Clinical Case Report

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Angioimmunoblastic T-cell lymphoma and hypereosinophilic syndrome with *FIP1L1/PDGFRA* fusion gene effectively treated with imatinib

A case report

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Abstract

Rationale: Hypereosinophilic syndrome (HES) is a rare disorder characterized by hypereosinophilia and organ damage. Some cases of HES are caused by the *FIP1L1/PDGFRA* fusion gene and respond to imatinib. *FIP1L1/PDGFRA*-positive HES occasionally evolves into chronic eosinophilic leukemia or into another form of myeloproliferative neoplasm; however, the development of a malignant lymphoma is very rare. We present a rare case of angioimmunoblastic T-cell lymphoma (AITL) and HES with the *FIP1L1/PDGFRA* gene rearrangement.

Patient concerns: A man in his 30s presented to our hospital with fever, hypereosinophilia, widespread lymphadenopathy, and splenomegaly. Laboratory tests showed hypereosinophilia, increased soluble interleukin-2 receptor, and increased vitamin B12. Positron-emission tomography with ^{18}F fluorodeoxyglucose (FDG) showed positive FDG uptake in multiple enlarged lymph nodes throughout the body and the red bone marrow. A bone-marrow biopsy showed hypereosinophilia without dysplasia and an increased number of blasts. The FIP1L1/PDGFRA fusion gene was positive upon fluorescence in situ hybridization (FISH) analysis of the peripheral blood. Furthermore, biopsy of a lymph node from the neck revealed restiform hyperplasia of capillary vessels, with small lymphoma cells arranged around the capillaries. Lymphoma cells were positive for CD3, CD4, and CD10, and negative for CD20. Lymphoma cells were also positive for the FIP1L1/PDGFRA fusion gene by FISH analysis.

Diagnoses: From these findings, the patient was diagnosed with HES and AITL with FIP1L1/PDGFRA.

Interventions: After the diagnosis, corticosteroid was administered but was ineffective. Imatinib was then administered.

Outcomes: Imatinib was very effective for treating HES and AITL, and complete remission was achieved in both.

Lessons: This report presents the first case in which the *FIP1L1/PDGFRA* fusion gene was positive both in peripheral blood and lymph nodes, implying the possibility that the tumor cells acquired the *FIP1L1/PDGFRA* fusion gene in the early stage of hematopoietic progenitor cell developments. Imatinib was very effective in treating both HES and lymphoma, suggesting that the *FIP1L1/PDGFRA* fusion gene plays a key role in the pathogenesis of both HES and lymphoma.

Abbreviations: AITL = angioimmunoblastic T-cell lymphoma, CEL = chronic eosinophilic leukemia, CI = conflicts of interest, CR = complete remission, CT = computed tomography, FDG = ^{18}F-fluorodeoxyglucose, FDG-PET = positron-emission tomography with ^{18}F-fluorodeoxyglucose, FISH = fluorescence in situ hybridization, HE = hypereosinophilia, HES = hypereosinophilic syndrome, IL = interleukin, LDH = lactate dehydrogenase, MPN = myeloproliferative neoplasm, SD = standard deviation, sIL-2R = soluble interleukin-2 receptor, TCR = T-cell receptor.

Keywords: angioimmunoblastic T-cell lymphoma, *FIP1L1/PDGFRA*, hypereosinophilic syndrome, imatinib

1. Introduction

Hypereosinophilic syndrome (HES) encompasses a group of rare disorders characterized by the presence of marked peripheral blood eosinophilia, tissue eosinophilia, or both, resulting in organ damage attributable to the eosinophilia.[1–3] HES can be treated with steroids, hydroxyurea, and interferon-α; however, when the *FIP1L1/PDGFRA* fusion gene is present, imatinib is an effective treatment alternative.[1,2] HES sometimes arises in combination with chronic eosinophilic leukemia (CEL), myeloproliferative neoplasms (MPNs), and malignant lymphoma, making it a life-threatening condition. From previous reports, the *FIP1L1/PDGFRA* fusion gene is sometimes found in CEL or MPN with HES[1], but very rarely in malignant lymphoma. Here, we report a case of HES with lymphoma in which the *FIP1L1/PDGFRA* fusion gene was present in both diseases. Moreover, imatinib effectively treated both diseases.

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The authors declare no conflicts of interest.

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Table 1

Laboratory findings at admission.

WBC	12890	/μL	TP	7.4	g/dL	IgG	2106.7	mg/dL
Neut	22.0	%	Alb	3.8	g/dL	IgA	417.9	mg/dL
Lymp	18.0	%	T-Bil	0.3	mg/dL	IgM	89.2	mg/dL
Mono	1.0	%	D-Bil	0.1	mg/dL	IgE	3	IU/mL
Eos	55.0	%	ALP	302	IU/L	ferritin	406.4	ng/mL
Baso	2.0	%	AST	9	IU/L	sIL-2R	2581.0	U/mL
Myelo	2.0	%	ALT	7	IU/L			
blast	0	%	LDH	194	IU/L	Vit B12	4700	pg/mL
RBC	225×10^4	/μL	γ-GTP	75	IU/L	Folic acid	4.8	ng/mL
Hb	7.5	g/dL	BUN	9.5	mg/dL			
Ht	22.2	%	Cre	0.61	mg/dL	IL-2	<5	pg/mL
MCV	98.7	fL	Na	139	mEq/L	IL-3	<31	pg/mL
MCH	33.3	pg	K	4.0	mEq/L	IL-5	7.0	pg/mL
MCHC	2.8	%	Cl	103	mEq/L			
Plt	12.4×10^4	/μL	Ca	8.6	mg/dL			
			CRP	0.71	mg/dL			

2. Case report

A man in his 30s visited a local clinic because of fever and cervical lymphadenopathy. Computed tomography (CT) revealed widespread lymphadenopathy and splenomegaly. His laboratory tests showed increased lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) levels, and hypereosinophilia (HE), indicating a possible hematological disorder. He was then referred to our hospital. The patient had a pre-existing condition of epilepsy, for which he had been receiving sodium valproate and carbamazepine for more than 10 years without adverse effects. His family history was negative for hematological abnormalities, including HE. He had a temperature of 38.2°C, but his other vital signs were within the normal range. When he visited our hospital, several lymph nodes were palpable in his neck (the largest of which measured approximately 20 mm).

A complete blood count showed leukocytosis with HE (55.0% of white blood cells), anemia, and mild thrombocytopenia. Blasts were not observed in the peripheral blood. Biochemical testing showed increased vitamin B_{12} and sIL-2R levels (Table 1). Tested cytokine (such as interleukin [IL]-2, IL-3, or IL-5) levels were within the normal range. The *FIP1L1/PDGFRA* fusion gene was positive (68%) by fluorescence in situ hybridization (FISH) analysis in the peripheral blood (Fig. 1A).

A bone-marrow biopsy was performed to test for HE. A bone-marrow biopsy showed HE (30.8% of nucleated cell counts) without dysplasia and a number of blasts was not increased (0.8% of nucleated cell counts). Furthermore, no lymphoma cells were detected in the bone marrow. No evidence of monoclonal tumor cells was found by flow cytometry analysis. A chromosomal analysis revealed a normal G-band karyotype. The T-cell receptor (TCR) gene rearrangement was negative based on Western blot analysis of the bone marrow, whereas the *FIP1L1/PDGFRA* fusion gene was positive in segmented nucleated cells (82%) based on FISH analysis (Fig. 2). The patient had high fever, anemia, and splenomegaly most likely from the eosinophilia; thus, he was diagnosed with *FIP1L1/PDGFRA*-positive HES.

In addition, a CT from the previous hospital revealed widespread lymphadenopathy and splenomegaly; thus, positron-emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) was performed. As shown in Figure 3A, FDG-PET showed

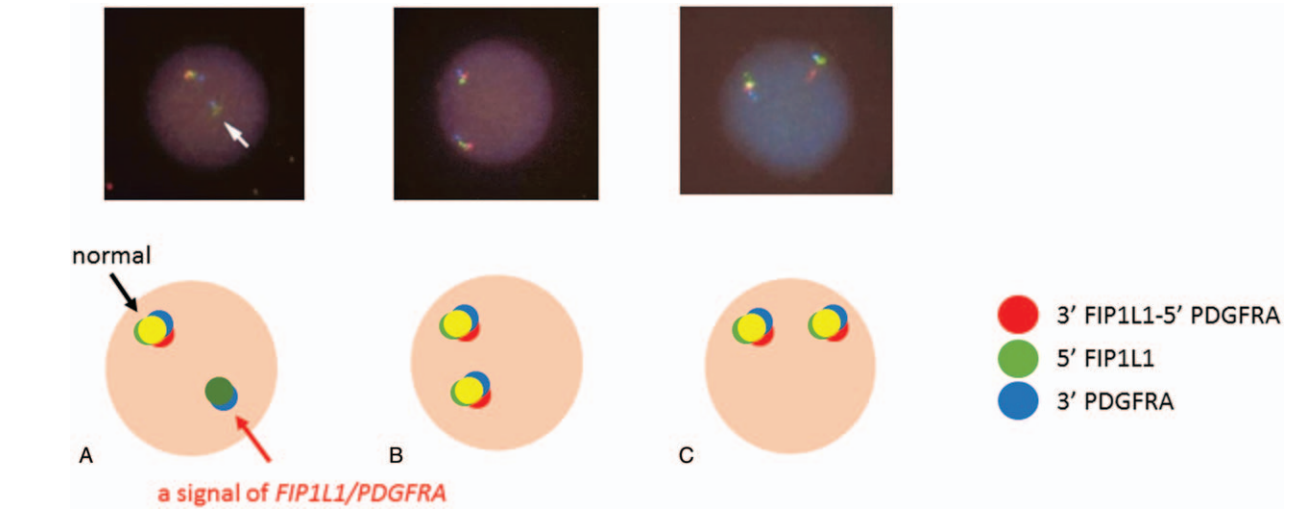

Figure 1. (A) FISH analysis of peripheral blood before imatinib treatment. The *FIP1L1/PDGFRA* fusion gene was positive in 86% of nucleated cells. The white arrow indicates the *FIP1L1/PDGFRA* fusion signal in the image of FISH. The black arrow indicates the normal signal and the red arrow indicates the *FIP1L1/PDGFRA* fusion signal in the illustration. (B) Six months after initiating imatinib therapy, the *FIP1L1/PDGFRA* fusion gene was negative. (C) One year after initiating imatinib therapy, the *FIP1L1/PDGFRA* fusion gene was also negative.

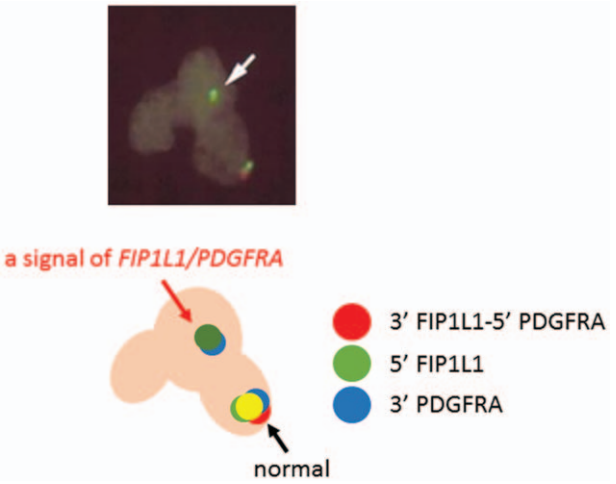

Figure 2. FISH analysis of the bone marrow. The *FIP1L1/PDGFRA* fusion gene was positive in 82% of segmented nucleated cells. The white arrow indicates the *FIP1L1/PDGFRA* fusion signal in the image of FISH. The black arrow indicates the normal signal and the red arrow indicates the *FIP1L1/PDGFRA* fusion signal in the illustration.

positive FDG uptake in multiple enlarged lymph nodes throughout body and in the red bone marrow. Because the FDG-PET findings strongly suggested malignant lymphoma, we performed a lymph-node biopsy of the neck. Microscopy revealed restiform hyperplasia of the capillary vessels, and small lymphoma cells with clear nucleoli were arranged around the capillaries (Fig. 4A). Lymphoma cells were immunohistochemically positive for CD3 (Fig. 4B), CD4, and CD10. These cells were also focally positive for CD21, and negative for CD20 and Epstein–Barr virus-encoded small nuclear RNA. The TCR gene rearrangement was positive based on Western blot analysis, and the *FIP1L1/PDGFRA* fusion gene was positive (86%) based on FISH analysis (Fig. 4C). From these findings, the patient was diagnosed with *FIP1L1/PDGFRA*-positive angioimmunoblastic T-cell lymphoma (AITL). All these findings suggested that the *FIP1L1/PDGFRA* fusion gene was involved in both hypereosinophilia in the peripheral blood and the development of AITL. From these findings, the clinical entity fell into the WHO 2016 category of myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*.

After lymph-node biopsy, corticosteroid (prednisolone) (0.5 mg/kg/day) was administered but was ineffective. After imatinib initiation (100 mg/day), the patient's symptoms, hypereosinophilia, and lymphadenopathy rapidly improved (Fig. 5) without any adverse events. Three months after imatinib initiation, FDG-PET revealed complete remission (CR) of AITL (Fig. 3B). A further 3 months later, the *FIP1L1/PDGFRA* fusion gene was negative based on FISH analysis in the peripheral blood (Fig. 1B). FDG-PET (Fig. 3C) and FISH analysis of the peripheral blood (Fig. 1C) after 1 year revealed CR of both HES and AITL, suggesting the successful treatment of HES and AITL by imatinib.

3. Methods

This study was approved by the ethics committee of Asahikawa Medical University (approval number 15208), and informed consent was obtained from the patient.

Peripheral blood and neck lymph nodes were processed by Carnoy's fixation, and FISH analysis was performed using a *FIP1L1/PDGFRA* probe (Vysis LSI 4q12 Tricolor, Rearrangement Probe; Abbott Japan, Tokyo, Japan). FISH analysis of the bone-marrow smear was performed using the *FIP1L1/PDGFRA* probe. One hundred cells were examined for each analysis and the number of cells that were positive for the *FIP1L1/PDGFRA* fusion gene was counted.

4. Discussion

HES encompasses a group of rare disorders characterized by the presence of marked peripheral blood eosinophilia, tissue eosinophilia, or both, resulting in organ damage attributable to the eosinophilia.[1–3] Blood HE should be diagnosed as absolute eosinophil count in peripheral blood of $>1.5 \times 10^9$/L observed on at least 2 examinations. Tissue HE should be defined

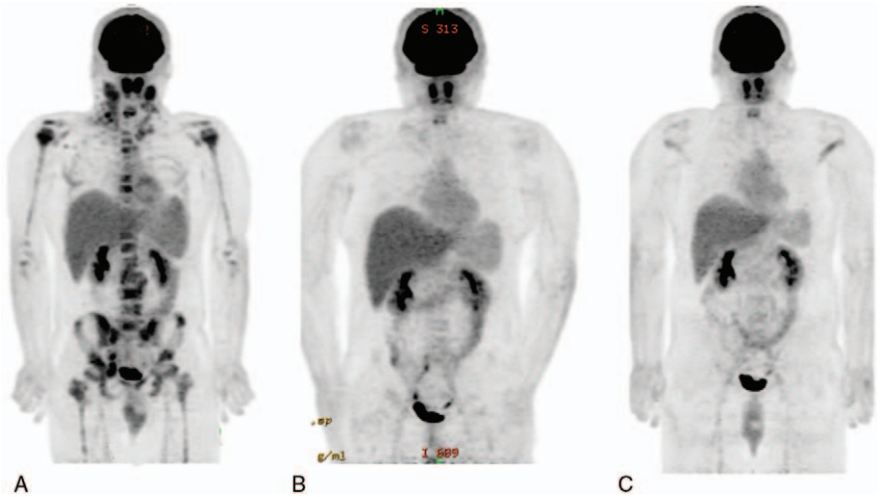

Figure 3. (A) Before imatinib treatment, positron-emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) revealed FDG uptake in multiple lymphadenopathies throughout the body and the red bone marrow. (B) Six months after initiating imatinib therapy, the FDG-PET scan showed no FDG uptake in the lymph nodes or the red bone marrow. (C) One year after initiating imatinib therapy, the FDG-PET scan also showed no FDG uptake in the lymph nodes or the red bone marrow.

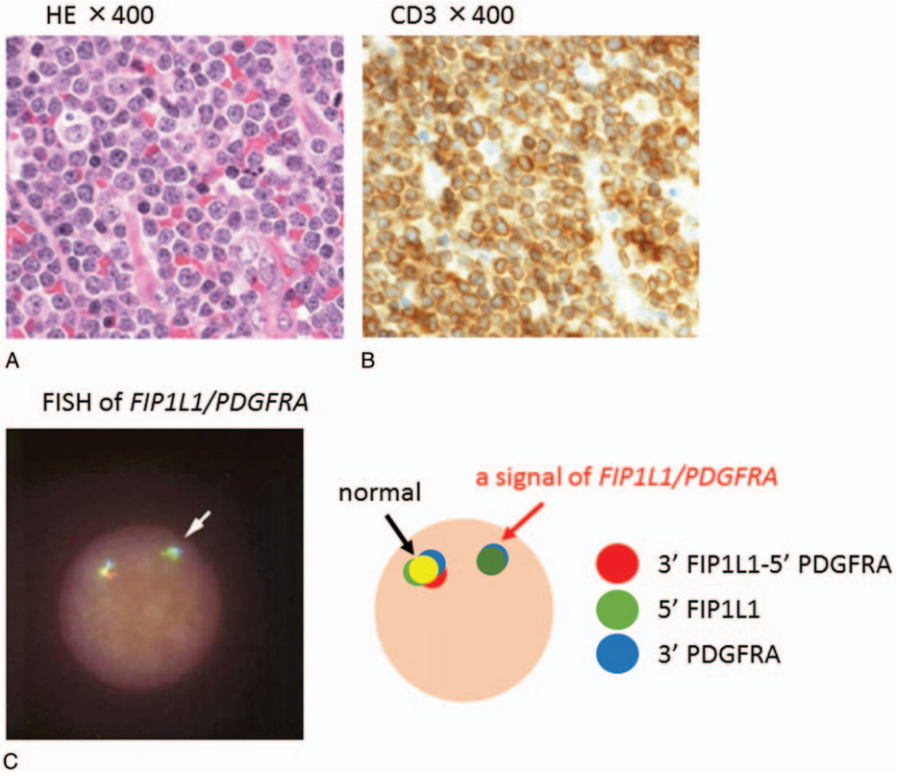

Figure 4. (A) Pathology findings from a lymph node revealed restiform hyperplasia of capillary vessels around which were small lymphoma cells with clear nucleoli. (B) Immunohistochemical findings were positive for CD3. (C) The *FIP1L1/PDGFRA* fusion gene was positive by FISH analysis. The white arrow indicates the *FIP1L1/PDGFRA* fusion signal in the FISH image. The black arrow indicates the normal signal and the red arrow indicates the *FIP1L1/PDGFRA* fusion signal in the illustration.

by the following findings: (1) eosinophil in the bone marrow exceeds 20% of all nucleated cells, (2) infiltration of eosinophils in the tissue is extensively increased confirmed by the experienced pathologist, and/or (3) the observation of remarkable extracellular deposition of eosinophil granule-derived protein in the tissue[1,2] HES can be diagnosed if patients have organ damage attributable to tissue HE, with the exclusion of other reasons for organ damage, in addition to fulfilling the criteria for blood HE.[2] It is ideal that persistent HE for >6 months is shown before the diagnosis of HES, but patients can be diagnosed with HES before passing the 6 months if they exhibit organ damage attributable to HE.[1] In the current report, the patient was diagnosed with HES because he fulfilled the criteria of HE and had fever, anemia and splenomegaly caused by HE.

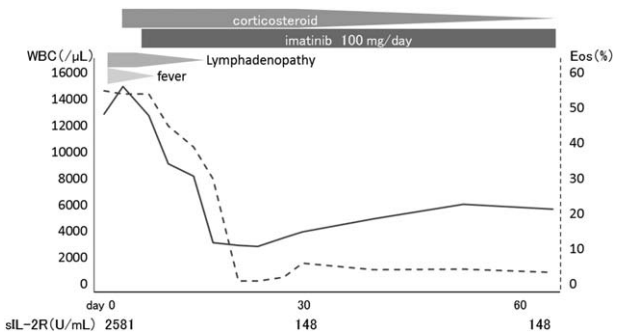

Figure 5. After lymph-node biopsy, corticosteroid (0.5 mg/kg/day) was administered, but was ineffective. Imatinib (100 mg/day) was initiated, and the fever and lymphadenopathy rapidly resolved. The patient's white blood cell and eosinophil counts also normalized.

A previous report classified HES into 6 clinical variants according to the clinical course and laboratory findings: myeloproliferative HES (M-HES), lymphocytic variant HES (L-HES), overlap HES (which involves a single organ in addition to eosinophilia), associated HES (which has eosinophilia as a secondary phenomenon), familial HES, and idiopathic HES (which cannot to be classified into the above categories).[1] M-HES and L-HES were classified according to the cellular origin. M-HES has features of a myeloproliferative process. M-HES is characterized by dysplastic eosinophils, circulating myeloid precursors, anemia, thrombocytopenia, splenomegaly, elevated serum vitamin B_{12} and/or tryptase levels, and atypical mast cells.[1,3] In addition, M-HES often progresses to CEL or acute myeloid leukemia. The *FIP1L1/PDGFRA* fusion gene has been reported in a few cases of M-HES.[1,4] This gene encodes an active tyrosine kinase that drives clonal eosinophil proliferation, and results from a microdeletion on chromosome 4q12.[4] This fusion gene is often detected in HES or CEL[4] but very rarely in malignant lymphoma.[5,6] Imatinib, a tyrosine kinase inhibitor, is reported to be very effective in *FIP1L1/PDGFRA*-positive HES or CEL.[1] By contrast, L-HES is reported to exhibit clones of an aberrant lymphocyte population producing cytokines (IL-5 and/or IL-3), which are the driving force of eosinophilia.[1,3] L-HES is characterized by a high prevalence of skin and soft tissue manifestations, elevated serum IgE, and thymus and activation-regulated chemokine levels, and progresses to lymphoma or

Table 2

Past cases of lymphoma with HES.[8–15].

case No	age/sex	pathology of lymphoma	complication of HES	*FIP1L1-PDGFRA* fusion gene	treatment	outcome	year
1	64 / M	LyP →T cell lymphoma	heart	NA	PUVA, PSL, HU, IFN-α, CHOP	PR	2000[8]
2	25 / M	ATCL	heart, CNS	NA	CHOP, HD-AraC	death	2001[9]
3	43 / F	PTCL	none	NA	CHOP, IMVP-16, ESHAP	death	2006[10]
4	35 / M	PTCL	none	negative	PSL, INF-α, CsA, CHOP	CR	2006[11]
5	48 / M	mycosis fungoides	heart	NA	PSL, IFN-α, PUVA	CR	2007[12]
6	63 / F	DLBCL	vasculitis	negative	THP-COP	CR	2009[13]
7	60 / F	PTCL	eosinophilic pneumonia	negative	CHOP, DeVIC, CHASE, HD-MTX	death	2011[14]
8	65 / M	PTCL	none	negative	CHOP, imatinib, mepolizumab, IFN-α	PR	2013[15]
9	30's / M	AITL	none	positive	PSL, imatinib	CR	current case

AITL = angioimmunoblastic T-cell lymphoma, ATCL = anaplastic T-cell lymphoma, CHASE = cyclophosphamide + high-dose cytarabine + dexamethasone + etoposide, CHOP = cyclophosphamide + doxorubicin + vincristine + prednisolone, CNS = central nerve system, CR = complete remission, CsA = cyclosporine, DeVIC = dexamethasone + etoposide + ifomide + carboplatine, DLBCL = diffuse large B-cell lymphoma, ESHAP = etoposide + methylprednisolone + cisplatin + cytarabine, HD-AraC = high-dose cytarabine, HD-MTX = high-dose methotrexate, HES = hypereosinophilic syndrome, HU = hydroxyurea, IFN-α = interferrone-α, IMVP-16 = ifosfamide + methotrexate + etoposide, LyP = lymphomatoid papulosis, NA = not available, PR = partial remission, PSL = prednisolone, PTCL = peripheral T-cell lymphoma, PUVA = psoralen ultraviolet A, THP-COP = cyclophosphamide + pirarubicin + vincristine + prednisolone.

leukemia.[1] The current patient had characteristics of both M-HES (positive for the *FIP1L1/PDGFRA* fusion gene, anemia, splenomegaly, and elevated serum vitamin B_{12} levels) and L-HES (progression to AITL), both of which responded well to imatinib. These findings suggest that the tumor cells have developed the *FIP1L1/PDGFRA* fusion gene at the earlier stage of hematopoietic progenitor cell development than in other cases of HES. In fact, previous reports have suggested that the *FIP1L1/PDGFRA* fusion gene mutation arises from pluripotent hematopoietic progenitor cells that may give rise to many different lineages, including eosinophils, mast cells, T-cells, B-cells, and others.[4,7] In the current case, the *FIP1L1/PDGFRA* fusion gene was detected in myeloid cells and lymphoid cells that developed tumorigenic transformation, but it might have also developed in cells of another lineage. Therefore, we should carefully observe whether cells of another lineage, in addition to eosinophil and lymphoid cells, develop tumorigenic transformation.

So far, 9 cases of lymphoma with HES have been reported (Table 2),[8–15] among which, this patient is the first case of lymphoma and HES with *FIP1L1/PDGFRA* fusion gene involvement. In addition, 2 previous reports have demonstrated the effectiveness of imatinib in treating *FIP1L1/PDGFRA*-positive lymphoma,[5,6] but those patients did not have eosinophilia. The most striking point in this case is that the *FIP1L1/PDGFRA* fusion gene was detected both in the peripheral blood and in the lymph nodes, strongly suggesting that *FIP1L1/PDGFRA* plays a key role in the pathogenesis of both HES and AITL. Imatinib alone induced CR of not only the HES but also the lymphoma in the current clinical case, which may further support the above speculation.

5. Conclusion

We have presented a rare case of AITL and HES that were both positive for the *FIP1L1/PDGFRA* fusion gene. In the current case, the *FIP1L1/PDGFRA* fusion gene was considered to cause neoplastic changes not only in myeloid cells but also in lymphoid cells. We therefore speculate that these tumor cells developed the gene at an earlier stage of hematopoietic progenitor cell development compared with other cases of HES.

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