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EOSINOPHILIC GRANULOMA OF BONE*

EXPERIENCE WITH 20 CASES

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EOSINOPHILIC granuloma of bone is especially interesting to radiologists because it occurs in any part of the skeleton and presents a wide variety of appearances. It is a benign process, but sometimes the roentgenographic picture is so similar to that of a malignant tumor that neoplastic disease must be considered in differential diagnosis. Although it was classified as a distinct entity only recently, eosinophilic granuloma has an interesting history. This report will review the background of our present concept of the disease, record some information from previously reported cases, and review experience at the Ochsner Clinic with 20 patients seen during a period of 20 years ending December, 1965.

HISTORICAL REVIEW

The term "eosinophilic granuloma" was introduced in 1940 by Lichtenstein and Jaffe,[12] who reported a case of a solitary tumor of the femur. The same issue of the same journal contained an article on the same disease by Otani and Ehrlich,[14] who referred to their cases as solitary granulomas of bone. Only 2 years later, Green and Farber[8] reported 10 cases of eosinophilic granuloma, some of which were in patients with multiple lesions. They stressed that eosinophilic granuloma of bone, Hand-Schüller-Christians' disease, and Letterer-Siwe's disease were various manifestations of a similar pathologic process. More recently, these lesions have come to be known as reticulosis, reticulo-endotheliosis, or histiocytosis.[11]

In addition to the evolving concept of an underlying unity of these various osseous manifestations, reports have shown that other nonskeletal organs or systems may contain similar eosinophilic granulomatous masses. Arnold[1] reported eosinophilic granuloma of bones with associated pulmonary involvement. In 1952, Lackey and associates[10] reported cases of eosinophilic granuloma limited to the lung. In 1951, Booher and Grant[2] collected 11 cases of gastric granulomas and noted that they usually involved the antrum of the stomach and tended to grow from submucosal nodules into polypoid masses.

It is the relatively frequent involvement of the skeletal system, however, that gives the disease its chief importance. Apparently, any bone in the body may be affected, but most lesions are found in the skull, ribs, spine, or long bones.

PATHOLOGIC FINDINGS

In their initial report, Lichtenstein and Jaffe[12] described the pathologic alterations so accurately that little has been added since. They described the tumor as a "localized, single lesion, starting in the medullary cavity and tending to erode, expand and perforate the cortex in the bony site affected." The mass may extend into the neighboring soft tissues and "the roentgenographic and clinical findings may lead one to suspect the presence of a malignant bone tumor. Surgical exploration shows that the affected portion of the bone has been extensively replaced by a more or less soft, yellowish or brownish tissue." The microscopic appearance is "characterized essentially by the presence of compacted, tumor-like aggregates of large phagocytic cells, with conspicuous collections of eosinophilic leukocytes interspersed." In addition, they reported "an appreciable number of large multinucleated (giant) cells." They stated that this type of lesion previously had been "regarded provisionally as a

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peculiar, inflammatory granulomatous lesion of indeterminate nature."

In 1941, Farber[7] presented his concept that eosinophilic granuloma is one of a group of related granulomatous diseases, including Hand-Schüller-Christian and Letterer-Siwe disease. It is interesting to notice, in retrospect, that in the discussion of Farber's paper, Lichtenstein, Jaffe, and Otani individually expressed disagreement with this concept. Nevertheless, Farber's theory has been generally accepted. Indeed, by 1953, Lichtenstein[11] espoused the idea completely and introduced the term "histiocytosis X," to specify the common pathologic denominator. He suggested that the disease is a specific inflammatory histiocytosis. Eosinophilic granuloma was considered the localized form, Letterer-Siwe disease the acute or subacute disseminated form, and Hand-Schüller-Christian disease the chronic disseminated form. Dundon and co-workers[5] pointed out that in an early phase of development, these lesions may undergo partial liquefaction and appear as a cystic mass.

In a more recent discussion, Jaffe[9] expressed the opinion that eosinophilic granuloma has little relationship to xanthogranuloma and heals by resolution (if it heals) and not by conversion into a xanthomatous lesion. He also stated that solitary osseous lesions in Hodgkin's disease may be difficult to differentiate cytologically from eosinophilic granuloma.

INCIDENCE

Most reports of eosinophilic granuloma stress the frequency of the disease in young persons.[5] Sbarbaro and Francis,[16] for instance, reported that 34 per cent of 50 patients were younger than 4 years old and 74 per cent were younger than 20 years of age. Although most of the patients in the present series also were young, 2 patients were 45 years old, so that this disease must be considered in the middle-aged patient with an osteolytic lesion of bone.

The incidence according to sex varies in reported series. Fifteen of our 20 patients were females. Most patients seen at the Ochsner Clinic are white; only 1 of the patients in our series was a Negro. Sbarbaro and Francis[16] considered it significant that all 50 cases at Memorial Hospital in New York occurred in the white race.

TABLE I

SKELETAL SITE IN 20 PATIENTS WITH EOSINOPHILIC GRANULOMA OF BONE

Site	No. of Cases
Skull	6
Rib	3
Spine	3
Mastoid	2
Pelvis	2
Femur	2
Mandible	1
Humerus	1

CLINICAL MANIFESTATIONS

These patients have few, if any, constitutional symptoms. The osseous lesion usually causes localized pain, so that the original clinical diagnosis revolves around the question of the possible causes of pain in a particular anatomic area. Some patients have a palpable mass, as well as localized pain. Fever, elevation of erythrocyte sedimentation rate, and leukocytosis with relative eosinophilia are rare and not ordinarily helpful in diagnosis.

The skeletal sites in our 20 cases are shown in Table 1. The skull, ribs, and spine were the most common sites.

ROENTGENOGRAPHIC OBSERVATIONS

The essential lesion is identified by roentgenographic examination. In essence, the granuloma produces a localized area of rarefaction in the diseased bone. This radiolucency starts in the medullary region. As it expands, it progressively erodes the inner side of the denser cortical bone, producing a smooth, irregular, or scalloped defect in the inner cortical profile. The involved cortex becomes progressively thinner, and the radiolucent medullary defect progres-

sively larger. Eventually, the cortex may break and cause a pathologic fracture. As the pathologic fracture attempts to heal, or as the granulomatous process separates the periosteum from the cortex, formation of new bone may be seen roentgenographically, as "periosteal reaction" adjacent to the abnormal cortex. Progression of lesions is usually slow but may be rapid.[11] Lesions in specific bones may have certain features worthy of note.

Skull. One-third of our patients had cranial granulomas. The eosinophilic granuloma produces a clearly defined area of radiolucency, usually with a sharp border and involving both the inner and outer tables of the bone. A "bevelled edge" may be found. There is neither sclerosis of the border of the defect nor adjacent hyperostosis or cortical thickening. Meningeal or periosteal calcification was not seen in any of our patients. Vascularity of the surrounding skull was normal. None of the defects showed the peculiar granularity that is sometimes seen in hemangiomas. Only one showed the central "button of bone" that Wells[18] reported in several eosinophilic granulomas, and it is interesting that this disappeared in the 6 month interval between initial recognition and final proof by local resection (Fig. 1, *A* and *B*).

Mastoid. Eosinophilic granulomas of the mastoid do not present a specific roentgenographic appearance. A radiolucent area appears in the bone. Clinical as well as radiologic diagnosis is likely to be cholesteatoma, which presents the same general appearance and is more common. Two of our patients had this type of lesion, one a solitary lesion and the other secondary involvement several years after a mandibular lesion had disappeared after radiation therapy.

Mandible. A relatively large, fairly well defined, radiolucent area may develop in the mandible. A 4 year old boy in our series had such an eosinophilic granuloma, involving the horizontal ramus and producing a "cyst-like area," in which one of the teeth seemed to be almost floating. The lesion disappeared after radiation therapy and the bone was so completely reconstituted that it appeared normal on subsequent roentgenograms (Fig. 2, *A* and *B*).

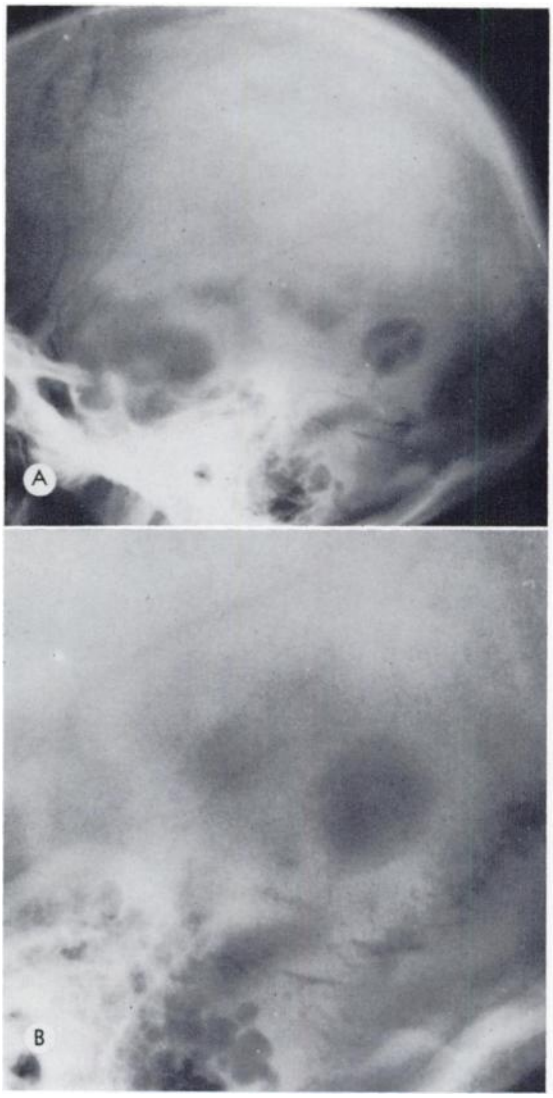

FIG. 1. (*A*) Roentgenogram of skull shows well defined radiolucent lesion in parietal bone. (*B*) Central opaque button disappeared in 6 months, but note bevelled edge of lesion.

Spine. The roentgenographic appearance of vertebrae affected by eosinophilic granulomas comes closer to being pathognomonic than any other roentgenographic manifestation of the disease. The vertebral body is generally affected, loses some of its

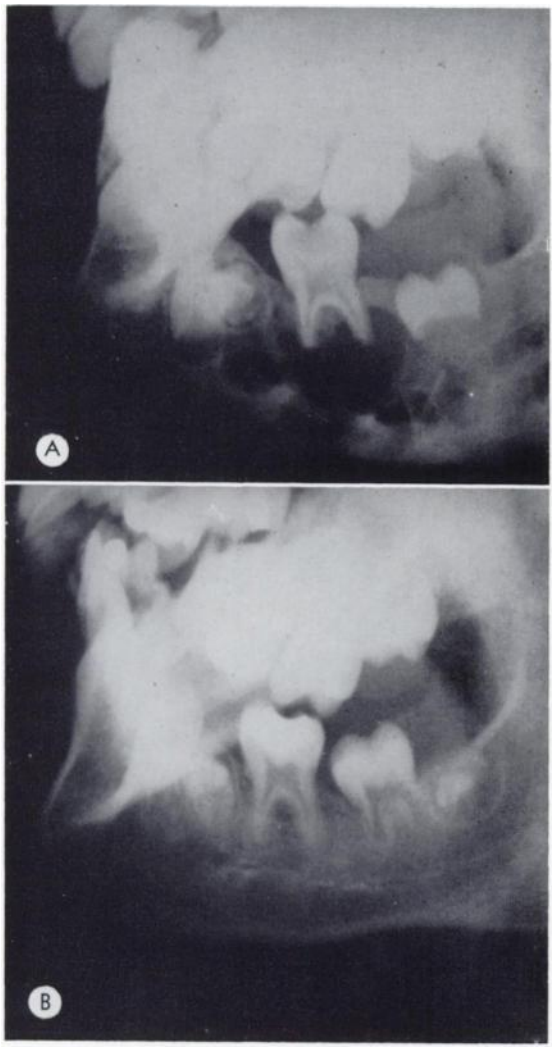

FIG. 2. (*A*) Eosinophilic granuloma of mandible before treatment, and (*B*) 2 years after biopsy and radiation therapy (600 r).

structural bony strength, and collapses to some degree. Vertebra plana is the result. Flattening may be extreme and only a thin wafer of bone remains. It is usually denser, and therefore whiter, in the roentgenogram than the adjacent vertebra (Fig. 3). These granulomas may occur in any portion of the spine and usually a single vertebra is affected. In discussing Compere and coworkers'[4] statement that vertebra plana is characteristic in eosinophilic granuloma, Hillman pointed out that it is not pathognomonic and he showed a roentgenogram of a characteristic vertebra plana which developed within 1 month in a boy with sarcoma of bone.

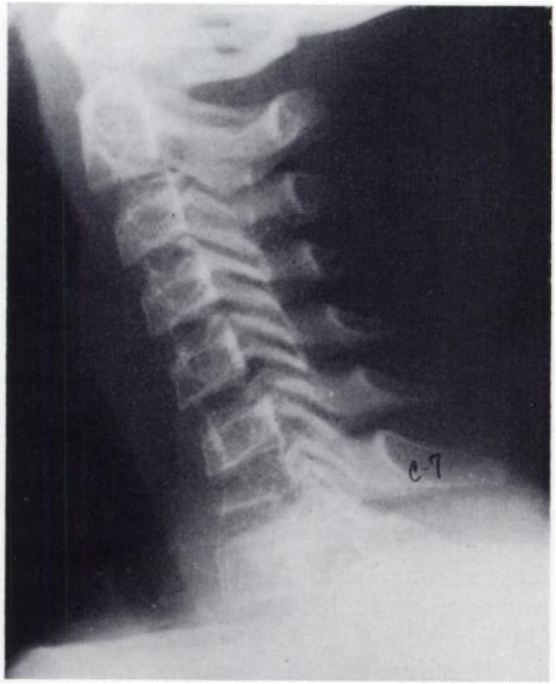

FIG. 3. Vertebra plana of cervical spine due to eosinophilic granuloma.

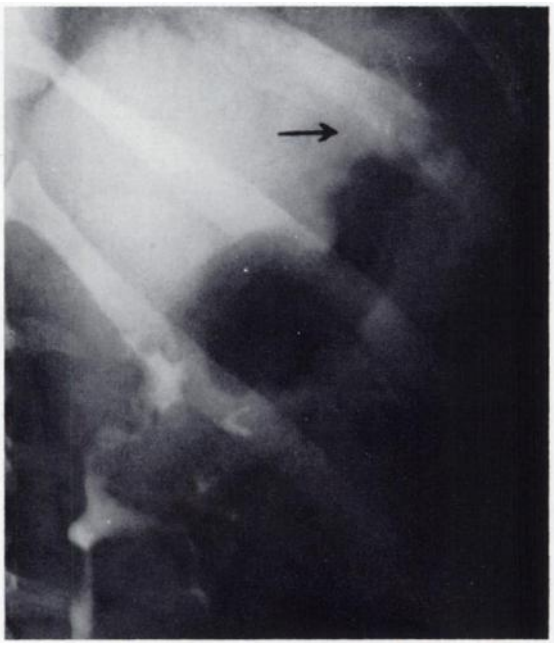

FIG. 4. Localized osteolytic tumor in rib which proved to be an eosinophilic granuloma.

Ribs. Three of our patients had granulomas of a rib. All 3 were older than 35 years of age. Each had a slightly painful, solitary osteolytic lesion and a pathologic fracture (Fig. 4). In each, the initial fear was that metastatic carcinoma was the cause. There is nothing characteristic about these radiolucent lesions.

Pelvis. Surpisingly large osteolytic areas may be present in the pelvis. The lesion usually has sharply defined borders, but they may appear irregular or scalloped, and inner bony ridges may produce a somewhat trabeculated appearance (Fig. 5, *A* and *B*). The lesion may look spongy or like a "soap bubble." In our patients, the roentgenographic appearance improved after radiation therapy.

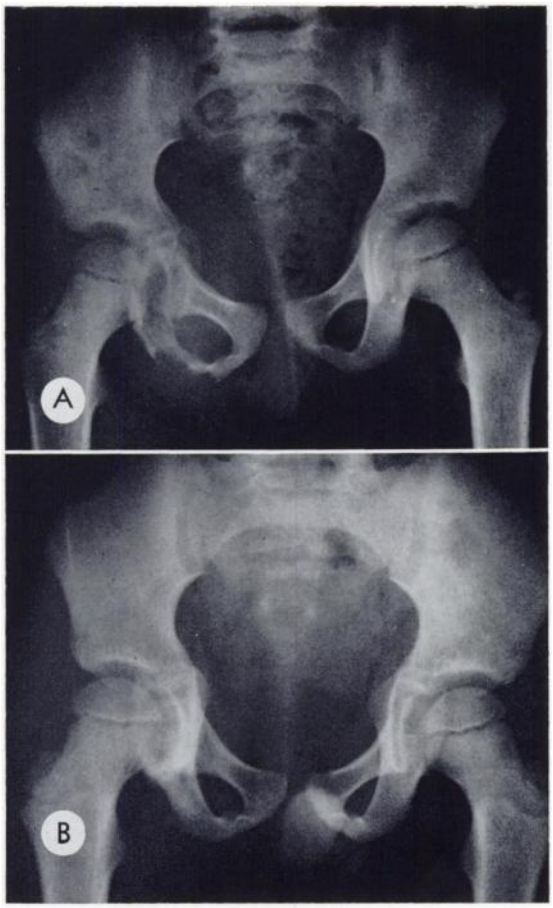

Fig. 5. (*A*) Eosinophilic granuloma in right ischium produces a large, irregular area of osseous destruction. (*B*) Improvement after biopsy and radiation therapy.

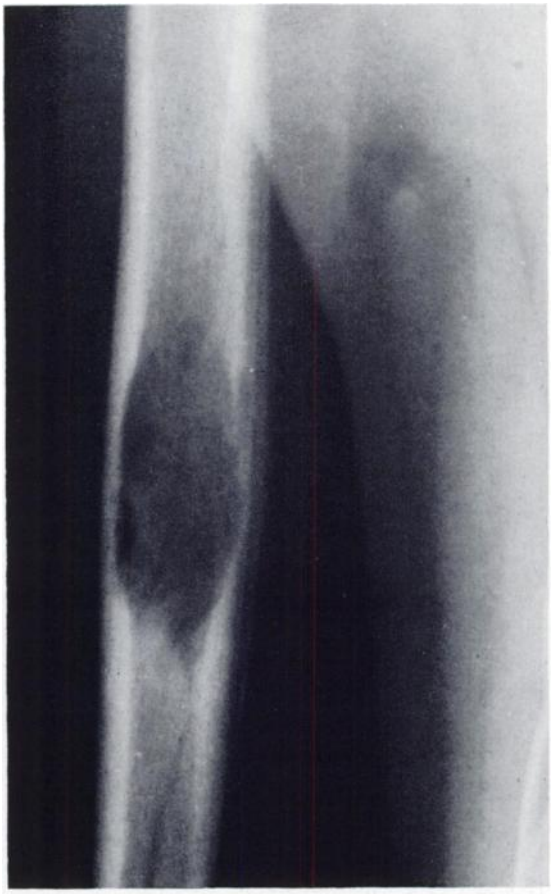

Fig. 6. Radiolucent eosinophilic granuloma of humeral diaphysis with periosteal reaction. Ewing's tumor was a differential diagnostic problem.

Long Bones. Of the eosinophilic granulomas involving the long bones, those of the femur are most frequent. Among reported cases, roentgenograms of the femur present some of the most bizarre and challenging appearances. Simple osteolytic lesions may suggest bone cyst or sarcoma of bone. Jaffe[9] noted that bone cysts usually are oriented to the end of the diaphysis, and are larger and less painful than granulomas. Relatively long lesions in eosinophilic granuloma may suggest fibrous dysplasia, and destructive lesions with adjacent sclerosis may suggest osteomyelitis. Those with surrounding periosteal reaction may mimic Ewing's sarcoma, especially in the

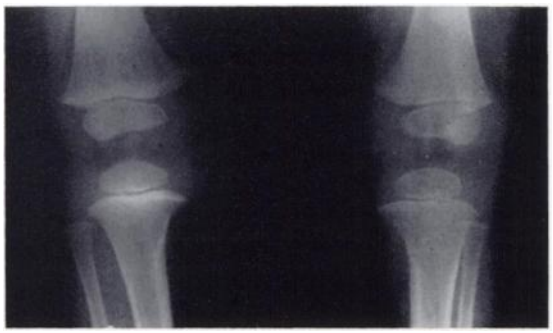

FIG. 7. Round radiolucent area in lower left femoral epiphysis: a rare site of eosinophilic granuloma.

earlier phases of the tumor, and Jaffe[9] suggested that some "cured" cases of Ewing's tumor may have, in truth, been eosinophilic granulomas. In a 9 year old girl in our series, the humeral eosinophilic granuloma mimicked Ewing's sarcoma (Fig. 6). Simple curettage resulted in complete cure.

Young persons are frequently affected and so the differential diagnosis of malignant bone tumor is a genuine problem. The tragedy of amputating an extremity for a localized benign tumor can be avoided only if the possibility of eosinophilic granuloma is kept in mind when the differential diagnosis of bone lesion is under consideration.

Epiphyses. In one of our patients, a 4 year old boy, an eosinophilic granuolma involved the lower femoral epiphysis (Fig. 7). Apparently, the epiphyses are rarely affected, as this site was not encountered in 2 of the largest reported series of cases.[13,16] In our patient, a round, radiolucent lesion occurred in the center of the epiphysis. After curettage, through a transmetaphyseal approach, the lesion healed and normal epiphyseal growth continued (Fig. 8, *A* and *B*). If the disease is not recognized and treated, the epiphysis probably would collapse and produce deformity of the articulating surface.

Lung. After the first reports that pulmonary lesions could occur in patients with eosinophilic granuloma, Farinacci and coworkers[6] described similar lesions in persons who did not have osseous manifestations. The lesions have been a mixture of stippled or finely nodular opacities, combined with reticular and patchy infiltrations. Sometimes small, cyst-like shadows give the lung a honeycombed appearance. In only one of our patients was pulmonary disease manifest. The lesions later cleared and the lungs assumed an essentially normal appearance.

Gastrointestinal Tract. None of our pa-

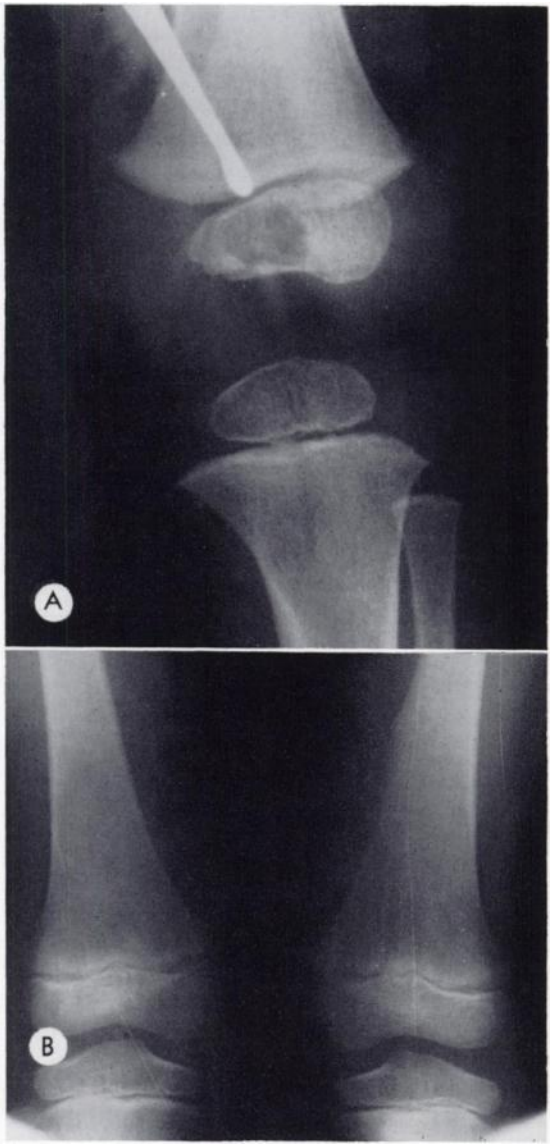

FIG. 8. Epiphyseal eosinophilic granuloma (same as Fig. 7). (*A*) Surgical transmetaphyseal approach. (*B*) Essentially normal appearance 4 years later.

tients had gastrointestinal granuloma. Rigler *et al.*[15] presented 9 cases with roentgenograms illustrating isolated polypoid lesions of the stomach.

DISCUSSION

Although multiple lesions may occur in one patient, and despite the similar histopathologic appearance of eosinophilic granulomas and other reticuloses, such as Hand-Schüller-Christian and Letterer-Siwe diseases, we would perhaps be wise to maintain an open mind regarding the degree of underlying similarity of these diseases. After a recent review of a relatively large group of cases, for example, McGavran and Spady[13] could find no patients whose disease progressed to a more complex form. Until the cause of the disease is discovered, therefore, they believed that doubt must remain about the extent of relationship between this group of diseases.

One of our patients had successive lesions in the mandible and mastoid in a 3 year interval. None of the others in this series had any evidence that the disease would progress to other than solitary osseous lesions.

The importance of prompt recognition and careful treatment is indicated by the tragic complication of permanent paralysis that resulted from damage to the spinal cord which followed sudden collapse of the involved thoracic vertebra in one of our patients.

TREATMENT

Relatively conservative management is undoubtedly desirable. Biopsy for diagnosis can be readily followed by simple curettement, or small lesions may be excised at biopsy. Roentgen-ray therapy has been used to relieve pain or promote healing. Favorable results have been reported after doses as small as 500 to 1,500 rads.[3] In our series, radiation therapy seemed particularly useful in patients with mandibular, vertebral, and pelvic lesions, in doses of 600 to 1,000 rads. McGavran and Spady[13] concluded that the lesions healed regardless of the type of treatment, including several patients who had no specific treatment.

SUMMARY

Eosinophilic granuloma of bones is of special interest to radiologists because it is first identified in roentgenograms and may mimic many benign and malignant conditions. Since this entity was first described 26 years ago, it has been reported in many skeletal locations. In our 20 cases, the skull, ribs, and spine were the most frequent sites; an unusual site in the femoral epiphysis is recorded. Local pain and disability are the usual symptoms, but vertebral granulomas may damage the spinal cord, and pathologic fracture of long bones may occur. Correct diagnosis usually requires biopsy. Results of conservative treatment are good; it is important not to overtreat this benign tumor in the fallacious assumption that it is a malignant tumor. The most frequently advocated treatment is curettage, with or without postoperative radiation therapy in moderate dosage.

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REFERENCES

1. Arnold, H. L. Eosinophilic granuloma of bone; preliminary report of case complicated by lung lesions. *Proc. Staff Meet. Clin., Honolulu*, 1946, *12*, 183–185.
2. Booher, R. J., and Grant, R. N. Eosinophilic granuloma of stomach and small intestine. *Surgery*, 1951, *30*, 388–397.
3. Childs, D. S., Jr., and Kennedy, R. L. J. Reticuloendotheliosis of children: treatment with roentgen rays. *Radiology*, 1951, *57*, 653–659.
4. Compere, E. L., Johnson, W. E., and Coventry, M. D. Vertebra plana (Calvé's disease) due to eosinophilic granuloma. *J. Bone & Joint Surg.*, 1954, *36-A*, 969–980.
5. Dundon, C. C., Williams, H. A., and Laipply, T. C. Eosinophilic granuloma of bone. *Radiology*, 1946, *47*, 433–444.
6. Farinacci, C. J., Jeffrey, H. C., and Lackey, R. W. Eosinophilic granuloma of lung; report of 2 cases. *U. S. Armed Forces M. J.*, 1951, *2*, 1085–1093.

7. FARBER, S. Nature of "solitary or eosinophilic granuloma" of bone. *Am. J. Path.*, 1941, *17*, 625–629.
8. GREEN, W. T., and FARBER, S. "Eosinophilic or solitary granuloma" of bone. *J. Bone & Joint Surg.*, 1942, *24*, 499–526.
9. JAFFE, H. L. Tumors and Tumorous Conditions of the Bones and Joints. Lea & Febiger, Philadelphia, 1958, pp. 629.
10. LACKEY, R. W., LEAVER, F. Y., and FARINACCI, C. J. Eosinophilic granuloma of lung. *Radiology*, 1952, *59*, 504–512.
11. LICHTENSTEIN, L. Histiocytosis X; integration of eosinophilic granuloma of bone, "Letterer-Siwe disease," and "Schüller-Christian disease" as related manifestations of single nosologic entity. *A.M.A. Arch. Path.*, 1953, *56*, 84–102.
12. LICHTENSTEIN, L., and JAFFE, H. L. Eosinophilic granuloma of bone, with report of case. *Am. J. Path.*, 1940, *16*, 595–604.
13. MCGAVRAN, M. H., and SPADY, H. A. Eosinophilic granuloma of bone; study of twenty-eight cases. *J. Bone & Joint Surg.*, 1960, *42-A*, 979–992.
14. OTANI, S., and EHRLICH, J. C. Solitary granuloma of bone simulating primary neoplasm. *Am. J. Path.*, 1940, *16*, 479–490.
15. RIGLER, L. G., BLANK, L., and HEBBEL, R. Granuloma with eosinophils; benign inflammatory fibroid polyps of stomach. *Radiology*, 1956, *66*, 169–176.
16. SBARBARO, J. L., JR., and FRANCIS, K. C. Eosinophilic granuloma of bone. *J.A.M.A.*, 1961, *178*, 706–710.
17. TEPLICK, J. G., and BRODER, H. Eosinophilic granuloma of bone. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1957, *78*, 502–507.
18. WELLS, P. O. Button sequestrum of eosinophilic granuloma of skull. *Radiology*, 1956, *67*, 746–747.