature of these diseases in most patients in our cohort led to a favourable clinical course and prolonged survival.

Our study has several limitations inherent to its retrospective design and small sample size. The heterogeneity of lymphoma subtypes precludes definitive conclusions about specific SM-lymphoma associations. Detailed molecular characterisation was not uniformly available for all patients. The follow-up duration was variable, and data on long-term outcomes are limited.

The co-occurrence of SM and lymphoproliferative disorders appears to reflect coincidental detection rather than shared clonality. Routine bone marrow examination in SM patients may facilitate the detection of lymphoma. However, accurate characterisation of both components remains clinically important for treatment planning and prognostication. Further multi-institutional studies with molecular characterisation are warranted.

Informed Consent. All patients provided written informed consent for the collection and use of their clinical data and for the publication of this case series.

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References:

1. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. luglio 2022;36(7):1703–19. https://doi.org/10.1038/s41375-022-01613-1
2. Valent P, Akin C, Hartmann K, Alvarez-Twose I, Brockow K, Hermine O, et al. Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal. HemaSphere. novembre 2021;5(11):e646. https://doi.org/10.1097/HS9.0000000000000646
3. Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. Am J Hematol. luglio 2023;98(7):1097–116. https://doi.org/10.1002/ajh.26962 PMID: 37309222.
4. Iqbal MF, Soriano PMK, Nagendra S, Sana S. Systemic Mastocytosis in Association with Small Lymphocytic Lymphoma. Am J Case Rep. 3 ottobre 2017;18:1053–7. https://doi.org/10.12659/ajcr.905759 PMID: 28970467; PMCID: PMC5637574.
5. Du S, Rashidi HH, Le DT, Kipps TJ, Broome HE, Wang HY. Systemic mastocytosis in association with chronic lymphocytic leukemia and plasma cell myeloma. Int J Clin Exp Pathol. 23 aprile 2010;3(4):448–57. PMID: 20490336; PMCID: PMC2872752.
6. Hauswirth AW, Födinger M, Fritz M, Müllauer L, Simonitsch-Klupp I, Streubel B, et al. Indolent systemic mastocytosis associated with atypical small lymphocytic lymphoma: a rare form of concomitant lymphoproliferative disease. Hum Pathol. giugno 2008;39(6):917–24. https://doi.org/10.1016/j.humpath.2007.10.022 PMID: 18448146.
7. Horny HP, Sotlar K, Stellmacher F, Valent P, Grabbe J. An unusual case of systemic mastocytosis associated with chronic lymphocytic leukaemia (SM-CLL). J Clin Pathol. marzo 2006;59(3):264–8. https://doi.org/10.1136/jcp.2005.026989 PMID: 16505276; PMCID: PMC1860346.
8. Ault P, Lynn A, Tam CS, Medeiros LJ, Keating MJ. Systemic mastocytosis in association with chronic lymphocytic leukemia: a rare diagnosis. Leuk Res. dicembre 2007;31(12):1755–8. https://doi.org/10.1016/j.leukres.2007.04.002 PMID: 17521719.
9. Fernández-Torres R, Verea MM, Álvarez A, Torres P, Fonseca E. Systemic Mastocytosis Associated with Splenic Marginal Zone Lymphoma with Villous Lymphocytes. Dermatol Res Pract. 2011;2011:385074. https://doi.org/10.1155/2011/385074 PMID: 21785582; PMCID: PMC3137984.
10. Meyer KM, Landthaler M, Hafner C, Geissinger E. Systemic mastocytosis associated with cutaneous B-cell lymphoma. Br J Dermatol. novembre 2013;169(5):1165–7. https://doi.org/10.1111/bjd.12471 PMID: 23773144.
11. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 15 settembre 2022;140(11):1200–28. https://doi.org/10.1182/blood.2022015850 PMID: 35767897; PMCID: PMC9479031.
12. Schipper EM, Posthuma W, Snieders I, Brouwer RE. Mastocytosis and diffuse large B-cell lymphoma, an unlikely combination. Neth J Med. marzo 2011;69(3):132–4. PMID: 21444939.
13. John MV, Simonitsch-Klupp I, Griss J, Waldstein C, Herrmann H, Gaiger A, et al. Bone marrow mastocytosis associated with primary cutaneous follicle center lymphoma: an unusual case report. Ann Hematol. ottobre 2025;104(10):5543–8. https://doi.org/10.1007/s00277-025-06588-4 PMID: 40913208; PMCID: PMC12619747.
14. Sanz MA, Valcárcel D, Sureda A, Muñoz L, Espinosa I, Nomdedeu J, et al. Systemic mast cell disease associated with B-chronic lymphocytic leukemia. Haematologica. ottobre 2001;86(10):1106–7. PMID: 11602421.
15. Zagaria A, Anelli L, Coccaro N, Tota G, Brunetti C, Minervini A, et al. Systemic Mastocytosis with Associated Chronic Lymphocytic Leukemia: A Matter of Diseases or Prognostic Factors? Turk J Haematol Off J Turk Soc Haematol. 2 agosto 2017;34(3):276–7. https://doi.org/10.4274/tjh.2017.0014 PMID: 28351827; PMCID: PMC5544054.
16. Lee HY, Lee JS, Koo DW. A case report of primary cutaneous marginal zone B-cell lymphoma with mastocytosis. SAGE Open Med Case Rep. 2021;9:2050313X211042527.

https://doi.org/10.1177/2050313X211042527
PMID: 34471539; PMCID: PMC8404676.
17. Tournilhac O, Santos DD, Xu L, Kutok J, Tai YT, Le Gouill S, et al. Mast cells in Waldenstrom's macroglobulinemia support lymphoplasmacytic cell growth through CD154/CD40 signaling. Ann Oncol Off J Eur Soc Med Oncol. agosto 2006;17(8):1275–82.
https://doi.org/10.1093/annonc/mdl109
PMID: 16788002.
18. Jawhar M, Schwaab J, Schnittger S, Sotlar K, Horny HP, Metzgeroth G, et al. Molecular profiling of myeloid progenitor cells in multi-mutated advanced systemic mastocytosis identifies KIT D816V as a distinct and late event. Leukemia. maggio 2015;29(5):1115–22.
https://doi.org/10.1038/leu.2015.4
PMID: 25567135.
19. Frederiksen JK, Shao L, Bixby DL, Ross CW. Shared clonal cytogenetic abnormalities in aberrant mast cells and leukemic myeloid blasts detected by single nucleotide polymorphism microarray-based whole-genome scanning. Genes Chromosomes Cancer. aprile 2016;55(4):389–96.
https://doi.org/10.1002/gcc.22342
PMID: 26865278.
20. Sotlar K, Colak S, Bache A, Berezowska S, Krokowski M, Bültmann B, et al. Variable presence of KITD816V in clonal haematological non-mast cell lineage diseases associated with systemic mastocytosis (SM-AHNMD). J Pathol. aprile 2010;220(5):586–95.
https://doi.org/10.1002/path.2677
PMID: 20112369.
21. Wang SA, Hutchinson L, Tang G, Chen SS, Miron PM, Huh YO, et al. Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease: clinical significance and comparison of chomosomal abnormalities in SM and AHNMD components. Am J Hematol. marzo 2013;88(3):219–24.
https://doi.org/10.1002/ajh.23380
PMID: 23440662; PMCID: PMC4188390.
22. Kim Y, Weiss LM, Chen YY, Pullarkat V. Distinct clonal origins of systemic mastocytosis and associated B-cell lymphoma. Leuk Res. dicembre 2007;31(12):1749–54.
https://doi.org/10.1016/j.leukres.2007.04.008
PMID: 17544505.
23. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 21 giugno 2018;131(25):2745–60.
https://doi.org/10.1182/blood-2017-09-806398
PMID: 29540348.
24. Olszewski AJ, Castillo JJ. Survival of patients with marginal zone lymphoma: analysis of the Surveillance, Epidemiology, and End Results database. Cancer. 1 febbraio 2013;119(3):629–38.
https://doi.org/10.1002/cncr.27773
PMID: 22893605.
25. Costanzo G, Marzio V, Cavaglià E, Paoletti G, Heffler E. New treatments for systemic mastocytosis in 2025. Curr Opin Allergy Clin Immunol. agosto 2025;25(4):277.
https://doi.org/10.1097/ACI.0000000000001079