

## Case Report

# Chronic Lymphocytic Leukemia Transdifferentiates into Neuroendocrine Carcinoma: A Case Report of a New Phenomenon

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**Richter's Transformation of chronic lymphocytic leukemia (CLL) to diffuse large B-cell lymphoma or Hodgkin lymphoma (both are B-cell origin) are well described in literature. Recently, transformation of CLL into histiocytic/dendritic/Langerhans cell sarcoma (all are myeloid origin), dubbed as "transdifferentiation", has also been reported. The mechanisms behind this phenomenon are not clear. Here we report the discovery of the first case of CLL evolving into a neuroendocrine carcinoma (NEC). A patient with long history of CLL developed a rectal mass and a liver mass. Biopsies confirmed rectal poorly differentiated NEC compositing with CLL, and liver metastatic NEC. FISH for CLL panel revealed trisomy 12 in both CLL and NEC. B-cell heavy chain rearrangement study on blood sample (pure CLL) and liver metastatic NEC (pure NEC, no contamination from CLL) revealed that these two tumors shared similar monoclonal peaks. Therefore, the patient's CLL and NEC were clonally related, and likely the NEC was transdifferentiated from CLL. This is the first case of transdifferentiation of CLL into carcinoma.**

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**Key Words:** chronic lymphocytic leukemia, neuroendocrine carcinoma, transdifferentiation

## INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation and proliferation of monoclonal B cells with a characteristic immunophenotype (CD5+, CD19+, CD23+, FMC-7-, and CD20 weak+). CLL is the most common leukemia in adults in the Western world.<sup>1</sup> Richter's transformation is a clinicopathological term used to describe the rapid development of a histologically proven aggressive lymphoma in a patient with CLL.<sup>2</sup> The most common lymphoma seen in patients with Richter's transformation is diffuse large B-cell lymphoma (frequency 2-8%), and to a less extent, Hodgkin's lymphoma (frequency < 1%).<sup>2-6</sup> Recently, CLL/SLL transforming into histiocytic/dendritic cell sarcomas has also been reported. This phenomenon is dubbed "transdifferentiation".<sup>7-13</sup> Here we report a case of transformation of CLL/SLL into neuroendocrine carcinoma with cytogenetic and molecular evidence. To our knowledge, this is the first case report for CLL/SLL transdifferentiating into different cell lineage other than lymphoid or myeloid origin.

## CASE REPORT

A 72 years old male patient was diagnosed as CLL 9 years ago by flow cytometry analysis, Cytogenetic and FISH studies. He was not treated. Recently the patient presented with rectal obstruction and a liver mass radiologically. Colonoscopic examination revealed a rectal mass. Biopsy specimen showed that the rectal mucosa was diffusely infiltrated by atypical small lymphocytes with an immunophenotype of CD5+, CD20+, CD23+, Bcl-2+, Bcl-6-, and Cyclin D1-, consistent with rectal involvement by CLL. In addition to that, mixed with the CLL cells there was a population of atypical epithelioid cells forming many nests.

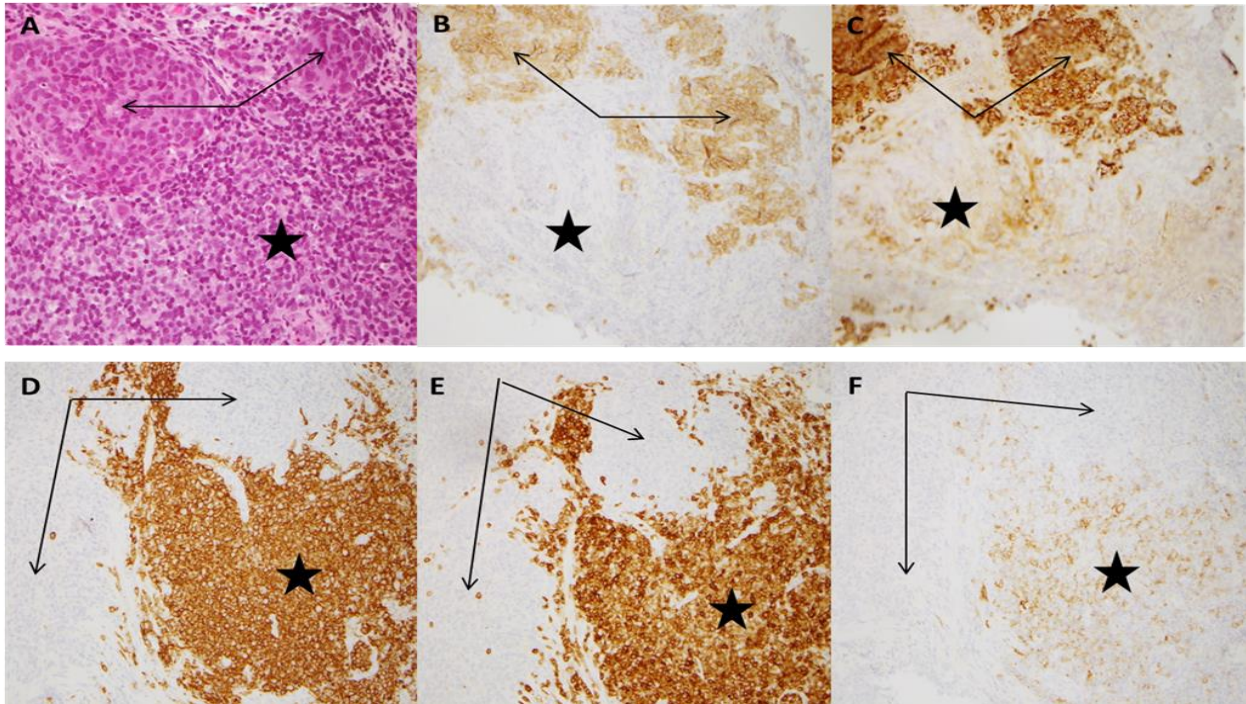
Immunohistochemistry study revealed these atypical cells were positive for CD56, Synaptophysin, and Chromogranin, consistent with a neuroendocrine carcinoma (NEC) (**Figure 1**). Needle core biopsy of the liver mass revealed a metastatic NEC (**Figure 2**). To explore the potential clonal relationship of these 2 populations in the rectal mass, we applied FISH for CLL-panel on the tissue section, due to the fact that the CLL cells in blood had been documented with trisomy 12. FISH results showed that the NEC cells, together with CLL cells, had trisomy 12 (**Figure 3**). To further investigate the lineage origin of the NEC cells, the liver biopsy of the metastatic NEC was tested for B-cell clonality (the specimen contained virtually no CD20+ lymphocytes by immunostaining),

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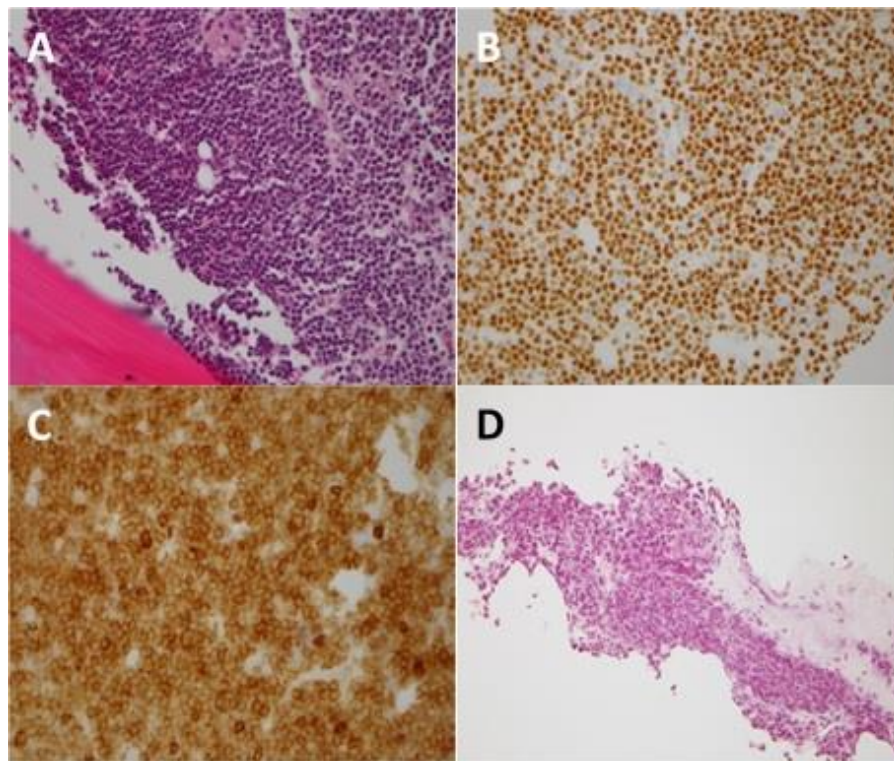
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together with patient's blood (contains CLL cells only) as comparison. Results showed that the NEC cells demonstrated monoclonal peaks in IGH V<sub>H</sub>-J<sub>H</sub>: tube C and IGH D<sub>H</sub>-J<sub>H</sub>: tube

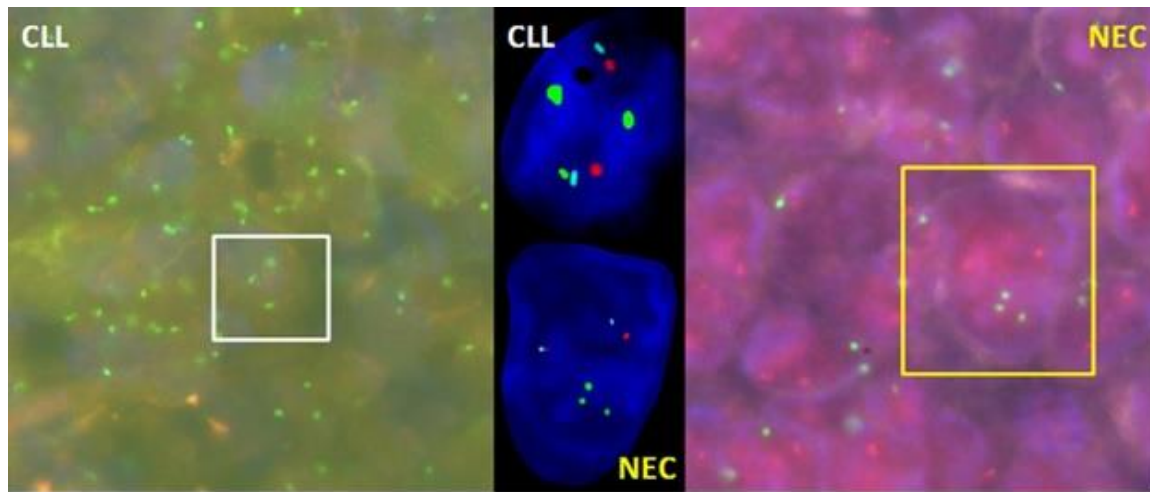
E, with similarity to that of the blood sample (**Figure 4**).<sup>21</sup> This provided further evidence that the NEC cells and the CLL cells were clonally related.



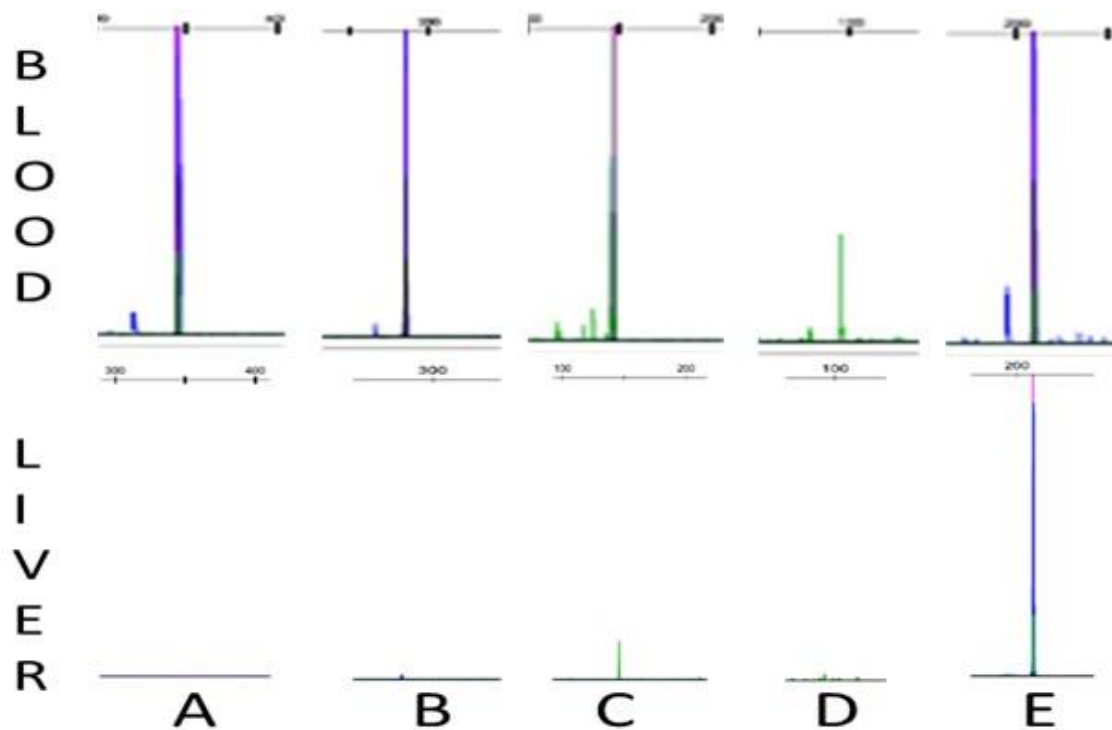
**Figure 1.** CLL and neuroendocrine carcinoma (NEC) in colorectal biopsy. **A.** H&E section of Colorectal biopsy (400X). Arrow: NEC; Star: CLL. NEC positive for Synaptophysin (**B**) and Chromogranin (**C**). CLL positive for CD20 (**D**), CD5 (**E**) and CD23 (**F**).



**Figure 2.** Bone marrow (current) and liver mass biopsies (400X). **A.** Bone marrow biopsy. The marrow is replaced by CLL that are positive for PAX-5 (**B**), and CD5 (**C**). **D.** Liver core biopsy (400X). All are NEC cells. Virtually no CLL cell seen by immunostaining with CD20 (data not shown).



**Figure 3.** FISH for CLL panel on tissue section. Both CLL and NEC showed trisomy 12. Left: CLL cell; right: NEC cell. Middle top: one CLL cell with trisomy 12, green color. Middle bottom: one NEC cell with trisomy 12, green color. The FISH probes are as follow: Vysis LSI D13S319 SpectrumOrange/LSI 13q34 SpectrumAqua/CEP 12 SpectrumGreen Probes.



**Figure 4.** B-cell clonality test on current peripheral blood (pure CLL), upper panel, and liver biopsy (pure NEC), bottom panel. IGH V<sub>H</sub>-J<sub>H</sub>: tube A, B, and C. IGH D<sub>H</sub>-J<sub>H</sub>: tube D and E. In liver biopsy, tube C (100-170bp) and tube E (100-130bp) showed monoclonal peak. Based on EuroClonality Algorithm, NEC has CLL clonal peak. The Relatively long products in A (310-360bp), B (250-295bp), and D (110-290bp) were not achieved possibly due to poor DNA quality in the liver biopsy.

## DISCUSSION

The development of aggressive lymphoma in CLL patients was originally reported by Maurice N. Richter in 1928,<sup>14</sup> and the term “Richter's syndrome” was coined in 1964 by Lortholary et al to describe the development of malignant reticulopathy in 14 patients with CLL.<sup>2</sup> Studies have shown

that the diffuse large B-cell lymphoma that develops in Richter's transformation can be clonally related to the original CLL (true Richter's transformation; 78% of cases) or can be clonally unrelated (20% of cases).<sup>15,16</sup> The latter is usually called “composite lymphoma” and is generally

discarded as a real Richter's transformation event. Feldman et al. provided the first evidence of clonal evolution or transdifferentiation of B-cell lymphoma into histiocytic/dendritic cell sarcoma, in which both neoplasms shared a common IGH gene rearrangement and carried the same BCL2/IGH translocation.<sup>7</sup> Of note, dendritic cell sarcoma is of myeloid origin, which differs from real Richter's transformation - a transformation happened within the lymphoid lineage. Here we report a case of transdifferentiation of CLL into NEC. NEC is believed to arise from various neuroendocrine cells (epithelial lineage). Therefore, this would be the first report of a transformation/transdifferentiation of CLL into a non-lymphoid, non-myeloid lineage.

The exact mechanisms of transformation/transdifferentiation are not fully elucidated, although several hypotheses have been proposed. The first possibility is of the direct lineage switch of neoplastic B-cells into other lineage cells. This is supported by the experimental data showing that enforced expression of some transcription factors such as C/EBP $\alpha$  and/or C/EBP $\beta$  can lead to direct transdifferentiation of mature B-cells into macrophages.<sup>17</sup> A second hypothesis is that this transformation/lineage switch is achieved through multiple steps, which mainly involve de-differentiation of neoplastic lymphocytes to early progenitors, followed by re-differentiation of these progenitor cells to other lineage cells. The potential for de-differentiation and re-differentiation of B-cells has been well documented. For example, in vitro deletion of PAX-5, a critical regulator for B-cell development, can lead to de-differentiation of mature B-cells into progenitor cells, and then differentiate into T-cells under certain conditions.<sup>18,19</sup>

Studies on pathogenesis of Richter's transformation revealed that CLL with cytogenetic/molecular events, such as negative for del(13q14), negative for translocation involving 14q32/IGH, high prevalence of TP53 disruption, and a lower prevalence of mutated IGHV, etc, have relatively high risk for Richter's transformation.<sup>11,20</sup> There is no similar study so far regarding transdifferentiation to histiocytic/dendritic sarcoma. Interestingly, our patients showed a deletion of TP53 on chromosome 17, intact DLEU1/DLEU2 on 13q14, and no translocation involving 14q32/IGH in CLL FISH panel. It's unclear if this cytogenetic/molecular profile of our case contributed to the transdifferentiation to NEC. Location-wise, most of the Richter's transformation to aggressive lymphoma or transdifferentiation to histiocytic/dendritic sarcoma were reported in lymph nodes or bone marrow. In contrast, our case happened in rectum. This might suggest that the microenvironment, the cytokines and growth factors in the tissue, contribute to transformation/transdifferentiation, as well as the intrinsic genetic changes in the CLL cells.

In summary, we discovered the first case of transdifferentiation of CLL into NEC. Our finding expanded the spectrum of transformation/transdifferentiation to a non-lymphoid, non-myeloid area.

#### CONFLICT OF INTEREST

None.

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