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پروپوزال نویسی
Appearance and Disappearance of Chronic Myeloid Leukemia (CML) in Patient with Chronic Lymphocytic Leukemia (CLL)

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ABSTRACT
Chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML) are the most common leukemias of the elderly (>43 year). However, the sequential occurrence of CML followed by CLL in the same patient is extremely rare. In our report, a 52-year-old female was diagnosed with CLL (type of bone marrow (BM) infiltration was nodular and interstitial) and was treated with chlorambucil. 64 months after the diagnosis of CLL, she developed CML. She was treated with imatinib (400mg/day). After a few months, signs of CML were disappeared and CLL became dominant. This is first reported case.

KEYWORDS: Chronic lymphocytic leukemia, Chronic myeloid leukemia, Dry tap

INTRODUCTION
CLL is the most common leukemia of adults in the western world. CML, the most common myeloproliferative disorder, has a characteristic t(9:22) cytogenetic abnormality that involves fusion of the BCR gene on chromosome 22 with the ABL gene on chromosome 9. The BCR/ABL fusion results in constitutive activation of tyrosine kinase, which leads to uncontrolled proliferation of myeloid cells.¹

The coexistence of CML and B-cell chronic lymphocytic leukemia (B-CLL) in the same patient is rare.²

In the present study we report an additional patient who developed CML several years after the diagnosis of B-cell chronic lymphocytic leukemia (B-CLL). Until now, 18 patients have been reported in whom CML developed after the diagnosis of CLL (Table 1).

Case report
A 52-year-old female referred to oncology clinic in January 2008 due to excessive sweating. Her performance status was good. The patient had no history of any disease, tobacco, ethanol, or illicit drug use. The initial blood chemistry tests and metabolic screening (e.g., liver function test (lactate dehydrogenase and creatine), lipids level, platelet, hemoglobin level) were normal. But WBC count was 30000 count/µL (lymphocytes=54% and neutrophils=42%). Computed tomography (CT) scanning revealed bulky cervical lymphadenopathy (CL).

One month later, flow cytometry analysis (CD20+,CD19+,CD3+,CD10- and CD5+) and pathological report showed that she had B-CLL with generalized lymphadenopathy (CT revealed the enlargement of cervical, axillary, mediastinal,
Diagnosis of bone marrow trephine biopsy showed hypercellular marrow (75% cellularity) with interstitial nodules. (Fig. 1) WBC count was 30000 count/µL. Patient had stage 4 and was treated with chlorambucil (three times a day). Table 2 shows the laboratory reports from January 2008 to February 2014.

### Table 1: Reports of patients with chronic myeloid leukemia and chronic lymphocytic leukemia

| Reference | Category                        | Age (year) | Gender | Treatment            | Interval (month) |
|-----------|---------------------------------|------------|--------|----------------------|------------------|
| 3         | CML and CLL Simultaneously      | 58         | M      | Bus, PDN            | 0                |
| 3         | CML and CLL Simultaneously      | 55         | M      | Bus                 | 0                |
| 3         | CML and CLL Simultaneously      | 69         | M      | Hu, Chl, PDN        | 0                |
| 3         | CML and CLL Simultaneously      | 69         | M      | Chl, Hu             | 0                |
| 3         | CML and CLL Simultaneously      | 71         | F      | Hu, DXR, VCR, PDN   | 0                |
| 3         | CML and CLL Simultaneously      | 64         | M      | Hu                  | 0                |
| 3         | CML and CLL Simultaneously      | 68         | M      | Hu, IFN             | 0                |
| 4         | CML and CLL Simultaneously      | 53         | M      | IM                  | 0                |
| 5         | CML and CLL Simultaneously      | 50         | M      | IM                  | 0                |
| 6         | CML and CLL Simultaneously      | 77         | M      | IM                  | 0                |
| 7         | CML and CLL Simultaneously      | 57         | M      | IM                  | 0                |
| 3         | CML after diagnosis of CLL      | 51         | F      | IM, Dasa            | 96               |
| 3         | CML after diagnosis of CLL      | 55         | M      | Chl, Bus            | 84               |
| 3         | CML after diagnosis of CLL      | 43         | M      | TBI, Chl, PDN, Bus  | 73               |
| 3         | CML after diagnosis of CLL      | 47         | F      | Chl, VCR, BLM       | 72               |
| 3         | CML after diagnosis of CLL      | 66         | M      | Chl, Hu             | 72               |
| 3         | CML after diagnosis of CLL      | 55         | M      | Chl, Hu, Bus        | 61               |
| 3         | CML after diagnosis of CLL      | 82         | F      | Hu, Bus             | 60               |
| 3         | CML after diagnosis of CLL      | 81         | F      | Dasa                | 42               |
| 3         | CML after diagnosis of CLL      | 62         | M      | TBI                 | 36               |
| 3         | CML after diagnosis of CLL      | 52         | F      | FAMP, CTX, Rituximab, TBI, IM | 29 |
| 3         | CML after diagnosis of CLL      | 74         | M      | None                | 24               |
| 3         | CML after diagnosis of CLL      | 68         | F      | FAMP, Rituximab, PDN | 24             |
| 3         | CML after diagnosis of CLL      | 76         | F      | Hu                  | 12               |
| 3         | CML after diagnosis of CLL      | 83         | M      | Bus, Chl            | 2                |
| 3         | CML after diagnosis of CLL      | 52         | F      | Chl, IM, Hu         | 64               |
| 8         | CML after diagnosis of CLL      | 57         | M      | Several months      |                  |
| 9         | CML after diagnosis of CLL      | 60         | M      | Dasa, IM            | 6                |
| 10        | CML after diagnosis of CLL      | 59         | F      | CLB+PDN             | 36               |

### The present case

| Reference | Category                        | Age (year) | Gender | Treatment            | Interval (month) |
|-----------|---------------------------------|------------|--------|----------------------|------------------|
| 3         | The present case                | 52         | F      | Chl, IM, Hu          | 64               |
| 8         | The present case                | 57         | M      | Several months       |                  |
| 9         | The present case                | 60         | M      | Dasa, IM            | 6                |
| 10        | The present case                | 59         | F      | CLB+PDN             | 36               |

### Table 2: Laboratory Data

| Variable(s)                     | Value          | Normal range          |
|---------------------------------|----------------|-----------------------|
| WBC(count.µL⁻¹)                 | 3307±x±3000    | 4000–9000             |
| Hemoglobin (g.dL⁻¹)             | 8.9±x±13.9     | 120–15.2              |
| Platelet(count.µL⁻¹)            | 153000±x±131700 | 117–329 × 10³         |
| Lactate dehydrogenase(IU.L⁻¹)  | 357±x±639      | 119–229               |
Sweating reduced in July 2009, and there was CL (cervical lymphadenopathy), yet. But CL reduced and spleen was not palpable in April 2010. One year later, there was axillary lymphadenopathy and CL, and after a few months, patient got headache and hemoglobin level had been reduced. In May 2013, patient referred to clinic and she had heel pain. Her tonsils were swollen. After sixteen months, gastrointestinal pain, nausea, vomiting, fever and gastritis appeared in patient. The platelet increased until 1317000 count/µL. Size of lymph nodes reduced. In peripheral blood smear due to leukocytosis with shift to left CML recommended for her, (Fig. 2) and her treatment was initiated with hydroxyurea. Bone marrow aspiration was dry tap but in bone marrow biopsy CML was recommended and reverse transcriptase-polymerase chain reactions (RT-PCR) showed (9:22) (p210-P190) and then CML was documented. Patient was treated with Imatinib (400mg/day) tablet. The platelet decreased after one month until 157000 count/µL. Now, WBC count is 6700 count/µL (lymphocytes 70% and neutrophils = 30%) and patient has been came back to previous picture of CLL presentation. But she doesn’t have any sign of dominant lymphadenopathy.

**DISCUSSION**

This case report describes a rare occurrence of sequential CLL and CML in the same patient. CLL is a lymphoid malignancy characterized by progressive accumulation of mature lymphocytes in the peripheral blood, bone marrow, liver, and lymphoid organs. B-CLL is a disease of an accumulation of mature B cells which are highly dependent on the microenvironment for maintenance and expansion.

Coexistence of CML in CLL can mainly be classified into three types; CML preceding CLL, CLL preceding CML, and simultaneous occurrence, and the most common, as in this case, long progression CLL preceding CML.

This case report describes a rare occurrence of CML after the diagnosis of CLL in the same patient. Table 1 shows the same reports of diagnosis of CML after the diagnosis of CLL.

The patients mean age of diagnosis of CLL in Iran is 63.7±8.9, 69.8% are males. Time of diagnosis CLL, our patient had 52 year.

CML is a myeloproliferative disease induced by the BCR-ABL oncogene. Pathologically, CML patients develop granulocytosis and splenomegaly.

Patients reported as having concurrent CML and CLL, including the present patient, are classified into three groups according to the interval between the diagnoses of CLL and CML (Table 1). Some published case reports, in which patients with coexistent CLL and CML were studied at the genomic level, already hypothesized that the two diseases originate in two different cell clones, as indirectly suggested by the
negativity of a molecular marker in one of the two clones examined. Therefore, both diseases may have arisen simultaneously and the CLL and CML clones may occur randomly and independently in patients, too. But Table 1 shows that simultaneous CML and CLL is more in male and our case is female, and also patients with CLL are at increased risk of secondary malignancies because their immune systems are impaired and this raises the possibility that an abnormality in pluripotent stem cells could lead to leukemic proliferation of both myeloid and lymphoid cells. Therefore, in the present case, CML may have arisen after CLL. Further studies are needed to identify an etiology.

18 patients (age group with 43-83) in Table 1 had CML after the diagnosis of CLL and 50% of patients were treated with hydroxyurea and chlorambucil in interval of diagnosis between CLL and CML. Also, a research showed that treatment with HU alone is associated with a leukemic risk of approximately 3.5% and chlorambucil is a potent mutagen in escherichia coli. On the other hand, Chlorambucil effectively induces deletion mutations in mouse germ cells and mutagenic effect of chlorambucil varies markedly among different post-stem-cell stages. To study BCR and immunoglobulin gene rearrangement, the chimeric BCR-ABL messengers, coding for p190 or p210 proteins, were detected on total RNA extracted from bone marrow and peripheral blood mononuclear cells collected at the time of diagnosis, by nested reverse transcriptase-polymerase chain reactions (RT-PCR). It has been suggested that co-expression of p190 and p210 may be a pathway of CML progression in adult patients. In our study, The CML phenotype was characterized by t(9;22) and the presence of both p210 and p190 BCR-ABL chimeric transcripts. Four different types of bone marrow (BM) infiltration were recognized in CLL: nodular (N), interstitial (I), nodular and interstitial (mixed) and diffuse (D). In addition, the pattern of BM infiltration correlates very well with the International Staging System for CLL, and the pattern of BM positivity in CLL patients also has prognostic significance. In our patient, type of BM was mixed with stage 4. In conclusion, we report a patient who developed CML 6 year after the diagnosis of CLL and after a few months, signs of CML were disappeared and she appeared CLL. This is first reported case of the appearance and disappearance of CML in patient with CLL.

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