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Multiple skeletal fibroxanthomas: radiologic-pathologic correlation of 72 cases*

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Abstract. Out of a series of 900 biopsy-proven cases of skeletal "fibroxanthoma" (nonossifying fibroma, fibrous cortical defect), we studied 72 patients with more than one lesion. Age, sex, coexistent conditions such as neurofibromatosis, and histologic and radiographic appearance of the lesions were evaluated. Multiple skeletal fibroxanthomas are probably more common than previously suspected. (At least 8% of the 900 patients in our archives had multiple lesions). Only a small percentage (5%) of patients with multiple skeletal fibroxanthomas had coexistent neurofibromatosis. These lesions are histologically indistinguishable from their solitary counterparts and most commonly present in the lower extremities. Four radiographic patterns were noted: (1) clustered lesions – usually about the knee. (2) nonclustered lesions – in opposite ends of long bones. (3) coalescent lesions – several lesions coalescing over time. This observation has not been previously reported. (4) emergent lesions – lesions appearing in previously unaffected bone. Familiarity with these features may obviate biopsy.

Key words: Fibroxanthoma, multiple – Metaphyseal fibrous defects – Nonossifying fibroma – Fibrous cortical defects – Fibrous histiocytoma of bone – Neurofibromatosis

There are only a few reports of multiple skeletal fibroxanthomas (MSF) in the literature. Most involve patients having coexistent neurofibromatosis, a well-established association, but these reports lack histologic confirmation of the lytic skeletal lesions [2–8]. The purpose of this paper is to analyze a large group of histologically-proven fibroxanthomas with the intention of (a) determining approximate frequency of MSF, (b) assessing the microscopic findings in MSF, and (c) emphasizing the four radiographic patterns of MSF. It is hoped that this knowledge will eliminate unnecessary biopsy. This study constitutes the largest series of multiple skeletal fibroxanthomas yet reported.

Materials and methods

Our archives contain 900 cases of skeletal fibroxanthomas collected over 40 years. These cases were histologically proven and radiographically correlated. A review of the radiographs established a subset of 72 patients having at least two separate fibroxanthomas.

Radiographs were available for every lesion that was biopsied. Occasionally, more than one fibroxanthoma was biopsied in a single patient. More frequently, only the largest lesion was biopsied. The histology was reviewed (DES, RPM) to confirm the diagnosis of fibroxanthoma of bone. For the diagnosis of fibroxanthoma of bone the histologic criteria were combination of proliferating spindle cells (often in a storiform configuration), clustered xanthoma cells, and interspersed multinucleated giant cells.

When available, the following data were analyzed: (a) age and sex at presentation, (b) presenting symptoms including pathologic fracture, (c) average number and size of lesions per patient, (d) lateralization to left or right side of the body, (e) localization to a specific site (epiphysis, metaphysis, metadiaphysis, diaphysis) in the bone, (f) presence of associated periosteal reaction, and (g) presence of neurofibromatosis or other coexistent conditions.

Results

The patient's age at presentation was known in 68 cases. The mean age was approximately 14 years for both males and females, with a range

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of 4 to 51 years. Of the 72 cases of MSF, 53 were males and 18 were females; in one case, the sex was not specified.

In six cases, radiographs obtained as a comparison view following trauma to one knee resulted in the incidental discovery of MSF in the contralateral knee. Nine patients presented with pathologic fractures. In all remaining cases where clinical information was available, the patient presented with pain (frequently as a result of trauma) in the area of skeletal abnormality. Biopsies were subsequently obtained.

The average number of fibroxanthomas was three per patient. There were 148 lesions in 53 males and 49 lesions in 18 females. The lesions varied in size from approximately 5 mm to 10 cm. Neither side of the body showed a preponderance of lesions; the most commonly affected bones (in decreasing frequency) were the femur, tibia, fibula, and humerus. The remaining lesions were scattered throughout the skeleton. There was no significant difference between involvement of the proximal or distal ends of long bones.

In long bones, the typical multiple fibroxanthoma presented radiographically as an eccentrically positioned lytic defect with a well-defined, sclerotic margin. The metadiaphysis was most commonly involved. The metaphysis or diaphysis was sometimes involved, but the epiphysis was never affected. The contour of the lesion was smooth or scalloped and had a sclerotic rim of varying thickness (Figs. 1–5). Radionuclide bone scans were performed in some cases and demonstrated increased radionuclide activity in the lesions.

Four radiographic patterns of multiple fibroxanthoma were found:

1. *Clustered fibroxanthomas* (Figs. 1, 2): Clustered lesions were most commonly encountered about the knee (distal femur alone, combination of distal femur and proximal tibia, or proximal tibia and proximal fibula). Often the clustered lesions were bilateral and relatively symmetric. After the knee, the ankle was most commonly affected; clustered lesions were seen in the distal tibia and fibula but not in the tarsal bones.

2. *Nonclustered fibroxanthomas* (Fig. 3): Nonclustered lesions were located at opposite ends of long bones, especially the femur, tibia, and fibula.

3. *Coalescent fibroxanthomas* (Fig. 4): Clustered lesions (pattern 1) progressively coalescing. This pattern has never been reported.

4. *Emergent fibroxanthomas* (Fig. 5): New lesions developed in previously unaffected areas.

Periosteal reaction was detected in only two cases, both with pathologic fracture. Seven patients had associated findings. Four patients (three males, one female) had neurofibromatosis. Three other patients had coexistent small osteochondromas. The histologic and radiographic appearances of the skeletal fibroxanthomas in these seven patients were indistinguishable from those in the remaining 65 patients.

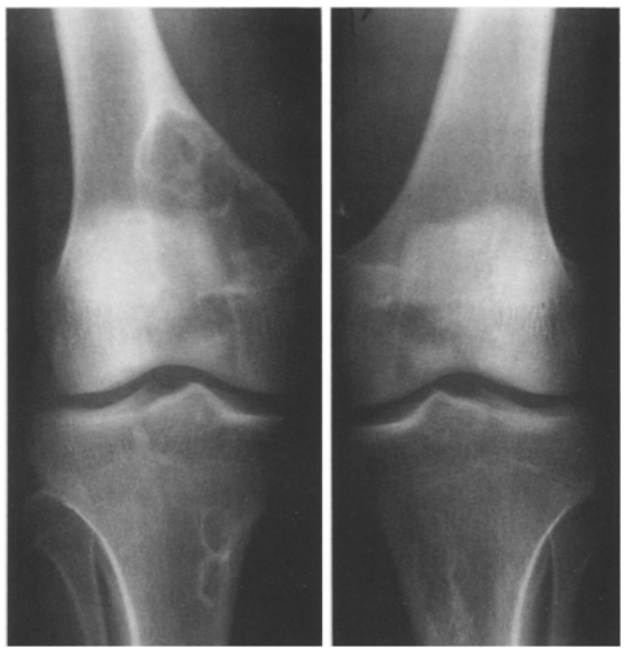

Fig. 1. Anteroposterior (AP) radiograph of both knees demonstrates typical multiple skeletal fibroxanthomas – eccentric lytic lesions that are well-defined, have sclerotic margins of variable thickness, and are located in the metadiaphyseal regions of long bones of the lower extremities. There is a large fibroxanthoma in the distal right femur and relatively symmetric fibroxanthomas in the proximal contralateral tibia

Discussion

The literature on multiple skeletal fibroxanthomas is scant. Previous studies involve small numbers of patients and often lack pathologic correlation. Most papers focus on the association between neurofibromatosis and MSF. No one has described the four patterns of MSF nor speculated on the frequency of their occurrence [1, 6, 9].

The fact that approximately 8% of our 900 patients had multiple lesions suggests that multiple skeletal fibroxanthomas are probably more common than has hitherto been recognized. Only in a small percentage of the 900 cases was total skeletal screening obtained, either by radiograph or radionuclide bone scan. Therefore, this series undoubtedly underestimates both the number of patients with MSF and the total number of lesions

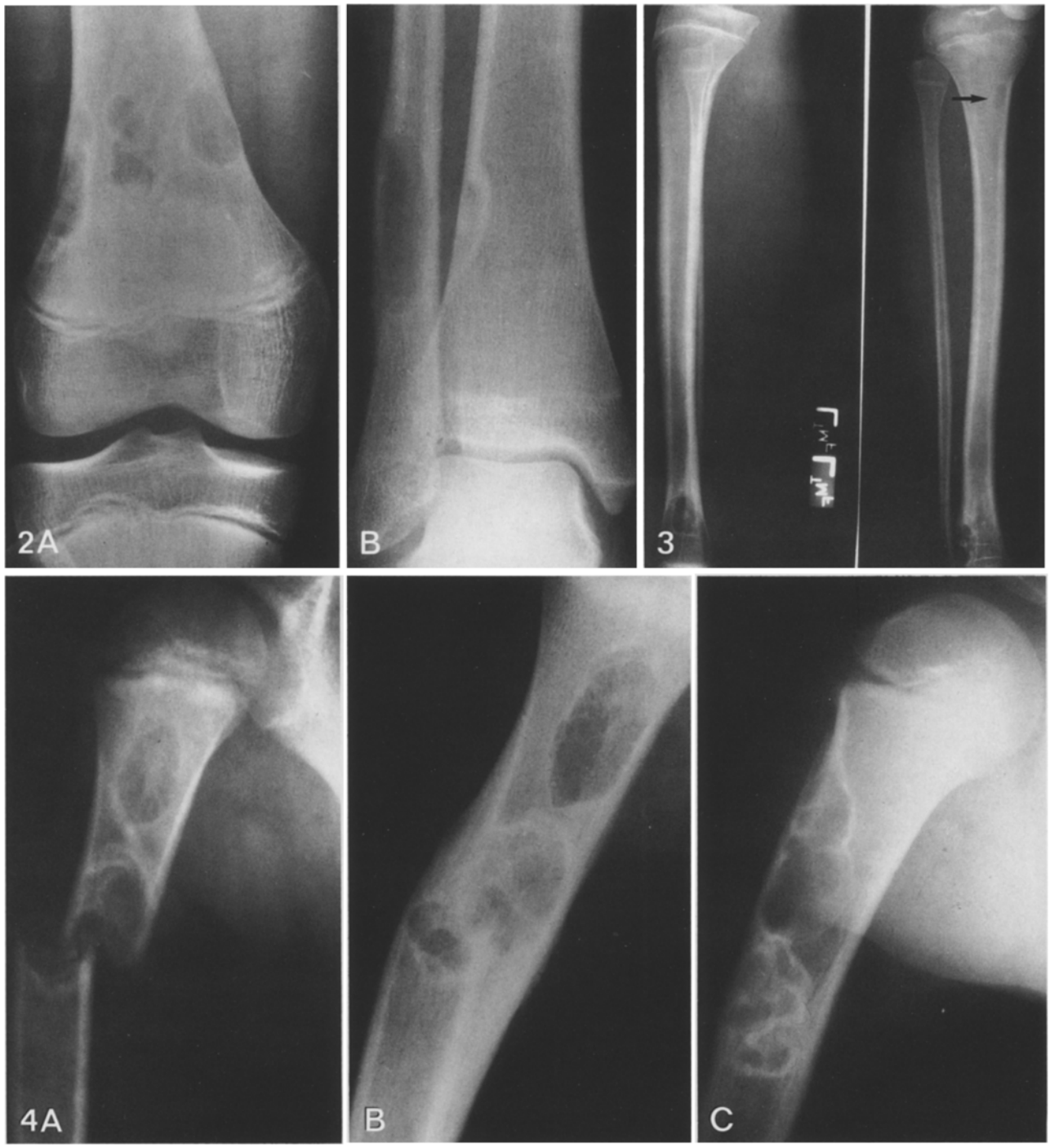

Fig. 2A, B. "Clustered" fibroxanthomas in two patients: **A** Three separate "clustered" fibroxanthomas in the distal femur. **B** Adjacent fibroxanthomas in the distal tibia and fibula

Fig. 3. "Nonclustered" fibroxanthomas are seen at opposite ends of the tibia. The proximal tibial lesion is best seen on the AP view (*arrow*)

Fig. 4A–C. "Coalescent" fibroxanthomas: previously separate "clustered" fibroxanthomas may "coalesce" on subsequent radiographs. This concept has not been reported. **A** Initial AP view demonstrates two separate "clustered" fibroxanthomas in the proximal humerus with pathologic fracture through the larger distal lesion. **B** Follow-up radiograph 4 months later demonstrates healing of the fracture. Fibroxanthomas remain separate. **C** A radiograph 17 months after initial examination demonstrates coalescence of the fibroxanthomas that were clearly separate lesions on the original film

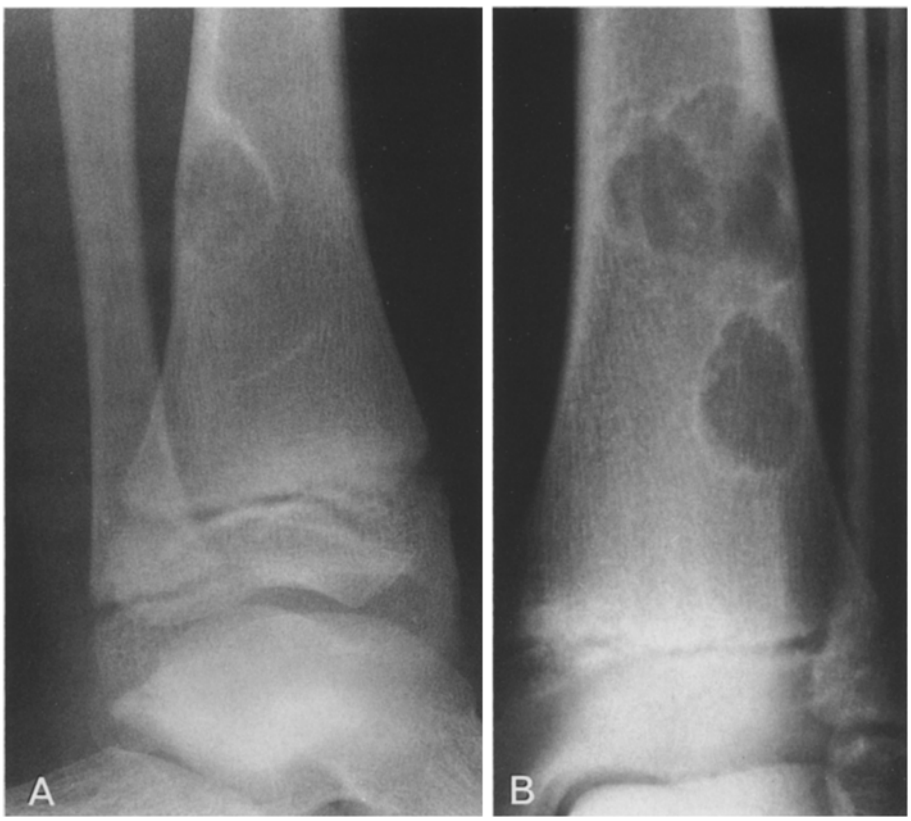

Fig. 5A, B. "Emergent" fibroxanthoma: **A** A single fibroxanthoma is seen on initial study in the distal tibia of a 14-year-old boy (oblique view). **B** On examination 25 months later, there are two fibroxanthomas in the distal tibia (AP view)

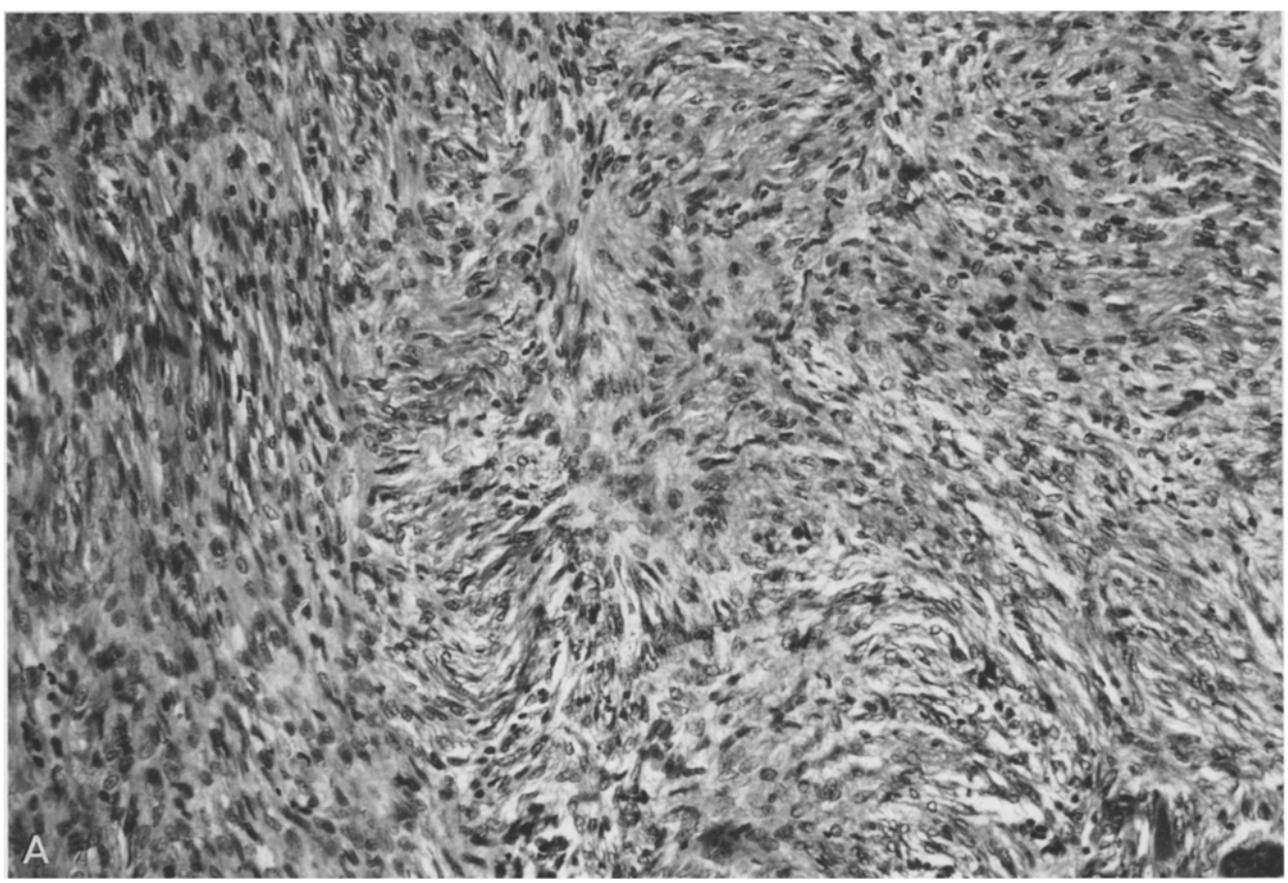

Fig. 6A–C. Typical histology from a fibroxanthoma in a patient with MSF: **A** Proliferating spindle cells arranged in a storiform pattern (×160). **B** In this field (×160) there is a sprinkling of multinucleated giant cells (*arrows*). **C** In this field (×160), there is a predominance of xanthoma cells (*arrows*)

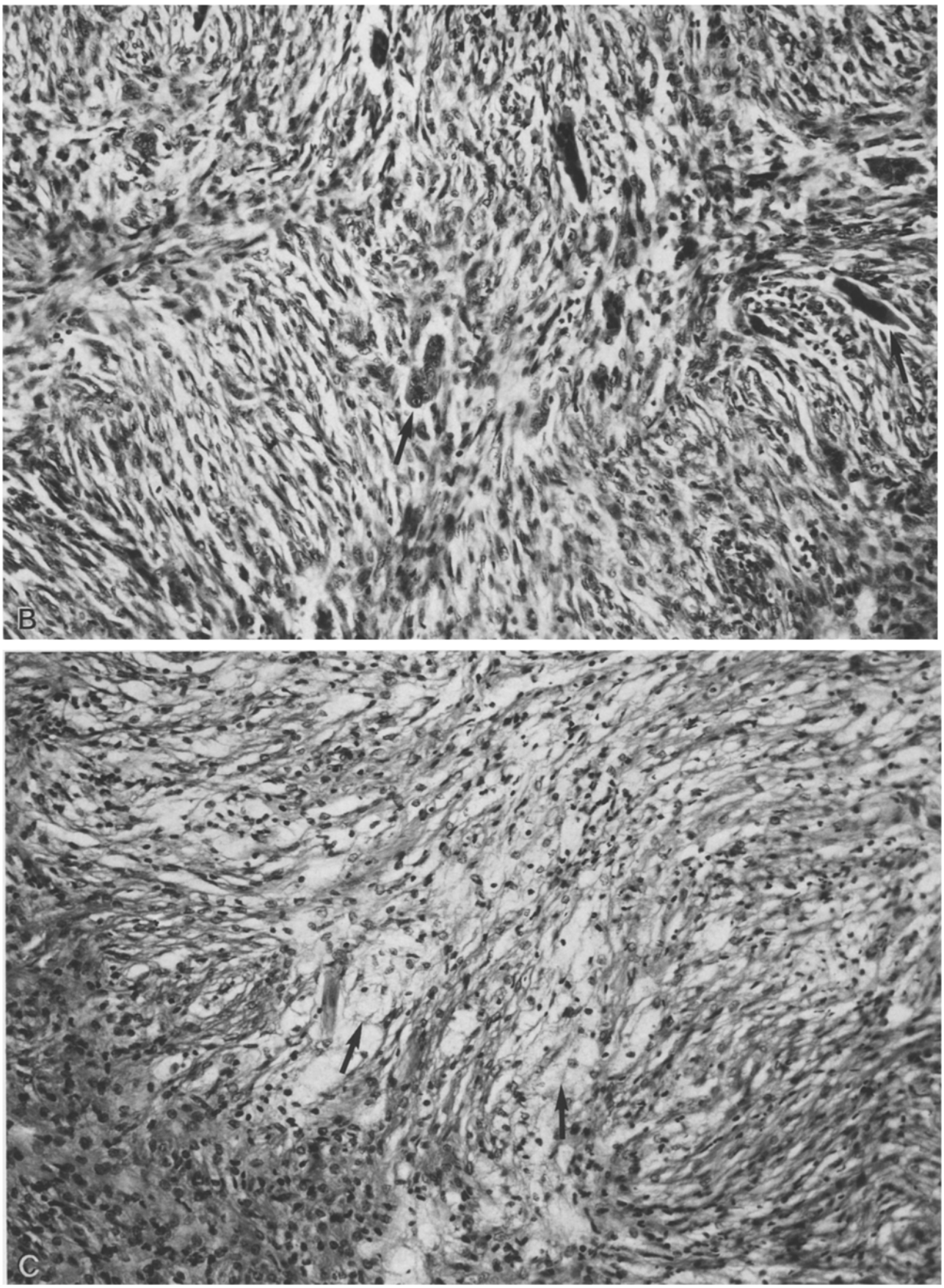

Fig. 6B, C.

per patient. In any case, absolute incidence of MSF is probably impossible to determine and is not critical.

Previously published studies have emphasized that multiple fibroxanthomas are among the many skeletal findings encountered in neurofibromatosis. In this series only 4 of 72 patients had neurofibromatosis, a finding which indicates that it is more common for the two conditions to exist independently than was previously suspected. This conclusion is qualified by the unlikely possibility that MSF could precede other manifestations of neurofibromatosis.

The question arises whether or not the histology of MSF differs from that of solitary lesions. Apparently it does not, according to the histologic analysis of the lesions in this series. Like their solitary counterparts, MSF are characterized histologically by proliferating spindle cells in a storiform configuration (Fig. 6A). Within these cells varying numbers of scattered multinucleated osteoclastic-like giant cells (Fig. 6B) and clustered xanthoma cells (Fig. 6C) are encountered. The multinucleated giant cell and xanthoma cell components appear inversely proportional to one another; the first type is associated with moderate to dense stroma and the second with loosely-packed stroma. In an individual lesion both patterns may be equally present, or one pattern may predominate. In all patients where biopsies were taken from two or more lesions, there were no significant differences in the histologic findings between the different sites.

The radiographic nomenclature of benign fibrous defects of bone (exclusive of fibrous dysplasia) is confusing. Wilner's classification [10] is based primarily on the size of the lesion and includes (a) fibrous cortical defect (a lytic lesion less than 2 cm in diameter, confined to the cortex); (b) fibrous endosteal defect (a persistent fibrous cortical defect 2–4 cm in diameter that has "expanded" the cortex and bulged into the endosteum, but has not actually invaded the medullary cavity); and (c) fibrous medullary defect (a well-defined lytic defect 4 cm or greater in diameter that involves the medullary space). Dr. Jaffe introduced the term "nonossifying fibroma" for this latter group. Since the lesion occasionally ossifies, Jaffe's terminology forces the awkward, self-contradictory expression of "ossifying, nonossifying fibroma". The terminology has been further confused by the use of the term "benign fibrous histiocytoma", which assumes that all xanthoma cells in bone originate from histiocytes. This hypothesis has not been firmly established. It fails to take into account the fact that normal development of fat cells includes both spindle cells and xanthoma cells and that the xanthomatous phase of fat cell development is well-established in embryology and histology. To avoid confusion, we prefer the term "fibroxanthoma of bone", which describes the actual cell types in this lesion.

The typical patient with MSF is an adolescent male with knee pain. The characteristic radiographic patterns are illustrated in Figs. 1–5. The frequency of lower extremity trauma in adolescents could explain, in part, the predominance of lower extremity long bone involvement, as well as its incidental discovery on subsequent radiographs. Strenuous biomechanical demands on the lower extremity in growing adolescents may or may not be a site-localizing factor.

In some patients in our series, sequential radiographs clearly demonstrate multiple, smaller fibroxanthomas coalescing into a single larger lesion, a pattern of growth not previously described (Fig. 4). Therefore, large, apparently solitary fibroxanthomas may actually result from the coalescence of several smaller ones.

Fibroxanthomas are among the most commonly encountered lytic skeletal defects and are usually not biopsied. The differential diagnosis for fibroxanthoma includes a variety of entities. Cortical desmoid, intracortical fibrous dysplasia (ossifying fibroma of long bone), and cortical chondromas must be distinguished from small fibroxanthomas or fibrous cortical defects. The differential diagnosis of the larger "intramedullary" fibroxanthoma includes chondromyxoid fibroma, brown tumors of hyperparathyroidism, giant cell tumor or bone cysts, and fibrous dysplasia. The latter (bone cysts and fibrous dysplasia) are usually central intramedullary lesions that may mimic fibroxanthoma when they present eccentrically. Fortunately, many of these possibilities are usually easy to eliminate.

1. If the patient has no other clinical, radiographic, or chemical evidence of hyperparathyroidism, then multiple brown tumors are unlikely.

2. Exclusive diaphyseal involvement would be uncommon for giant cell tumor.

3. Chondromyxoid fibroma is less easily excluded but predominates in the lower extremity, especially in the proximal tibia and in the feet.

4. Most important, giant cell tumor, chondromyxoid fibroma, and bone cysts are almost always solitary.

Since a "radiographic diagnosis" of fibroxanthoma is usually sufficient, the fact that we were able to accumulate 72 biopsy-proven cases of mul-

tiple skeletal fibroxanthoma probably results from the fact that the entity of multiple skeletal fibroxanthomas is not well-recognized. Our study emphasizes the following: multiple skeletal fibroxanthomas are probably more common than previously suspected; associated neurofibromatosis is distinctly less common than previously suspected; and MSF lesions assume four typical radiographic patterns. The radiologist's awareness of these principles should decrease and, perhaps, eliminate the need for biopsy in most cases.

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