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Letter to the editor

Unbalanced t(2;19) and t(2;16) in a neurofibroma

Neurofibromas are a benign heterogeneous group of tumors arising from peripheral nerve sheaths; they consist of a mixture of Schwann cells, fibroblasts, perineurial cells, neuronal processes, and mast cells. Neurofibromas may present as dermal (cutaneous or subcutaneous) or plexiform (diffuse growths, spinal tumors, nodular or diffuse) tumors. They may present as isolated sporadic tumors in the general population or occur as a part of an autosomal dominant tumor diathesis in von Recklinghausen neurofibromatosis type 1 (NF1). Malignant transformation of neurofibromas gives rise to nerve sheath tumors (MPNSTs) and neurofibrosarcoma in NF1 patients [1]. Although the genetic basis of neurofibromas associated with NF1 has been well established, similar genetic basis of sporadic neurofibromas is poorly understood [2]. Loss of both alleles of NF1 occurs in MPNSTs and associated tumors [3], but such evidence in benign neurofibromas is lacking. Loss of heterozygosity (LOH) at the NF1 locus has been detected in a minority of dermal neurofibromas of NF1 syndrome [2]; however, no such evidence exists in sporadic neurofibromas. Thus, these findings suggest that sporadic neurofibromas may arise through a mechanism different from that of NF1 tumors and the understanding of the genetic mechanisms that underlie tumorigenesis remains elusive.

At the cytogenetic level, only five cases of neurofibroma with karyotype abnormalities have been reported [4]. These studies did not identify any nonrandom chromosome aberrations in this tumor type. We report a case of neurofibroma with unbalanced translocations involving chromosomes 2, 16, and 19 and discuss the possible significance of these changes. The patient is a 63-year-old woman who was evaluated for a 3.5-cm mass in her right axilla. At surgery, a well-circumscribed lobulated mass was excised without technical difficulty. Histologic examination revealed a uniformly low-cellularity tumor composed of bland spindled cells without nuclear pleomorphism or mitotic activity. These cells were amidst areas of jumbled collagen and stromal mucin. The tumor was generally encapsulated, although focal infiltration of adipose tissue was seen. Immunohistochemistry was positive for S100 in the thin spindled cells. These findings are diagnostic of an intramural neurofibroma, clinical solitary.

Fresh tumor tissue obtained for cytogenetic analysis was dissociated with collagenase and grown in short-term culture in complete RPMI medium supplemented with insulin–transferrin–sodium selenate. Metaphase preparations, made using standard methods, were analyzed on G-banded preparations. Twenty-two metaphases were analyzed and the karyotype was described according to standard International System for Human Cytogenetic Nomenclature (ISCN 1995) [5]. Spectral karyotype (SKY) analysis was performed on metaphase preparations using a human SKYPaint kit (Applied Spectral Imaging, Carlsbad, CA) according to manufacturer’s protocol. SKY images were acquired with a SD200 Spectra cube mounted on a Nikon Eclipse 800 microscope equipped with a SKY optical filter (Chroma Technology, Brattleboro, VT); the images were analyzed using SkyView software (Applied Spectral Imaging). Fluorescence in situ hybridization (FISH) was performed using whole-chromosome paint probes WCP 2, WCP 16, and WCP 19 (Vysis, Downers Grove, IL) and standard hybridization methods. Hybridization signals were analyzed using a Nikon Eclipse 600 microscope attached to a CytoVision imaging system (Applied Imaging, Santa Clara, CA).

In the present case, a combination of G-banding, SKY, and chromosome painting identified the karyotype as: 46,XX,der(2)t(2;19)(p25;p13.2),der(16)t(2;16)(p25;q24), del(19)(p13.2)[22] (Fig. 1; Table 1). The SKY analysis followed by chromosome painting allowed us to identify the derivative chromosomes precisely.

Cytogenetic abnormalities have been reported in only five cases of neurofibroma with clonal changes, but without any recurrent chromosomal aberrations (Table 1). Comparative genomic hybridization (CGH) studies showed that chromosome 22 losses predominate in both sporadic and NF1-associated neurofibromas [6,7]. Most notably, losses of 17, 19p13.2, and 22q (22q12–qter) losses predominate in both sporadic and NF1-associated neurofibromas [7]. A minimal deletion on 19 was reported at 19p13.2–p 13.3, which was observed more frequently in NF1-associated neurofibromas than in the sporadic cases. It has been suggested that a candidate tumor suppressor gene maps to this locus on chromosome 19 [7].

In the present case, we found unbalanced translocations der(2)t(2;19)(p25;p13.2) and der(16)t(2;16)(p25;q24). The
breakpoint on 19p13.2 is at the same region of loss found with CGH in NF1-associated neurofibromas [7]. Based on our karyotype, however, it is unlikely that there is a net loss of genetic material on 19p. The effect of the structural abnormality at 19p13.2 in activating or inactivating genes of importance to neurofibroma in the present case remains unknown.

Table 1

| Case no. | Site         | Karyotype                                                                 | Reference                  |
|----------|--------------|---------------------------------------------------------------------------|----------------------------|
| 1        | Spinal cord  | 45,XX, – 22                                                               | Chadduck et al., 1991–1992 [9] |
| 2        | Nasopharynx  | 47,XY, + der(?)(7,12)(?;q15)                                               | Mertens et al., 2000 [10]   |
| 3        | Soft tissue  | 45–46,XX,t(1;17)(q21q21),r(3;7)(p5q29;?), add(5)(q14),der(9)t(4;9)ins(9;?),del(9)t(5;9)(q13;p13), (15)(q22), + der(?)(7;7)(q11), +mar | Molenaar et al., 1997 [11]   |
| 4        | Soft tissue  | 46,X,t(X;2)(p22q21),del(1)(q11,t(1;22)(p32;q11)c,(8)(1;8)(q11;q274)/46,XX,t(1;22)c,add(5)(q14),der(16)(p12)/45,XX,t(1;22)c,inv(8)(p23;q12), der(9)(3;9)(q12;p22)del(3)(q26–q28),del(10)(3;10)(p11;p12),del(12)(q14) | Rey et al., 1987 [12]       |
| 5        | Soft tissue  | 47,XX, + 18                                                               | Riccardi and Elder, 1986 [13] |
| 6        | Axillary mass| 46,XX,der(2)t(2;19)(p25;p13.2),der(16)t(2;16)(p25;q24),del(19)(p13.2)[22] | Present case                |
The 19p13.2–p13.3 region contains a number of genes relevant to cell growth and proliferation, including two related mitogen-activated protein kinase genes, MAP2K2 and MAP2K7, which play a critical role in mitogen growth factor signal transduction, and neurturin (NRTN), a member of the TGF-β subfamily. The NRTN gene may be more relevant. This gene, which signals through RET and a GPI-linked coreceptor, promotes survival of neuronal populations. A neurturin mutation has been described in a family with Hirschsprung disease [8]. NRTN is a neuromodulator that regulates the development of the neuromuscular synapse. Thus, the molecular nature of 19p13 alterations in the development and proliferation of neurofibromas remains to be elucidated.

Description of the karyotypic abnormalities identified in the present case may aid in identifying nonrandom chromosome changes in neurofibroma and in understanding the underlying genetic mechanisms of transformation.

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