

## Case Report

# Pulmonary leucostasis and trisomy 12 in a young patient with chronic lymphocytic leukemia: a case report and review of literature

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Received July 18, 2016; Accepted September 10, 2016; Epub November 15, 2016; Published November 30, 2016

**Abstract:** Chronic lymphocytic leukemia (CLL) is the most prevalent type of adult leukemia in the Western world. CLL is predominantly a disease of the elderly and affects men twice as often as women. It is rare before the fourth decade of life, and its incidence increases exponentially after age 40. The occurrence of CLL in younger patients accounts only for 10% to 20% of newly diagnosed cases. In CLL there is a predominance of mature lymphocytes, which usually does not result in occlusion of microvasculature. Leucostasis in the lungs of a patient with CLL has been rarely documented, especially in younger patients, in the literature to our knowledge. We present a 25-year-old man initially diagnosed with CLL who had pulmonary leucostasis with excessive lymphocytes, and trisomy 12 by whole genome sequencing, and received complete remission after four cycles of FCR.

**Keywords:** Chronic lymphocytic leukemia, younger, leucostasis, excessive lymphocytes, trisomy 12

## Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world and affects mostly elderly patients. The clinical course of patients with CLL is heterogeneous, ranging from highly indolent to relatively aggressive. CLL can be divided into two subtypes based on the occurrence of somatic hypermutation in the immunoglobulin heavy-chain variable (IGHV) genes [1]. The subtype with mutated IGHV genes (M-CLL) has an improved overall survival compared to the subtype with unmutated IGHV genes (U-CLL) [2, 3]. CLL is still incurable without allogeneic stem cell transplantation (ASCT), but chemo-immunotherapy can significantly improve survival [4]. In this article, we describe the case of a young patient with leucostasis in the lungs and trisomy 12 by whole genome sequencing, and received complete remission after four cycles of FCR.

## Case report

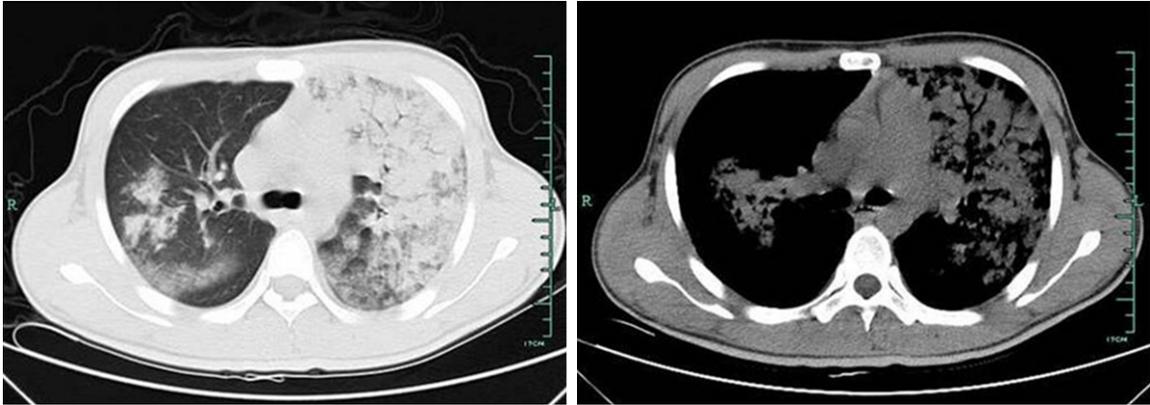
A 25-year-old man presented to the emergency department with a fever, increasing fatigue and

weight loss. The patient was in his usual health until approximately 1 year earlier, when he felt much tired than before. However he hadn't have any examination until presentation to the emergency department.

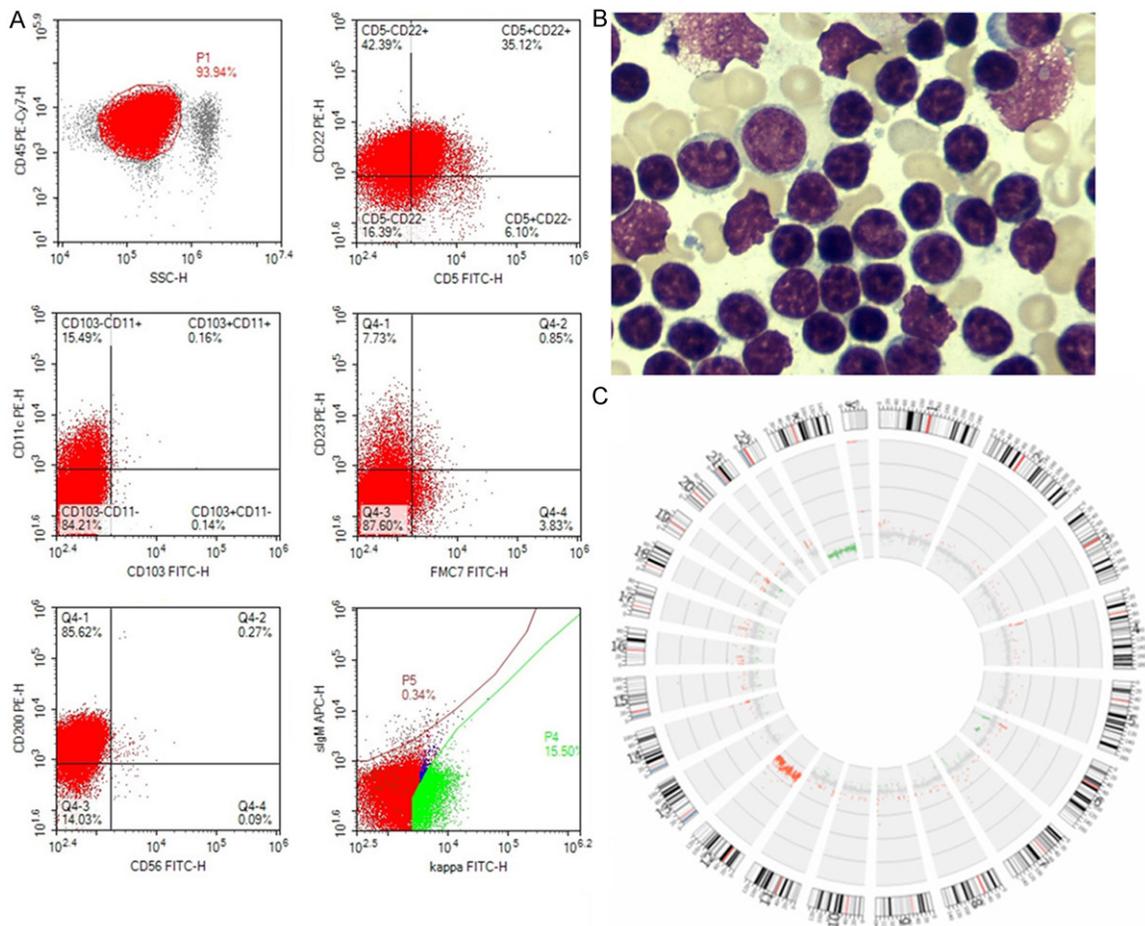
On examination, he had moderate anemia appearance, bilateral tonsillar enlargement and splenomegaly with a fahrenheit temperature reached 102.7 (39.3 centi-degree) and his weight was 10 kg less than 1 year earlier. The patient had no known medical history and was not on any medications.

On admission, complete blood count (CBC) with differential showed: total white blood cell count (WBC)  $981.9 \times 10^9/L$  ( $4.0 \times 10^9/L$ - $10.0 \times 10^9/L$ ) with 46% aberrant cells, haemoglobin (Hb) 68 g/L (120-160 g/L), haematocrit 26.7% and a platelet count of  $92 \times 10^9/L$  ( $100 \times 10^9/L$ - $300 \times 10^9/L$ ). Immunoglobulin level was below the lower limit and lactic dehydrogenase (LDH) was increased obviously with normal erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and liver and renal function. Serologic investigation for HBV, HCV, CMV, EBV was nega-

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**Figure 1.** The computer tomography (CT) of lungs. The CT scan suggested pulmonary infective disease and a small amount of pleural effusion on the left.



**Figure 2.** Aspirate of bone marrow and peripheral blood. A: The flow cytometry immunophenotyping showed CD5, CD22, CD200, CD23 (dim) and membrane kappa light chain positive and negative for CD103, FMC7, CD56. B: Cytology of bone marrow showed a high level of aberrant mature lymphocytes in bone marrow. C: Aberrant chromosome of trisomy 12 by whole genome sequencing. Red region of inner ring are detected as copy number gain; green region of inner ring are detected as copy number loss region and have little significance in the patient.

tive for acute infections. The computed tomography (CT) suggested pulmonary infective dis-

ease and a small amount of pleural effusion on the left (**Figure 1**). On the second day of admis-

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sion, his saturation of blood oxygen decreased with white blood cell count  $1290 \times 10^9/L$  and we took an endotracheal intubation for mechanical ventilation in intensive care unit (ICU).

Bone marrow aspirate demonstrated 88% aberrant mature lymphocytes (**Figure 2B**) and flow cytometry immunophenotyping was reported as follows: 93.94% of total cells were monoclonal B cells, expressing the following antigens: CD19, HLA-DR, CD5, CD22, CD20, CD200, CD21 (dim), CD23 (dim) and membrane kappa light chain. The B cells were negative for CD103, FMC7, CD56 (**Figure 2A**). The cells were also positive for ZAP-70 and negative for CD38, with mutated IgV<sub>H</sub> status.

We took the peripheral blood of the patient for whole genome sequencing and found trisomy 12 by chromosome analyses (**Figure 2C**). The final diagnosis was chronic lymphocytic leukemia (Binet C and Rai stage IV). Therefore, the patient was treated with 7 times of peripheral blood leukocytes separation technique and 4 cycles of FCR (rituximab, fludarabine, cyclophosphamide) and received complete remission.

### Discussion

Chronic lymphocytic leukemia is a neoplastic disease of small, mature lymphocytes, which infiltrate the bone marrow, peripheral blood and lymphoid organs, showing the unique immunophenotypes CD5+, CD19+, CD20+ and CD23+. The disease is more common in men with a 2:1 male-female predominance [5]. A wide range of genetic variations like hypermutation of the immunoglobulin heavy-chain genes (IGHV), genomic aberrations, and recurrent gene mutations in oncogenes and tumor suppressor genes reflect the clinical and biological heterogeneity of the disease with survival times from 3 to 20 years [6]. CLL is still incurable without allogeneic stem cell transplantation, although treatment outcome has considerably improved by using risk stratification and novel therapeutic agents [7, 8].

The median age at diagnosis of CLL is 72 with 56.5% of cases between the ages of 65 and 84 years with a median age at death of 79 years (<http://seer.cancer.gov/statfacts/html/leuks.html>). Younger patients (defined as patients younger than 50-55 years of age) repre-

sent a small group of newly diagnosed patients with CLL, accounting only for 10% to 20% of newly diagnosed cases. Based on the National Cancer Institute's Surveillance and Epidemiology End Results (SEER) program estimates, 0.3% of the 15,490 patients diagnosed with CLL in 2009 in the United States were age 34 or younger [9]. When the young man presented to our department, we gave him the diagnosis of acute lymphocytic leukemia (ALL) firstly before bone marrow biopsy. After receiving the reports of biopsy, we were still in doubt of the CLL and excluded mantle cell lymphoma (MCL), prolymphocytic leukemia (PLL), splenic marginal zone lymphoma (SMZL) and hairy cell leukemia (HCL). However, the whole genome sequencing showed trisomy 12 without any mutated gene. Finally, the diagnosis of the young man was CLL (Binet C and Rai stage IV).

Within the hierarchical model of genetic subgroups commonly used in clinical practice, trisomy 12, the third most frequent aberration, confers an intermediate prognosis [6]. The mechanism, however, by which trisomy 12 contributes to lymphoproliferation remains unknown. Landau et al. [10] found that trisomy 12, del(13) and MYD88 were consistently clonal and specific drivers of CLL or B cell malignancies. Thus, trisomy 12 became a driver event of CLL based on pretransformation mutagenesis. In addition, Garcia-Marco JA et al. [11] has shown trisomy 12 to be associated with cells with a high proliferative index and consequently a key role in disease progression has been postulated. That's can explain our patient's high level of WBC count.

Through our extensive Medline search, pulmonary leucostasis with a high level of WBC count has been rarely described, especially in young patient of CLL. Awad, et al. [12] reported a case of pulmonary leucostasis in a 71-year-old woman with developed respiratory failure requiring intubation, whose WBC was  $>1789.4 \times 10^9/L$ . Our patient had a similar symptom with saturation of blood oxygen decreased when his WBC count  $1290 \times 10^9/L$ . After four cycles of FCR, his lung was as clear as normal.

Our patient was treated with four cycles of FCR and received complete remission. For symptomatic, untreated younger patients, two studies suggest that durable remissions seem to occur in patients with IGHV-mutated disease

and favorable interphase cytogenetics [ie, del(13)(q14) and trisomy 12], who received treatment with FCR [13, 14]. Compared with BR (bendamustine and rituximab), the GCSG still considers FCR to be its standard therapy for young, fit patients with CLL, while BR is associated with less toxic effects [15]. Byrd et al. [16] suggested FCR-based therapy seems most justified for younger, more fit patients lacking del(17)(p13.1) at the present time. With this therapy, assessment of bone marrow MRD-negative status offers the opportunity for extended remission and justifies this procedure after therapy. Nevertheless, there is no evidence for how many cycle needs. Moreover, allogeneic stem-cell transplantation (ASCT) is the only curative treatment modality for patients with CLL. The European Group for Blood and Marrow Transplantation released guidelines for consideration for SCT in patients with CLL, including younger patients [17].

In conclusion, younger patients are usually have a different attitude toward the diagnosis of CLL and available treatment options and better performance status, lower incidence of severe comorbidities than elderly. Much importance should be attached to accurate diagnosis, prognostic analysis and appropriate treatment.

### Acknowledgements

This work was supported in part by the Research Plan from the National Natural Science Foundation of China (No. 81372256).

### Disclosure of conflict of interest

None.

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