Clinical response to dabrafenib and chemotherapy in clonally-related histiocytosis and acute lymphoblastic leukemia

Histiocytoses encompass a heterogeneous group of disorders characterized by tissue infiltration of cells with morphological and phenotypic features of macrophages or dendritic cells, which have been reclassified into five groups: i) L group - Langerhans cell histiocytosis (LCH)/Erdheim Chester disease (ECD); ii) C group - cutaneous histiocytoses; iii) M group - malignant histiocytoses; iv) R group - Rosai-Dorfman disease and v) H group - hemophagocytic lymphohistiocytosis (HLH).[1] Histiocytoses rarely occur during acute lymphoblastic leukemia (ALL) treatment, potentially due to trans-differentiation[2] or a common progenitor cell,[3] and there is no standard treatment in this particular situation. We herein report a case of *BRAF*-mutated non-LCH arising during T-ALL therapy who responded to dabrafenib and chemotherapy combination.

Our patient was a 7-year-old boy diagnosed in March 2020 with central nervous system (CNS)-positive T-ALL harboring the oncogenic *STIL-TAL1* fusion. He initially presented with right facial nerve palsy and hyperleukocytosis with an initial white blood cell count at 205x10^9/L. He received four-drug induction chemotherapy, achieved morphologic remission with positive end-induction minimal residual disease (MRD) by flow cytometry. He then received post-induction therapy according to Arm D of AALL0434 protocol,[4] with a negative flow-based end-consolidation MRD. In October 2020, during delayed intensification (DI), he developed persistent thrombocytopenia refractory to corticosteroids and intravenous immunoglobulins. Extensive investigation for refractory thrombocytopenia came back negative. However, a positron emission tomography (PET) scan showed hypermetabolic focal lesions in the mediastinum, 5th right rib and right tibial tuberosity. In December 2020, 7 months from T-ALL diagnosis, biopsy of the rib lesion revealed proliferation of multinucleated giant cells with emperipolesis that were CD68+, CD163+, S100+, fascin+, lysozyme+ and BRAF+, suggestive of Rosai-Dorfman disease (RDD). Whole-transcriptome analysis of the rib lesion revealed a *BRAF* V600E mutation and the *STIL-TAL1* fusion present at T-ALL diagnosis, suggesting a common clonal origin. Since RDD and T-ALL were clonally-related, leukemia treatment was prioritized and our patient pursued DI and maintenance therapy, including cranial irradiation. A follow-up PET scan in March 2021 showed histiocytosis progression despite ALL-based chemotherapy, which provided the rationale to introduce a BRAF inhibitor. Considering pre-existing transaminitis and thrombocytopenia, ALL maintenance chemotherapy was stopped and dabrafenib monotherapy at 5.25 mg/kg/day was initially started in April 2021, with a rapid metabolic response 1 month post-dabrafenib. In order to pursue T-ALL therapy, low-dose ALL maintenance chemotherapy was combined with dabrafenib in June 2021 and titrated based on patient's tolerance (monthly vincristine 1.5 mg/m^2/dose, prednisone 20 mg/m^2/dose twice a day for 5 days every month, daily 6-mercaptopurine 20 mg/m^2/dose, weekly methotrexate was omitted because of thrombocytopenia). Combination of dabrafenib and chemotherapy was well-tolerated. Unfortunately, the patient experienced an isolated CNS relapse in September 2021, 17 months from T-ALL diagnosis and 9 months from onset of histiocytosis. Dabrafenib was stopped at the time of relapse to begin ALL reinduction chemotherapy. Of note, thrombocytopenia <50x10^9/L without clinically active bleeding persisted from October 2020 to September 2021. PET scans prior to relapse showed progressive hypermetabolic uptake in the liver. A liver biopsy was inconclusive for etiology. Relapse was treated with intrathecal chemotherapy and daratumumab, to provide systemic therapy and potentially address his refractory thrombocytopenia,[5] followed by two cycles of the NECTAR regimen.[6] After a conditioning regimen with VP-16, anti-thymocyte globulin and total body irradiation, he proceeded to a matched-sibling donor hematopoietic stem cell transplantation (HSCT) in December 2021. At the time of this report, the patient is 7 months post-HSCT without evidence of T-ALL and histiocytosis.

Histiocytoses arising during ALL therapy are exceedingly rare, although they can also occur at diagnosis or following treatment completion. Our case is unique in several ways and expands the paradigm of molecularly-targeted therapies in histiocytic neoplasms. First, we report a rapid metabolic response in *BRAF*-mutated histiocytic lesions refractory to conventional chemotherapy after only 1 month of dabrafenib monotherapy. Donadieu *et al.*[7] previously reported rapid response within 2 months of vemurafenib in children with *BRAF* V600E-mutated refractory LCH. Given the co-existence of clonally-related *BRAF*-mutated RDD and T-ALL, ALL-directed therapy was prioritized prior to histiocytosis treatment. However, since RDD lesions were refractory to conventional chemotherapy, we report the feasibility of combining dabrafenib and low-dose maintenance ALL therapy to treat both diseases simultaneously. Combination of dabrafenib and chemotherapy was well-tolerated, without worsening pre-existing hematologic and hepatic toxicities. Although this

Table 1. Clinical characteristics and outcome of children with co-occurrence of histiocytic neoplasms during acute lymphoblastic leukemia therapy excluding H group disorders.

Article	Journal	Age[a] (yr)	Sex	ALL immuno-phenotype	Histiocytoses	Organ involved	Delay[b] (mth)	ALL treatment phase	*BRAF* mutation	Proven clonal relationship[c]	Treatment	Outcome
Alten 2015	Pediatric Blood & Cancer	6	M	T	HS (+HLH)	na	12	Maintenance	No	Yes	Treatment for secondary HLH (DEX, VP16, ATG, Basiliximab)	DOH
Aparicio 2008	Pediatric Dermatology	3	M	B	JXG	Skin	6	na	na	na	None	DOL (relapse)
Bleeke 2019	Pediatric Blood & Cancer	11	na	B/myeloid MPAL	HS	Liver, spleen	5	na	No	Yes	na	DOH
Cheon 2017	Pediatric and Developmental Pathology	16	M	B	JXG	Skin, bone, bone marrow	4	Interim Maintenance	na	na	ALL treatment continued	Alive, RH and RL, 14 mth
Chiles 2001	J Am Acad Dermatol	5	M	T	LCH	Skin then bone marrow/pleura	7	Maintenance	na	na	PRED,VBL,VP16/topical nitrogen mustard	DOH
Egeler 1998	Hematology/ Oncology Clinics of North America	3	M	na	LCH	na	12	Maintenance*	na	na	Chemotherapy NOSRadiotherapy	Alive, RL but not RH, 2 yrs
Egeler 1998	Hematology/ Oncology Clinics of North America	6	M	na	LCH	na	6	na	na	na	Chemotherapy NOS	Alive, RH and RL, 2 yrs
Egeler 1998	Hematology/ Oncology Clinics of North America	4	F	na	LCH	na	12	Maintenance	na	na	Chemotherapy NOS	DOH
Egeler 1998	Hematology/ Oncology Clinics of North America	10	M	na	LCH	na	12	Maintenance	na	na	Chemotherapy NOS	DOH
Egeler 1998	Hematology/ Oncology Clinics of North America	3	M	na	LCH	na	12	Maintenance	na	na	Chemotherapy NOS	DOH
Egeler 1998	Hematology/ Oncology Clinics of North America	9	M	na	LCH	na	6	na	na	na	Surgery	DOL (relapse)
Egeler 1998	Hematology/ Oncology Clinics of North America	13	M	na	LCH	na	6	na	na	na	Chemotherapy NOS	Alive, RL but not RH, 6 mth
Feldman 2004	Lancet Oncology	14	M	B	HS	Spleen, kidney, bone	21	Maintenance	na	Yes	VCR, CPM, DAUNO, MTX, VP16, CYTA, PRED then HSCT	Alive, RL, 10 mth
Ganapula 2014	Indian J Hematol Blood Transfus	4	M	T	HS	Pleura, bone	18	Maintenance	na	na	None	Died NOS
Jansen 2020	Pediatric Blood & Cancer	4	F	T	LCH	Bone then pleura, digestive tract, pancreas, kidney	6	Maintenance	No	na	ALL treatment continued then LCH-IV protocol (PRED, VBL) then Clofarabine	DOH

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Article	Journal	Age[a] (yr)	Sex	ALL immuno-phenotype	Histiocytoses	Organ involved	Delay[b] (mth)	ALL treatment phase	*BRAF* mutation	Proven clonal relationship[c]	Treatment	Outcome
Kanter 1976	Oral Surg	3	M	na	LCH	Bone	4	na	na	na	ALL treatment continued, surgery, CPM	DOH (concomittant ALL relapse)
Kato 2015	British Journal of Hematology	8	F	T	LCH	Skin, lungs	8	Maintenance	No	Yes	na	Died NOS
Kumar 2011	Pediatric Blood & Cancer	4	M	B	HS	Bone	7	Maintenance	na	Yes	DEXA, CPM, MTX, IFO, CYTA, VP16 then palliative radiation therapy	DOH
Onciu 2004	Am J Clin Pathol	13	M	B	HS	Spleen	3	na	na	Yes	Surgery	na
Pastor Jané 2011	Am J Dermatopathol	18	M	B	Indeterminate	Skin, bone, bone marrow, liver, spleen	3	Consolidation	na	na	ALL treatment continued then CYTA and Cladribine	Died of infection, histiocytosis not in remission
Pawińska-Wąsikowska 2020	Frontiers in Oncology	15	M	B	JXG (+ HLH)	Bone, skin	3	Consolidation	na	Yes	HLH2004 (PRED, VP16, CSA) then Tocilizumab and HSCT	Alive, RH and RL, 2 1/2 yrs
Perez Becker 2010	Pediatric Blood & Cancer	5	F	T	JXG (atypical)	Nodes then liver, kidney, lungs, digestive tract	5	na	na	Yes	ALL treatment continued then LCH-III protocol (MTX, VBL, PRED)	DOH
Rodig 2008	American Journal of Hematology	3	F	T	LCH (then LS)	Skin	18	Maintenance	na	Yes	na	Died of infection, histiocytosis not in remission
Soslow 1996	Blood	8	M	B	THL	Paraspinal mass	10	Maintenance	na	na	VP16, PRED	DOH
Soslow 1996	Blood	6	M	na	THL	Bone	20	Maintenance	na	na	VP16, IFO, CARBO	Alive, RL but not RH, 16 mth
Vallonthaiel 2016	World Journal of Radiology	6	F	B	ECD	Bone	24	Maintenance	No	na	None	Alive, RL but not RH
Venkataraman 2020	Pediatric Blood & Cancer	0,5	M	T	HS	Temporal mass	14	Maintenance	Yes	Yes	Targeted therapy (dabrafenib, trametinib)	Alive, RH and RL, 14 mth
Wang 2021	European Journal of Nuclear Medicine and Molecular Imaging	12	M	T	LCH	Bone marrow, nodes, liver, spleen	10	na	na	na	na	na
Wongchan-chailert 2002	Med Pediatr Oncol	8	F	na	THL	Extradural mass, bone	6	Maintenance	na	na	CHOP regimen (CPM, DAUNO, VCR, PRED)	Died of infection, histio-cytosis and ALL not in remission
Yokokawa 2015	Genes Chromosomes and Cancer	7	M	T	LCH	Skin then lungs	22	Maintenance	na	Yes	JLSG-02 protocol (CYTA, VCR, PRED)	DOH

[a] Age at ALL diagnosis (years [yr] old); [b] Delay between ALL diagnosis and onset of histiocytosis (months [mth]), [c] Proven clonal relationship between ALL and histiocytosis: same TCR gene rearrangement and/or same mutation identified at ALL diagnosis. ALL: acute lymphoblastic leukemia; ATG: anti-thymocyte globulin; CARBO: carboplatin; CPM: cyclophosphamide; CSA: cyclosporin; CYTA: cytarabine; DAUNO: daunorubicin; DEXA: dexamethasone; DOH: died of histiocytosis; DOL: died of leukemia; ECD: Erdheim-Chester disease; HLH: hemophagocytic lymphohistiocytosis; HS: histiocytic sarcoma; HSCT: hematopoietic stem cell transplantation; IFO: ifosfamide; JXG: juvenile xanthogranuloma; LCH: Langerhans cell histiocytosis; LS: Langerhans sarcoma; MTX: methotrexate; na: not available; NOS: not otherwise specified; PRED: prednisone; RH: remission of histiocytosis; RL: remission of leukemia; VBL: vinblastine; VCR: vincristine; THL : true histiocytic lymphoma.

combination resulted in a significant metabolic response of RDD lesions, leukemia remission was not durable as patient experienced CNS relapse 3 months following combination therapy. Of note, Gaspari *et al.*[8] also reported the safety and efficacity of vemurafenib combined with vinblastine/prednisone in a newborn with multisystem LCH.

A literature review of children with co-diagnosis of histiocytosis (excluding H group disorders) during ALL treatment identified 30 cases. Median age at ALL diagnosis was 6 years old (range, 0.5-18 years) and median time between ALL diagnosis and histiocytosis onset was 7.5 months (range, 3-24 months). Most patients were boys. Leukemia immunophenotype included ten T-ALL. Histiocytic disorders arising during ALL treatment comprises LCH (47%), histiocytic sarcoma (23%), juvenile xanthogranuloma (13%), true histiocytic lymphoma (10%), Erdheim-Chester disease (ECD) (3%) and indeterminate (3%). Prognosis was poor with 19 deaths (12 related to histiocytosis). Twenty-one patients did not achieve remission of histiocytosis. ALL treatment alone in this context appeared ineffective (remission in 1/5 cases). Four children experienced ALL relapse following diagnosis of histiocytosis, with two dying of ALL progression.

The clinical course of our patient is consistent with key findings summarized above. Although the morphologic appearance of our patient's histiocytic lesions is highly suggestive of RDD, the *BRAF* V600E mutation is not characteristic of RDD, but rather represents a molecular hallmark of LCH and/or ECD.[9] This morphologic/molecular discrepancy is reminiscent of mixed histiocytosis arising as part of malignant hemopathy associated with clonal hematopoiesis previously reported in adults with ECD.[10,11] It

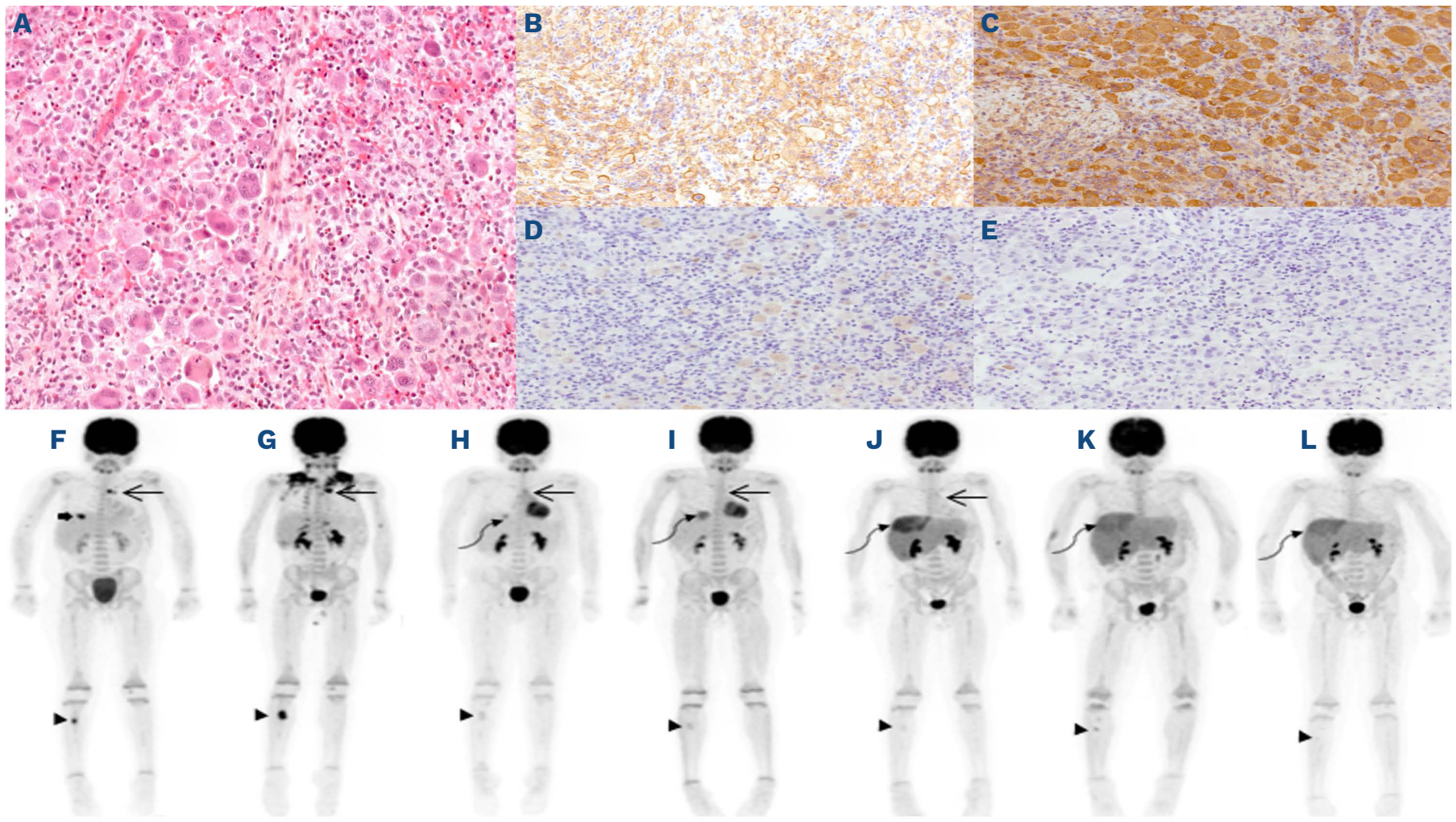

Figure 1. Pathology of rib lesion and evolution of metabolic response over the course of therapy. (A) Rib lesion depicting predominant infiltration of large, multinucleated histiocytic cells with evidence of emperipolesis in the absence of necrosis or mitosis. The histiocytic cells are strongly positive for CD68 (not shown), (B) CD163, (C) Fascin, (D) weak and focal S100 staining and (E) negative for CD1a and CD207 (not shown). The following immunostains are negative: CD15, CD20, CD30, CD45, CD117, ALK, PAX5, EMA, HLA-DR, and MPO (not shown). Evolution of metabolic response by ^{18}F-fluorodeoxyglucose positron emission tomography (PET) scans over the course of therapy. (F) At diagnosis of histiocytosis: mediastinal nodules (long arrow) SUV_{max} 4.2 and 8.2, right tibial diaphysis lesion (arrowhead) SUV_{max} 6.8 and 5th rib lesion (thick arrow) SUV_{max} 8.1; (G) post-rib biopsy and continuation of ALL therapy: progressive disease in the mediastinum SUV_{max} 10.1 and 12.4 and tibia SUV_{max} 11.5; (H) 1 month post-dabrafenib monotherapy: almost complete metabolic response in the mediastinum SUV_{max} 3.0 and right tibia SUV_{max} 1.5, new hepatic focus SUV_{max} 3.4 (curvilinear arrow) with remaining liver SUV_{max} 1.6 and liver size 14.5 cm CC; (I) 3 months post-dabrafenib and maintenance chemotherapy combination: complete metabolic response in the mediastinum and stable uptake in right tibia SUV_{max} 2.0. Progressive uptake of liver lesion SUV_{max} 4.3 with remaining liver SUV_{max} 2.0; (J) at isolated central nervous system relapse: no significant uptake in mediastinum or right tibia, progression in the uptake of liver lesion SUV_{max} 5.6 with diffuse hyperactivity of the remaining liver SUV_{max} 3.5; (K) after re-induction chemotherapy with nelarabine: no mediastinal lesion. Discrete uptake right tibia SUV_{max} 2.6. Persistent increased uptake in liver lesion SUV_{max} 4.0 and remaining liver SUV_{max} 3.2; (L) 100 days post-hematopoietic stem cell transplantation: no mediastinal or tibial lesions. Stable uptake in liver lesion SUV_{max} 4.0 and remaining liver SUV_{max} 3.0.

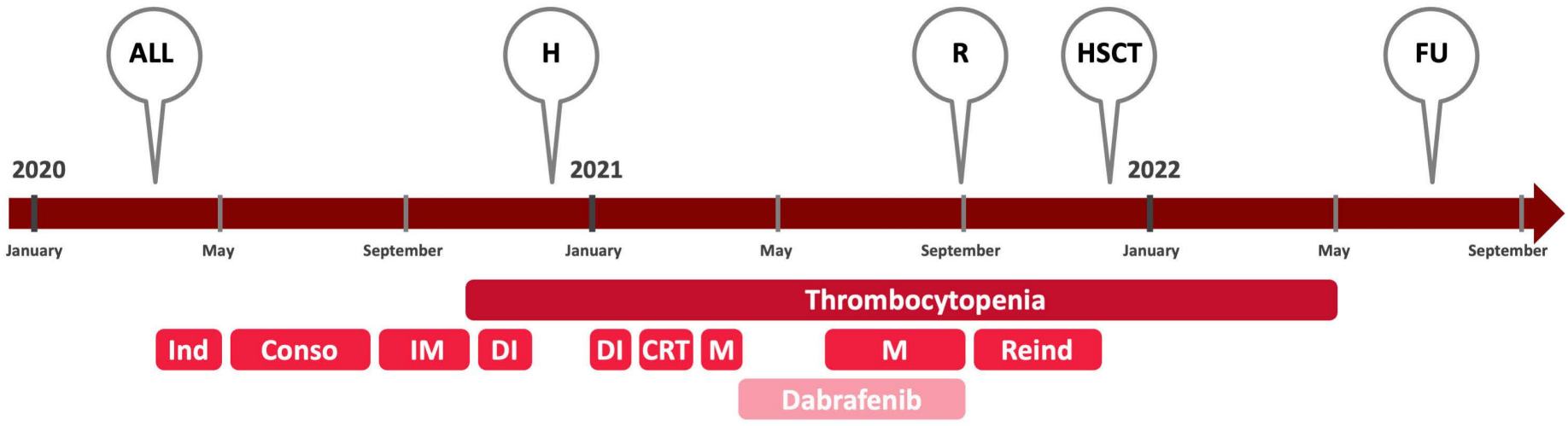

Figure 2. Timeline illustrating different events and treatments of the case report. ALL: diagnosis of acute lymphoblastic leukemia; Conso: consolidation; CRT: cranial irradiation; DI: delayed intensification; FU: last follow-up; H: diagnosis of histiocytosis; HSCT: hematopoetic stem cell transplantation; Ind: induction; IM: interim maintenance; M: maintenance, R: relapse of acute lymphoblastic leukemia; Reind : reinduction.

remains unclear whether co-occurrence of histiocytosis confers a worse prognosis when associated with ALL or *vice versa*, although our literature review signals a high rate of histiocytosis-related mortality. Recent evidence of MAPK pathway activation in most histiocytic disorders paves the way for molecularly-targeted therapies in combination with conventional chemotherapy, as illustrated in this case, to treat leukemic and histiocytic entities concomitantly. This therapeutic combination strategy warrants further validation; however, prospective assessment of such strategy is unforeseeable due to the rarity of these pathologies. Therefore, our case provides a proof-of-concept demonstrating safety of dabrafenib in combination with chemotherapy, and may represent an alternative therapeutic option for *BRAF*-mutated histiocytosis arising during ALL therapy, either as a definitive treatment or as a bridge to HSCT consolidation, given their poor outcome. Furthermore, since ALL maintenance chemotherapy is similar to LCH-based backbone, future prospective evaluation of BRAF inhibitor in combination with conventional chemotherapy for high-risk *BRAF*-mutated multisystemic LCH may be warranted.

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Contributions

GH and THT designed the study, reviewed the literature, analyzed the data and wrote the manuscript; SL, AR, SC, DS and THT performed molecular analysis; DDS and ST provided pathology and radiology review; HB, CL, PT, SC and THT provided patient care and clinical information. All authors revised and approved the manuscript.

Data-sharing statement

Additional data can be requested via the corresponding author by email.

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