

Common ancestral origin of indeterminate dendritic cell tumor and chronic myelomonocytic leukemia in clonal hematopoiesis

Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), and indeterminate dendritic cell tumor (IDCT) have been reported to be frequently associated with additional hematopoietic malignancies.¹⁻³ A retrospective analysis of patients with ECD has shown that those harboring clonal hematopoiesis (CH) are more likely to develop myeloid hematopoietic malignancies.⁴ However, the timing of CH acquisition and its impact on the development of additional hematopoietic malignancies remain unclear.⁵ Herein, we report that IDCT, chronic myelomonocytic leukemia (CMML), and hematopoietic stem cells (HSC) share two major drivers, *IDH2*^{p.R140Q} and *RUNX1*^{p.S167R}. Our results indicate that, although IDCT and CMML share common driver mutations, clonal divergence had occurred long before disease onset, as revealed by trajectory analysis based on whole-genome sequencing (WGS). This observation suggests that transdifferentiation is unlikely to be the underlying mechanism and instead supports the association of CH-related mutations, such as *IDH2*, with the development of hematopoietic malignancies, including histiocytic neoplasms.

A 68-year-old woman was referred to our hospital for a cutaneous mass and pain. The mass was initially suspected to be LCH, and thrombocytopenia had persisted for 1 year before the skin lesions appeared. She was under regular follow-up for her diabetes mellitus and showed decreased white blood cell (WBC) and platelet levels 3 years ago (Figure 1A). The patient had anemia just before she visited us, in addition to bleeding and pain from the skin tumor, explaining her poor performance status (PS3). Peripheral blood examination upon admission to our hospital revealed the following: WBC count, $12.9 \times 10^9/L$ (neutrophils 48.5%, monocytes 25.5%, eosinophils 1.5%, metamyelocytes 1.5%, myelocytes 1.5%, promyelocytes 0%, blasts 0%); red blood cell count, $2.15 \times 10^{12}/L$; hemoglobin, 6.3 g/dL; hematocrit, 20.5%; and platelets, $141 \times 10^9/L$ (Figure 1B). Skin biopsy performed at diagnosis showed massive mononuclear cell infiltration in the dermis, which was positive for CD1a, S-100, CD1c, and VE1 (*BRAF*^{V600E} mutation-specific antibody), and negative for CD207 (langerin) and CD115 (colony-stimulating factor 1 receptor [CSF1R]) (Figure 2A). Based on these findings, we diagnosed her with IDCT. Infiltration of IDCT cells was also observed in the bone marrow (BM) (Figure 2B). BM-infiltrating CD1a-positive, CD207-negative cells – such as those observed in IDCT – were positive for CD1c and negative for CD115, supporting their classification as dendritic cell neoplasms rather than monocyte/macro-

phage-lineage tumors (Figure 2C). Multiple lesions with ¹⁸F-fluoro-2-deoxyglucose (FDG) uptake were detected in the bone, skin, and muscle by positron emission tomography/computed tomography (PET/CT). Following two cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) therapy, the skin mass reduced, and the IDCT cells disappeared from the BM. However, an increase in monocytes in the peripheral blood persisted for 3 months, and marrow examination revealed CMML. We confirmed that the patient fulfilled all the essential criteria and one of the desirable criteria (clonal cytogenetics) with monocyte counts of $1.55 \times 10^9/L$ ($>1.0 \times 10^9/L$). Peripheral blood examination at first visit to our hospital revealed a WBC count of $12.9 \times 10^9/L$ and supported the diagnosis of myelodysplastic CMML diagnosis. After five cycles of CHOP therapy, complete metabolic remission was confirmed by PET/CT, and normalization of soluble interleukin-2 (sIL-2R) was observed. Considering the poor prognosis of disseminated IDCT and complications caused by CMML, we planned to perform unrelated cord blood transplantation (uCBT). However, 1 month after the sixth CHOP therapy cycle, CMML progressed to acute myeloid leukemia (AML), and the IDCT skin lesions relapsed. Venetoclax and azacitidine reduced AML cells; however, IDCT-related cutaneous masses showed progressive enlargement. To achieve deeper remission of IDCT, we used Dabrafenib 150 mg and Trametinib 1 mg (BRAF/MEK inhibitors) as a bridge therapy to uCBT. There was complete regression of the skin lesion, and the sIL-2R levels normalized after 21 days of the bridge therapy. The *BRAF*^{V600E} mutation in peripheral blood cell-free DNA (plasma cf*BRAF*^{V600E}) became negative. The patient underwent uCBT after conditioning with TBI (4 Gy), busulfan, fludarabine, and G-CSF-cytarabine. Acute graft-versus-host disease (GVHD) prophylaxis was initiated using cyclosporine A and mycophenolate mofetil. Engraftment was achieved on day 20, and she developed grade 3 GVHD (skin stage 1, intestine stage 2, liver stage 0), which was successfully treated with prednisolone. Plasma cf*BRAF*^{V600E} levels remained negative after the uCBT. Maintenance therapy with BRAF/MEK inhibitors was resumed on day 62. The patient has chronic GVHD of the skin, which is controllable. However, she was negative for both AML and IDCT on day 300 after uCBT. Figure 1 summarizes the patient's clinical course.

This study was approved by the Ethics Committee of the Institutional Review Board of the Institute of Medical Science, University of Tokyo (approval numbers: 2021-63-1222

CASE REPORT

and 2022-12-0616) and was conducted according to the principles of the Declaration of Helsinki. Clinical samples were collected after obtaining written informed consent from the patient.

To investigate the clonal relationship between IDCT and CMML, we isolated CD34⁺ and CD14⁺ cells from the BM by fluorescence-activated cell sorting (FACS) (Figure 3A) and skin biopsies of the IDCT lesions. We conducted whole-exome sequencing (NextSeq 2000; Illumina, San Diego, CA, USA) using the patient's nail-derived DNA as a germline control. Using the Genomon 2.6.2 pipeline,⁶ we identified mutations in (i) *IDH2*^{p.R140Q} with a variant allele frequency (VAF) of 33% in skin, 53% in CD14⁺ BM, and 52% in CD34⁺

BM, (ii) *RUNX1*^{p.S167R} in VAF of 30% in skin, 51% in CD14⁺ BM, and 51% in CD34⁺ BM, and (iii) *BRAF*^{p.V600E} with VAF of 25% in the skin (Figure 3B). The VAF values for *IDH2* and *RUNX1* mutations in CD34⁺ BM cells (nearly 50%) indicated that almost all stem/progenitor cells of the hematopoietic system were composed of *IDH2*/*RUNX1*-mutated clones; and the expansion of this clone may explain the thrombocytopenia that preceded IDCT. No CMML-specific myeloid driver mutations were identified. The absence of *BRAF*^{p.V600E} alleles in CD34⁺ BM was confirmed by targeted sequencing at a depth of 1,233, suggesting that skin and BM IDCT originated from differentiated cells. Given that IDCT and CMML were developed within a short period of 12

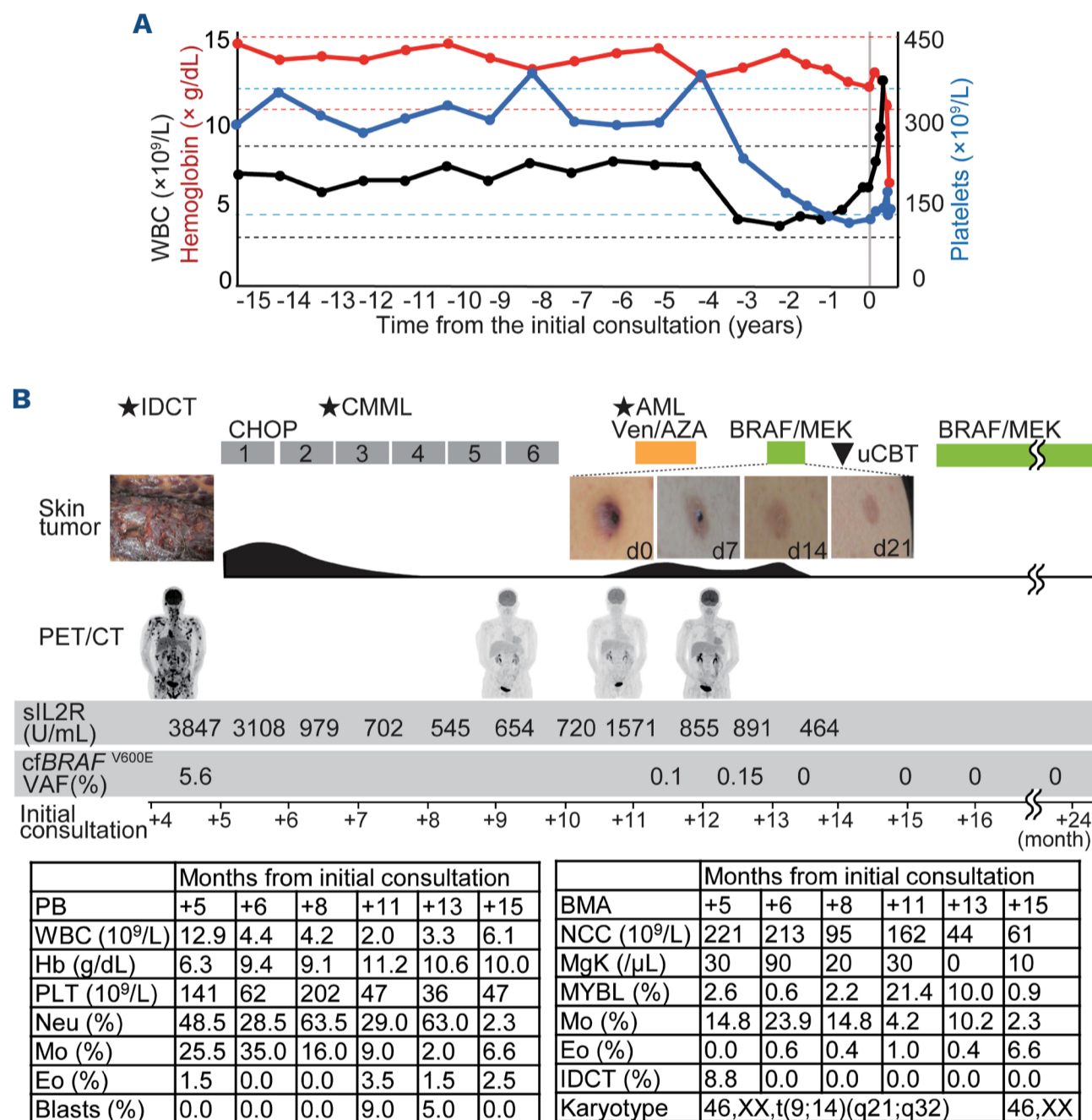


Figure 1. Clinical course of the patient. (A) Longitudinal changes in blood cell counts prior to indeterminate dendritic cell tumor (IDCT) diagnosis. Dashed lines indicate the reference ranges over time for each parameter: black for white blood cell (WBC), red for hemoglobin (Hb), and blue for platelets (PLT). (B) Clinical course and treatment; skin tumor of IDCT; axial images from combined positron emission tomography/computed tomography (PET/CT) with ¹⁸F-fluorodeoxyglucose (FDG) before treatment, after 5 cycles of doxorubicin, vincristine, cyclophosphamide, and prednisolone (CHOP) therapy, before venetoclax and azacitidine (Ven/AZA) therapy, and before BRAF inhibitor (Dabrafenib) and MEK inhibitor (Trametinib) combination therapy; trends in serum interleukin 2 receptor (sIL2R) (U/mL), variant allele frequency (VAF) of *BRAF*^{V600E} in peripheral blood (PB) plasma cell-free DNA (cfDNA) (*BRAF*^{V600E}); and trend in peripheral blood cell counts and bone marrow aspiration (BMA) findings at time point defined by months since the initial consultation. CMML: chronic myelomonocytic leukemia; AML: acute myeloblastic leukemia; uCBT: unrelated cord blood transplantation; BMA: bone marrow aspiration; Neu: neutrophils; Mo: monocytes; Eo: eosinophils; NCC: nucleated cell count; MgK: megakaryocytes; MYBL: myeloblasts.

CASE REPORT

months and they had *RUNX1/IDH2* mutations in common, we initially assumed that the IDCT and CMML clones had bifurcated recently. We, therefore, examined the trajectories of these clones by WGS of skin (IDCT) and CD14⁺ BM (CMML) samples. WGS libraries were prepared using a TruSeq Nano DNA Library Prep kit with 100 ng of input DNA and sequenced on a NovaSeq 6000 platform with 150-base paired-end reads (Illumina; San Diego, CA, USA). After filtering out single nucleotide polymorphisms and error calls, 564 events (524 variant types) were identified from two samples. Contrary to expectations, the two samples shared only 40 mutations, while the remaining 484 (86%) were private mutations (Figure 3C). Next, we estimated the time of the most recent common ancestors (MRCA) appearance of these clones (T(MRCA)) based on the ratio

of shared/private variants using the formula below:

$$T(\text{MRCA}) = \left[A \frac{c}{c + \frac{p1}{f}}, A \frac{c}{c + \frac{p2}{f}} \right]$$

where A is the age at sampling, c is the number of common mutations, p1 and p2 are the number of private mutations, and f represents clone fitness.

Assuming that the rate of mutation acquisition remained constant irrespective of driver mutation acquisition (f=1) and given that the patient was 68 years old at the time of sample collection, the MRCA of these clones was estimated to have existed at the age of 9.3 to 10.1, more than 50 years before the onset of these diseases (Figure 3E). This finding is consistent with the high VAF values of

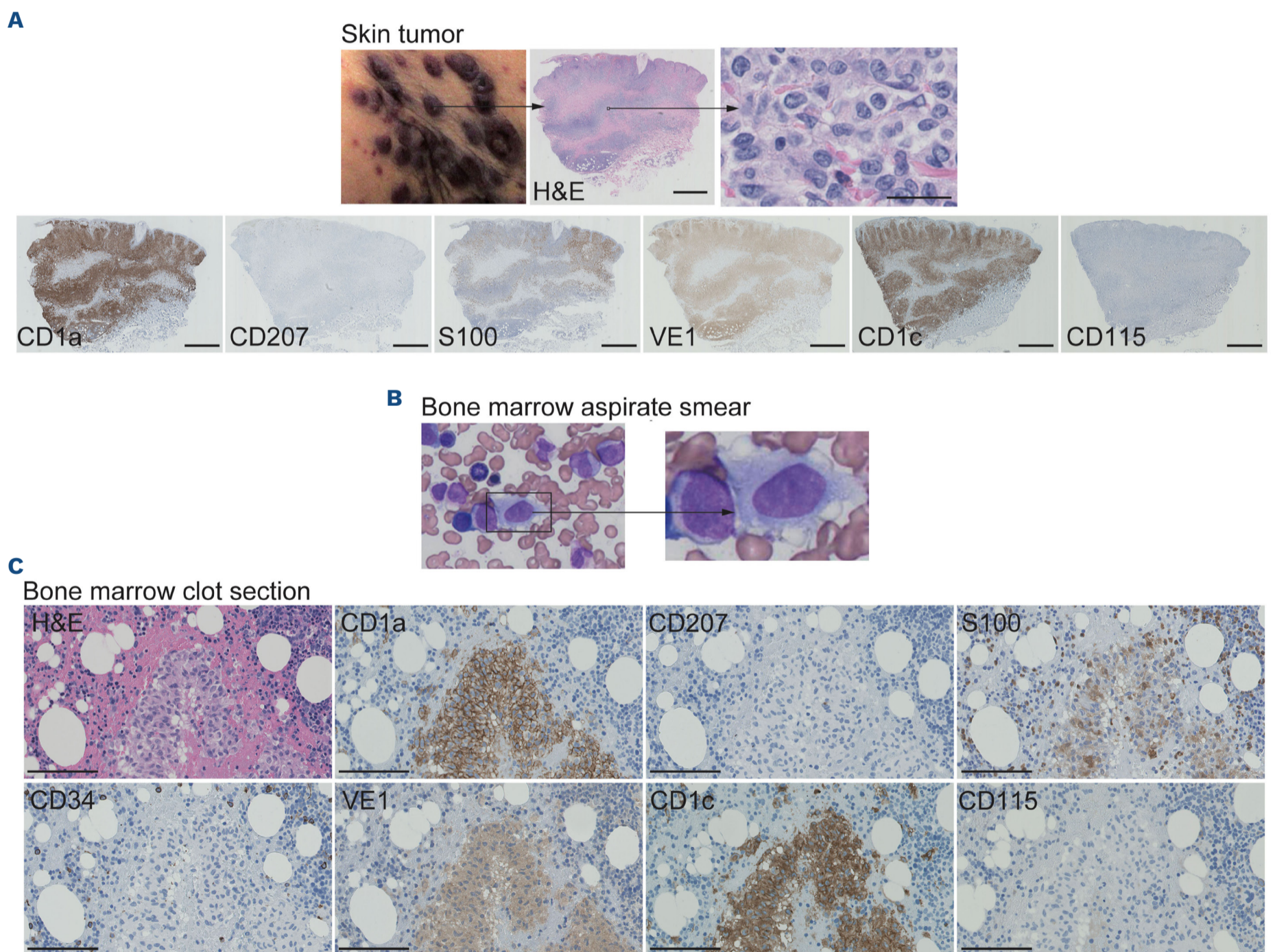


Figure 2. Tumor histological image. Histological images of tumors were created using NDP. View 2 (Hamamatsu Photonics, Shizuoka, Japan). (A) Hematoxylin and eosin (H&E) staining of the indeterminate dendritic cell tumor (IDCT) in the skin tumor. Low magnification: scale bar 1 mm. High magnification: scale bar 25 μ m. Immunohistochemical analysis of CD1a, CD207 (Langerin), S100, VE1, CD1c, and CD115 (CSF1R). Scar bar 1 mm. (B) Wright-Giemsa-stained bone marrow smears at diagnosis. Arrow: IDCT cell. (C) H&E staining of bone marrow clot sections and immunohistochemical analysis of CD1a, CD207 (Langerin), S100, CD34, *BRAF*^{V600E} mutation-specific antibody (VE1), CD1c, and CD115 (colony-stimulating factor 1 receptor [CSF1R]) in the same samples. Scar bar 100 μ m.

IDH2/RUNX1 mutations in CD1a⁻/CD34⁺ cells. If higher clone fitness ($f > 1$) is assumed for the IDCT or CMML clones, T(MRCA) becomes more recent but remains considerably earlier than the disease onset (Figure 3F).

IDCT is a rare histiocytic neoplasm of dendritic cell progenitor origin, which is CD1a positive and langerin negative. Like other histiocytic neoplasms, IDCT has been reported to co-exist with other hematologic neoplasms, accounting for 22-42% of cases.^{3,7} The most common hematological malignancies that co-exist with IDCT are

lymphoid tumors and CMML.

The exact reasons for the high rate of multiple hematological neoplasms in patients with IDCT remain elusive. However, evidence suggests that the transdifferentiation of lymphoid neoplasms into dendritic cells may be a potential cause. In one reported case, both IDCT and the co-existing chronic lymphocytic leukemia had variable diversity-joining (VDJ) rearrangements of the same clonotype.⁸ In another case, diffuse large cell lymphoma and IDCS, an IDCT-related neoplasm, shared *MYC* translocations.⁹ These cases

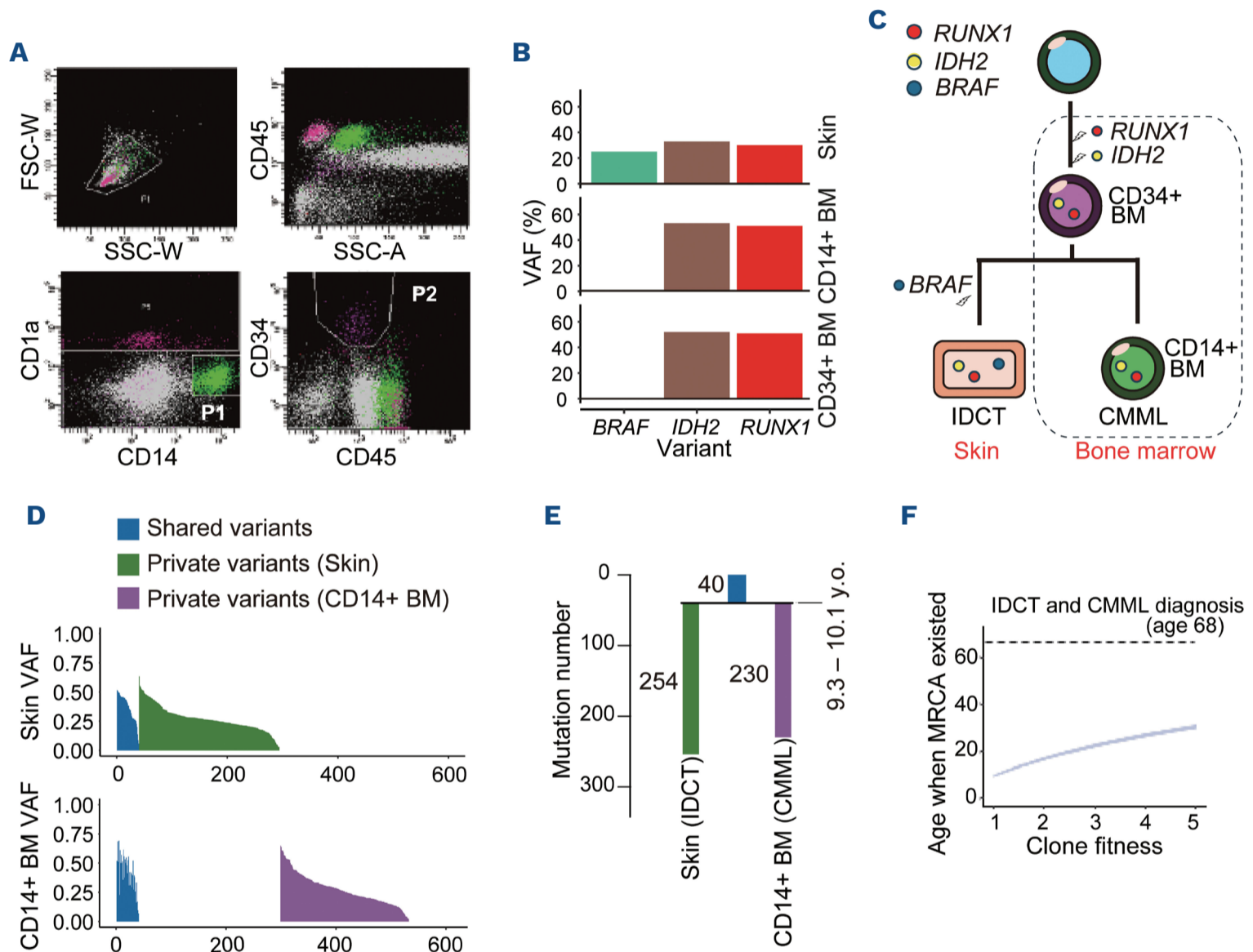


Figure 3. Genetic analysis of indeterminate dendritic cell tumor, chronic myelomonocytic leukemia, and hematopoietic progenitor cells. (A) Fluorescence-activated cell sorting of bone marrow samples after 2 cycles of doxorubicin, vincristine, cyclophosphamide, and prednisolone (CHOP) therapy. Cell sorting of chronic myelomonocytic leukemia (CMML) cells (P1), gating on CD14-positive and CD1a-negative, and hematopoietic progenitor cells (P2), gating on CD34-positive. (B) Variant allele frequencies (VAF) of driver mutations detected by whole-exome sequencing of the sorted fractions of bone marrow (BM) cells and skin samples. (C) Clonal evolution inferred from WES. The dotted box indicates BM cells. (D) Waterfall plots showing the somatic mutations detected by WES from the CD1a⁺ fraction of skin and CD14⁺ fraction of BM cells. The y-axis shows the size (VAF) of mutations. Blue colors indicate shared mutations, and private mutations of CD1a⁺ and CD14⁺ cells are shown in green and purple, respectively. (E) Estimation of the time of separation of the CMML (CD14⁺ fraction) and indeterminate dendritic cell tumor (IDCT) (CD1a⁺ fraction) clones. Length of branches represents the number of mutations. (F) Estimation of time when most recent common ancestor (MRCA) existed: where A is the age at sampling, c is the number of common mutations, p1 and p2 are the number of private mutations, and f is clone fitness. The estimated time of MRCA existence, T(MRCA), is given by the following equation.

$$T(MRCA) = \left[A \frac{c}{c + \frac{p1}{f}}, A \frac{c}{c + \frac{p2}{f}} \right]$$

Gray ribbon indicates the range of estimated time when MRCA existed for the clone fitness values shown on the x-axis. SSC: side scatter; FSC: forward scatter.

support the role of transdifferentiation between IDCT and co-existing neoplasms, as lymphoid neoplasms exhibit irreversible signs of lymphoid cell differentiation or lymphoid neoplasm development.

In contrast, there is no evidence supporting the role of transdifferentiation in cases of CMML co-occurring with IDCT, although shared mutations are often detected between the two.¹⁰ Compared with lymphoid tumors, proving that IDCT cells originate from cells that were previously differentiated into CMML is difficult since myeloid cells do not leave any trace of differentiation in the genome. Instead, given the chronological proximity of onset and the presence of shared driver mutations between IDCT and CMML, we suspected that these tumors were clonally related and examined their genetic relationship using trajectory analysis based on WGS. Our results showed that although IDCT and CMML shared driver mutations, clonal bifurcation occurred long before disease onset, making transdifferentiation an unlikely explanation.

Instead, our results highlighted CH as an underlying environmental factor of both tumors. Specifically, CH harboring the *RUNX1/IDH2* mutation serves as the source of myeloid neoplasm development. *RUNX1*- and *IDH2*-mutated CH carries a significantly higher risk of myeloid neoplasm development than the overall CH-positive population, with hazard ratios of 14.28- and 13.32-fold for *RUNX1* and *IDH2*, respectively.¹¹ While CH generally induces an inflammatory environment that confers selective advantage of CH clones,¹² each genetic alteration representing CH has distinct mechanisms: *RUNX1* deficiency is associated with the overproduction of tumor necrosis factor α (TNF- α), macrophage inflammatory protein 1 α , and interleukin (IL)-1 α ,¹³ and *IDH2* mutation induces hypermethylation phenotype through the overproduction of 2-hydroxyglutarate and functional inhibition of ten-eleven translocation-2.¹⁴ Therefore, *RUNX1/IDH2*-mutated CH may have played a significant role in the development of these tumors in this case. When CMML and/or IDCT developed, substantial secretion of pro-inflammatory signals (granulocyte-macrophage-colony-stimulating factor, TNF- α , IL-6, IL-17, and IL-1 β) was achieved from both CMML¹⁵ and histiocytic neoplasms,¹⁶ which consequently promoted both tumors' proliferation.^{16,17} This explains the chronological proximity of the development of these tumors despite the long-standing CH environment.

IDCT is a rare disease, and standard treatment guidelines have not yet been established. In cases of IDCT with coincidental non-histiocytic hematopoietic neoplasms, treatment is administered not for IDCT itself, but for the concomitant tumors that have a greater impact on prognosis. In addition, IDCT with non-histiocytic hematopoietic neoplasms has a significantly poorer prognosis^{3,18} and hematopoietic stem cell transplantation (HSCT) is considered whenever available. The pre-HSCT treatment strategy primarily focuses on control of coincidental non-histiocytic hematopoietic neoplasms. However, in cases of IDCT with

a *BRAF*^{V600E} mutation, combination therapy using BRAF/MEK inhibitors is a less toxic modality for debulking the IDCT burden before HSCT. Specific considerations for CH environment-derived IDCT and coincidental tumors have not yet been established. If SASP- or CH-related inflammatory signals play an important role in tumor development within a CH environment, suppressing these signals may be effective and worth considering.

Although this is only a single case report, the next-generation sequencing and trajectory analysis of the isolated cell fractions are expected to elucidate the mechanism of disease onset and optimize molecular targeted therapy.

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Contributions

AS contributed to the study design, manuscript drafting, and the

data analysis and interpretation. YN conceived the experiments, interpreted data, and supervised the study. NY, HT, ES, KY, and SI performed the experiments. All authors interpreted the data, critically revised the report, commented on drafts of the manuscript, and approved the final version.

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Data-sharing statement

Individual participant data will not be shared.

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