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Letter to the editor

A case of acute myeloid leukemia initially treated as chronic lymphocytic leukemia: what do we know about t(4;12)(q12;p13)?

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with incidence approaching 13,000 cases in the United States in 2008. It is diagnosed based on the percentage of blasts in the peripheral blood or bone marrow smear, in addition to specific cytogenetic findings. The standard therapy in the United States is anthracycline with cytarabine in a 7+3 protocol. Among the rare chromosomal translocations reported in AML is t(4;12)(q12;p13), which has been documented in several reports (see, for example, references [1,2]) and has poor prognosis. This entity is characterized by atypical myeloblasts, which may be reported as lymphocytes and therefore can be described also as *pseudo-lymphocytes*. Here we describe a case of t(4;12)(q12;p13) AML that was resistant to conventional chemotherapy. Imatinib was also tried as a possible therapy targeted to the protein transcript CHIC2–ETV6, but was not effective.

A 64-year-old man of European origin presented to a local hospital with progressive generalized weakness in July 2008. He also reported a weight loss of ~9 kg (20 pounds) over 3 months, with intermittent night sweats. No petechiae, rash, hepatosplenomegaly, or obvious lymphadenopathy were observed upon physical examination. At presentation, his white blood cell count was elevated (307×10^9/L); his hemoglobin was 7.2 g/dL, and platelets were 170×10^9/L. The differential was read as 60% lymphocytes and ~30% prolymphocytes. A peripheral blood smear was reported to show lymphocytes, prominence of prolymphocytes, few blasts, and many smudge cells, compatible microscopically with chronic lymphocytic leukemia (CLL). Flow cytometry and cytogenetic analysis from the peripheral blood were recommended and ordered, but were never done. A computed tomography scan confirmed the absence of any masses or enlarged nodes. A hematology consultation was ordered, and treatment for CLL was initiated.

The patient initially had leukapheresis performed, to reduce the tumor burden before initiation of chemotherapy, and his white blood cell count dropped to 10×10^9/L. No bone marrow biopsy was performed. After discussion of therapeutic options, the patient received a standard fludarabine, cyclophosphamide, and rituximab regimen (FCR) for a total of five cycles. During therapy, neutropenia resulted in several delays in therapy. His white blood cell counts ranged from 2.3×10^9/L to 12×10^9/L between cycles of chemotherapy, with a rapid elevation of the count toward the end of each cycle. No increase in blast number was noted on the differential, but lymphocyte counts remained elevated (70% of total) during the majority of complete blood count readings, including both lymphocytes and prolymphocytes. Basophil counts ranged from 1% to 20% of white blood cells toward the end of each cycle. After initial treatment with FCR failed to achieve an adequate response, the patient was referred to a local cancer center for further treatment recommendations, including stem cell transplant options.

On initial consultation, the patient was found to have a good performance status, although his blood tests indicated trilineage myelosuppression. His white blood count was noted to be 164×10^9/L with 92% blasts; his hemoglobin was 9.1 g/dL, and his platelets were 94×10^9/L. The patient was admitted for leukapheresis, and a white blood cell count of 7×10^9/L was obtained. The peripheral blood smear (Fig. 1) showed numerous white cells with a vaguely lymphoid appearance, moderate in size and with mildly clumped chromatin, a single nucleolus, and a moderate amount of agranular basophilic cytoplasm. A comparison with the patient's original blood smear from July 2008 indicated similar appearance. His first bone marrow biopsy was reviewed, and the blast count was noted to be >90%, all previously and mistakenly identified as "atypical lymphocytes." Flow cytometry confirmed the myeloid lineage of the blasts. HLA typing identified a possible matched unrelated donor with an ABCDR match, and HLA DQ1 AG mismatch.

The patient received induction therapy using standard idarubicin and cytarabine on a 7+3 protocol. At day 13, a bone marrow biopsy revealed persistent blasts with no hypoplasia, and the peripheral blood differential indicated 90% myeloid blasts. Cytogenetic analysis (Fig. 2) revealed t(4;12)(q12;p13) in all 20 metaphases analyzed and del(5q)(35) in 2 of 10 metaphases (not shown). After failure with two lines of therapy (i.e., the idarubicin and cytarabine 7+3 and the fludarabine-based FCR protocols), the patient was put on an imatinib and gemtuzumab chemotherapy regimen. The rationale for this third line of treatment included that (a) the blasts were >80% positive for CD 33 and (b) the patient's translocation included the protein transcript of the *ETV6* gene. Patients with similar transcripts of the ETV6 protein have been reported to be responsive to imatinib, such as t(5;12) in chronic

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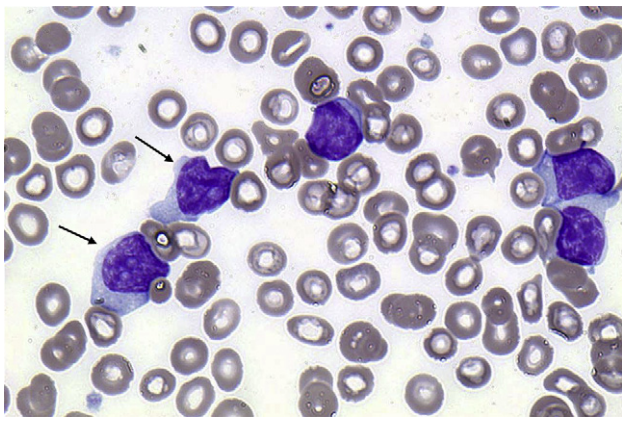

Fig. 1. Peripheral blood smear. Arrows indicate myeloblasts (pseudolymphocytes).

myelomonocytic leukemia (CMML) (see, for example, references cited by Han et al. [3]). The present patient was given one dose of gemtuzumab at 9 mg/m^2 with continuous imatinib therapy at 400 mg daily. A repeat bone marrow biopsy on day 9 indicated persistent AML. Fourth-line therapy included gemtuzumab, intermediate-dose cytarabine, and mitoxantrone (MIDAM protocol), with an increase in imatinib dose to 800 mg. A repeat bone marrow aspirate indicated no leukemic response. The patient was placed on palliative care and sent home.

Acute myeloid leukemia is defined by the World Health Organization (WHO) as myeloblasts exceeding 20% or more of bone marrow white cells [4]. The determination of the myeloid lineage is usually done through at least three-color flow cytometry or by traditional immunohistochemistry. Myeloid origin may also be suggested if the myeloperoxidase (CD13, CD33) or monocytic markers (NSE, CD11c, CD14, and CD64) are positive. In the peripheral blood smear, myeloblasts are traditionally large cells with high nuclear-to-cytoplasm ratio and with nucleoli. Although these cells can contain a pink or red rodlike structure (Auer rods), Auer rods are not found all the time. Auer rods are the only indicator of myeloid origin by light microscopy.

The International Workshop on Chronic Lymphocytic Leukemia defined CLL as the presence of an absolute lymphocyte count exceeding 5,000/cm^2 [5]. The clonality of B-cells in CLL should also be confirmed by flow cytometry. In CLL, cells coexpress CD5 and B-cell surface antigens (CD19, CD20, and CD23). A bone marrow examination is not required for the diagnosis of CLL, although it is recommended before therapy was initiated. In the peripheral blood smear the leukemic cells are commonly small, mature lymphocytes with dense nuclei and aggregated chromatin but without discernible nucleoli; there is a narrow border of clear basophilic cytoplasm. Atypical cells,

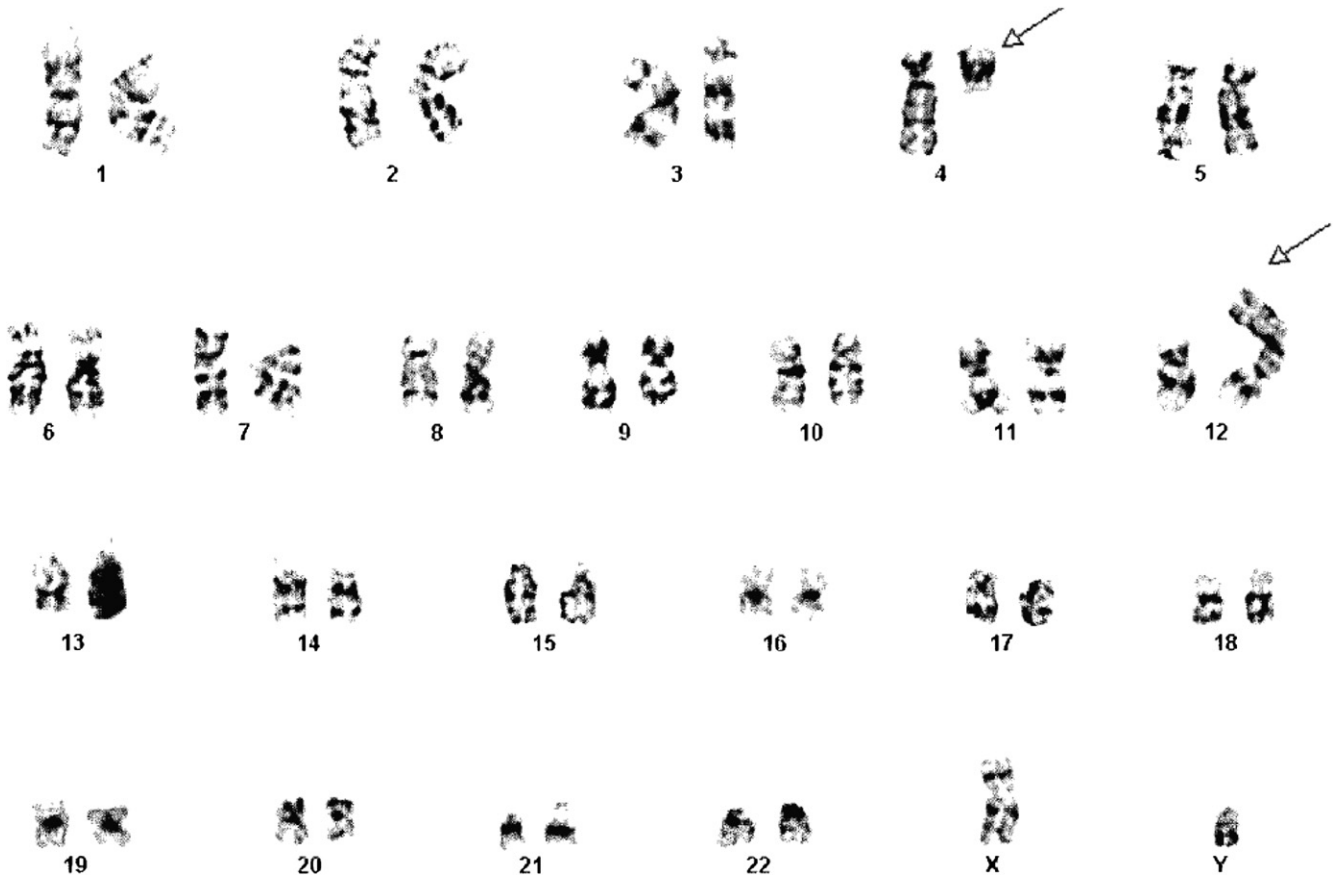

Fig. 2. Karyogram. Arrows indicate translocated chromosomes.