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Molecular cytogenetic analysis of dicentric chromosomes in acute myeloid leukemia

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ABSTRACT

Dicentric chromosomes (DCs) have been described in many hematological diseases, including acute myeloid leukemia (AML). They are markers of cancer and induce chromosomal instability, leading to the formation of other chromosomal aberrations and the clonal evolution of pathological cells. Our knowledge of the roles and behavior of human DCs is often derived from studies of induced DCs and cell lines. It is difficult to identify all the DCs in the karyotypes of patients because of the limitations of metaphase cytogenetic methods. The aim of this study was to revise the karyotypes of 20 AML patients in whom DCs were found with conventional G-banding or multicolor fluorescence in situ hybridization (mFISH) with (multi)centromeric probes and to characterize the DCs at the molecular cytogenetic level. FISH analyses confirmed 23 of the 29 expected DCs in 18 of 20 patients and identified 13 others that had not been detected cytogenetically. Fourteen DCs were altered by other chromosomal changes. In conclusion, karyotypes with DCs are usually very complex, and we have shown that they often contain more than one DC, which can be missed with conventional or mFISH methods. Our study indicates an association between number of DCs in karyotype and very short survival of patients.

1. Introduction

Human centromeres are characterized by large arrays of α-satellite DNA, in which the canonical histone H3 is replaced by a variant, centromere protein A (CENP-A), to create unique centromeric nucleosomes [1,2]. The abnormal fusion of two chromosomal segments, each with a centromere, produces a dicentric chromosome. Dicentric chromosomes (DCs) are present in many cancers, particularly hematological disorders, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) [3,4]. These chromosomes are markers of cancer and are known to induce chromosomal instability, leading to the formation of other chromosomal aberrations and the clonal evolution of pathological cells.

Barbara McClintock first described the unstable behavior of chromosomes with two functional centromeres. The segregation of the two centromeres to opposite spindle poles can lead to chromosomal mis-segregation or breaks, followed by alterations in the genes located in or around the breakpoint. The formation of new DCs can result in a cascade of chromosomal damage (the breakage–fusion–bridge cycle) and consequently in a complex unbalanced rearrangement of the karyotype [3,5,6]. In myeloid diseases, complex karyotypes (≥ three unrelated chromosomal aberrations) are indicators of very poor prognoses [7–10].

However, some DCs seem to be stable in mammals. Three possible mechanisms of dicentric stabilization have been described: epigenetic inactivation, reduction in the intercentromeric distance, and shortening/deletion of a centromere [4]. DCs with one inactivated centromere are called “pseudodicentric”. The inactivated centromere lacks the key centromeric and kinetochore proteins, and at metaphase, often loses the form of primary constriction that is typical of functional centromeres [11].

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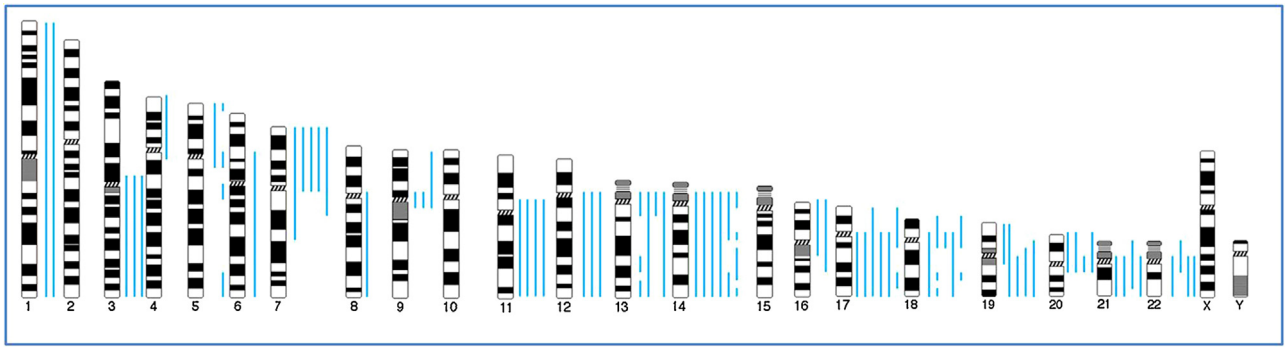

Fig. 1. Schema of the regions involved in dicentric chromosomes.

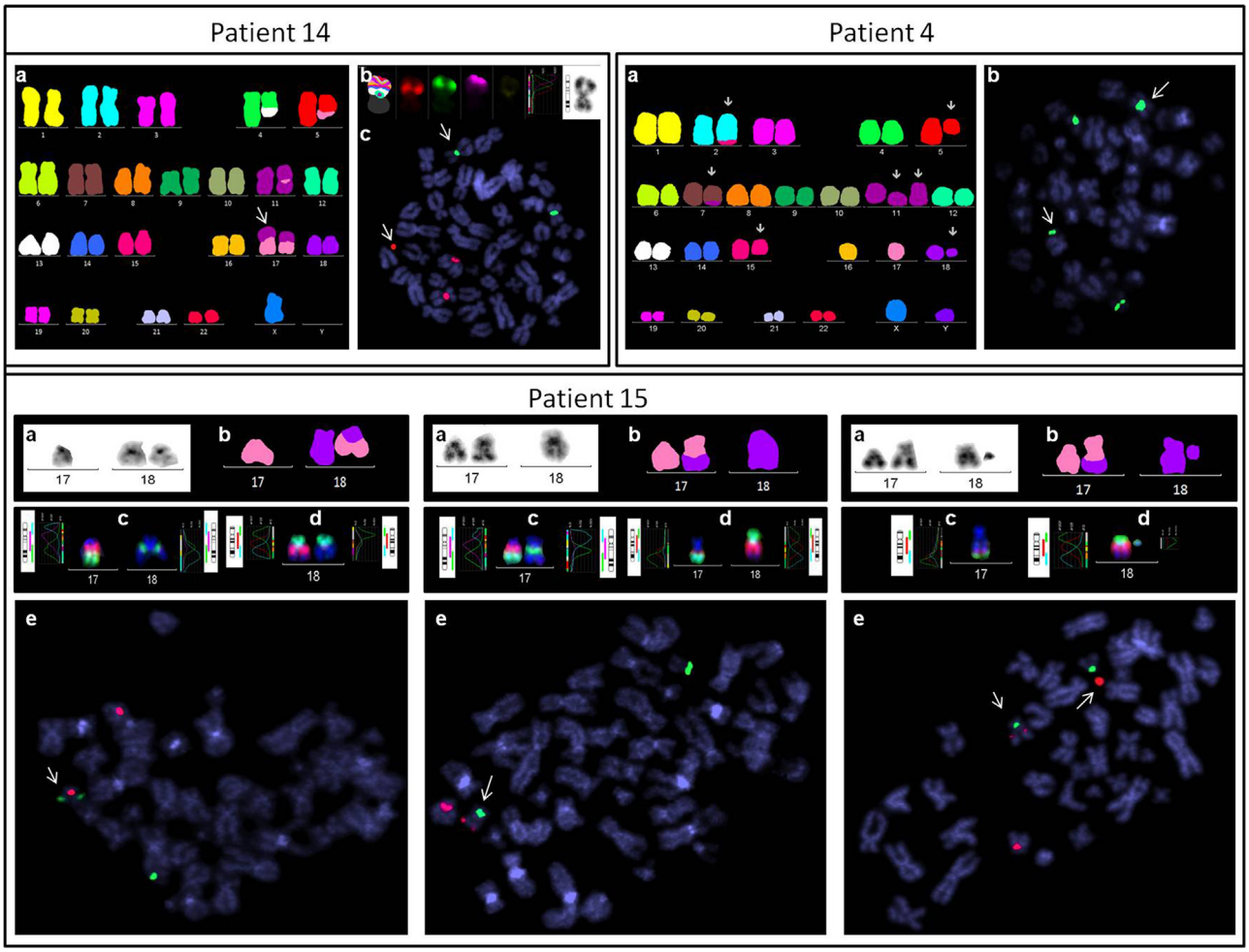

Fig. 2. Patient 14: mFISH (a); mBAND XCyte11 (b); FISH with CEP 17 (green)/11 (orange) (c); expected psu dic(17;11)(p11.2;p11.1) (a,b) (marked by arrow) revised as der(17)(17qter→17p11.2::11p11.2::11q11.2→11qter), accompanied by the separately localized centromere of chromosome 11, apparent as a small marker chromosome (c). Patient 4: mFISH (a); FISH with CEP 11 (green) (b); dicentric dic(11)(p11.2) without any reduction of centromere 11 and a fragment of additional chromosome 11 centromeric material (marked by arrows). Patient 15: partial karyotype (a); partial mFISH result (b); mBAND XCyte17 (c) and XCyte18 (d); FISH with CEP 17 (green)/18 (orange) (e); clone 1 (on the right), psu der(18;17)(17pter→17q11.2::17q23→17q25::18q22::18q11.1→18pter), inactivated centromere 17; clone 2 (in the middle), psu der(17;18)(17pter→17q11.2::17q23→17q25::18q22::18q11.1→18pter), inactivated centromere 18; clone 3 (on the left), psu der(17;18)(17pter→17q11.2::17q23→17q25::18q22::18p11.2::18q22→18q21.3::18q11.1→18pter), inactivated centromere 18, and small centromeric marker of chromosome 18.

Many studies have examined the roles of induced DCs, but only a few have summarized their occurrence and behavior in natural malignant cells. In this study, we characterized the DCs verified in AML at the molecular cytogenetic level. We evaluated the most frequently involved chromosomes and the secondary changes they entail.

2. Materials and methods

2.1. Patients

In 2006–2014, we examined 468 adult patients with AML (excluding the specific type AML-M3). A complex karyotype