

Virus-like Intranuclear Inclusions in Giant Cell Tumor of Bone

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An ultrastructural study of 13 cases of typical giant cell tumor of bone (GCT) revealed the presence of virus-like intranuclear inclusions (INI), morphologically identical to those reported in Paget's disease of bone. In two giant cells of two different patients, INI were found only after careful survey of a great number of cells. This finding, coupled with the scarcity of GCT with similar inclusions reported in the literature, reveals the extreme rarity of this finding and leaves open to discussion the specificity of these INI even in Paget's disease, as well as the possible etiological significance in giant cell tumor of bone.

The presence of characteristic intranuclear inclusions (INI) in the osteoclasts of Paget's disease of bone, which resemble the nucleocapside of paramyxoviridae virus, has been repeatedly demonstrated by ultrastructural studies in recent years. Their presence was reported for the first time by Rebel *et al.*²⁰ and later corroborated by him and his associates²¹ and by other research groups,^{7,15,25-28} including Schajowicz *et al.*,²⁴ and have been considered characteristic of Paget's disease. However, morphologically similar INI were previously described in 1970 by Welsh and Meyer³² in two genuine giant cell tumors of bone (GCT). Other studies on the presence of INI in GCT were performed later. Their presence was reported in one case by Le Charpentier *et al.*,¹⁴ in seven cases by Vacher-Lavenu *et al.*,³¹ in a case of GCT associated with Paget's disease by Mirra *et al.*,¹⁸ and in a case of osteosarcoma.⁶

It is surprising that such inclusions were detected in so few cases, in spite of the numerous ultrastructural studies of GCT performed.^{1-3,5,9,11,13,23,29,30} Accepting that these INI reveal an evidence for a viral etiology of Paget's disease of bone, it seems extremely important to confirm their presence and real incidence in GCT, which is the aim of this study.

MATERIALS AND METHODS

The samples were obtained from 13 patients with GCT either by puncture or by surgical biopsy, from lesions in femur, tibia, and radius.

All pieces were fixed for light microscopy in formaline 10%, embedded in paraffin and stained with hematoxylin-eosin. For electron microscopy, they

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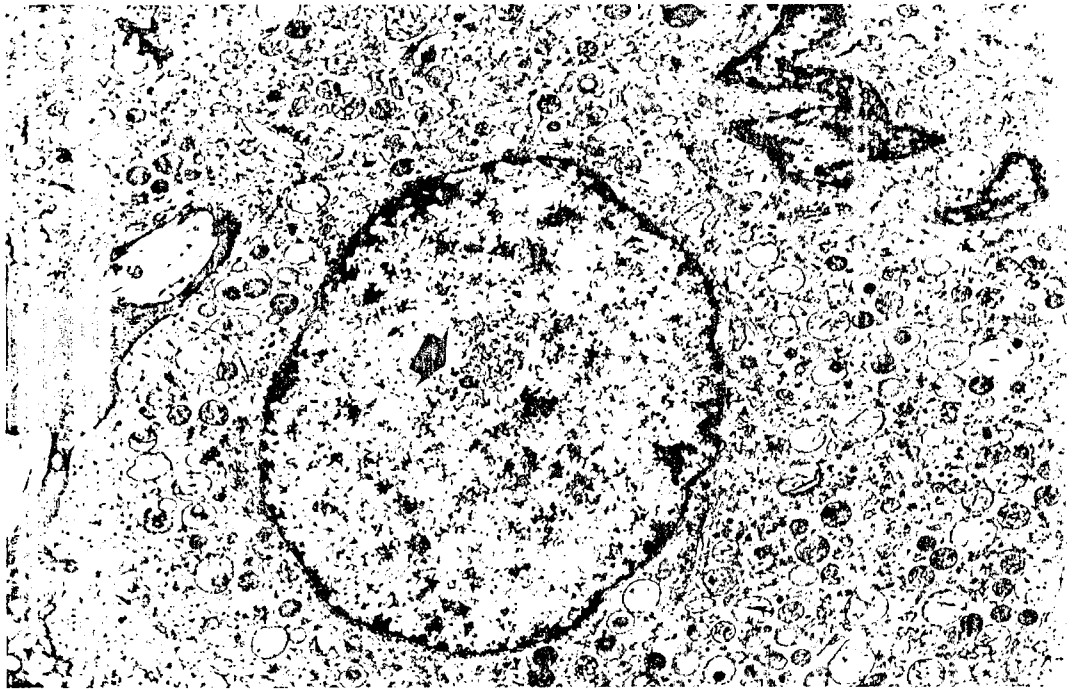


FIG. 1. Nucleus of a giant cell of an GCT showing an intranuclear inclusion (arrow) (Original magnification, $\times 15,000$.)

were fixed at surgery in Karnowsky's solution, post-fixed in osmium tetroxide 1% and embedded in EPON 812 (Ladd Research Industries, Inc., Burlington, Vermont). Giant cells were localized in thin sections stained with toluidine blue. Ultrathin sections obtained from at least five blocks of each case were counterstained with uranyl acetate and lead citrate according to Reynold's technique.

RESULTS

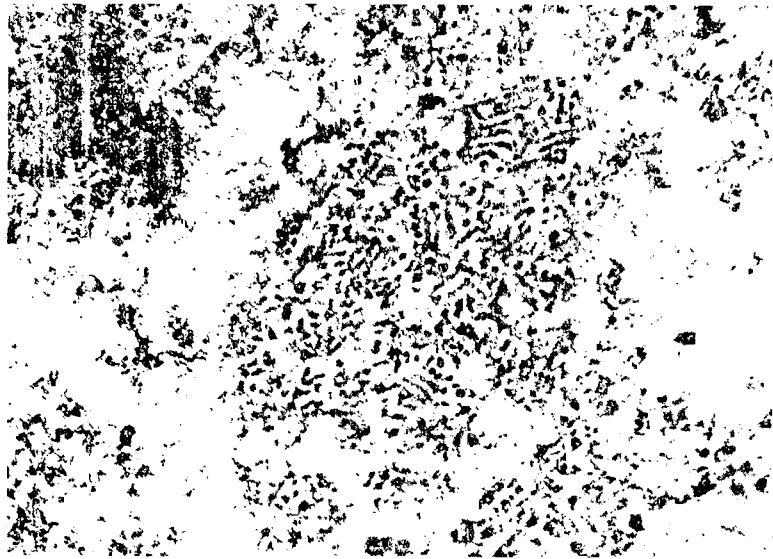
INI formed by filamentous structures packed in bundles in a paracrystalline array and sectioned transversally or longitudinally, essentially identical to those of Paget's disease of bone, were found in a scarce number of nuclei of giant cells (Fig. 1). Filaments exhibited a constant diameter of 12–15 nm, separated from each other by a space of 20 nm. When cut transversally and observed at high magnification, they showed a clear central core (Fig. 2). The image of INI in GCT was not so clear as that found by the authors in nuclei of osteoclasts of Paget's disease (Fig. 3). In all of

the 13 cases of GCT, nuclei corresponding to a minimum of 10 giant cells were scanned, *i.e.*, a total of 130 giant cells analyzed. The inclusions were found only in three nuclei corresponding to two giant cells of two different cases. This represents an incidence of 15% of the cases, 1.53% of the cells and 0.16% of the nuclei, thus revealing its extreme rarity in giant cell tumor.

DISCUSSION

The present ultrastructural study of 13 cases of GCT revealed the presence of INI, essentially similar to those of Paget's disease, in giant cells of two different patients. They were found, after a careful search, in only two of the great number (130) of such cells scanned. The incidence found in this work reached 15% of the cases; a value similar to that afforded by Vacher-Lavenue *et al.*,³¹ who reported INI in 22% of the cases. These find-

FIG. 2. INI found in a giant cell of GCT (Original magnification, $\times 78,000$.)



ings, and the fact that INI were reported in only 11 patients of GCT,^{14,18,31,32} one of them with lesions arising from a focus of Paget's disease,¹⁸ demonstrated the rarity of these inclusions in GCT. It is interesting that such inclusions have not been mentioned at all in the numerous ultrastructural studies of GCT,^{1,2,5,9,11-13,23,29,30} and it seems possible that a more exhaustive search of these structures would reveal a greater number of positive cases. Their demonstration in GCT reveals

that the presence of INI found in the osteoclasts of patients with Paget's disease must be considered as highly characteristic but not specific of Paget's disease. This fact thus detracts from the diagnostic value of INI for Paget's disease. In recent years immunocyto-logic studies of bone biopsies and cultured bone cells in Paget's disease have demonstrated positive responses with antisera against the measles virus and/or respiratory syncytial virus.^{4,8,10,17,19,22,28,32} Based on these findings,

FIG. 3. INI found in an osteoclast of Paget's disease (Original magnification, $\times 87,000$.)



Paget's disease has been suggested to be a slow viral infection, although the etiologic factor of this virus has not yet been proved. The presence of similar INI in giant cells of GCT, although rare, would suggest a similar etiology for both diseases, which, in our opinion, is a highly debatable hypothesis that needs further immunocytochemical investigations to be confirmed or refuted.

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