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CASE REPORT

A 23-year-old woman with 11q-chronic lymphocytic leukemia

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Case report

Chronic lymphocytic leukemia (CLL) is characterized by accumulation of monoclonal CD5+ B lymphocytes in blood, bone marrow and lymphoid tissues. The incidence of CLL is about five cases per 100,000 people per year, increasing with age. In most series, CLL is more frequent in males than in females [1].

In a recent report from the Hospital Clinic of Barcelona, Abrisqueta et al. [2] described the findings of 929 patients, with a median age at diagnosis of 67, with a range of 24–97 years. Only 13.3% were under the age of 50; the youngest patient was 24 years old. In another investigation, Mauro et al. [3] reported the age distribution of 1,011 patients with CLL. Among the patients studied, 11% were ≤50 years of age and 1.5% was less than 40 years. In this distribution, the youngest one was 31 years old. Gribben et al. [4] described 162 patients with poor prognosis CLL who have undergone hematopoietic stem cell transplantation. The median age was 49 with a range of 19–66 years [4]. Lugassy et al. [5] reported six cases under the age of 30 years. We studied 426 patients with CLL in the Laboratory of Flow Cytometry from the University Hospital of Medical School at Ribeirão Preto. The median age at diagnosis was 66.3 (range 23–91), only 10.6% were under the age of 50 years; 2.6% was ≤40 years and only 0.7% ≤30 years. Therefore, CLL is a rare disease in young patients.

We describe a case of a 23-year-old woman with CLL diagnosed in May 2008 who referred cervical, axilar and inguinal lymphadenopathy since 2005 when she was 20 years old. At time of the diagnosis, she complained diarrhea, vomiting and abdominal distension. Physical examination showed cervical, axilar and inguinal bilateral lymphadenopathy, hepatomegaly (6 cm below the right costal margin), but the spleen was not papable. Peripheral blood counts revealed hemoglobin 6.5 g/dl, platelets 78.000/mm^3, WBC 69 × 10^9/L with 77% of lymphoid cells. Immunophenotype studies showed CD19+, CD5+, FMC7−, CD79b-, CD23+, *kappa* chain of low intensity, CD38+ (35%), CD10−, TdT−, ZAP70+(33%) (Matutes score 5). Cyclin D1 was negative as determined by RT-PCR analysis. Metaphase induction was performed by using 10^7 peripheral blood mononuclear cells that were cultured in RPMI 1640 medium (Invitrogen, Gaithersburg, MD) with 20% fetal calf serum in the presence of the immunostimulatory CpG-oligonucleotide DSP30 (TIB-MolBiol, Berlin, Germany) and interleukin 2 (IL-2). After 72 h, colcemid (Sigma, Munich, Germany) was added before chromosome preparation. Peripheral blood mononuclear cells for FISH analysis were not submitted to any stimuli. Chromosome preparations were obtained by using standard procedures and the subsequent cytogenetic analysis and interpretation were made according to ISCN 2005 [6]. G-banding analysis showed 11q deletion in all 20 analyzed cells, 46,XX,del(11)(q23)[20] (Fig. 1a).

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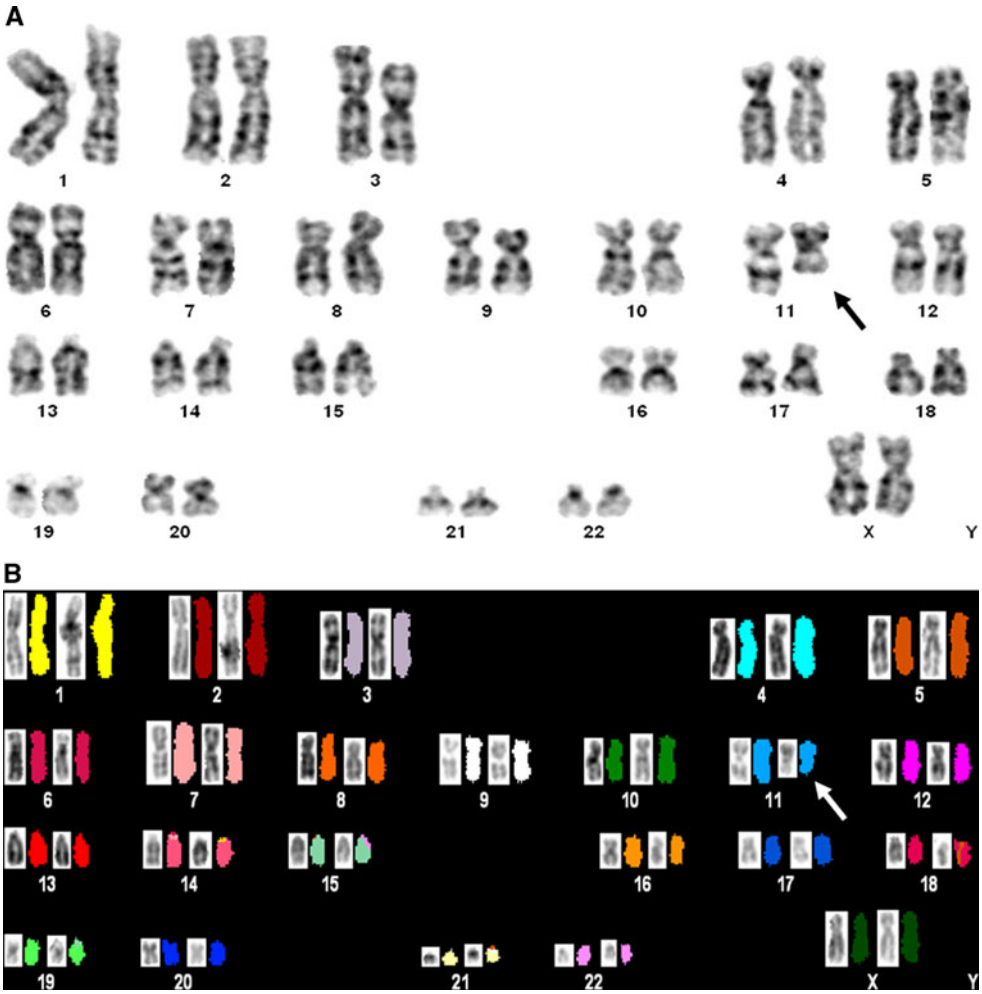

Fig. 1 **a** Karyotype showing del(11)(q23) (*arrow*) (G-banding with trypsin—Giemsa). **b** SKY karyotype from a leukemia cell at time of diagnosis, showing the inverted DAPI (*left*) and the classified (*right*) profiles for each chromosome. Deletion 11q23 is illustrated (*arrow*)

Chromosome labeling was performed with the SKY fluorescent labeling kit (Applied Spectral Imaging, Migdal HaEmek, Israel) according to the manufacturer's protocol. Image acquisition was performed with a SD200 Spectracube (Applied Spectral Imaging, Inc.) mounted on an Axio Imager M2 microscope using a custom designed optical filter (SKY-1; Chroma Technology, Brattleboro, VT, USA). Automatic identification of chromosomes was based on the measurement of the spectrum for each chromosome. A minimum of twenty metaphases were analyzed using the SkyView 5.5 software (ASI, Carlsbad, CA, USA). Spectral karyotyping analysis confirmed previously abnormalities seen by G-banding analysis (Fig. 1b). FISH analysis using Vysis LSI ATM (11q22.3) SpectrumOrange confirmed the presence of del(11)(q23), previously seen in G-banding and SKY analysis (data not shown). The parents' karyotypes revealed a normal profile. Bone marrow aspiration showed 90% infiltration with mature lymphocytes. The bone marrow trephine biopsy revealed extensive and diffuse infiltration by CLL, with scarce hematopoietic reserve total bilirubin of 3.4 mg/dl, direct f 0.4 mg/dl and indirect 3.0 mg/dl. The Coombs test was strongly positive and the diagnosis of autoimmune hemolytic anemia (AIHA) was settled.

The patient was treated with rituximab, at dose of 375 mg/m^2 i.v. on day 1 (D-1), cyclophosphamide, 750 mg/m^2 i.v. on D-2, and dexamethasone, 20 mg i.v. on D-1, D-2 and orally from D-3 to D-7 as suggest by Gupta et al. [7]. It was observed a slow though continuous improvement of the nodal enlargement and lymphocytes levels. At the end of 6 cycles, there was no lymphadenopathy, however, leukocytes levels remained high 30×10^9/l. Soon after this event, the leucocytes levels increased to 200×10^9/l, and the platelets decreased to 15×10^9/l. The treatment with alentuzumab was thus proposed, aiming a tumoral reduction, before proceeding the allogenic bone marrow transplantation—since the patient has a sibling donor.

Expressions of ZAP70 and CD38 are considered as two important prognostic markers for CLL. Their high expression is always associated with an aggressive clinical course and, consequently poor prognosis [8]. Both ZAP70

and CD38 were positive (*cut off* 20%). Furthermore, patients with deletion 11q are generally younger and typically associated with severe lymphadenomegaly [9]. The *ATM* gene, located on 11q22, codes for a protein that acts upstream of p53 in the DNA damage response pathway. Mutations on *ATM* are associated with an unfavorable outcome in CLL [10]. Inactivation of the *ATM* by deletion is usually a somatic event, but can also be present in the germline cells. Although this event suggests a predisposition of heterozygous *ATM* mutation carriers to develop CLL, the parents karyotype showed a normal profile. However, not all patients with a deletion 11q show a disruption of the remaining *ATM* allele [9], so the search for additional genes in 11q22–23 is necessary.

In this study, we report a 23-year-old patient with poor risk CLL [del(11q), ZAP70+, CD38+], but with lymphadenopathy since she was 20 years old. To the best of our knowledge, this is the second youngest patient reported in the literature, except for a 19-year-old case reported by Gribben et al. [4].

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