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Epithelioid Granulomata in a Nonossifying Fibroma

The Possible Drug-Induced Mechanism

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Summary. A 13-year-old boy affected by bursitis of the R knee and nonossifying fibroma of the distal metaphysis of the R femur, was treated in the weeks prior to surgical intervention with water-soluble aspirin tablets to relieve local pain. Unexpected epithelioid cell granulomata were observed inside the neoplastic fibrous stroma of the nonossifying fibroma.

The coincidental appearance of a slight blood eosinophilia (7%) and perioral fixed drug eruption are clues that suggest that the histological bone findings may represent an expression of the hypersensitivity response elicited by aspirin. It cannot be ruled out that this unusual finding may be related to documented previous trauma, resulting in interstitial hemorrhages and subsequent reactive resorptive processes.

Key words: Bone neoplasms – Pathology-granuloma – Pathology-fibroma – Pathology-hypersensitivity delayed – Drug hypersensitivity

Epithelioid cell granulomata were found in large numbers throughout a nonossifying fibroma located in the distal metaphysis of the right femur in a 13-year-old boy.

After an extensive review of the pertinent literature, we were not able to identify a similar case.

Case Report

A 13-year-old boy was admitted to the Giannina Gaslini Children's and Women's Hospital in November 1980 for a bursitis of the R knee secondary to local trauma sustained some weeks previously. The R knee was swollen with a 5 cm increase of the circumference, in comparison to the unaffected controlateral knee and did not demonstrate articular effusion. Routine serum chemistry and urinalysis were normal. Blood white cell count was 4,500 with 49% neutrophils, 43% lymphocytes and 7% eosinophils. Roentgenographically a 3 cm well

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Fig. 1. This histological section illustrates the typical appearance of nonossifying fibroma: a whorled stroma interspersed with multinucleated giant cells. Haematoxylin and eosin ×40

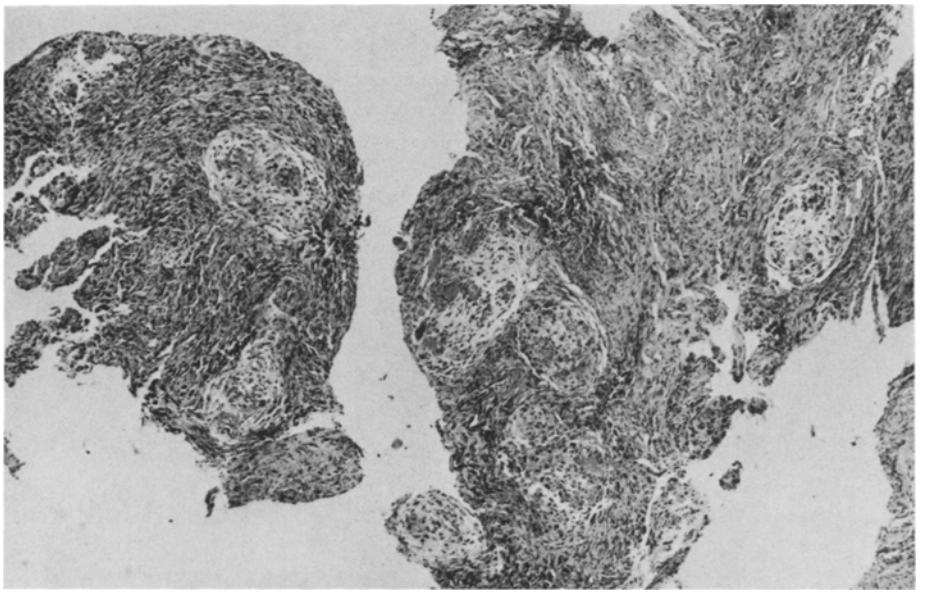

Fig. 2. Several epithelioid cell granulomata lie in close proximity each to other inside the tumor stroma. Haematoxylin and eosin ×150

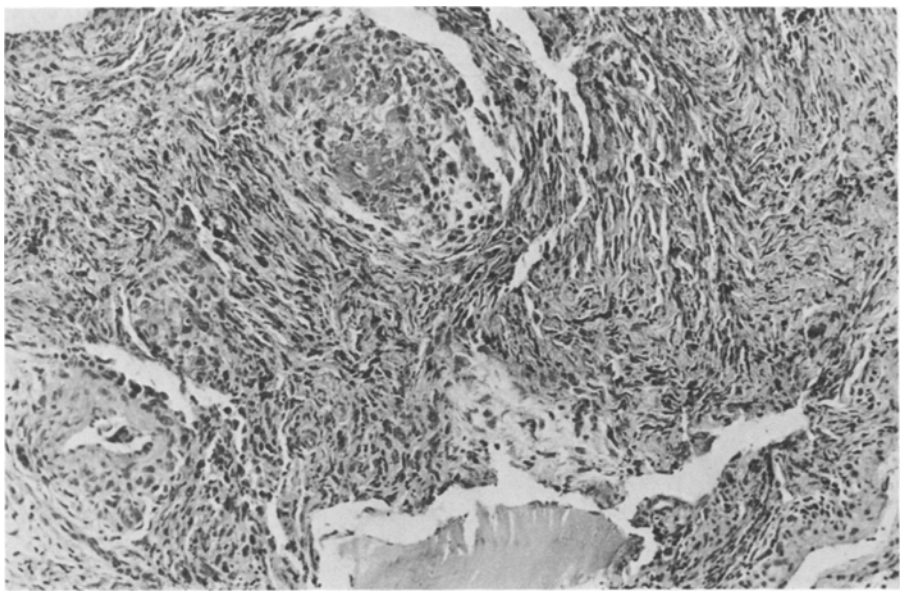

Fig. 3. An epithelioid granuloma (upper) surrounded by the fibrous stroma. A bone spicule is seen at bottom. Abundant intercellular fibrin-like material is seen inside the granuloma. Haematoxylin and eosin ×150

demarcated cortical defect with a sclerotic margin was demonstrated in the distal metaphysis of the R femur.

A peri-oral fixed drug eruption was noted characterized by oval, erythematous plaques and hyperpigmented macules. A drug history revealed that aspirin had been administered for several weeks for relief of the local pain.

At operation, the inflamed prepatellar bursa was removed. From the osteolytic defect of the femur abundant, yellow material was curetted. After discontinuation of aspirin therapy and discharge from the hospital both the skin eruption and eosinophilia resolved completely.

The child was said by his mother to be intolerant of aspirin. She reported several instances of malaise of the child following aspirin ingestion.

Pathologic Findings

Histological examination of the tissue specimen removed from the osteolytic area revealed cellular whorled connective tissue interspersed with multinucleated giant cells (Fig. 1). New bone formation and inflammatory infiltrates were absent. Rare foam cells were seen.

Numerous clearly defined round to oval epithelioid cell granulomata were found either scattered or clustered throughout the fibrous tissue (Fig. 2). They averaged 200–300 microns in diameter and were composed of epitheliod cells arranged in nests (Figs. 2 and 3).

The cells had round to oval nuclei and abundant, defined, and intensely eosinophilic cytoplasm. Some small multinucleated giant cells of the foreign body type were also present inside the granulomata (Fig. 4). Streaks and fragments of an intensely eosinophilic and bright material were scattered

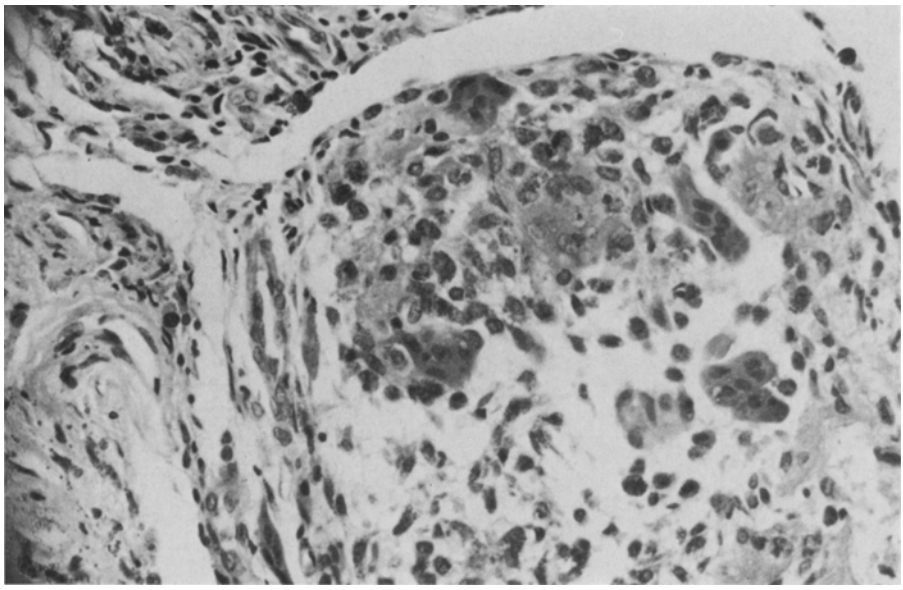

Fig. 4. At high magnification, intercellular amorphous fibrin-like material, and several giant cells of the foreign body type can be seen. The epitheliod appearance of the other cells can also be noted. Haematoxylin and eosin ×400

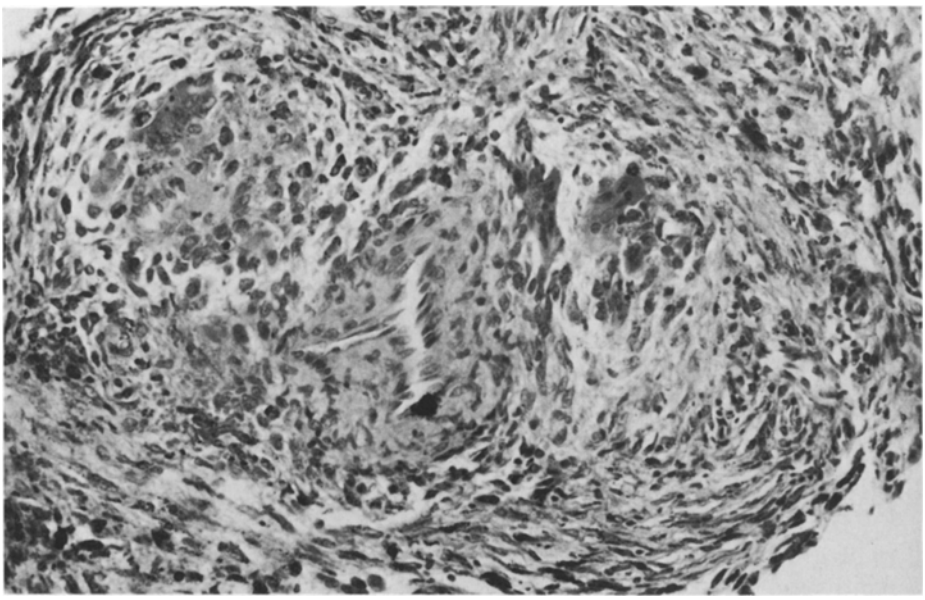

Fig. 5. Some granulomata are tightly clustered against the wall of a small arteriole. Haematoxylin and eosin ×400

in the center of each granuloma (Fig. 4). This fibrin-like material stained very weakly with PAS and with PTAH for fibrin. Several granulomata were centered around capillary or small arteriolar vessels and had inside a well defined onion-like arrangement of macrophages (Fig. 5). Intense intercellular oedema was an additional constant finding inside the granulomata. Numerous haemosiderin-laden histiocytes were scattered in the fibrous stroma of the tumor as well as inside the granulomatous formations. The PAS, Gomori-Crocott, Giemsa, Ziehl-Neelsen stains were negative for fungi, acid resistant bacilli, and other microorganisms. Birefringent structures in the granulomatous tissue were not observed under polarized light.

Discussion

Hypersensitivity to acetylsalicylic acid has been known for a long time. The term "aspirin triad" has been used for nasal polyposis and bronchial asthma associated with intolerance to aspirin. Several hypotheses other than of immune or allergic nature have been advanced to explain the hypersensitivity to aspirin (Samter and Zeitz 1978).

Salicylates are included among the drugs that cause common skin drug eruptions (Ackerman 1978). It is noteworthy that they can produce erythema nodosum, in which histiocytic nodules and giant cells can appear in older lesions (Ackerman 1978; Lever 1967).

The criteria dictated by Irey for considering a drug to be responsible for an adverse drug reaction are met in the present case (Irey 1976). The use of aspirin as the only drug therapy, the appearance of a fixed cutaneous eruption several days after administration, the absence of other clinical symptoms or diseases and the disappearance of the skin lesion after the discontinuation of aspirin therapy are all findings in agreement with the criteria of Irey (Irey 1976).

Moreover, the association of eosinophilia with allergic granulomatosis, and epithelioid granulomata as an expression of a hypersensitive state are well recognized entities (Adams 1976; Churg and Strauss 1951; Goldgraber and Kirsner 1958; Nezelof and Wilde 1976; Unanue 1978). Recently aspirin-induced granulomatous hepatitis has been reported (McMaster and Ennigar 1981). It is suggested that the changes observed in the bone could be correlated with the drug hypersensitive mechanism caused by aspirin. The perivascular location of the nodules and the fibrin-like material could support this contention. However, this remains a very speculative suggestion. Another explanation of the granulomata could be the previous trauma which caused interstitial haemorrhages and clustering of haemosiderin-laden histiocytes; but in several granulomata haemosiderin was scanty while oedema and fibrin-like material were abundant. Stromal haemorrhages in bone tumors may result in focal accumulation of haemosiderin-laden macrophages and giant cells, and eventually may form islands of xanthoma cells, but not such sharply outlined granulomas as in the present case.

Independently of the mechanisms involved in the present case, the finding of epithelioid granulomata inside a non-ossifying fibroma or other bone

tumors is noteworthy, and is not reported in standard treatises (Jaffe 1958; Aegerter and Kirkpatrick 1968; Spjut et al. 1971; Huvos 1979; Mirra 1980). Although the bone marrow and the cancellous bone can be infiltrated by inflammatory granulomatous tissue in a wide range of infectious or neoplastic conditions (Dehner 1975; Hamilton 1954; Hovde and Sundberg 1950; Nugent et al. 1976; Pease 1956), we were unable to find any similar previously reported case.

Finally, it is interesting to note that some fibrinoid imbibition of the collagen, a finding similar to that seen in the present case, has been described in erythema nodosum.

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