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# Is Bruton tyrosine kinase a potential target to treat mast cell neoplasms? Systemic mastocytosis associated with chronic lymphoid leukemia successfully treated with acalabrutinib monotherapy: a case report and review of the literature

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**RUNNING TITLE: Successful Acalabrutinib Monotherapy in Systemic Mastocytosis associated with Chronic Lymphoid Leukemia**

Systemic mastocytosis (SM) is a category of rare hematologic neoplasms which encompasses both indolent (ISM), smoldering (SSM) and advanced (AdvSM) subcategories. Most cases are characterized by *KIT* mutations, particularly *cKITD816V*, which promotes MCs maturation rather than proliferation[1]. SM can be associated with others hematologic neoplasm (SM-AHNMD). Myeloid AHNs are frequent and often *cKIT(+)*; lymphoid AHNs are rare and generally *cKIT(-)*[1].This gives evidence of a shared clonal origin only with associated myeloid diseases. Cases of SM-CLL have been sporadically reported in literature [2–7] and have documented unsatisfactory outcomes on SM component with available therapies. Whether there is a link between these two diseases is still debated but the perturbances that mast cells (MCs) cause in the bone marrow (BM) microenvironment can justify a potential connection. The treatment depends on both risk features and symptoms but in most cases SM component tends to persist. Bruton tyrosine kinase (BTK) plays an important role in both B cell development and MCs activation, and this could provide a rationale for the employment of BTK inhibitors (BTKIs) in SM-CLL. By describing the case of a patient treated with acalabrutinib monotherapy who achieved partial remission (PR) of both CLL and SM (coupled with complete symptom resolution) we aim to analyze the role of BTK in SM and to suggests BTKIs as new potential strategy in this peculiar setting of patients. To our knowledge this is the 1st case report in literature describing such a strategy in SM-CLL. We guarantee that this case report complies with national ethical guidelines and that written informed consent was obtained from the patient for publication of this article and accompanying images.

The patient, a 76 years old Caucasian woman, began experiencing urticaria pigmentosa in 2014 and was initially treated at Fondazione IRCSS-Policlinico "San Matteo" in Pavia. Blood analysis reported an increased serum tryptase level: 95.5 microg/L (n.r. 0.1-11.4 microg/L) and medical imaging showed moderate splenomegaly (≃15 cm) and osteoporosis. The BM biopsy documented MCs aggregates with a CD2-/+, CD25+, CD117+, CD30- immunophenotype and molecular tests confirmed *cKITD816V* mutation. Therefore, the patient was diagnosed with ISM and began anti-H1/H2, antiresorptive and anti-mediator therapy. She experienced spleen resizing and clinical improvement for nearly a decade. In March 2023, the patient presented again with cutaneous, constitutional and gastrointestinal (GI) symptoms (diarrhea, gastritis). Restaging analysis showed a higher serum tryptase level (281 microg/L), moderate anemia and lymphocytosis (25.000/mm3). Medical imaging revealed the presence of organomegalies (lymph nodes, spleen and liver). A second BM biopsy confirmed the presence of neoplastic MCs (20%) and documented the appearance of monoclonal CD5+, CD200+, CD79+/-CD23+, CD20+, CD19+ lymphoid B cells (50%). FISH showed deletion (del) (13q14) and del(17p13) in CLL, while NGS confirmed both *TP53* mutation (VAF: 88%) and unmutated immunoglobulin heavy chain variable region *(IGVH)*; SM persisted *cKIT816V(+)* but with a higher variant allele frequency (VAF) assessed on peripheral blood (7.0368%). No *KIT* mutation was found on CLL cells. A complete myeloid NGS panel was performed (*FIP1L1-PDGFRα* and *β*, *JAK2 V617F, CALR, MPL, BCR-ABL p210/190/230*) and resulted negative. Thus, the patient was diagnosed with SSM-CLL, and CLL stage resulted as very high risk according to CLL-International Prognostic Index (CLL-IPI). Morphological images of BM cellularity captured with optical microscopy are shown in **Figure 1**. In March 2024, follow-up analyses documented CLL progression, with severe anemia and absolute lymphocytosis (44.000/mm$^3$). Molecular analyses for SM showed a discrepancy between *c-KIT* VAF on PB (29.14%) and on BM (0.5922%) due to the fact that 95.6% of BM mononuclear cells were CD19+ lymphocytes which resulted *c-KIT* wild type. In order to start a specific hematologic therapy, the patient moved to Catania for proximity to her permanent address in order to be treated at "Policlinico G.Rodolico", which is regional reference center for SM. Our initial intention was to combine a type-1 tyrosine kinase inhibitor (TKI) (avapritinib, for SM) with a BTK inhibitor (acalabrutinib, for CLL). However, considering progressive thrombocytopenia (PLT 48.000/mm3) with subsequent hemorrhagic risk, we decided to avoid avapritinib and start acalabrutinib in monotherapy at a dose of 100 mg/die. For good tolerance, we increased the drug dose to 200 mg one month later. The patient experienced a gradual improvement in blood count and after 4 months she became transfusion-independent. Medical imaging confirmed progressive hepatic, spleen and lymph-nodes resizing (≥50% from baseline). We therefore considered the opportunity to embricate midostaurin to specifically address SM. Although it is less specific for the *cKITD816V* mutation, midostaurin allows flexible dose adjustments in cases of thrombocytopenia rather than mandatory drug discontinuation. However, given the potential GI adverse effects (including nausea, vomiting, and diarrhea), the patient firmly declined this therapeutic option, citing the pre-existing SM-related GI manifestations from which she had particularly suffered. Consequently, the idea to employ midostaurin was not pursued further. By February 2025, we assessed that CLL had reached a partial remission (PR) according to international guidelines. Most

surprisingly, despite no specific SM treatment, we observed a progressive serum tryptase decrease, from 155 to 64.3 to 45.6 microg/L within 6 months of starting CLL therapy. Moreover, the patient obtained a complete resolution of SM-related manifestations. Therefore, also SM was considered in PR according to international response criteria. At the latest follow-up visit (October 2025) blood counts were as follows: hemoglobin (Hb) 10 g/dL, PLTs 267.000/$mm^3$, and WBCs 13.900/$mm^3$ (lymphocytes 62%). This represented the best hematologic profile recorded to date and confirmed the enduring PR of CLL. A further decrease in serum tryptase was also observed (36.5 microg/L). BM analyses were proposed to reassess the SM component. However, the patient declined the procedure due to poor tolerance during previous examinations. Consequently, we decided to re-evaluate the *KIT* mutation *status* using PB. NGS analysis revealed the absence of the *KITD816V* mutation (previously detected at 29.14%). The patient proceeds with treatment maintaining a good performance *status*. Our case and the other cases of SM-CLL available in literature are here summarized in **Table.1.**

It can be deduced from literature that, in SM-CLL cases, SM may favor CLL progression and aggressiveness. Indeed, by secreting several pro-tumoral factors, MCs are able to orchestrate the neoplastic stromal microenvironment. For example: histamine and IL-10 exerts an immunosuppressive effect; tryptase stimulates endothelial cells proliferation (neo-angiogenesis); vascular endothelial and fibroblast growth factors (VEGF and FGF-2) further promote tumor vascularization [8]. On this regard, Molica et al. have demonstrated that the percentage of tryptase+ MCs in CLL correlates with major microvascular density, unfavorable genetic aberrations (i.e. 11q and 17p) and thus, disease progression [9]. Therefore, MCs have been hypothesized as a potential therapeutic target in order to avoid neo-vascularization and delay tumor growth. For example, several patients treated in 2007 with both fludarabine and alemtuzumab (anti-CD52 monoclonal antibody employed to address the CLL-associated inflammatory component), achieved a parallel reduction of both BM angiogenesis and MCs percentage [10]. MCs originate from CD34+, CD117+ (*KIT*) and CD13+ progenitor cells. The stem cell factor (SCF), also known as *KIT*-ligand, binds to CD117 promoting differentiation and survival [11]. Ligand-independent activation of *KIT* occurs as the result of activating somatic mutations such as *cKITD816V* which is detectable in the majority of patients with SM and is considered to contribute to the differentiation of neoplastic MCs[11]. Consequently, TKIs such as midostaurin and avapritinib represent the pillar of SM therapy. However, *cKITD816V* alone is not a fully transforming oncoprotein. Thus, it is not sufficient to justify disease progression from ISM to more aggressive subtypes. In order to address this issue, Gleixner et al. focused their attention on other tyrosine kinases (TYKs). In 2011, they proved that 2 TYKs, namely p-Lyn and p-BTK, are constitutively activated (phosphorylated) only on neoplastic MCs [both *cKIT(+)* and *(-)*], especially in AdvSM. Furthermore, they confirmed that these TYKs are involved in neoplastic survival by witnessing the inhibition of proliferation in p-Lyn and p-BTK knocked-out human neoplastic MCs (HMCs). In addition, they showed that while midostaurin blocks *cKIT* phosphorylation but is not able to downregulate p-Lyn and p-BTK, other TKIs [such as *BCR-ABL* inhibitors (bosutinib and dasatinib] exert the opposite effect. Therefore, they decided to combine both drugs to address neoplastic *cKIT(+)* MCs. As a result, they demonstrated that both bosutinib and dasatinib determined a midostaurin-sensibilizing effect leading to increased apoptosis [12]. At present, no such studies have been carried out with BTKIs. However, judging from the outcome of our patient after 6 months of acalabrutinib monotherapy, it is reasonable to speculate that specifically targeting both p-BTK and *cKIT* would allow a much synergistic effect. Unfortunately, our patient couldn't receive avapritinib due to thrombocytopenia, but it would be ideal to try this drug combination in a younger, fit patient. Moreover, considering that our patient had *TP53* mutated but *KIT* wild type CLL cells, our choice to employ acalabrutinib and avoid avapritinib or another *KIT*-inhibitor is further justified. To refine therapeutic strategies in this subset of patients, it may be valuable to perform NGS investigation to identify potentially targetable non-*KIT* mutations. One of this mutations is *SF3B1* which leads to altered splicing patterns in both CLL and SM. In SM, *SF3B1* mutations, though less frequent, have been identified in patients with aggressive phenotypes often characterized by mutated genes of the *S/A/R* panel[1]. However, no studies to date have explored the potential occurrence of these mutations as a shared genetic signature in SM-CLL cases. In our case, a comprehensive NGS panel

was performed at the time of progression from ISM to SSM, and no additional mutations, including *SF3B1*, were identified.

Focusing on BTK inhibitors, it is also important to emphasize the symptomatic benefit that our patient obtained from acalabrutinib administration. Ibrutinib and acalabrutinib are respectively 1st and 2nd generation, oral, irreversible BTKIs approved for the treatment of CLL either as 1st or subsequent line and acalabrutinib represents a primary choice in case of *TP53* mutation and del(17p). Already in past years, several studies have been carried out to assess BTKIs function against allergy and anaphylaxis [13,14]. In order to understand their potential role in SM, it is necessary to specify that p-BTK is involved in MCs activation. More specifically, human MCs express the receptor for IgE: FcεRI [15]. Once activated, the transduction of FcεRI crosslinking signals is propagated by the kinase network (Lyn, SyK, MAPK and PI-3K) [15] and can be further upregulated by p-BTK, which is a member of Tec kinases family [together with Etk (BMX), Itk, Rlk, and Tec][15]. As discussed above, BTK can also be activated by SCF or be constitutively activated in case of SM [12]. This process culminates in the secretion of preformed and newly synthesized MCs' mediators. Therefore, by using acalabrutinib to target p-BTK we were able to counteract mediator-induced SM symptoms and allowed a complete clinical improvement. In order differentiate between a merely symptomatic advantage and a potentially disease-modifying effect of acalabrutinib on SM, we have recently reassessed *cKIT* allele burden. Due to patient's refusal to undergo BM examinations, we decided to perform NGS analysis on PB. Results showed the absence of the mutation and allowed us to hypothesize that BTKIs may impact the course of the disease.

In conclusion, the coexistence of SM and CLL, though rare, has been documented and may involve reciprocal promotion despite clonal independence. While dual targeted therapy would be ideal, safety concerns often limit its use. In such scenarios, BTKIs monotherapy may provide an effective strategy. In line with this statement, we have hereby described a case of SM-CLL treated with acalabrutinib single-agent achieving CLL response, SM partial remission, and full symptomatic relief. So far, two clinical trials have explored BTKIs in SM. The first is NCT04655118 [ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT02415608. Last updated 20 Sept 2018], an ongoing Phase 2 multicenter study evaluating TL-895 in patients with relapsed/refractory myelofibrosis or ISM. The oral administration and favorable pharmacokinetics of this drug make it a promising candidate for long-term disease control in ISM. The second study is NCT02415608 [ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04655118. Last updated 27 Oct 2025], a Phase 2 trial evaluating the ability of ibrutinib to reduce MCs burden in AdvSM (including more aggressive subtypes). Although the study was terminated due to slow accrual, it offers preliminary insights into the feasibility of BTKIs in this setting. Results of both studies are eagerly awaited. Therefore, BTKIs seem potential candidates to enter SM *armamentarium* and further studies are warranted to evaluate their effectiveness and safety in combination with TKIs.

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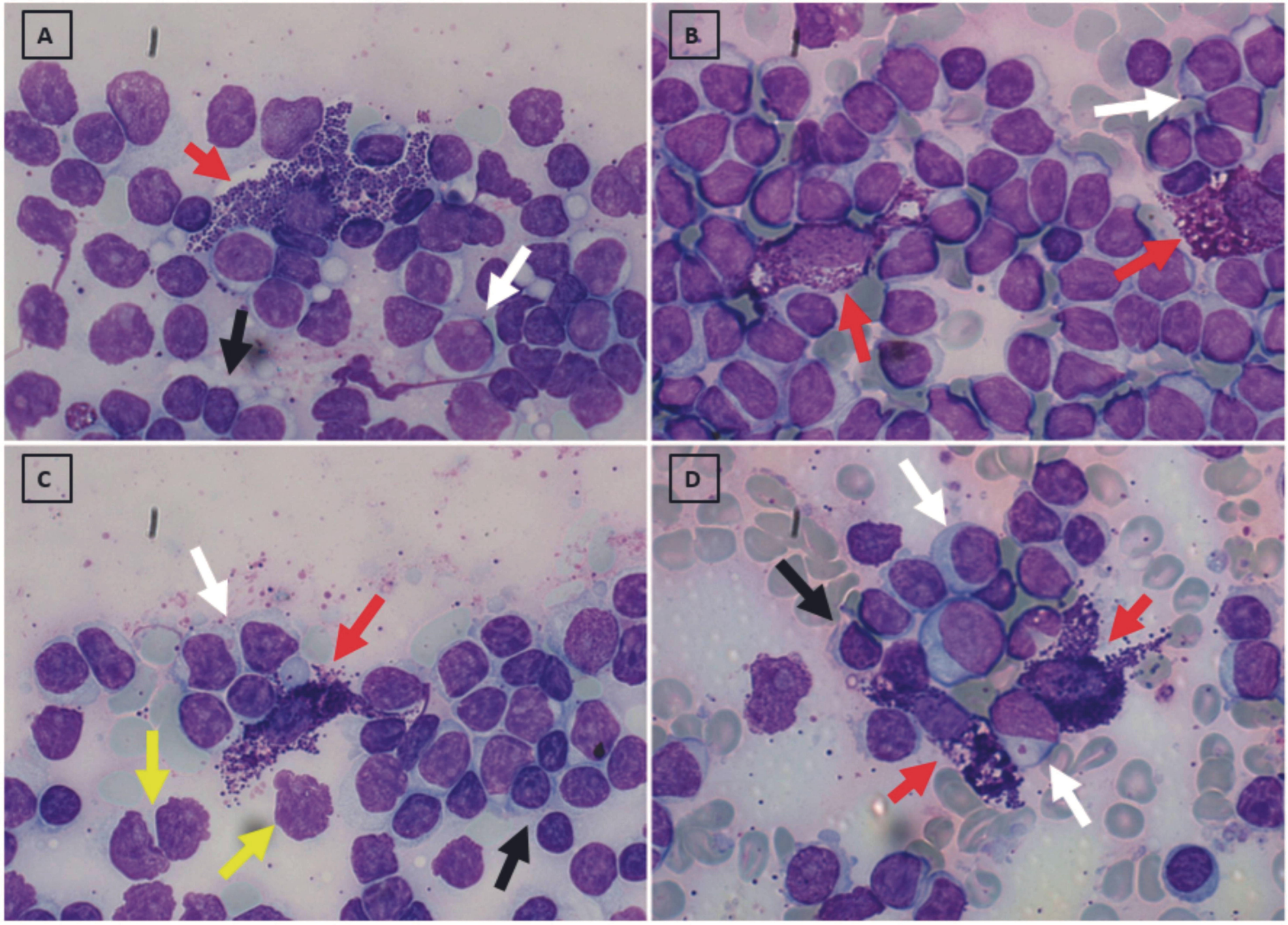
## TABLE 1

| Ref | N° | Diagnosis | tryptase (ng/mL) | SM symptoms | CD2+ MCs | CD25+ MCS | CD30+ MCs | Biology | CLL Therapy | SM Therapy | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [2] | 2<br>1st<br><br>2nd | <br>CLL (2001)<br>SM (2006)<br><br>CLL (2003)<br>PCM + SM (2009) | <br>10.3<br><br><br>21.4 | <br>none<br><br>rash | <br>no<br><br>NA | <br>yes<br><br>yes | <br>NA<br><br>NA | In both cases:<br>SM: *D816V(-)*<br>CLL:<br>del(13q14.3) | R-Benda x 3<br>FCR+AlloSCT<br><br>R-Lena | AlloSCT (MUD)<br>for both diseases<br><br>none | CLL: CR<br>SM: SD<br><br>CLL: PR<br>SM: PD |
| [3] | 1 | SM (1993)<br>CLL (2000) | NA | urticaria<br>osteolysis | yes | yes | NA | NA | none | H1/H2 blockers<br>agents | CLL: SD<br>SM: CI |
| [4] | 1 | SM-SLL (2005)<br>(CM from childhood) | 163 | diarrhea<br>flushing<br>headache<br>urticaria | no | yes | NA | *SM: D816V(+)*<br>SLL: *D816V(-)*<br>+12; IGHR | FC (without R) | H1/H2 blockers | CLL: CR<br>SM: SD |
| [5] | 1 | RAI 0 CLL (2001)<br>RAI 3 CLL+SM<br>(2007) | 4xULN | osteolysis<br><br>vertebral<br>fractures | yes | yes | NA | SM: *D816V(+)*<br>CD52+ MCs<br>CLL: del(11q)<br>ZAP-70+ | FCR (x 6) +<br>Anti-CD52 | 1st line:<br>Imatinib<br><br>2nd line:<br>Anti-CD52 (x 6) | SM: SD<br><br>CLL: CR<br>SM: SD |
| [6] | 1 | SM-CLL in 2005<br>(urticaria >25 years)<br>with CD25+, *KIT(-)*<br>MCs in GI mucosa | 130 | urticaria<br>pruritus<br>GI tract | yes | yes | NA | SM: *D816V(+)*<br>CLL: IGHR | NA | NA | NA |
| **our case** | 1 | ISM in 2014<br><br>In 2023/2024<br>SSM+high risk CLL | 95.5<br><br>281 | urticaria<br>spleen >15cm<br>osteoporosis<br>GI tract<br>pruritus | yes | yes | no | SM: *D816V(+)*<br>CLL:<br>del(13q14)<br>del(17p13) | **Acalabrutinib**<br>**Single agent** | H1/H2 blockers<br>Denosumab<br>(TKI avoided→<br>low PLT) | **CLL: PR**<br>**SM: PR**<br>**No more symptoms**<br>**NGS:**<br>***KIT(-)* PB** |

**TABLE 1. This table summarizes major characteristics of patients affected by SM associated with CLL/SLL, extrapolated from those few case reports present in literature.** We have also included data from our case. A recurrent characteristic in all cases is that SM diagnosis generally anticipates CLL/SLL one. To our knowledge, our case is the only one reporting a more significative therapeutic outcome (PR) compared to other cases which reported SM persistence (even after matched unrelated donor AlloSCT). **ABBREVIATIONS**: SM (systemic mastocytosis); CD (cluster of differentiation); MCs (mast cells); CLL (chronic lymphoid leukemia); PCM (plasma cell myeloma); NA (not assessed); del (deletion); R (rituximab); FCR (fludarabine, cyclophosphamide, rituximab); benda (bendamustine); lena (lanalidomide); AlloSCT (MUD) (allogenic stem cells transplant from matched unrelated donor); CR (complete remission); PR (partial remission); CI (clinical improvement); SD (stable disease); SLL (small lymphocytic lymphoma); CM (cutaneous mastocytosis); +12 (trisomy 12); IGHR (immunoglobulin heavy chain rearrangement); H1/H2 (histamine receptor 1 and 2); RAI (CLL staging system); ULN (upper limit of normal); ZAP-70 (Zeta-chain-associated protein kinase 70); anti-CD52 (alemtuzumab); GI (gastrointestinal); ISM (indolent SM); TKI (tyrosine kinase inhibitors); PLT (platelets); NGS (next generation sequencing); PB (peripheral blood).

**Figure 1. Optical microscopy morphology of bone marrow of SM-CLL (A-D).** Regarding the CLL component, all 4 images show a cellularity predominantly represented by two cell types: 1) small lymphocytes with eccentric nuclei, coarse and dense chromatin and a narrow, weakly basophilic cytoplasmic rhyme **(black arrows)**; 2) numerous medium-sized prolymphocytes, larger than B-CLL cells, characterized by prominent nucleoli, pale weakly basophilic cytoplasm (sometimes with a reinforced blue-purple contour indicating an abundance of RNA and protein) and moderately condensed chromatin (but more open than in B-CLL) **(white arrows)**. The classic "Gumprecht Shadows" or "smudge cells" are also visible. These elements results from mechanical disruption of lymphocytes during smear preparation **(yellow arrows)** and represent an hallmark of CLL. Regarding the SM component, all images show the presence of atypical, generally spindle-shaped mast cells (MCs) with polar cytoplasmic elongations (atypical MCs type 1) **(red arrows)**. The nucleus is oval and eccentric; the cytoplasm is basophilic and typically obscured by densely packed granulations which stain strongly with metachromatic dyes (such as toluidine blue, Giemsa stain, and methylene blue). **Figure A** shows an activated atypical mast cell with diffusely scattered blue-purple granules infiltrating intercellular spaces.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