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Review/Praca poglądowa

Duplication 1q as primary and 3q in t(3;13) as secondary aberration in Fanconi anemia: Implications and literature review

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ABSTRACT

Fanconi anemia (FA) is a genetic disorder of chromosomal instability. One of the routine methods of confirmation for FA includes chromosome breakage analysis, using cross-slink-inducing agents. Bone marrow karyotyping at diagnosis and further follow-up will aid in detecting aberrations. If present, they might be indicative of a possible karyotype evolution, leading to poor prognosis. We report a FA patient with two distinct karyotypes: 46,XY,dup(1)(q21q31) in the first diagnostic sample and 46,XY,dup(1)(q21q31),der(13)t(3;13)(?q26;p12) in the second, after a span of two years. We discuss the possible karyotypic evolution, the implications of chromosome 13 involvement and regions/genes on chromosomes 1q and 3q in FA. The importance of periodic examination of bone marrow in these patients, for detection of cryptic aberrations which might lead them to MDS/AML, is also discussed.

Introduction

Fanconi anemia (FA) is a chromosome instability syndrome with progressive bone marrow (BM) failure and increased risk of cancers. Karyotyping of BM, forms an essential investigation at diagnosis, prior to bone marrow transplantation (BMT). Periodic karyotyping is beneficial, besides testing for breakage scoring alone, which is one of the confirmatory methods to differentiate between FA and aplastic anemia. Clinical observation showed that detectability of chromosomal aberrations in BM aspirates of FA patients can vary over time, with clones becoming transiently undetectable. This has led to underestimation of clinical relevance of chromosomal aberrations in FA [1]. Better clinical relevance and biological implications of

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chromosomal aberrations in FA, were achieved in a larger case series by advanced molecular cytogenetic technologies along with conventional karyotyping [2–5]. Clonal evolution and associated chromosomal aberrations in FA are important for understanding malignant transformation mechanisms; therefore, they had wider implications. That led to the identification and delineation of a specific pattern of chromosomal aberrations in FA, characteristically unbalanced, with gain/loss of chromosomal material during clonal evolutions. We report a patient who developed secondary additional chromosome abnormalities 2 years after the initial diagnosis, and thus indicating possible karyotypic evolution. The possible implications are discussed.

Patient details

A 22-year-old male patient was admitted with febrile episodes and diarrhea. Clinical examination indicated dysmorphic features; deformities of the chest wall, with grade one clubbing and scar from previous surgeries, and abnormal thumbs, hands and abnormally placed ears. Ultrasound investigation revealed abnormal kidneys. He was also operated earlier for esophageal atresia and cardiac lesions and labeled VATER syndrome (Vertebrae, Anus, Trachea, Esophagus, Renal). His cognitive function was average. Peripheral smear findings and bone marrow aspiration (BMA) exhibited dysplasia. The family history indicated that the patient had a brother with FA who died 15 years back, after it transformed to AML.

Methods, results and discussion

Breakage scoring on peripheral blood using caryolysin (0.05 μg/ml) showed chromosome breakage, chromatid exchanges, and dicentric and triradial images, in 98% of cells (controls 2%). A year later, a repeat also showed the same rearrangements of breakage. These results were consistent with the diagnosis of FA.

Karyotype on diagnostic bone marrow in 2012 showed dup(1)(q21q31) (Fig. 1(a)) as a sole clonal abnormality. Two years later, in 2014, a repeat cytogenetics showed persistence of dup(1)(q21q31) with a secondary additional structural abnormality – add(13)(p12) (Fig. 1(b)). This indicated a possible clonal karyotype evolution (transformation). Spectral karyotyping (SKY) identified the additional abnormality on 13p, as part of chromosome 3 and hence, the karyotype was redefined as 46,XY,dup(1)(q21q31),der(13)t(3;13)(?q26;p12)[18] (Fig. 2).

FA patients are known to have chromosomal aberration in bone marrow, which might later transform to MDS or AML. Partial duplications/triplications of chromosome 1q have been documented [6–8]. The most frequently involved region is 1q21 which harbors fragile sites and oncogenes involved in AML [6]. Cells with chromosome triplication are considered to have evolved from a previous duplication. The duplication region in our patient was (1)(q21q31). The consequence is a genomic amplification of a specific chromosomal region. In one report, dup(1)(q21q42) was found in the first sample and 7 months later when patient had transformed to AML, the second sample showed del(1)(q32) [9]. Our patient showed dup(1)(q21q31) on diagnostic sample, while a repeat after 2-years showed an additional abnormality der(13)t(3;13). Clonal evolution observed in FA after initial diagnosis is frequent gains of 1q and 3q, characteristically unbalanced with gain and loss of chromosomal material [2–4, 10], as observed in our patient, with the occurrence of der(13)t(3;13). 3q gain is a particular characteristic for FA and its clinical implications indicate transformation to MDS/AML and FA related myelodysplasia [2–4, 10]. Chromosomal aberrations, such as inversions or translocations involving the 3q, are well documented in myeloid malignancies from non-FA patients, particularly adults [11, 12]. Gene expression resulting from FA-specific gain in 3q26-3q29 has been studied to understand the important role of

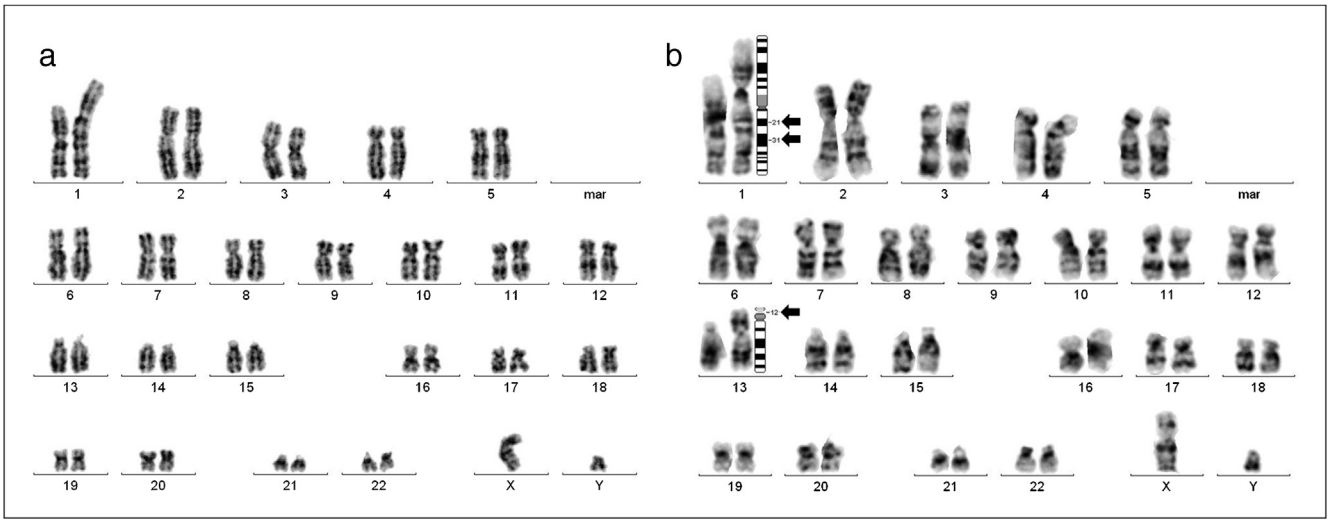

Fig. 1 – (a) Karyotype of bone marrow at diagnosis showing dup(1)(q21q31) as sole abnormality; (b) karyotype of repeat (follow-up) bone marrow (2 years after the initial diagnosis), showing dup(1)(q21q31) (arrow) and an additional add(13)(p12)

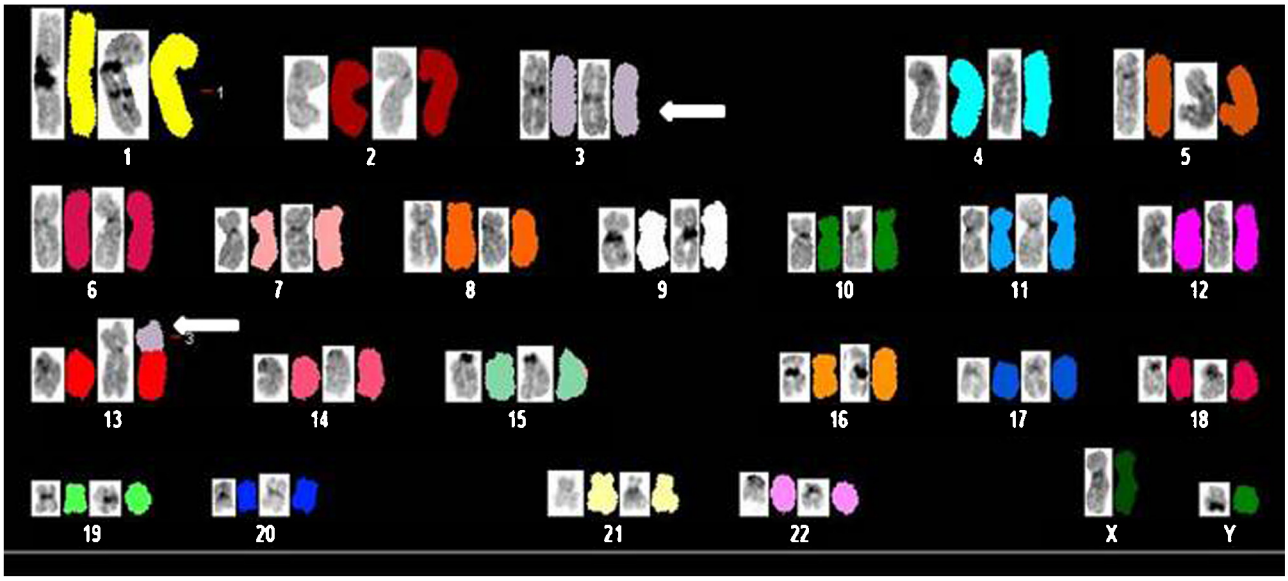

Fig. 2 – Spectral karyotype showing add(13)(p12) as part of chromosome 3 (arrow heads)

transcriptional regulator EVI1 (ecotropic viral integration site 1) for leukemic transformation in FA [13, 14]. The EVII (MECOM) gene analysis could not be performed in our patient. Gain of 1q is often the sole finding in the early stages of clonal evolution, as observed in our patient, which can persist for years. It also occurs frequently with 3q gain and other aberrations. An evolution of similar nature might have occurred over a span of 2 years in our patient; hence the additional aberration of 3q was observed. Tönnies et al. [2] observed high incidence of 3q aberrations in FA patients, with subtle aberrations due to unbalanced translocations of distal 3q to various other chromosomes, including chromosome 13 as in our patient.

The evolution of karyotypic change after 2 years is evidenced by the fact that 1q aberration was the diagnostic observation which later evolved as t(3;13) in the form of der (13)t(3;13). The characteristic clonal evolution of FA with dominance of chromosomal gain and loss is at least likely to be a specific result of the disruption of the FA/BRCA pathway and partially caused by FA-related unresolved DNA damage during S-phase [15, 16]. The striking overrepresentation of 1q and 3q could imply that these chromosomal regions are particularly susceptible to FA/BRCA disruption-associated damage.

Those with unbalanced translocation of a segment of chromosome (3)(q26q29) leading to gain showed extremely poor survival, compared to FA patients without such aberrations [2]. Hence, routine FISH screening for 1q and 3q gain is advisable for all FA-BM samples [4] which might help determine patients at high risk. The ultimate goal is to detect clonal abnormality and its involvement in the disease progression, which might facilitate the development of targeted therapies in FA. The FA-characteristic 3q gain harbors leukemogenic oncogenes, *EVI1*, first detected to be amplified and overexpressed in FA-derived AML transformation in patients with biallelic *FANCD1/BRCA2* mutations [2, 3]. This suggests that FA-associated leukemia shares its biology with one of the most aggressive forms of sporadic AML [11, 12]. FISH probes for break-apart *EVII* and *RUNX1* might increase the sensitivity of early detection of transformed cells.

Close monitoring for the presence and evolution of chromosomal aberrations is essential in patients with BM failures [14]. However, cytogenetic analysis should include karyotyping and monitoring by FISH, for FA-characteristic chromosomal aberrations. Techniques like aCGH and SKY are valuable complementary tests, targeting FA-specific chromosomal gain and loss [14]. Therefore, it is important to investigate patients, by regular BM examination for these chromosomal regions at diagnosis, later monitored for karyotype evolution. Thus, patients at high risk can be identified for a better management.

Authors' contributions/Wkład autorów

UAM – study design, data collection and interpretation, manuscript preparation, literature search. KN-B – data collection, literature search. SAl-K – data collection.

Conflict of interest/Konflikt interesu

None declared.

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None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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