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CASE REPORT

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Extraskeletal myxoid chondrosarcoma: multimodal diagnosis and identification of a new cytogenetic subgroup characterized by t(9;17)(q22;q11)

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Abstract Extraskeletal myxoid chondrosarcoma is a rare malignant soft tissue tumour that can be difficult to diagnose correctly, especially preoperatively. We describe four cases of extraskeletal myxoid chondrosarcoma of the extremities diagnosed by a multimodal approach. The cytological examination of fine-needle aspirates showed small and round, mildly pleomorphic cells lying in sheets and cords, but also dispersed within a myxoid and metachromatic intercellular substance. Histological, electron microscopic and immunocytochemical examination also yielded findings compatible with the diagnosis of extraskeletal myxoid chondrosarcoma. Cytogenetic analysis demonstrated a t(9;22)(q22;q12) in two tumours and a t(9;17)(q22;q11) in the third and fourth. The translocation t(9;22)(q22;q12) has been described repeatedly in extraskeletal myxoid chondrosarcoma but never in other tumours; hence, the detection of this pathognomonic chromosome abnormality in short-term cultured cells from fine-needle aspirates verified the diagnosis in two of the cases. The t(9;17)(q22;q11) found in the last two cases probably represents a new cytogenetic subgroup of extraskeletal myxoid chondrosarcoma as it, too, is unknown in other contexts. The multimodal approach taken in these four cases enabled a definite diagnosis of a rare malignant tumour whose cytological and histological features alone are usually not sufficiently distinct to rule out other differential diagnostic possibilities.

Key words Karyotype · Cytogenetic analysis · Extraskeletal myxoid chondrosarcoma · Pathology · Soft tissue tumours

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Introduction

Extraskeletal myxoid chondrosarcoma (EMC) is a rare malignant soft-tissue tumour first described by Stout and Verner in 1953, after which Enzinger and Shiraki, in 1972, delineated the entity more precisely [8, 34]. The tumour is mostly detected in the extremities, but other, more unusual, tumour locations have also been reported, including the tongue, chin, epiglottis, brachial plexus, chest wall, pleura, abdomen, buttock, inguinal region, testis and synovia [7, 20, 32]. EMC is most commonly found in middle-aged and elderly men, but has also been described in children [18]. Long-term follow-up studies have shown that metastases can develop, especially in the lungs. In one study of ten patients, seven died of their disease within 17 years, whereas the remaining three were all alive but with metastatic disease at the latest follow-up 13–16 years after their diagnosis [29].

The preoperative diagnosis of EMC is traditionally based on fine-needle aspiration (FNA) cytology and/or histological examination of biopsy specimens. However, it is often difficult to establish a definite diagnosis based on these analyses, not only because of the rarity of the tumour, but also because several other entities, for instance myxoid variants of liposarcoma and malignant fibrous histiocytoma, have a similar morphological appearance [26, 39]. Other methods have therefore been brought to bear, including chromosome banding analysis, and the translocation t(9;22)(q22;q11–12) has been found in 9 out of 20 cases of EMC examined [1, 2, 6, 13, 14, 23, 26, 33, 37]. Since the t(9;22) has not been seen in

other tumour types, it seems to constitute a pathognomonic EMC marker [24].

We describe four cases of extraskeletal myxoid chondrosarcoma. In the first two, the diagnosis was confirmed by the finding of the characteristic t(9;22). In the last two cases, a translocation t(9;17)(q22;q11) was found. This translocation is not known from any other diagnostic entities, and hence seems to identify a new cytogenetic subgroup of EMC.

Case reports

All four patients were referred to the Norwegian Radium Hospital. Cases 1–3 came without a prior biopsy at their local hospitals. Patient 4 had undergone FNA prior to referral.

Case 1

A 71-year-old man with a history of multiple subcutaneous lipomas was admitted in 1996 with a 6-month history of a painless tumour in the right vastus lateralis muscle. FNA cytology showed that the tumour was a myxoid sarcoma, possibly an EMC. There were no signs of metastases. The treatment consisted of marginal excision followed by postoperative radiation therapy.

Case 2

A 47-year-old man presented in 1996 with a 3-month history of a growing, painful tumour in the left vastus lateralis muscle. FNA cytology and histological examination of a biopsy showed a myxoid sarcoma. There were no signs of metastases. A marginal excision was performed. No postoperative radiation or other therapy was given.

Case 3

A 60-year-old man presented in 1997 with a tumour in the left lower arm. Five years previously he had noticed a lump in the same region after an injury. The tumour in the left pronator quadratus muscle infiltrated adjacent subcutaneous tissue and the interosseous membrane between the radius and ulna. FNA cytology and histological examination of a biopsy both suggested a diagnosis of extraskeletal myxoid chondrosarcoma. There were no signs of metastases. A marginal excision was done without any postoperative treatment.

Case 4

A 47-year-old man presented in 1998 with a tumour in the right thigh. The tumour was intermuscular and infiltrated the adjacent fascia. FNA cytology and histological examination of a biopsy showed a myxoid sarcoma, probably an EMC. There were no signs of metastases. A marginal excision was done without any postoperative treatment.

Materials and methods

Cytopathology

The aspiration biopsies were performed with a 23-G needle fitted to a 20-ml syringe in a handle. The aspirates were smeared on glass slides. Air-dried smears were stained by a modified Romanowsky stain (Diff-Quick) and May-Grünwald-Giemsa (MGG). Alcohol-fixed smears were stained by the Papanicolaou method (PAP). Additional aspirates were collected in tubes containing PBS, 0.9% sodium saline and McDowell's fixative for immunocytochemistry, cytogenetic analysis and electron microscopy, respectively.

Table 1 Antibodies used for immunocytochemistry

Antibodies	Dilution	Source
AE1/AE3	1:20	Signet Lab.
CAM5.2	25 µg/ml	Becton and Dickinson
Vimentin	1:25	Boehringer Mannheim
SMA	1:160	Biogenex
Muscle-specific actin	1:10	Biogenex
EMA	1:20	Dako
HMB-45	1:10000	Enzo Diagnostics
GFAP	1:50	Dako
S-100 protein	1:100	Dako

Histopathology

The surgical resection specimens were fixed in 10% buffered formalin, dehydrated and embedded in paraffin. Five-micron-thick sections were cut and stained with haematoxylin and eosin, Alcian blue at pH 1.0 and pH 2.5 with and without prior treatment with hyaluronidase, and periodic acid–Schiff (PAS).

Immunocytochemistry

Five-micron-thick sections, direct smears and cytospin preparations were used for immunostaining according to the avidin-biotin-peroxidase method, with relevant positive and negative histological controls [15]. The monoclonal antibodies applied were for cytokeratins (AE1/AE3 and CAM5.2), GFAP, vimentin (V9), muscle-specific actin (HHF-35), smooth muscle actin (SMA), epithelial membrane antigen (E29), melanoma marker (HMB-45) and polyclonal protein S-100 (Table 1).

Electron microscopy

Fresh tumour tissue was immersed in a cacodylate-buffered solution of 4% formalin and 1% glutaraldehyde (McDowell's fixative), postfixed in 1% OsO_4, dehydrated in graded ethanol and embedded in an Epon-Araldite mixture. Semi-thin sections cut with a glass knife and stained with toluidine blue were used for light microscopic orientation. Ultra-thin sections were cut with diamond knife and stained with uranyl acetate and lead citrate prior to examination under a Philips CM10 electron microscope.

Cytogenetics

The material for cytogenetic analysis consisted of both a preoperative FNA and an operation biopsy in cases 1 and 2 and the latter only in cases 3 and 4. The operation biopsies were minced with scissors and disaggregated enzymatically in 1,400 IU/ml collagenase II (Worthington) for 2 h, whereas the FNA specimens were only spun down and resuspended in medium before culturing. Short-term cultures were initiated in plastic flasks (operation biopsy material) and on plastic chamber slides (FNAs) using RPMI 1640 medium with HEPES buffer, supplemented with 17% fetal bovine serum, 2 mM L-glutamine, 100 IU/ml penicillin and 100 µg/ml streptomycin. After 5–7 days, the cultures were exposed to Colcemid and harvested by trypsinization, followed by hypotonic shock in 0.05 M KCl and repeated fixations in methanol:acetic acid (3:1). G-banding of the chromosomes was obtained using Wright stain. The criteria for clonality and the karyotype description followed the 1995 recommendations of the ISCN [16].

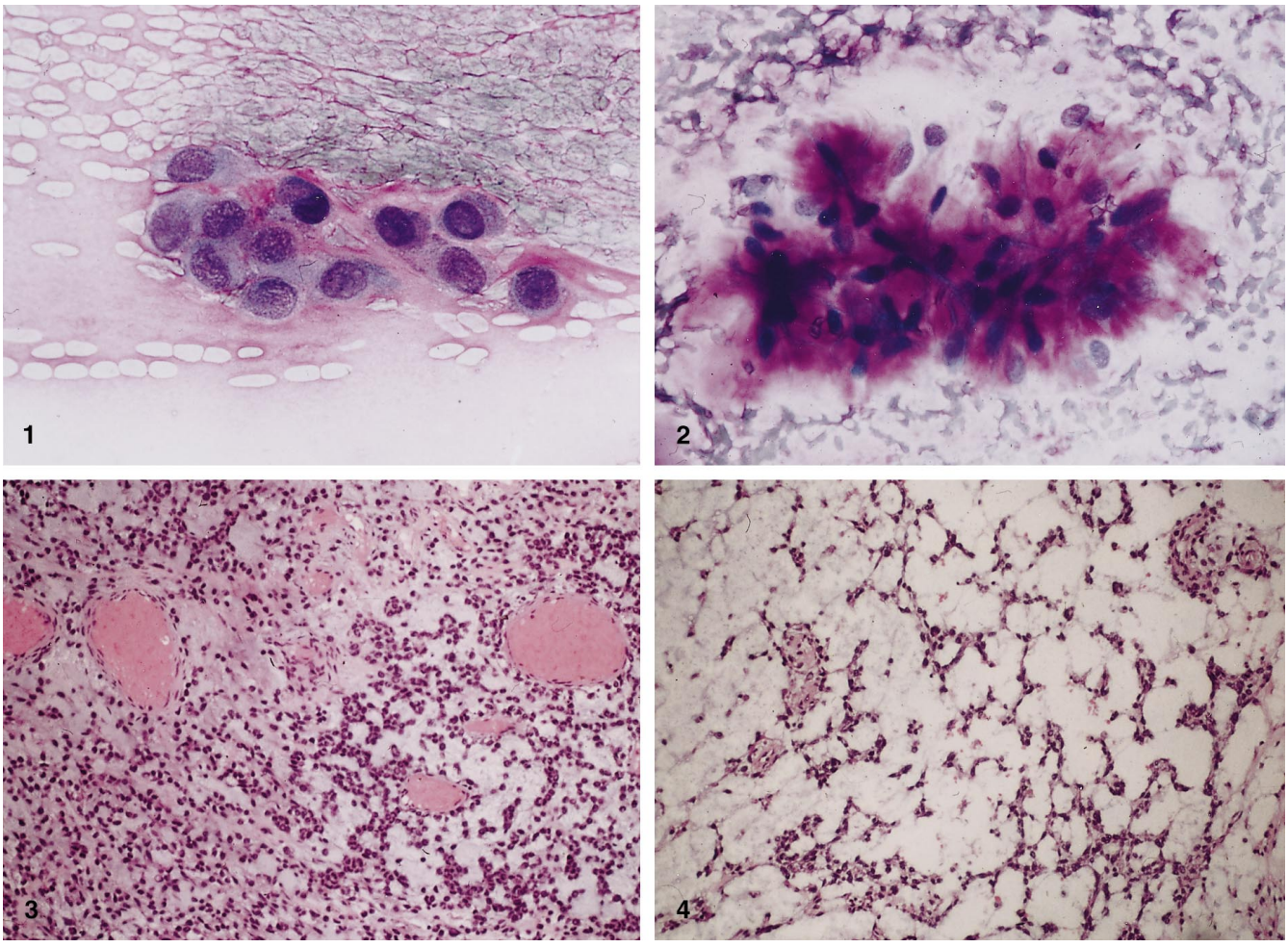

Fig. 1 Cytological smear from case 1 showing a cluster of cells with distinctive cytoplasm and round to oval nuclei. MGG, obj. ×40

Fig. 2 Cytological smear from case 3 showing round and spindle-shaped cells in an abundant myxoid stroma. MGG, obj. ×40

Fig. 3 Histopathological features of case 1 showing strands and cords of tumour cells within a myxoid material. H&E, obj. ×20

Fig. 4 Histological preparation of case 3 showing the tumour's lace-like growth pattern. H&E, obj. ×20

Results

Cytopathology

The material from all four tumours was of adequate cellularity. Within the metachromatic and myxoid intercellular substance seen in the Giemsa-stained preparations, abundant uniform epithelioid and spindle-shaped cells were seen dispersed or arranged in fragments (Figs. 1, 2). There were very few chondroid-like cells. Some capillaries could be identified. The nuclei were round to oval with a prominent nucleolus. The cytoplasm was eosinophilic. Mitotic figures were not seen. In case 4, necrotic cells were recognized. The cell size was small to moderate, and the cell membranes were distinct.

Gross pathology

All four tumours (8 cm, 9.5 cm, 5 cm and 8 cm in largest diameter, respectively) contained lobulated soft masses surrounded by a fibrous capsule. All but one of the tumours infiltrated skeletal muscle, and in cases 2 and 3 there was also infiltration of subcutaneous fat. The consistency of the tumours was gelatinous. The cut surfaces were grey to tan-brown with cysts and haemorrhages.

Histopathology

All tumours consisted of well-circumscribed, lobulated nodules. The epithelioid, round, ovoid or spindle-shaped cells had small, hyperchromatic and slightly pleomorphic nuclei and a narrow rim of deeply eosinophilic cytoplasm. They lay as single cells or in anastomosing strands and trabecula separated by variable amounts of mucoid ground substance (Figs. 3, 4). In case 1, foci with a pseudopapillary growth pattern of less highly differentiated tumour cells and up to 10 mitoses per 10 high-power fields were seen. In case 2, chondroid foci were noticed in the myxoid matrix. In case 4, large areas of necrosis were seen. Neither lipoblasts nor pro-

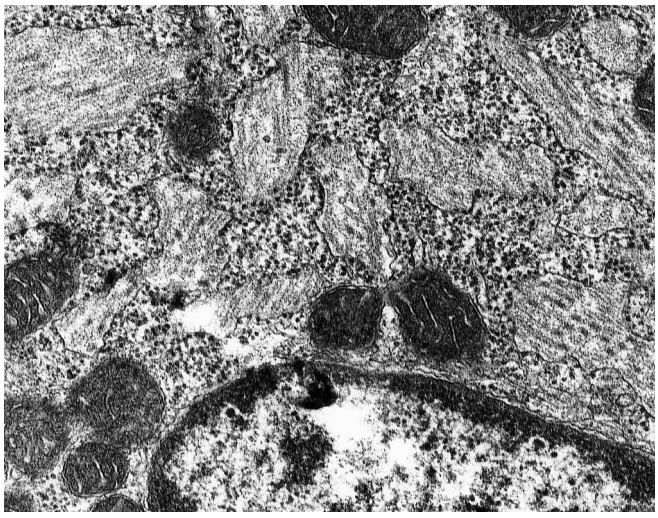

Fig. 5 Ultrastructural examination of case 1 showing tumour cells with cytoplasmic intracisternal microtubules. Uranyl acetate and lead citrate, original magnification ×21,560

nounced atypia was noted, nor was there any infiltration of tumour tissue into vessels.

Histochemistry and immunocytochemistry

Alcian blue at pH 1.0 and pH 2.5 stained the myxoid matrix blue, a reaction that was diminished by prior treatment with hyaluronidase. Only a few cells had intracellular PAS-positive and diastase-resistant globules. The tumours were strongly positive for vimentin and moderately positive for protein S-100 (the aspirate in case 1 was a partial exception, inasmuch as it was negative for protein S-100). There was a weak and scattered positivity for CAM5.2 but immunostaining with AE1/AE3 was negative. Muscle-specific actin, SMA, GFAP and HMB-45 were all negative. EMA was weakly positive in a few cells in cases 1 and 4.

Electron microscopy

In all four cases, tumour cells were present in an abundant intercellular matrix, in small groups or individually. No external lamina surrounded the cells. The tumour cells were elongated with irregular nuclei and inconspicuous nucleoli. The chromatin was finely dispersed. Abundant mitochondria were present in the cytoplasm. The rough endoplasmic reticulum (RER) was prominent. In cases 1 and 2, arrays of parallel microtubules were present within cisternae of the RER (Fig. 5). Parallel bundles of cytofilaments were seen in case 3. The surface of the tumour cells was either smooth or with scattered filipodia.

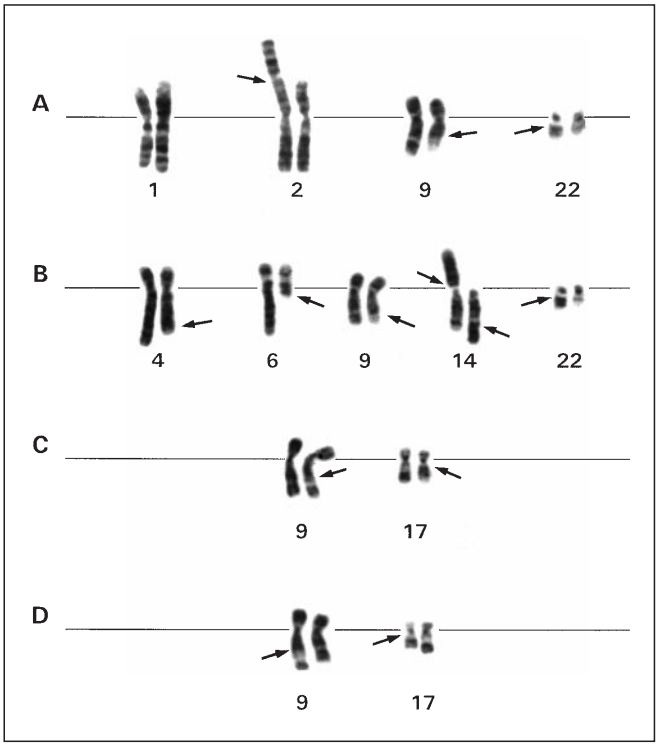

Fig. 6A–D Partial karyotypes illustrating the clonal chromosome abnormalities seen in cases 1–4. *Arrows* indicate breakpoints. **A** Case 1: der(2)t(1;2)(q21;p25) and t(9;22)(q22;q12). **B** Case 2: t(4;14)(q31;q32), t(6;14)(q15;p13) and t(9;22)(q22;q12). **C** Case 3: t(9;17)(q22;q11). **D** Case 4: t(9;17)(q22;q11)

Cytogenetic analysis

Case 1

Ten cells from the aspirated material and 15 cells from the operative specimen were analysed. The karyotype of the aspirate was 92,XXYY,der(2)t(1;2)(q21;p25)×2,t(9;22)(q22;q12)×2[10], whereas a mixture of pseudodiploid and pseudotetraploid cells was found in the operative specimen, corresponding to the karyotype 46,XY,der(2)t(1;2)(q21;p25),t(9;22)(q22;q12)[10]/92,idem ×2[5] (Fig. 6A).

Case 2

All the cells analysed from aspirated material (8 cells) and from the operative specimen (8 cells) showed the same chromosome aberrations corresponding to the karyotype 46,XY,t(4;14)(q31;q32),t(6;14)(q15;p13),t(9;22)(q22;q12)[16] (Fig. 6B).

Case 3

Of the 15 cells examined, 2 were normal, whilst 13 cells showed a balanced translocation. The karyotype was 46,XY,t(9;17)(q22;q11)[13]/46,XY[2] (Fig. 6C).

Case 4

All ten cells from the operative specimen showed a balanced translocation between chromosomes 9 and 17, giving the karyotype 46,XY,t(9;17)(q22;q11)[10] (Fig. 6D).

Discussion

We describe a multimodal approach to the diagnosis of four rare cases of soft tissue sarcoma. All tumours demonstrated cytological, histological, immunocytochemical and electron microscopic features suggestive of EMC [9, 25, 26]. The most striking cytological feature was the rich amount of metachromatic myxoid extracellular substance. The aspirates were cellular, with the cells lying freely or arranged in cords and sheets (Figs. 1, 2). The round, polygonal or spindle-shaped cells were fairly uniform in size, with a moderate amount of eosinophilic cytoplasm and round to oval nuclei. The chromatin was bland with insignificant atypia. Very few mitotic figures were found. In tissue sections a multinodular pattern was seen, consisting of cells in cords and strands surrounded by an abundant myxoid extracellular matrix with some more fibrous areas (Figs. 3, 4). The cells were rounded or elongated with small hyperchromatic nuclei and rather scant eosinophilic cytoplasm. Again, few mitotic figures were seen. The tumour cells were immunoreactive for vimentin and protein S-100 but were negative for cytokeratins. The positive staining of the myxoid ground substance with Alcian blue at both pH 2.5 and pH 1.0 and the reduced staining reaction in the matrix after prior treatment of the slides with hyaluronidase indicated the presence of chondroitin sulphates [10]. The results of the electron microscopic examination, which help significantly in the differential diagnosis of myxoid soft tissue tumours [39], were compatible with a diagnosis of EMC (Fig. 5), although the last two cases did not show parallel microtubules. That microtubules are not obligatory in EMC was also shown by Payne et al. [28], who found them in only four out of ten such tumours.

It may be difficult to separate EMC from other myxoid tumours on the basis of cytology and the other phenotype-related parameters discussed in the preceding paragraph. In our four cases, the most important differential diagnoses were myxoid type of malignant fibrous histiocytoma and myxoid liposarcoma. Other relevant differential diagnoses for tumours with abundant myxoid intercellular substance are intramuscular myxoma, mixed tumour of soft tissue, nodular fasciitis, ganglion cyst, chordoma and myxoid peripheral nerve sheath tumour [17, 36, 38]. Pleomorphic adenoma and mucinous carcinoma can also mimic a soft tissue tumour.

In recent years, chromosome banding analysis has become an important ancillary method in the diagnosis of soft tissue tumours, as several of the neoplastic entities that represent the most difficult differential diagnostic dilemmas are characterized by highly specific aberration patterns [11]. The tumour cells thus examined come from fine-needle aspirates, tissue biopsies or surgical specimens and are usually short-term cultured beforebeing processed for cytogenetic analysis [21]. Examples of highly disease-specific or pathognomonic translocations in sarcomas include t(11;22)(q24;q12) in Ewing sarcoma, t(X;18)(p11;q11) in synovial sarcoma, t(12;16)(q13;p11) in myxoid liposarcoma and t(2;13)(q35;q14) in alveolar rhabdomyosarcoma [22]. The diagnostic usefulness of the karyotype is particularly high for the group of small-round-cell tumours, in which the cytogenetic features may sometimes single out the correct diagnosis among the most relevant differential diagnostic possibilities much better than the tumour phenotype [11].

The cytogenetic literature records at least 20 cases of EMC in which karyotyping was done. In 9 of these tumours the translocation t(9;22)(q22;q11–12) was found [6, 13, 14, 26, 30, 33] and in 2 of them two different three-way translocations, t(9;22;15)(q31;q12.2;q25) and t(9;17;15)(q22;q11.2;q22), were found [23, 37]. The last 9 tumours showed other chromosomal rearrangements [1, 2, 33]. Since the translocation t(9;22)(q22;q11–12) has not been found in other tumours [24], it gives every impression of being pathognomonic for EMC. This made it possible to establish the diagnosis beyond any doubt in the first two cases of our series, in which the same 9;22 translocation was detected (Fig. 6A, B). It is particularly noteworthy that this could be done on fine-needle aspirated cells, thus circumventing the need for a surgical biopsy to obtain sufficient material for short-term culture and cytogenetic analysis.

The t(9;17)(q22;q11) of cases 3 and 4 (Fig. 6C, D) has not been seen in any other tumour types [24] and thus seems to define a new cytogenetic subgroup of EMC in addition to the more common subset carrying 9;22 translocations. Although this is the first description of t(9;17) in EMC, it is worthy of note that a three-way translocation involving the same breakpoints, t(9;17;15)(q22;q11.2;q22), has been seen [23]; it seems likely that this t(9;17;15) represents a variant translocation [11] of the two-way t(9;17) we now describe, in much the same way as the t(9;22;15) [23] is a variant translocation of the standard t(9;22). The der(17) resulting from the t(9;17;15) is cytogenetically identical to that of the two-way translocations of our cases 3 and 4, indicating that the pathogenetically important outcome of the 9;17 rearrangement, most likely a fusion gene, is located on the der(17) rather than the der(9).

The standard t(9;22)(q22;q12) of EMC causes a fusion of *TEC* (Translocated in Extraskeletal Chondrosarcoma) in 9q22 with the *EWS* gene in 22q12, although neither Labelle et al. nor Brody et al. were able to identify this fusion gene in all their examined cases [3, 19]. The *EWS* gene is also fused with various translocation partners in the Ewing family and other types of primitive neuroectodermal tumours (characterized cytogenetically by 11;22 or, much less frequently, 2;22, 21;22, 17;22 and 7;22 translocations), desmoplastic small-round-cell tumours (characterized cytogenetically by an 11;22 trans-

location, but with a different breakpoint in chromosome 11 from that of Ewing-type tumours), and clear-cell sarcomas (characterized cytogenetically by a 12;22 translocation).

Whereas it seems reasonable to assume that the gene in 9q22 that is rearranged in cases 3 and 4 must be *TEC*, the important locus in 17q is unknown. The breakpoint in 17q of the t(9;17) seems to be proximal to the corresponding breakpoint of the t(17;22) that characterizes giant-cell fibroblastoma [5]. It is, on the other hand, cytogenetically indistinguishable from the breakpoint of t(15;17) in acute promyelocytic leukaemia, which affects the *RARA* gene on chromosome 17 [35], and the breakpoint of the t(7;17) now known to be specific for endometrial stromal sarcoma [4, 12, 27, 31]. The 17q gene involved in the latter situation is unknown, but it, too, is a good candidate for a pathogenetic role in cases 3 and 4. The possibility exists, therefore, of using a candidate gene approach, working from the putative involvement of *TEC* to determine the nature of a 17q gene that plays a part not only in a subset of EMC but possibly also, more regularly, in endometrial stromal sarcoma.

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