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Unique Composite Hematolymphoid Tumor Consisting of a Pro-T Lymphoblastic Lymphoma and an Indeterminate Dendritic Cell Tumor: Evidence for Divergent Common Progenitor Cell Differentiation

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Established Facts

- Composite neoplasms of the lymphoid and dendritic cell lines have repeatedly been reported. They are usually genetically related. Direct lineage transdifferentiation or divergent common progenitor cell differentiation are the underlying mechanisms increasingly discussed to explain this phenomenon, while other cases are attributed to coincidence, some sort of reaction or the influence of therapy.

Novel Insights

- We present a unique case of a combined pro-T lymphoblastic lymphoma and indeterminate dendritic cell tumor, both bearing +21, a combination that has never been reported before. The mechanisms of transdifferentiation and especially of divergent common progenitor cell differentiation are discussed based on the case observations and on a review of the most recent literature.

Key Words
Lymphoblastic lymphoma · Indeterminate dendritic cell tumor · Transdifferentiation · Gene rearrangement · *NRAS* gene · PU.1

Abstract
Until recently, hematopoietic neoplasms were considered monoclonal proliferations belonging to one cell lineage. In the last years, evidence for transdifferentiation from one cell lineage to another or divergent common progenitor cell differentiation has accumulated, mainly based on composite hematolymphoid tumors, sharing common genetic abnormalities. We report the case of a 59-year-old woman with a composite pro-T lymphoblastic lymphoma (LBL) and indeterminate dendritic cell tumor infiltrating the lymph nodes, bone marrow and stomach. Genetic analyses revealed that both cell populations bore +21, while a G13D mutation of the *NRAS* gene and monosomy 18 were detected only in the pro-T LBL. The synchronous appearance of two distinct uncommon hematolymphoid tumors in the same patient, recurrent at three different anatomic locations, with an identifiable common genetic denominator, namely +21, but also with unique genetic anomalies in the pro-T LBL raises the hypothesis of a divergent common progenitor cell differentiation.

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Introduction

For a long time, hematopoietic tumors have been considered as neoplastic proliferations of a distinct cell line at various stages of differentiation. This is reflected in the classification of hematopoietic neoplasms, which is mainly based on the lineage of the respective postulated cell of origin [1]. Indeterminate dendritic cell tumor (IDCT) is a rare neoplastic proliferation of indeterminate cells, which phenotypically resemble Langerhans cells but lack Langerin expression and Birbeck granules [1, 2]. Patients predominantly present with skin lesions, but also cervical lymph node and bone marrow involvement in the absence of skin manifestations have been reported [2–4]. A few case reports describe IDCTs in association with other hematolymphoid tumors, mainly low-grade B-cell lymphomas [2, 5, 6]. To our knowledge, there is no published case of an IDCT in combination with a pro-T lymphoblastic lymphoma (LBL) to this date and no cases with in-depth molecular analysis of a possible clonal relationship between the two components.

Combined lymphoid and dendritic neoplasms in the same patient other than the above are rare but have been reported previously, most frequently cases of Hodgkin lymphomas or B- or T-cell lymphomas in combination with Langerhans cell histiocytosis (LCH). Initially, the association was taken either as a coincidence or as a peculiar reaction, such as an immune response [7, 8]. A possible influence of the therapy has also been suggested [9]. Other established causal factors for IDCTs or combined lymphoid and dendritic neoplasms have not been reported, while known exogenous exposures in acute lymphoblastic leukemia (ALL) include ionizing radiation, possibly high levels of electromagnetic field radiation, and abnormal or dysregulated immune response to infections [10]. More recent molecular data revealed clonal relationships between both components of such combined tumors. Transdifferentiation from one cell lineage to the other is anticipated [11]. Changes in transcription factor expression leading to transdifferentiation have been postulated [12, 13]. This hypothesis is supported by the well-known importance of interplays between transcription factors in normal hematopoietic lineage commitment [14].

Case Report and Materials and Methods

Case Report

We report the case of a 59-year-old woman who was admitted to Vilnius University Hospital with generalized lymphadenopathy and splenomegaly in November 2010. She had been a chemical industry worker for years. Pre-existing conditions were primary arterial hypertension, episodes of angina pectoris and depression (use of antidepressants). Lactate dehydrogenase (469 IU/l) and eosinophils (0.65×10^9/l) were elevated, whereas the platelet count (126×10^9/l) was low. The number of white blood cells (5.89×10^9/l) was normal, but the lymphocyte ratio was elevated (45.7%). Lymph node and bone marrow biopsies were performed at that time. Flow cytometry of the bone marrow aspirate revealed 35% undifferentiated blasts with the following phenotype: CD45RA+dim, CD7+, CD33+, CD34+dim, cTdT+dim, CD99+, HLA-DR+, CD1a–, CD2–, sCD3–, cCD3+dim, CD4–, CD8–, CD13–, CD117–, and MPO–. No *MLL/AF4, ETV6/RUNX1, E2A/PBX1,* or *SIL/TAL1* fusion products were detected. After a short period of refusing any chemotherapy, the patient was treated according to protocols for ALL, and the lymphadenopathy initially regressed. Due to refractory disease and histologically confirmed gastric involvement of the composite lymphoid and dendritic tumor, the treatment regimen was changed to palliation. The patient died of disease in 2013. No autopsy was performed.

Materials and Methods

The cervical lymph node biopsy specimens were routinely fixed in formalin and embedded in paraffin wax. Hematoxylin and eosin (HE) as well as immunohistochemical stainings for CD4, CD45RO, S100, CD68, CD1a, CD7, CD117, TdT, CD34, Ki67, Bcl2, CD43, CD2, CD3, CD5, CD8, CD56, LMO2, Langerin, and PU.1 were performed. Fluorescence in situ hybridization (FISH) analyses applying the UroVision [consisting of chromosome enumeration probes (CEP) 3, 7, 17 and a 9p21 locus-specific identifier probe; order No. 02J27-095 from Abbott/Vysis] and AneuVision (consisting of CEP 13, 18, 21, X and Y; order No. 05J38-050 from Abott/Vysis) as well as immunoglobulin heavy chain (*IGH;* chromosome 14q)/*C-MYC* (chromosome 8q)/CEP 8 (order No. 05J75-001 from Abbott/Vysis) probes were performed to assess common cytogenetic aberrations in both the larger cell component of the IDCT and the smaller cell component of the pro-T LBL. To properly consider the respective cellular populations, assessment of the FISH probes was performed after optical control of serial sections in areas particularly rich in CD1a (IDCT cells) or LMO2 (pro-T LBL cells) positively stained cells, respectively. To exclude constitutional chromosomal aberrations, tumor-free soft tissue structures from the periphery of the lymph node were examined by FISH as well.

Tissue samples for molecular analysis were obtained in a first step by scratching off cells from immunohistochemically stained uncovered glass slides. To identify the appropriate spots, serial sections were separately stained each for LMO2 as discerning marker for pro-T LBL and for CD1a as discerning marker for IDCT. In a second step, tissue sections were again immunohistochemically stained with the same markers, but then collected by laser capture microdissection. This step was crucial to exclude any contamination, since the pro-T lymphoblasts were diffusely distributed among the population of the IDCTs. In addition, tumor-free adipose tissue of the periphery of one slide was scratched off to exclude a possible germline mutation of the *NRAS* gene [15]. DNA was extracted and purified utilizing the QIAamp DNA Mini Kit (Qiagen), according to the manufacturer's recommendations. T-cell clonality was evaluated by our four-color semi-nested multiplex polymerase chain reaction assay and automated high-resolution fragment analysis. This assay is designed to determine clonal T-cell receptor *(TCR)* γ and *IGH* rearrangements as well as to de-

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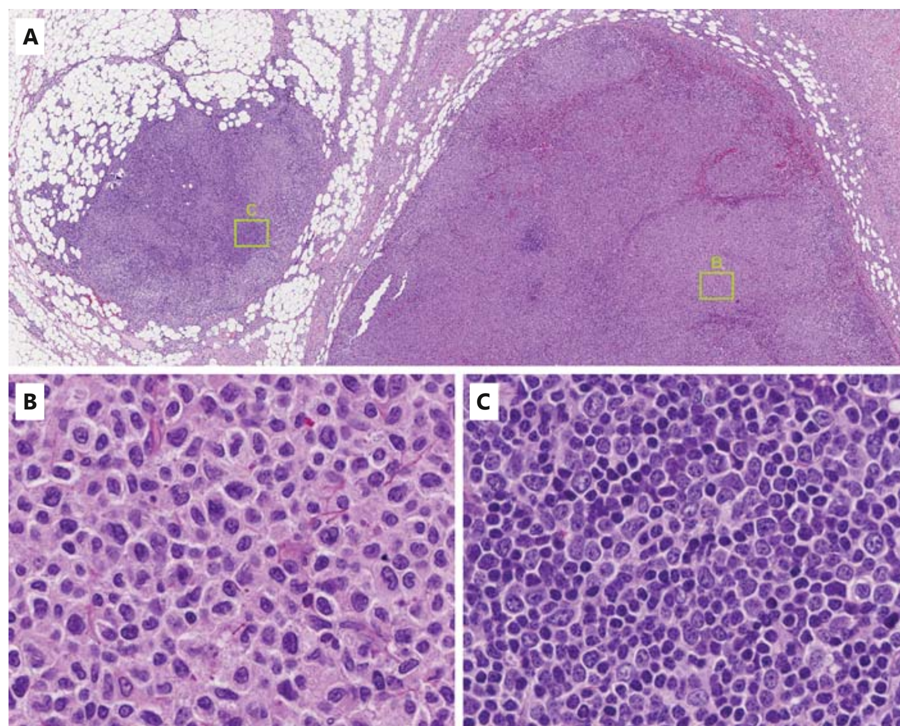

Fig. 1. Conventional histology of cervical lymph node biopsy specimen. **A** Low-power view of a cell-rich tumor with dark and light spots destroying the normal lymph node architecture and infiltrating the surrounding adipose tissue. HE. ×40. **B** Light spot showing large histiocytic cells with abundant eosinophilic cytoplasm and irregular nuclear grooves. HE. ×640. **c** Dark spot showing small lymphoid cells with sparse cytoplasm diffusely distributed between the histiocytic cells. HE. ×640.

tect the t(14;18) and t(11;14) [16]. Mutational analysis examined hotspots in genes known to be mutated in T-LBL or T-cell ALL [17, 18], including *KRAS* (exon 2, codons 12 and 13), *NRAS* (exon 1, codons 12 and 13), *BRAF* (exon 15, codons 600 and 601), *IDH1* (exon 4, codon 132), and *IDH2* (exon 4, codon 172). Sequence analysis was performed by capillary electrophoresis and laser-induced fluorescence detection on an ABI 310 Genetic Analyzer using the sequencing analysis software version 5.2.0 (Applied Biosystems). All products were sequenced bidirectionally.

Results

The lymph node biopsy specimens showed effacement of the architecture by a composite cell population infiltrating the perinodal tissue (fig. 1A). Large histiocytic cells with abundant eosinophilic cytoplasms showing some retraction artifacts represented the most prominent population. These cells had wrinkled and cleft nuclei with irregular nuclear grooves and distinct nucleoli (fig. 1B). The second population was composed of small immature lymphocytes with scant cytoplasm. Their nuclei were round to oval and had indistinct nucleoli (fig. 1C). CD1a (fig. 2A), S100, CD4, and PU.1 were positive in the histiocytic population. The lymphoid population was positive for CD7 (fig. 2B), TdT, CD34, LMO2, and CD43 and negative for CD1a, CD2, CD3, CD4, CD5, CD8, CD56, and PU.1. CD68 and Langerin (fig. 2D) were negative in both populations. MIB1 staining showed a proliferation index of about 40 and 70% in the histiocytic and lymphoid cell population, respectively (fig. 2C). The same applied to the bone marrow specimen, where both populations were present as well (data not shown). A gastric biopsy specimen obtained later on showed a dense infiltrate by the same composite cell population (fig. 2E), verified by the expression of CD7 in the more prominent pro-T LBL component (fig. 2F), and the expression of CD1a in the dendritic cell component (fig. 2G). Except for the presence of trisomy 21 in 50% of the cells of both cellular compartments (fig. 3) but not in the tumor-free soft tissue (non-constitutional aberration), a finding that was recently observed in one case of a similar series of composite LCH and acute leukemias [19], and monosomy 18 in 75% of the small cell compartment (T-LBL), FISH showed no further numeric aberrations. Since Langerin was negative in the histiocytic part of the tumor, and because an accompanying eosinophilic infiltrate was missing, this component was classified as IDCT (and not as LCH) [2, 20]. Considering the clinical presentation, the flow cytometry phenotype, the immunohistochemical expression pattern of the lymphoid part, and the cytogenetics,

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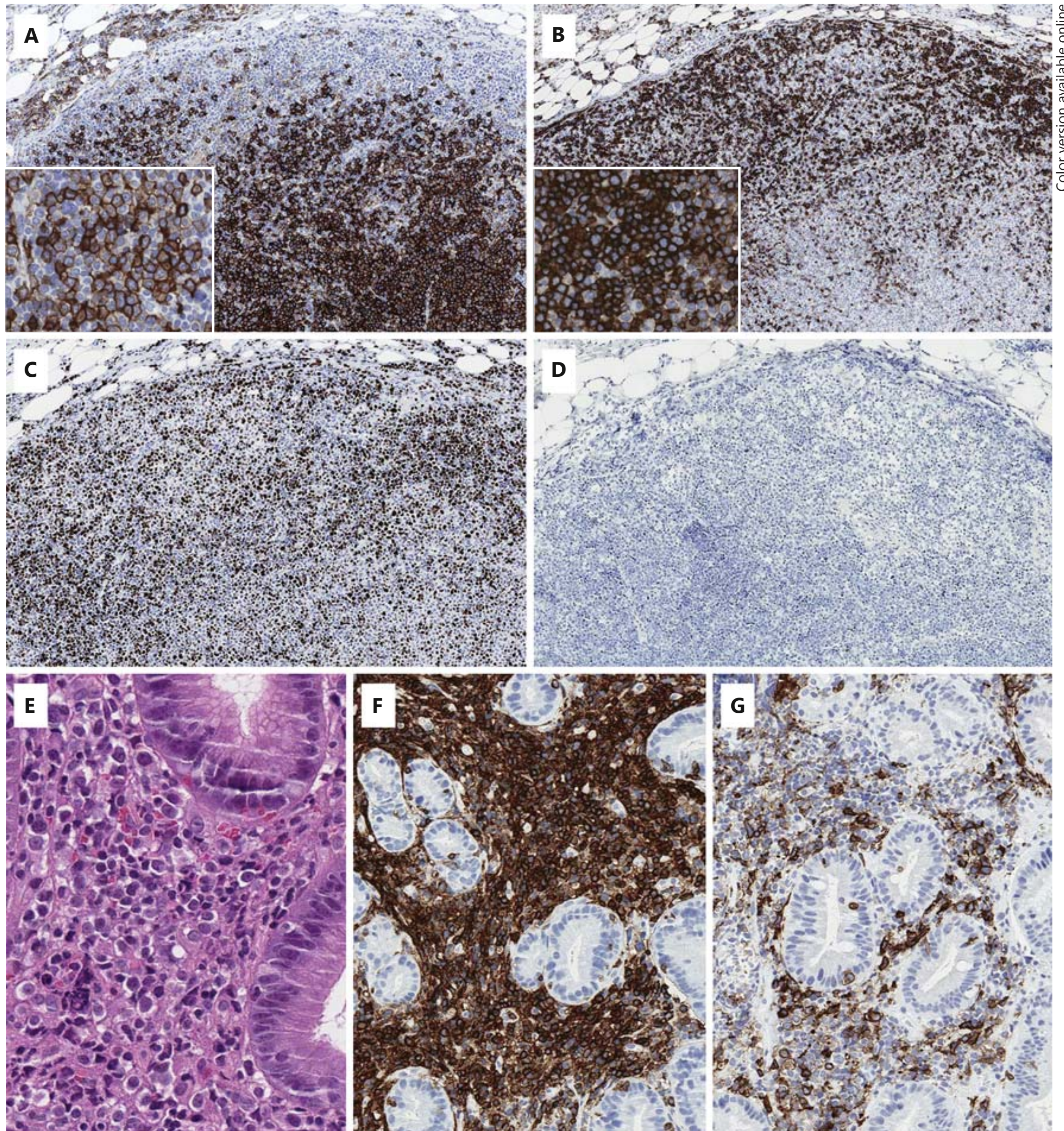

Fig. 2. Immunohistochemical characterization of the cervical lymph node and gastric involvement. **A** The atypical histiocytic cells are positive for CD1a and are mainly distributed in the lower area in this part of the cervical lymph node. ×80. **Inset** ×400. **B** The lymphoid cells strongly express CD7 and are accumulated in the upper area. ×80. **Inset** ×400. **C** The histiocytic cells in the lower part show a less pronounced Ki67 expression compared with the higher proliferation index of the lymphoid cells in the upper part, as demonstrated by MIB1 staining. ×80. **D** Langerin is negative in both components; only one scattered cell in the middle lower part of the figure shows a weak Langerin expression. ×80. **E** The gastric biopsy specimen shows a dense cellular infiltration. HE. ×640. **F** The infiltrate consists predominantly of lymphoid cells expressing CD7. ×400. **G** The histiocytic cell component is also present, as demonstrated in the CD1a staining. ×400.

the diagnosis of a pro-T LBL (early T-cell precursor LBL) [17, 21] for the second component was established. Criteria to diagnose an acute leukemia of ambiguous lineage – especially mixed-phenotype acute leukemia, T/myeloid – were not fulfilled, according to the WHO classification and the most recent molecular data on ALL, since (1) clinically, lymphadenopathy was the leading symptom and the patient was aleukemic, (2) phenotypically, the

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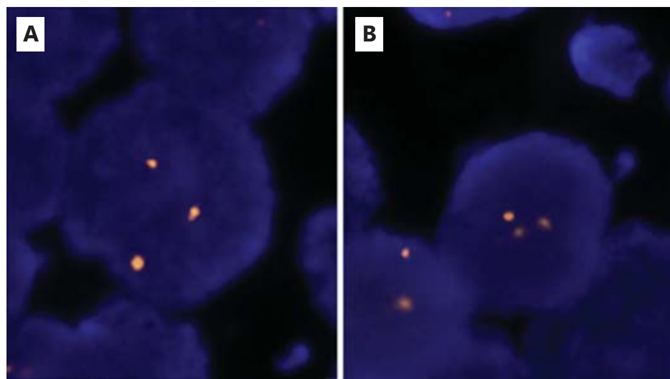

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Fig. 3. FISH applying chromosome enumeration probe 21. **A** Three paracentromeric orange FISH signals in a larger cell, corresponding to the indeterminate dendritic component of the composite neoplasm. ×1,600. **B** Three red FISH signals in the smaller cells, corresponding to the pro-T lymphoblastic component of the composite neoplasm. ×1,600.

blast did not express MPO, CD13 and CD117, but were positive for cCD3, CD7, CD99, and TdT, and (3) displayed a gain of chromosome 21, which has been described in both molecularly documented series of early T-cell precursor ALL [1, 17, 19, 21, 22].

The scratched-off sample with mainly LMO2-positive lymphoblasts showed a G13D point mutation of the *NRAS* gene, while the scratched-off sample with mainly CD1a-positive histiocytic cells showed a considerably smaller adenine signal at the second position of codon 13. Importantly, in the microdissected tissue samples, the CD1a-positive component did not show any mutated alleles of the *NRAS* gene. Therefore, we concluded that the IDCT did not harbor the G13D mutation and that contaminating lymphoblasts were responsible for the detectable adenine signal in the scratched-off specimens. Germline mutation could be excluded, since the adipose tissue showed wild-type configuration of the *NRAS* gene. Mutation analysis of the *KRAS, BRAF* and *IDH2* genes showed wild-type configuration in all samples. All attempts to determine mutations in the *IDH1* gene or clonal *TCR γ* gene rearrangements yielded in results that were not conclusive due to the limited DNA quality of the available tissue samples. In the applied assay to determine *TCR γ* gene rearrangements, most of the detectable peak heights were below the lower limit. However, the lack of any reproducible single peak and the presence of occasional peaks exceeding the lower limit rather suggested the presence of different *TCR γ* fragments, and therefore, lacking clonal rearrangements, or even that the *TCR γ* gene was not yet rearranged.

Discussion

We extend the spectrum of composite lymphoid and dendritic tumors by a novel combination of pro-T LBL and IDCT, both bearing a common cytogenetic aberration, i.e. +21. To the best of our knowledge, this is the first reported case of a synchronous pro-T LBL and IDCT at the same locations to this date.

Basically, there are two possibilities to explain the relationship between the two entities. First, there might be no clonal relationship between the two neoplasms, and the simultaneous appearance might be by chance or some sort of reaction [7, 8]. Such a reactive phenomenon was suggested by Quintanilla-Martinez et al. [23] reporting two similar cases of LBL with a very immature phenotype and a synchronous population of LCH in the same lymph node. Molecular genetic analysis revealed germline *TCR β* and *γ* chain genes. Christie et al. [24] investigated 5 examples of LCH-like proliferations occurring in the context of other lymphoproliferative disorders with the highly polymorphic human androgen receptor gene assay. Their results showed that, at least in a proportion of cases, Langerhans cells may represent reactive proliferation. Nonetheless, a coincidence seems very unlikely in our present case, since both cellular components bore a non-constitutional trisomy 21 and were histologically identified at three different anatomic sites (cervical lymph nodes, gastric mucosa and bone marrow). Further, a simple reaction would hardly explain the atypical cellular morphology, the distribution pattern and the high proliferation index of the respective components. Therapy influence, as proposed in similar combined tumors with different occurrence over time [9], can most likely be excluded, since both components occurred simultaneously and were detected in our patient before chemotherapy was started.

Second, in case a clonal relationship between both components is assumed as suggested by the common cytogenetic anomaly in the respective cells, i.e. +21 in our case, a direct lineage transdifferentiation or a divergent common progenitor cell differentiation might have played a role. This theory is supported by a considerably growing body of evidence postulating such processes. For example, Feldman et al. [11] suggested possible transdifferentiation in precursor T-LBL and LCH in children with confirmed identical clonal rearrangements of the *TCR γ* gene. It has been demonstrated that pre-T cells can be reprogrammed into dendritic cells by retroviral expression of the transcription factors C/EBPα and PU.1 [25]. Accordingly, overexpression of PU.1 in the IDCT

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might have led to reprogramming from the lymphoid to the dendritic cell phenotype in our patient. Vice versa, a switch from the dendritic cell to the lymphoid phenotype due to the loss of PU.1 expression would also be conceivable; however, reprogramming from the myeloid to the lymphoid lineage has never been observed [14]. The importance of transcription factor expression in transdifferentiation was also postulated in a study of 8 adults with follicular lymphoma and dendritic neoplasms with common clonal origin. Identical *IGH* gene rearrangements or *BCL2* gene breakpoints as well as the t(14;18) in both tumors have been identified in all patients. The authors postulated that changes in transcription factor expression may have led to transdifferentiation from a lymphoid to a dendritic phenotype [12]. Secondary genetic events leading to changes in transcription factor expression might be responsible for lineage transdifferentiation in such cases [13]. In support of this, a recent review summarizes the importance of cooperative or antagonistic interplays between single or multiple transcription factors as well as the timing of their expression for hematopoietic lineage fate decision [14].

The missing of a (clonal) *TCR γ* rearrangement in our patient is consistent with the immunohistochemical and molecular genetic characterization of early pro-T ALL [17, 21]. Garand et al. [26] found that only half of early pro-T ALL were *TCR β* and *γ* rearranged in comparison with more mature T-ALL. Moreover, loss of CD34 expression correlated with the start of *TCR* rearrangement. Thus, we suggest that in our case, with an early pro-T phenotype and the expression of CD34, the *TCR γ* has quite likely not yet been rearranged. The detected mutation of the *NRAS* gene and monosomy 18 only in the pro-T LBL component are in line with the well-known *RAS* gene family mutations in early T-cell-derived ALL [27] and with the reported cytogenetic anomalies in ALL [28]. Since the *NRAS* gene was not mutated in the IDCT, the G13D mutation might have represented a secondary genetic event in the pro-T LBL component, which corresponds with the putative role of *RAS* family member mutations as progression and not driver mutations [29]. The presence of monosomy 18 in the pro-T LBL is an important finding because it shows that, at least in our case, the IDCT could not have originated from the pro-T LBL cells by direct transdifferentiation, since genomic losses are irreversible. Instead, our result fits best with and further supports the most recently proposed model of a common progenitor clone giving rise to both neoplasms in composite histiocytic/dendritic and lymphoid tumors [30].

In conclusion, the present case is a unique representatition of the rare group of composite lymphoid and dendritic tumors, consisting of a pro-T LBL and an IDCT both bearing non-constitutional trisomy 21, a combination that has never been reported before. Our case provides further evidence in support of the existence of a putative common progenitor cell clone, in that particular case bearing +21, with the propensity to divergently differentiate into a dendritic and lymphoid neoplasm, which was accompanied by acquisition of monosomy 18 and *NRAS* mutation in the pro-T LBL component.

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References

1 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, IARC, 2008.
2 Rezk SA, Spagnolo DV, Brynes RK, Weiss LM: Indeterminate cell tumor: a rare dendritic neoplasm. Am J Surg Pathol 2008;32:1868–1876.
3 Martin Flores-Stadler E, Gonzalez-Crussi F, Greene M, Thangavelu M, Kletzel M, Chou PM: Indeterminate-cell histiocytosis: immunophenotypic and cytogenetic findings in an infant. Med Pediatr Oncol 1999;32:250–254.
4 Ratzinger G, Burgdorf WH, Metze D, Zelger BG, Zelger B: Indeterminate cell histiocytosis: fact or fiction? J Cutan Pathol 2005;32:552–560.
5 Vasef MA, Zaatari GS, Chan WC, Sun NC, Weiss LM, Brynes RK: Dendritic cell tumors associated with low-grade B-cell malignancies. Report of three cases. Am J Clin Pathol 1995;104:696–701.
6 Bettington A, Lai JK, Kennedy C: Indeterminate dendritic cell tumour presenting in a patient with follicular lymphoma. Pathology 2011;43:372–375.
7 Burns BF, Colby TV, Dorfman RF: Langerhans' cell granulomatosis (histiocytosis X) associated with malignant lymphomas. Am J Surg Pathol 1983;7:529–533.
8 Neumann MP, Frizzera G: The coexistence of Langerhans' cell granulomatosis and malignant lymphoma may take different forms: report of seven cases with a review of the literature. Hum Pathol 1986;17:1060–1065.
9 Egeler RM, Neglia JP, Aricò M, Favara BE, Heitger A, Nesbit ME, Nicholson HS: The relation of Langerhans cell histiocytosis to acute leukemia, lymphomas, and other solid tumors. The LCH-Malignancy Study Group of the Histiocyte Society. Hematol Oncol Clin North Am 1998;12:369–378.
10 Inaba H, Greaves M, Mullighan CG: Acute lymphoblastic leukaemia. Lancet 2013;381:1943–1955.

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11 Feldman AL, Berthold F, Arceci RJ, Abramowsky C, Shehata BM, Mann KP, Lauer SJ, Pritchard J, Raffeld M, Jaffe ES: Clonal relationship between precursor T-lymphoblastic leukaemia/lymphoma and Langerhans-cell histiocytosis. Lancet Oncol 2005;6:435–437.

12 Feldman AL, Arber DA, Pittaluga S, Martinez A, Burke JS, Raffeld M, Camos M, Warnke R, Jaffe ES: Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone. Blood 2008;111:5433–5439.

13 Shao H, Xi L, Raffeld M, Feldman AL, Ketterling RP, Knudson R, Rodriguez-Canales J, Hanson J, Pittaluga S, Jaffe ES: Clonally related histiocytic/dendritic cell sarcoma and chronic lymphocytic leukemia/small lymphocytic lymphoma: a study of seven cases. Mod Pathol 2011;24:1421–1432.

14 Iwasaki H, Akashi K: Myeloid lineage commitment from the hematopoietic stem cell. Immunity 2007;26:726–740.

15 De Filippi P, Zecca M, Lisini D, Rosti V, Cagioni C, Carlo-Stella C, Radi O, Veggiotti P, Mastronuzzi A, Acquaviva A, D'Ambrosio A, Locatelli F, Danesino C: Germ-line mutation of the *NRAS* gene may be responsible for the development of juvenile myelomonocytic leukaemia. Br J Haematol 2009;147:706–709.

16 Meier VS, Rufle A, Gudat F: Simultaneous evaluation of T- and B-cell clonality, t(11;14) and t(14;18), in a single reaction by a four-color multiplex polymerase chain reaction assay and automated high-resolution fragment analysis: a method for the rapid molecular diagnosis of lymphoproliferative disorders applicable to fresh frozen and formalin-fixed, paraffin-embedded tissues, blood, and bone marrow aspirates. Am J Pathol 2001;159:2031–2043.

17 Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, Easton J, Chen X, Wang J, Rusch M, Lu C, Chen SC, Wei L, Collins-Underwood JR, Ma J, Roberts KG, Pounds SB, Ulyanov A, Becksfort J, Gupta P, Huether R, Kriwacki RW, Parker M, McGoldrick DJ, Zhao D, Alford D, Espy S, Bobba KC, Song G, Pei D, Cheng C, Roberts S, Barbato MI, Campana D, Coustan-Smith E, Shurtleff SA, Raimondi SC, Kleppe M, Cools J, Shimano KA, Hermiston ML, Doulatov S, Eppert K, Laurenti E, Notta F, Dick JE, Basso G, Hunger SP, Loh ML, Devidas M, Wood B, Winter S, Dunsmore KP, Fulton RS, Fulton LL, Hong X, Harris CC, Dooling DJ, Ochoa K, Johnson KJ, Obenauer JC, Evans WE, Pui CH, Naeve CW, Ley TJ, Mardis ER, Wilson RK, Downing JR, Mullighan CG: The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 2012;481:157–163.

18 Andersson AK, Miller DW, Lynch JA, Lemoff AS, Cai Z, Pounds SB, Radtke I, Yan B, Schuetz JD, Rubnitz JE, Ribeiro RC, Raimondi SC, Zhang J, Mullighan CG, Shurtleff SA, Schulman BA, Downing JR: IDH1 and IDH2 mutations in pediatric acute leukemia. Leukemia 2011;25:1570–1577.

19 Yohe SL, Chenault CB, Torlakovic EE, Asplund SL, McKenna RW: Langerhans cell histiocytosis in acute leukemias of ambiguous or myeloid lineage in adult patients: support for a possible clonal relationship. Mod Pathol 2014;27:651–656.

20 Lau SK, Chu PG, Weiss LM: Immunohistochemical expression of Langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorders. Am J Surg Pathol 2008;32:615–619.

21 Coustan-Smith E, Mullighan CG, Onciu M, Behm FG, Raimondi SC, Pei D, Cheng C, Su X, Rubnitz JE, Basso G, Biondi A, Pui CH, Downing JR, Campana D: Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. Lancet Oncol 2009;10:147–156.

22 Béné MC, Porwit A: Acute leukemias of ambiguous lineage. Semin Diagn Pathol 2012;29:12–18.

23 Quintanilla-Martinez L, Zukerberg LR, Harris NL: Prethymic adult lymphoblastic lymphoma. A clinicopathologic and immunohistochemical analysis. Am J Surg Pathol 1992;16:1075–1084.

24 Christie LJ, Evans AT, Bray SE, Smith ME, Kernohan NM, Levison DA, Goodlad JR: Lesions resembling Langerhans cell histiocytosis in association with other lymphoproliferative disorders: a reactive or neoplastic phenomenon? Hum Pathol 2006;37:32–39.

25 Laiosa CV, Stadtfeld M, Xie H, de Andres-Aguayo L, Graf T: Reprogramming of committed T cell progenitors to macrophages and dendritic cells by C/EBP alpha and PU.1 transcription factors. Immunity 2006;25:731–744.

26 Garand R, Voisin S, Papin S, Praloran V, Lenormand B, Favre M, Philip P, Bernier M, Vanhaecke D, Falkenrodt A, et al: Characteristics of pro-T ALL subgroups: comparison with late T-ALL. The Groupe d'Etude Immunologique des Leucémies. Leukemia 1993;7:161–167.

27 Neri A, Knowles DM, Greco A, McCormick F, Dalla-Favera R: Analysis of RAS oncogene mutations in human lymphoid malignancies. Proc Natl Acad Sci USA 1988;85:9268–9272.

28 Udayakumar AM, Bashir WA, Pathare AV, Wali YA, Zacharia M, Khan AA, Soliman H, Al-Lamki Z, Raeburn JA: Cytogenetic profile of childhood acute lymphoblastic leukemia in Oman. Arch Med Res 2007;38:305–312.

29 Vogelstein B, Kinzler KW: Cancer genes and the pathways they control. Nat Med 2004;10:789–799.

30 Brunner P, Rufle A, Dirnhofer S, Lohri A, Willi N, Cathomas G, Tzankov A, Juskevicius D: Follicular lymphoma transformation into histiocytic sarcoma: indications for a common neoplastic progenitor. Leukemia 2014;28:1937–1940.

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