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Evidence for telomeric fusions as a mechanism for recurring structural aberrations of chromosome 11 in giant cell tumor of bone

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Abstract Giant cell tumor of bone (GCTB) is a benign but often aggressive tumor with a tendency toward local recurrence. Telomeric associations (tas) or telomeric fusions are common cytogenetic findings that have been implicated in the initiation of chromosome instability and tumorigenesis. We performed cytogenetic studies on 5 cases of GCTB to further characterize chromosome aberrations in these tumors. Four of the 5 cases showed abnormal karyotypes with clonal telomeric fusions involving chromosome 11. In 3 cases, the telomeric fusions of 11pter were apparently the precursor lesions to the progression of sub-clones with structural chromosome aberrations of 11p. Two tumors demonstrated a similar pattern of progression resulting in whole arm losses of 11p, including subclones with both whole-arm unbalanced translocations and whole-arm deletions. A third tumor with clonal tas of 11pter showed 2 additional subclones, one with ring chromosome 11 and the other with an extra copy of 1q. To our knowledge, the 2 cases with del(11)(p11) represent the first report of a recurring structural chromosome aberration in GCTB. These findings support the concept that telomeric instability is responsible for a large degree of intratumor heterogeneity and serves as a precursor lesion to subsequent clonal structural aberrations of chromosome 11 in GCTB.

1. Introduction

Giant cell tumor of bone (GCTB) is regarded as a benign neoplasm which occurs most often in the third and fourth decades of life and is typically localized in the epiphysis of the long bones [1]. GCTB can sometimes be an aggressive lesion with a propensity for local recurrence and in rare cases malignant transformation. The cytogenetic literature indicates that these tumors are not generally characterized by any particular chromosome aberration, with the notable exception of telomeric associations (tas) or telomeric fusions [2–11].

Recurring structural and numerical aberrations are rare in GCTB apart from extra copies of chromosomes 3 and 7, and losses of 11, 13, and 22 [12]. However, in contrast to the rare numerical aberrations, telomeric fusions are a characteristic finding, occurring in almost 75% of these tumors [7]. Telomeric fusions in GCTB have for the most part been reported as non-clonal random occurrences, although there are several reports of clonal telomeric fusions, dicentrics, and rings involving chromosome 11 [3,4,7,11].

Telomeric fusions are a cytogenetic phenomenon in which the telomeres of a single chromosome or 2 distinct chromosomes are associated or fused with minimal or no loss of material from either chromosome end. McClintock first showed that the telomeric fusions cause broken chromosome ends which create a series of breakage-fusion-bridge cycles (BFB) and chromosome instability [13,14]. These events lead to dicentric chromosomes which tend to pull apart during mitosis, resulting in deletions and unbalanced translocations. Increasing evidence suggests that most cancers are in fact genetically unstable, and in most cases this instability is observed at the chromosomal level, resulting in unbalanced chromosomal rearrangements [15]. Telomeric fusions have been implicated in the initiation of tumorigenesis and it has further been hypothesized that this type of genetic instability is a precursor for both tumor progression and heterogeneity in many types of cancer [16,17].

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2. Cytogenetic methods and results

Fresh tumor was collected and treated as previously described [18]. Chromosomes were stained by the trypsin-Giemsa band method. Spectral karyotyping (SKY) was performed as previously described [19].

SKY (not shown) was used to confirm the rearrangements identified in case 1 (Fig. 1). Karyotype aberrations are presented in accordance with the International System for Human Cytogenetic Nomenclature [20].

Cytogenetic findings are summarized in Table 1. The study included 5 tumors, 4 of which (cases 1, 3–5) showed clonal structural aberrations (Figs. 1–4), and one case showing only normal metaphase cells (case 2). In 3 cases recurrent lesions were studied (cases 1, 3, and 4), all of which showed clonal structural aberrations. Two of these tumors (cases 1 and 4) showed clonal aberrations only in the recurrent lesions, and one (case 3) was not analyzed as a primary lesion. Both non-clonal and clonal telomeric fusions were observed in all of the abnormal cases.

The most frequent cytogenetic findings were clonal telomeric fusions of chromosome 11 in 4 patients (cases 1, 3–5), and of chromosome 19 in 2 patients (cases 3 and 5). Specific aberrations found clonally in more than one tumor included tas of 11p15 in 3 patients (cases 1, 4, and 5), 2 patients with tas of 19q13 (cases 3 and 5), and 2 patients with del(11)(p11) (cases 4 and 5).

3. Discussion

The role of telomeric fusions in the progression of tumor cells remains undetermined. It is believed that the demonstration

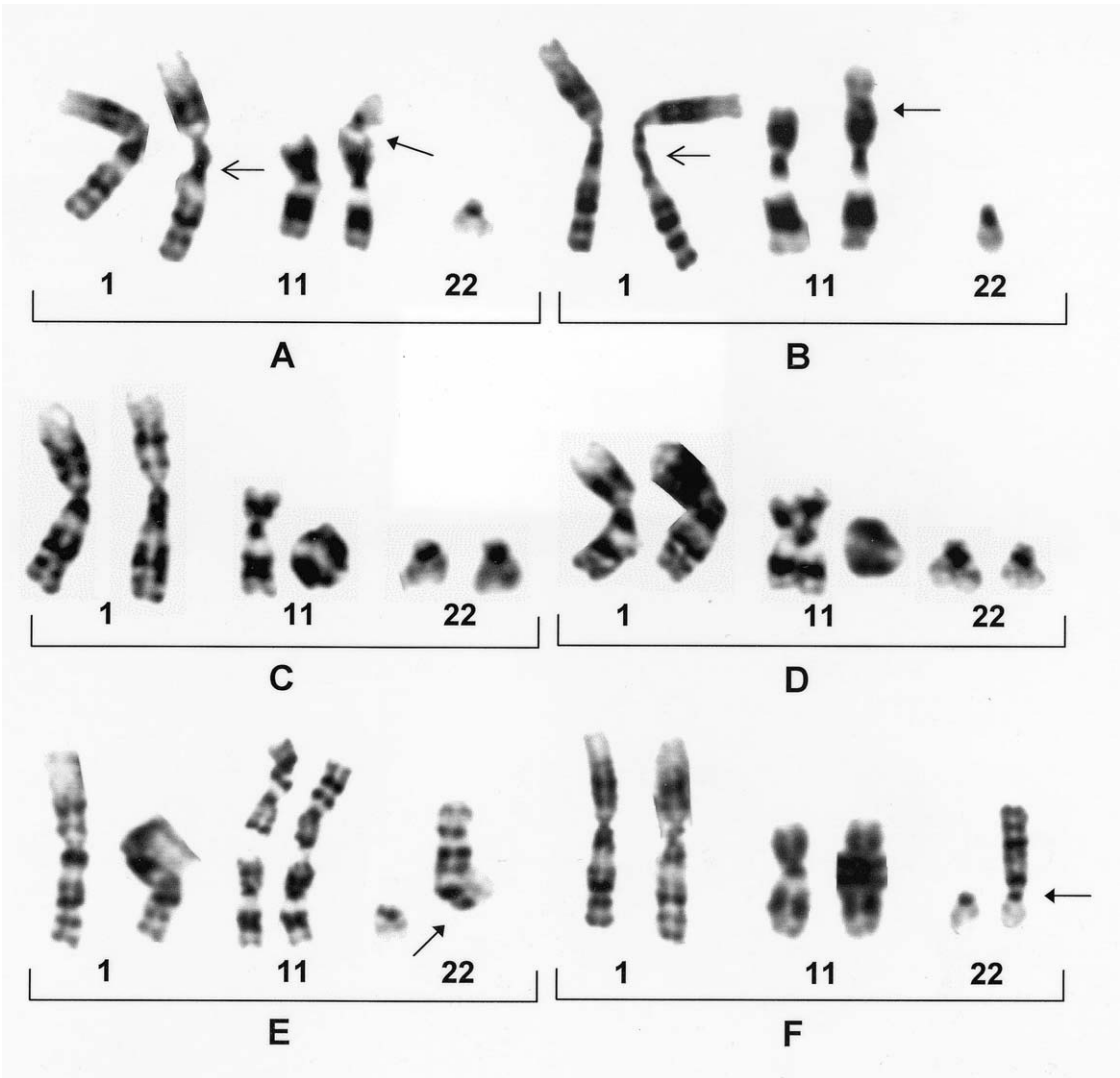

Fig. 1. Partial G-band karyotypes of case 1 showing 6 different cells (A–F) demonstrating the recurring clonal aberrations involving chromosomes 1, 11, and 22. In cells A and B, note the telomeric associations in cells with tas of 11pter and 22pter (closed arrows), and also subtle pericentromeric decondensation of chromosome 1 (on right, open arrows). In cells C and D, a cell line with ring chromosome 11 and normal chromosomes 22 is demonstrated. In cells E and F, a cell line with der(22)t(1;22)(q10;p11) (arrows) is demonstrated. Note tas of 7pter and 11pter (middle) in cell E.