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

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 mast cell (MC) maturation rather than proliferation.[1] SM can be associated with other hematologic neoplasms (SM-AHNMD). Myeloid associated hematologic neoplasms (AHN) are frequent and are often *cKIT*$^+$; lymphoid AHN 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 these 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 MC 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, the SM component tends to persist. Bruton tyrosine kinase (BTK) plays an important role in both B-cell development and MC activation, and this could provide a rationale for the employment of BTK inhibitors (BTKI) in SM-CLL.

We describe the case of a patient treated with acalabrutinib monotherapy who achieved partial remission (PR) of both CLL and SM (coupled with complete resolution of symptoms) in order to analyze the role of BTK in SM and to suggest BTKI as a new potential strategy in this particular patient setting. To our knowledge, this is the first case report in literature describing such a strategy in SM-CLL. This case report complies with national ethical guidelines. Written informed consent was obtained from the patient for the publication of this article and the accompanying images.

The patient, a 76-year old Caucasian woman, began experiencing urticaria pigmentosa in 2014 and was initially treated at the Fondazione IRCSS-Policlinico “San Matteo” in Pavia, Italy. Blood analysis reported an increased serum tryptase level (95.5 microg/L; normal range: 0.1-11.4 microg/L), and medical imaging showed moderate splenomegaly (≃15 cm) and osteoporosis. The BM biopsy documented MC aggregates with 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 gradual spleen resizing and maintained 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 (25x10^9/L). Medical imaging revealed the presence of organomegalies (lymph nodes, spleen and liver). A second BM biopsy confirmed the presence of neoplastic MC (20%) and documented the appearance of monoclonal CD5$^+$, CD200$^+$ CD79$^{+/-}$, CD23$^+$, CD20$^+$, CD19$^+$ lymphoid B cells (50%). Fluorescence *in situ* hybridization (FISH) showed deletion (del) (13q14) and del(17p13) in CLL, while next-generation sequencing (NGS) confirmed both *TP53* mutation (variant allele frequency [VAF]: 88%) and unmutated immunoglobulin heavy chain variable region (*IGVH*); SM persisted with *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-PDGFR*α and β, *JAK2 V617F, CALR, MPL, BCR-ABL p210/190/230*) and resulted negative. Thus, the patient was diagnosed with SSM-CLL, and very high risk CLL stage according to the CLL-International Prognostic Index (CLL-IPI) was confirmed. 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 (44x10^9/L). 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 back to her home in Catania, Sicily, in order to be treated locally at the “Policlinico G. Rodolico”, which is the 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 (platelets [PLT] 48x10^9/L) with subsequent hemorrhagic risk, we decided to avoid avapritinib and start acalabrutinib in monotherapy at a dose of 100 mg/die. Since the patient showed good tolerance, we increased the drug dose to 200 mg one month later. The patient experienced a

gradual improvement in blood count and after four months she became transfusion independent. Medical imaging confirmed progressive hepatic, spleen and lymph node enlargement (≥50% from baseline). We, therefore, considered the possibility of adding 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 suffered particularly badly. Consequently, the idea of using 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 decrease in serum tryptase (from 155 to 64.3 and then to 45.6 microg/L) within six months of starting CLL therapy. Moreover, the patient obtained a complete resolution of SM-related manifestations. Therefore, also SM was considered to be in PR according to international response criteria. At the latest follow-up visit (October 2025), blood counts were as follows: hemoglobin 10 g/dL, PLT 267x10^9/L, and white blood cell count 13.9x10^9/L (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). Bone marrow 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 is proceeding with treatment, and maintaining a good performance status. Our case and the other cases of SM-CLL available in literature are summarized in Table 1.

It can be deduced from literature that, in SM-CLL cases, SM

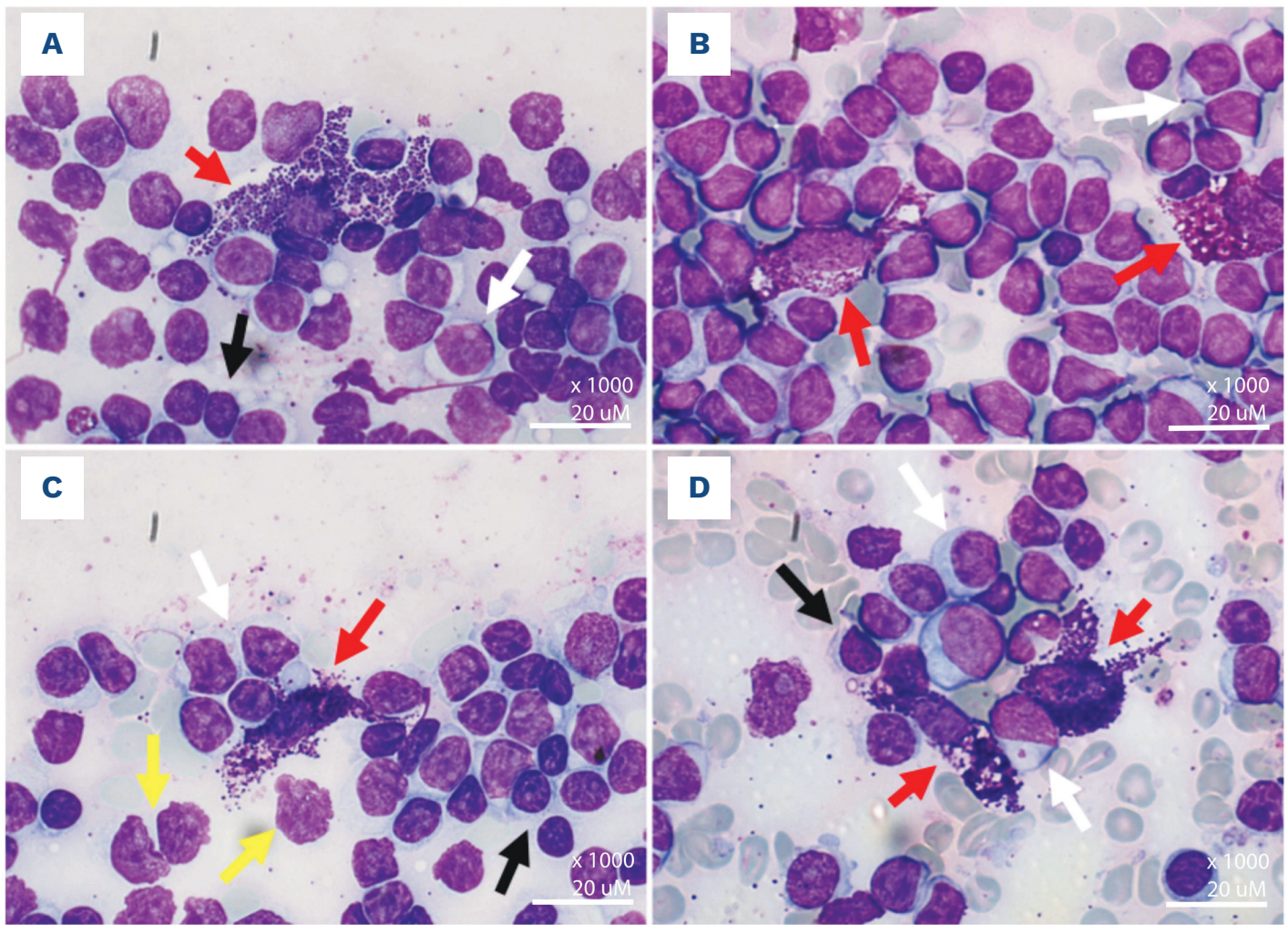

Figure 1. Optical microscopy morphology of bone marrow of systemic mastocytosis-chronic lymphoid leukemia. (A-D) Regarding the chronic lymphoid leukemia (CLL) component, these four images show a cellularity profile predominantly represented by two cell types: 1) small lymphocytes with eccentric nuclei, coarse and dense chromatin and a narrow, weakly basophilic cytoplasmic rhyme (black arrows, A, C, and D); 2) numerous medium-sized prolymphocytes, larger than B-cell CLL (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, A-D). The classic "Gumprecht Shadows" or "smudge cells" are also visible (C). These elements result from mechanical disruption of lymphocytes during smear preparation (yellow arrows) and represent a hallmark of CLL. Regarding the systemic mastocytosis (SM) component, all panels (A-D) show the presence of atypical, generally spindle-shaped mast cells (MC) with polar cytoplasmic elongations (atypical MC 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). (A) An activated atypical mast cell with diffusely scattered blue-purple granules infiltrating intercellular spaces.

may favor CLL progression and aggressiveness. Indeed, by secreting several pro-tumoral factors, MC are able to govern the neoplastic stromal microenvironment. For example, histamine and IL-10 exert an immunosuppressive effect, tryptase stimulates endothelial cell proliferation (neo-angiogenesis), and vascular endothelial and fibroblast growth factors (VEGF and FGF-2) further promote tumor vascularization.[8] In this regard, Molica *et al.* have demonstrated that the percentage of tryptase$^+$ MC in CLL correlates with major microvascular density, unfavorable genetic aberrations (i.e., 11q and 17p), and, thus, disease progression.[9] Therefore, MC 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 (an anti-CD52 monoclonal antibody used to address the CLL-associated inflammatory component) achieved a parallel reduction of both BM angiogenesis and MC percentage.[10] MC 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 *cKIT-D816V*, which is detectable in the majority of patients with SM and is considered to contribute to the differentiation of

TABLE 1. Summary of major characteristics of patients affected by systemic mastocytosis associated with chronic lymphoid leukemia / small lymphocytic lymphoma, extrapolated from those few case reports in the literature.

Ref	N	Diagnosis (year)	Tryptase ng/mL	SM symptoms	CD2$^+$ MC	CD25$^+$ MC	CD30$^+$ MC	Biology	CLL therapy	SM therapy	Outcome
2	1	CLL (2001) SM (2006)	10.3	None	No	Yes	NA	In both cases: SM: *D816V*$^-$	R-benda x 3 FCR+AlloSCT	MUD alloSCT for both diseases	CLL: CR SM: SD
	2	CLL (2003) PCM + SM (2009)	21.4	Rash	NA	Yes	NA	CLL: del(13q14.3)	R-lena	None	CLL: PR SM: PD
3	1	SM (1993) CLL (2000)	NA	Urticaria Osteolysis	Yes	Yes	NA	NA	None	H1/H2 blockers	CLL: SD SM: CI
4	1	CM from childhood SM-SLL (2005)	163	Diarrhea Flushing Headache Urticaria	No	Yes	NA	SM: *D816V*$^+$ SLL: *D816V*$^-$ +12; IGHR	FC (without R)	H1/H2 blockers	CLL: CR SM: SD
5	1	RAI 0 CLL (2001)	4xULN	Osteolysis	-	-	-	SM: *D816V*$^+$ CD52+ MCs	-	1st line: imatinib	SM: SD
		RAI 3 CLL + SM (2007)	-	Vertebral fractures	Yes	Yes	NA	CLL: del(11q) ZAP-70+	FCR (x 6) cases + anti-CD52	2nd line: anti-CD52 (x 6)	CLL: CR SM: SD
6	1	SM-CLL (2005) (urticaria >25 years) with CD25$^+$, KIT$^-$ MC in GI mucosa	130	Urticaria Pruritus GI tract	Yes	Yes	NA	SM: *D816V*$^+$ CLL: IGHR	NA	NA	NA
Our case	1	ISM (2014)	95.5	Urticaria	Yes	Yes	No	SM: *D816V*$^+$	-	H1/H2 blockers	CLL: PR SM: PR No more symptoms
		SSM + high-risk CLL (2023/2024)	281	Spleen >15 cm Osteoporosis GI tract Pruritus	Yes	Yes	No	CLL: del(13q14) del(17p13)	Single agent acalabrutinib	Denosumab (TKI avoided→ low PLT)	Loss of *cKIT* by NGS in PB

Data from our case are included. A recurrent characteristic in all cases is that systemic mastocytosis (SM) diagnosis generally anticipates that of chronic lymphoid leukemia (CLL) / small lymphocytic lymphoma (SLL). To our knowledge, our case is the only one reporting a more significative therapeutic outcome (partial remission [PR]) compared to other cases which reported SM persistence, even after matched unrelated donor (MUD) allogeneic stem cell transplant (alloSCT). +12: trisomy 12; anti-CD52: alemtuzumab; benda: bendamustine; CD: cluster of differentiation; CI: clinical improvement; CM: cutaneous mastocytosis; CR: complete remission; del: deletion; FCR: fludarabine, cyclophosphamide, rituximab; GI: gastrointestinal; H1/H2: histamine receptor 1 and 2; IGHR: immunoglobulin heavy chain rearrangement; ISM: indolent SM; lena: lanalidomide; MC: mast cells; N: number of cases described; NA: not assessed; NGS: next-generation sequencing; PB: peripheral blood; PCM: plasma cell myeloma; PLT: platelets; PR: partial remission; R: rituximab; RAI: CLL staging system; Ref: reference; SD: stable disease; TKI: tyrosine kinase inhibitors; ULN: upper limit of normal; ZAP-70: Zeta-chain-associated protein kinase 70.

neoplastic MC.[11] Consequently, TKI 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 (TYK). In 2011, they proved that two TYK, namely p-Lyn and p-BTK, are constitutively activated (phosphorylated) only on neoplastic MC (both *cKIT* positive and negative), especially in AdvSM. Furthermore, they confirmed that these TYK are involved in neoplastic survival by witnessing the inhibition of proliferation in p-Lyn and p-BTK knocked-out human neoplastic MC (HMC). In addition, they showed that while midostaurin blocks *cKIT* phosphorylation but is not able to down-regulate p-Lyn and p-BTK, other TKI, such as *BCR-ABL* inhibitors (bosutinib and dasatinib), exert the opposite effect. Therefore, they decided to combine both drugs to address neoplastic *cKIT* + MC. 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 BTKI. However, judging from the outcome of our patient after six months of acalabrutinib monotherapy, it is reasonable to speculate that specifically targeting both p-BTK and *cKIT* would allow a greater synergistic effect. Unfortunately, our patient could not receive avapritinib due to thrombocytopenia, but it would be useful 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 use NGS to identify potentially targetable non-*KIT* mutations. One of these 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 BTKI approved for the treatment of CLL either as 1st or subsequent line therapy, and acalabrutinib represents a primary choice in case of *TP53* mutation and del(17p). Several studies have already been carried out to assess BTKI 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 MC activation. More specifically, human MC 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 up-regulated by p-BTK, which is a member of the 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 MC mediators. Therefore, by using acalabrutinib to target p-BTK, we were able to counteract mediator-induced SM symptoms and achieve a complete clinical improvement. In order to 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 the 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 BTKI may impact the course of the disease.

In conclusion, the co-existence 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, BTKI 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 BTKI in SM. The first is an ongoing phase II 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 (https://clinicaltrials.gov/study/NCT04655118; last updated 27 October 2025). The second study is a phase II trial evaluating the ability of ibrutinib to reduce MC burden in AdvSM (including more aggressive subtypes). Although the study was terminated due to slow accrual, it offers preliminary insights into the feasibility of BTKI in this setting (https://clinicaltrials.gov/study/NCT02415608; last updated 20 September 2018). Results of both studies are eagerly awaited. Therefore, BTKI seem potential candidates to enter the SM armamentarium, and further studies are warranted to evaluate their effectiveness and safety in combination with TKI.

Authors

Manlio Fazio,[1,2] Chiara Elena,[3] Jacqueline Ferrari,[3] Virginia Camilotto,[4] Stefania Stella,[5,6] Dario Leotta,[1,7] Giuseppe Alberto Palumbo,[1,8] Francesco Di Raimondo[1,7,9] and Alessandra Romano[1,7,9]

[1]Division of Haematology and BMT, A.O.U. 'Policlinico G.Rodolico-San Marco', Catania; [2]Division of Hematology, Department of Human Pathology in Adulthood and Childhood "Gaetano Barresi", University

of Messina, Messina; [3]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo and University of Pavia, Pavia; [4]Department of Molecular Medicine, University of Pavia, Pavia; [5]Department of Clinical and Experimental Medicine, University of Catania, Catania; [6]Center of Experimental Oncology and Hematology, A.O.U. Policlinico "G.Rodolico-S.Marco", Catania; [7]Post-Graduation School of Haematology, University of Catania, A.O.U. 'Policlinico-San Marco', Catania; [8]Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G. F. Ingrassia", University of Catania, Catania, and [9]Dipartimento di Specialità Medico-Chirurgiche, CHIRMED, Sezione di Ematologia, Università degli Studi di Catania, Catania, Italy

Correspondence:
M. FAZIO - manliofazio@hotmail.it

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Disclosures

No conflicts of interest to disclose.

Contributions

AR and MF are responsible for study concept; MF carried out the literature research; MF and Dl prepared the original draft; AR, CE, JF and MF are responsible for clinical management; AR reviewed and edited the manuscript; SS is responsible for next-generation sequencing analyses; VC prepared the morphological images; AR, GAP and FDR revised the final version of the manuscript. All authors read and approved the final version of the manuscript for publication.

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Data-sharing statement

Data sharing is not applicable to this article as this is a single-patient case report and does not involve the generation of a dataset suitable for sharing in a public repository. All relevant clinical, laboratory, and therapeutic information necessary to understand and interpret the case has been fully reported within the manuscript.

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