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Paramyxovirus-like nuclear inclusions identical to those of Paget's disease of bone detected in giant cells of primary oxalosis

Paolo Bianco, Giuliana Silvestrini, Paola Ballanti, and Ermanno Bonucci

Dipartimento di Biopatologia Umana, Sezione Anatomia Patologica, Universita' La Sapienza, Viale Regina Elena 324 (Policlinico), I-00161 Rome, Italy

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Summary. Nuclear inclusions, identical to those characteristic of Paget's disease of bone, were observed in giant cells in four of eight cases of primary oxalosis. The giant cells containing nuclear inclusions were directly involved in phagocytosis of large oxalate crystals in the context of typical foreign body granulomas in the bone marrow. Cytochemically, all of them exhibited strong tartrate-resistant acid phosphatase activity, and a proportion of them also tartrate-resistant acid ATPase. The inclusions consisted of typical arrays of filamentous material as described in Paget's disease, admixed with variable proportions of electron-dense material closely reminiscent of nucleolar pars fibrillaris and fibrillary centres. These data indicate: (a) the occurrence of Paget-like inclusions in a bone disease unrelated to Paget's disease, not causally related to viral infection, and resulting from an inborn metabolic derangement; and (b) the occurrence of Paget-like inclusions in foreign body giant cells as opposed to osteoclasts. We suggest that the occurrence of paramyxovirus-like nuclear inclusions in either osteoclasts or giant cells may represent an epiphenomenon of cell fusion and giant cell formation whenever appropriate stimuli act on latently infected precursor cells. Furthermore, our data suggest that nucleoli may represent the specific site of virus-like inclusion formation.

Key words: Primary oxalosis – Paget's disease of bone – Nuclear inclusions – Paramyxovirus – Osteoclasts

Introduction

The hypothesis of a viral aetiology of Paget's disease of bone (Singer 1980; Mirra 1985) has been supported mainly by the demonstration of characteristic paramyxovirus-like intranuclear inclusions in pagetic bone osteoclasts (Rebel et al. 1974a, 1980a; Mills and Singer 1976; Gherardi et al. 1980a; Harvey et al. 1982; Howatson and Fornasier 1982; O'Driscoll and Anderson 1985) and of antigens related to either measles virus or respiratory syncytial virus (Rebel et al. 1980b; Mills et al. 1981, 1984; Basle et al. 1985; Mills and Singer 1987). Nuclear inclusions identical to those detected in pagetic osteoclasts can also be observed in osteoclasts in other bone diseases, such as osteopetrosis (Mills et al. 1988), pycnodysostosis (Beneton et al. 1987) and giant cell tumours (osteoclastomas) (Welsh and Mayer 1970; Aparisi et al. 1979; El Labban 1984; Schajowicz et al. 1985; Abelanet et al. 1986). These observations have not significantly challenged the hypothesis of a paramyxovirus-related, "slow virus" type of infection underlying the pathogenesis of Paget's disease. Rather, an involvement of the same viruses as in Paget's disease has been on occasion advocated in non-Paget bone disorders. Nonetheless, uncertainties over the significance of putative paramyxovirus infection in Paget's disease persist (Kahn 1990; Ralston et al. 1991).

The studies reported in this paper began with the incidental observation of typical paramyxovirus-like nuclear inclusions in the giant cells of oxalate crystal-induced bone marrow granulomas in one case of primary oxalosis. Primary oxalosis results from an inborn metabolic derangement, and the giant cells comprising its typical granulomas in the marrow and other tissues are regarded as foreign body giant cells. Therefore, the observation of paramyxovirus-like inclusions in this context appeared to be of potential importance for its bearing on current views on the nature and meaning of osteoclastic virus-like inclusions in both Paget's disease and non-Paget bone disorders. By examining our series of bone biopsies from cases of primary oxalosis retrospectively, we determined the consistency of our observation. We report here the ultrastructural features of virus-like inclusions found in primary oxalosis, together with cytochemical characterization of the giant cells in which they were observed. In addition, we suggest an alternate explanation for the nature and meaning of this finding in both Paget's disease and non-Paget bone disorders.

Correspondence to: P. Bianco

Materials and methods

The iliac crest bone biopsies from seven cases of primary oxalosis on file in our laboratory and the femoral head of a further patient who underwent hip replacement were studied by histology, enzyme cytochemistry and electron microscopy. The age range was between 18 and 37 years. Tissue samples processed for low-temperature glycol methacrylate (GMA) embedding and for electron microscopy were available from each of the seven retrospective cases. Additional samples for microradiography, electron microscopic cytochemistry, and tartrate-resistant acid ATPase (TRATPase) cytochemistry were obtained from the surgically removed femoral head (see below).

Low-temperature GMA embedding was performed as previously described (Bianco et al. 1987, 1988). Semi-thin sections from GMA blocks were used for morphology after staining with May Grunwald Giemsa (Bianco et al. 1987) as well as for enzyme cytochemistry. Samples for electron microscopy were fixed in 4% formaldehyde (freshly made from paraformaldehyde) in 0.1 M phosphate buffer for 2–6 h, post-fixed in osmium tetroxide, dehydrated in ethanol and embedded in araldite. Additional samples from the surgically removed femoral head were routinely processed for paraffin embedding.

Tartrate-resistant acid phosphatase (TRAP) was demonstrated according to a published protocol (Bianco et al. 1988). TRATPase activity was demonstrated using a slightly modified version of a published method (Andersson et al. 1986, 1989; Andersson and Marks 1989). We used GMA sections instead of paraffin sections, an incubation time of 90 min as opposed to 60 min, and 18 mg ATP in the incubation medium, instead of 12.6 mg as in Andersson's protocol. GMA sections were cut from undecalcified tissue blocks, then decalcified by immersion in 2% formic acid for 15 min before performing the cytochemical reaction.

Sections (100 μm thick) of the surgically removed femoral head were prepared using a Leitz circular saw and contact microradiographs were prepared from these sections.

Results

The pathological features of the bone/bone marrow observed in our cases of primary oxalosis were comparable to those previously reported (Fig. 1a). Basically, the noteworthy marrow change was the presence of typical aggregates of elongated, birefringent oxalate crystal, surrounded by a prominent population of giant cells. Bone changes with features of osteomalacia and hyperparathyroidism, resulting from associated renal osteodystrophy, were also present in all cases with varied prominence. Microradiographs were instrumental in revealing the spherical shape of oxalate aggregates, and in showing clearly the altered profile of bone trabecula resulting from increased bone resorption (Fig. 1b, c). Areas in which bone resorption had progressed to a complete effacement of trabecular structure were also apparent.

Both extensive formation of giant cell granulomas and increased osteoclastic bone resorption occur in the same environment in bone oxalosis. We therefore attempted to characterize the two distinct population of multinucleated giant cells (osteoclasts and granuloma cells) by means of enzyme cytochemistry. TRAP activity is highly enriched in osteoclasts, but also present in activated macrophages. TRATPase has been proposed as a specific osteoclastic marker, although it can also be demonstrated immunologically in macrophages. We found an extremely strong TRAP reaction in all the giant cells comprising the oxalate-induced granulomas (Fig. 2b), as well as in the extracellular space. The reaction was so intense that all giant cells were still strongly positive when the incubation time was reduced to 10 min

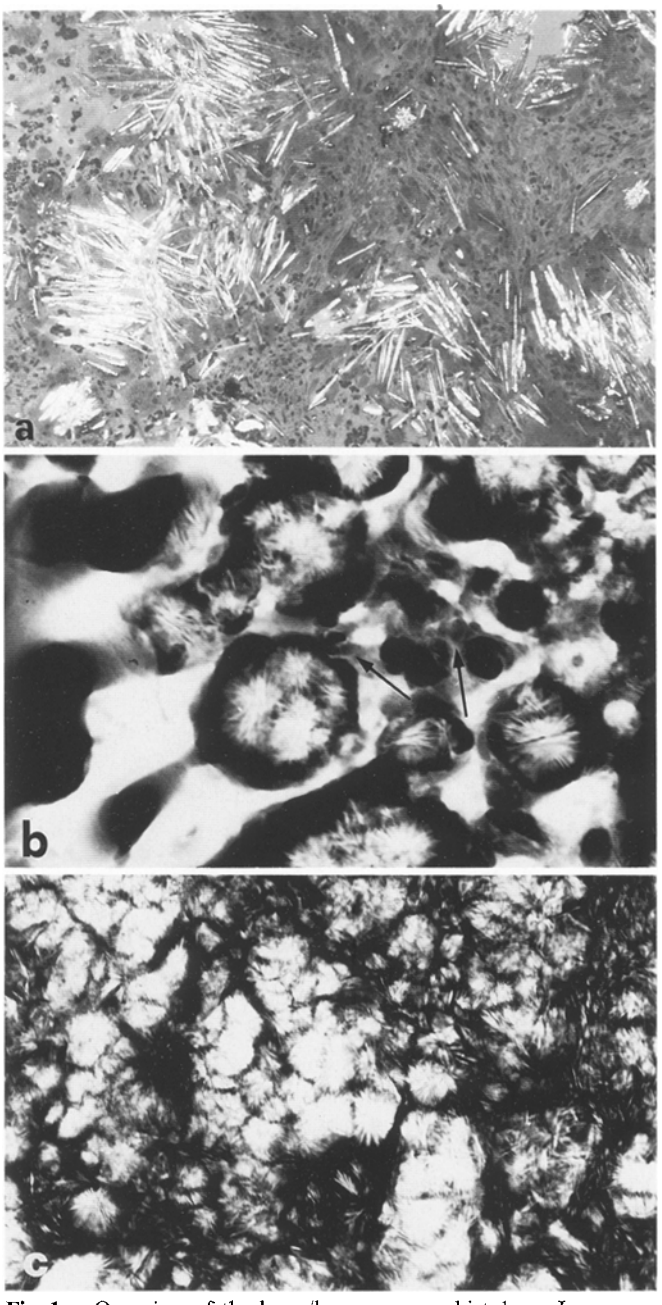

Fig. 1. **a** Overview of the bone/bone marrow histology. Large aggregates of oxalate crystals are obvious, as are the giant cells in the process of engulfing some of them. **b, c** Microradiographic images of the bone/bone marrow organ in the femoral head of a patient with primary oxalosis. **b** Spherical clusters of oxalate crystals are obvious in the marrow spaces. Many clusters are in direct contiguity with bone trabeculae. Note the extensive resorptive processes along the trabecular profile, indicated by many resorption bays (*arrows*), well-illustrated by microradiography. **c** In a distinct area of the femoral head section, bone resorption has progressed to a complete effacement of bone trabeculae. Spherical crystal aggregates are the only X-ray absorbing features. **a, b** × 210; **c** × 100

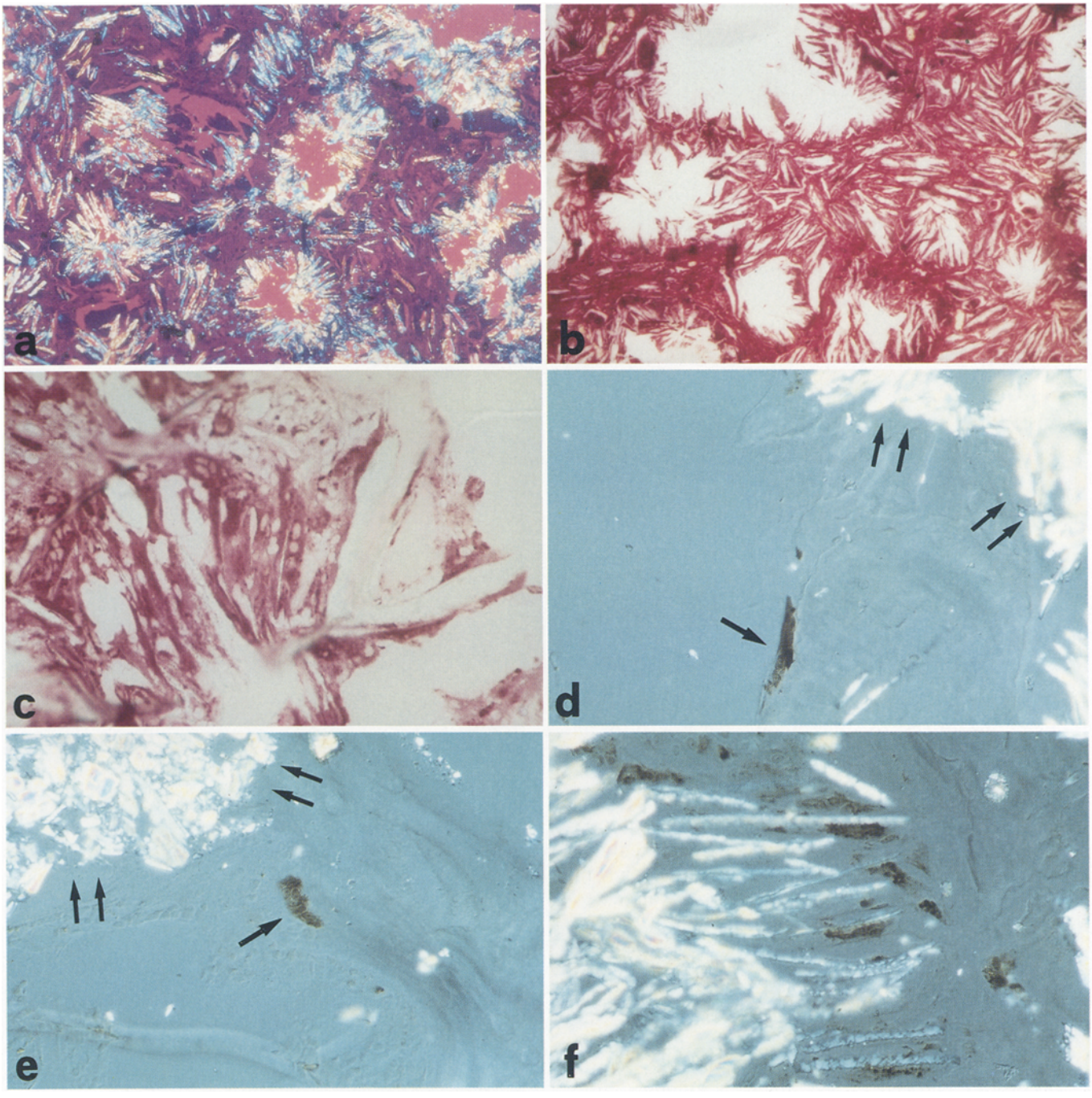

Fig. 2. a Typical appearance of oxalate crystals as seen under polarized light microscopy using a 1/4 lambda plate. **b** Tartrate resistant acid phosphatase (TRAP) reaction on a glycol methacrylate (GMA) section with standard incubation time. The reaction product is abundant all over the microscopic field, i.e. both within giant cells and in the interstitial space. **c** TRAP reaction, incubation time cut down to 10 min. All giant cells are still strongly positive. **d, e** Reaction for tartrate-resistant acid ATPASE (TRATPASE), demineralized GMA section, non-counterstained and viewed with Nomarski optics. Since Nomarski optics employs polarized light, the crystals are readily demonstrated, along with tissue structural features and cytochemical reaction product. Note the positive reaction in osteoclasts (*arrows*), and the absence of reaction product around the crystals (*double arrows*), at variance with the staining pattern of TRAP (compare with **c**). **f** shows, however, that occasional foreign body giant cells do react for TRATPASE. **a, b** × 210; **c–f** × 400

(Fig. 2c), a far shorter time than is required to demonstrate all osteoclasts in GMA sections. In contrast, TRATPase was stronlgy positive in all osteoclasts, and in a low proportion of giant cells. Most granulomas appeared completely devoid of TRATPase (Fig. 2d–e), although typical foreign body giant cells were positive in others (Fig. 2f). Osteoclasts, identified by their consistent TRATPase activity and above all by their location in resorptive lacunae, never contained oxalate crystals.

Microscopic fields with oxalate-induced granulomas

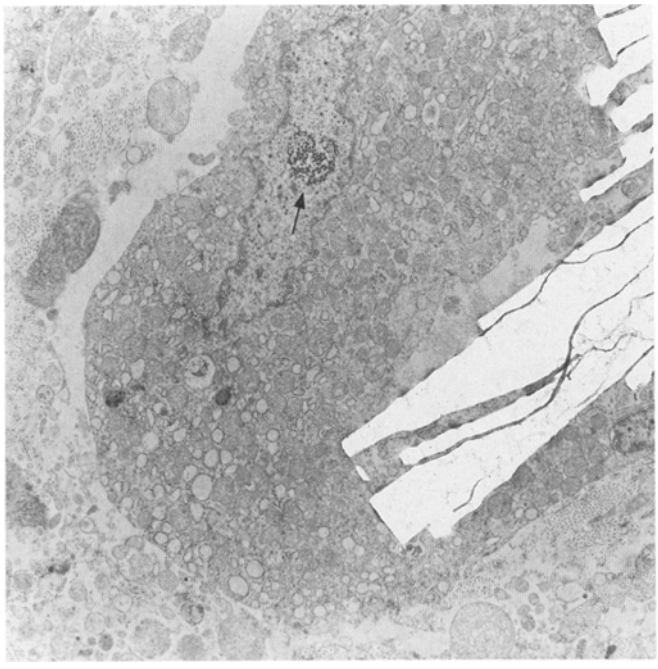

Fig. 3. A giant cell in the process of engulfing oxalate crystals. These appear empty since they sublimate under the electron beam. The nucleus contains virus-like particles admixed with nucleolar-like material (*arrow*; compare with Figs. 4 and 5a). ×6240

but devoid of trabecular bone were selected from semithin sections for electron microscopy. We looked for nuclear inclusions in giant cells proper. One such cell, in the process of engulfing oxalate crystals, is depicted in Fig. 3. Typical paramyxovirus-like inclusions were found in four of eight cases. Figure 4a shows a typical array of virus-like filaments, identical to those repeatedly described in osteoclasts of Paget's disease of bone. In some inclusions, the filaments were admixed with varied proportions of reticular, electron-dense material (Figs. 4b, 5). This material formed the bulk of the nuclear inclusion on occasion, accounted for approximately a half of it on other occasions, and for a minor fraction of the inclusion in other cells. This material was morphologically closely reminiscent of the pars fibrillaris of nucleoli (Figs. 5, 6a). Nuclear inclusions were also on occasion in close topographical association with roundish structures reminiscent of nucleolar fibrillary centres (Fig. 6b).

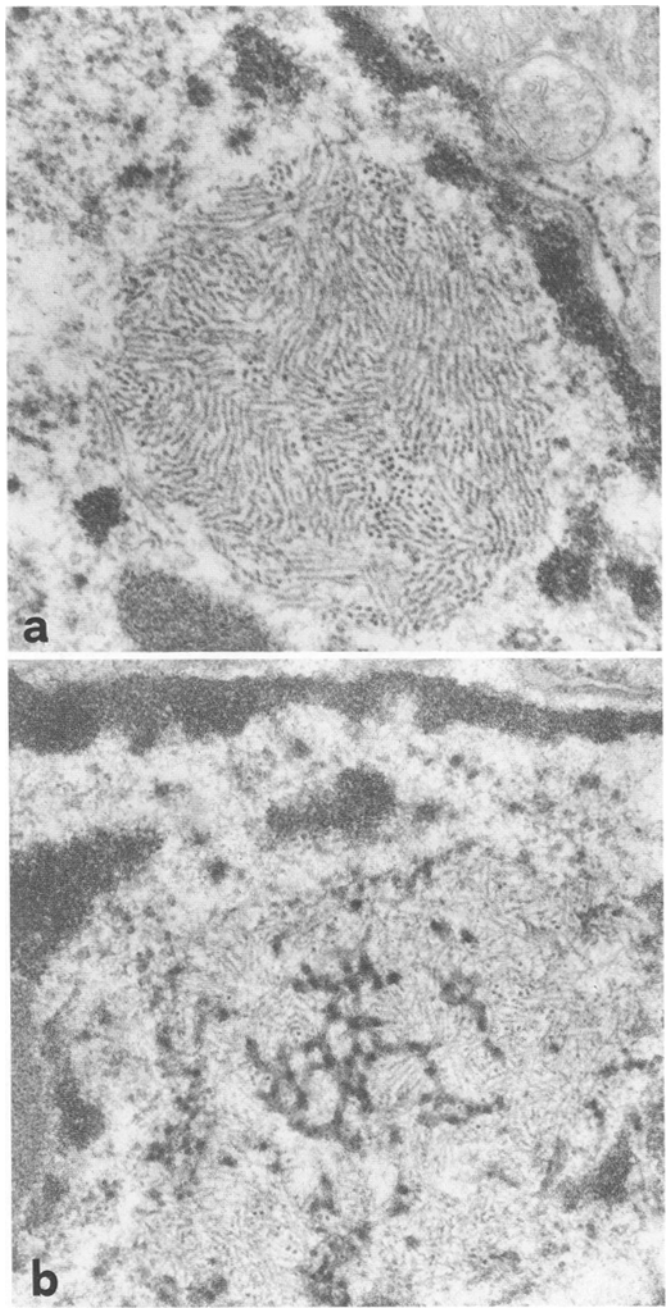

Fig. 4. a Paramyxovirus-like material in the nuclei of giant cells. Detail of a characteristic inclusion, indistinguishable from those described in Paget's disease. **b** A virus-like inclusion composed of typical filamentous material as in **a**, admixed with electron-dense material. **a** ×62400; **b** ×44800

Discussion

Primary oxalosis results from an inborn error of oxalate metabolism, which leads to the extensive deposition of oxalate crystals in the kidney as the first target organ. Renal failure ensues in the natural history of the disease, leading to uraemia. At this stage, deposition of oxalate crystals proceeds in non-renal tissues at an accelerated pace, and the bone/bone marrow organ becomes an important target of oxalate deposition (Hodgkinson and Zarembski 1968; Williams and Lloyds 1972; Chaplin 1977; Gherardi et al. 1980b; Breed et al. 1981; Lagier et al. 1982; Benhamou et al. 1987). Bone disease resulting from uraemia (renal osteodystrophy) is associated with and co-exists with the marrow damage induced by crystal deposition (Gherardi et al. 1980b; Benhamou et al. 1987; Canavese et al. 1990). In the marrow, as in kidney and other organs, the deposition of oxalate crystals elicits the formation of typical giant cell granulomas, commonly viewed as ordinary foreign body granulomas (Gherardi et al. 1980b; Benhamou et al. 1987). We have shown in this study that the giant cells involved

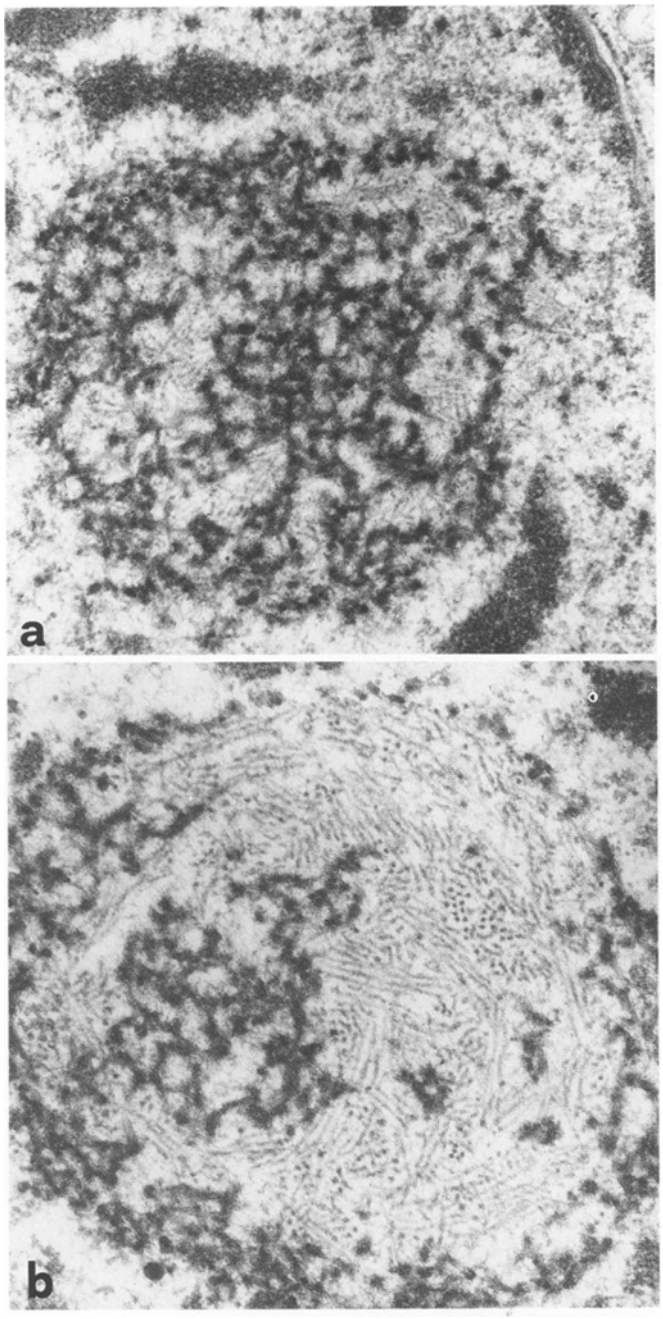

Fig. 5. a, b Variable amounts of filamentous virus-like particles and electron-dense material, reminiscent of nucleolar pars fibrillaris. Compare with Fig. 4b. **a** ×44800; **b** ×62400

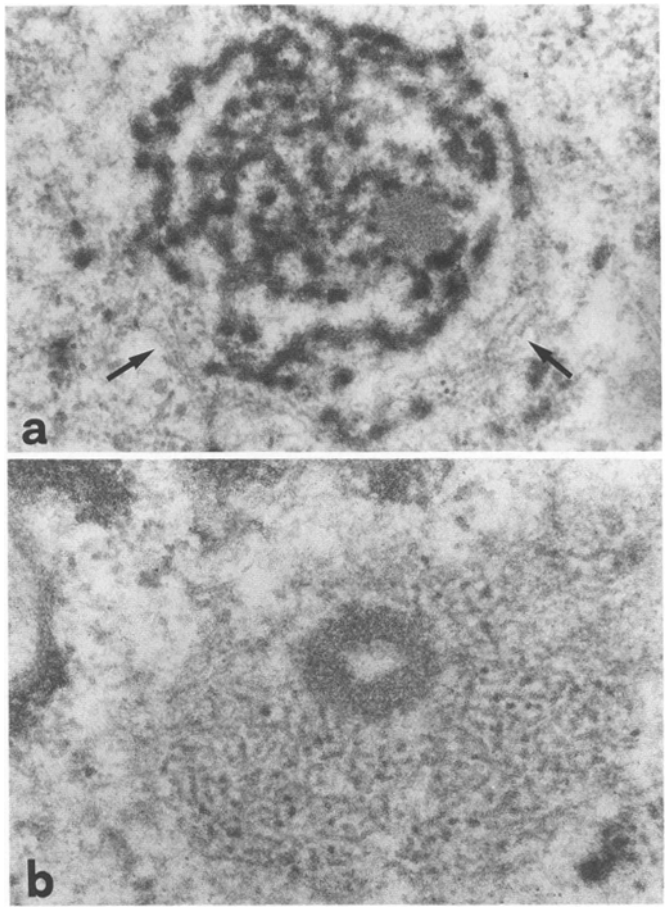

Fig. 6. a A nucleolus of a giant cell, in which a fibrillary centre and the pars fibrillaris are easily identified. Note the occurrence of scattered virus-like filaments in the close vicinity (*arrows*). **b** A cluster of virus-like filaments in close contact with material consistent with a nucleolar fibrillary centre. **a** ×62400; **b** ×83200

in the formation of such marrow granulomas contain nuclear inclusions identical to those described in osteoclasts of Paget's disease of bone (Rebel et al. 1974a, b; Mills and Singer 1976; Gherardi et al. 1980a; Rebel et al. 1980a). The interest of this observation stems from two circumstances. First, the nature of primary oxalosis as an inherited metabolic derangement provides a disease model as far removed from Paget's disease as one can think of. The concurrence of Paget's disease in four of eight young patients with oxalosis is extremely unlikely. Second, previous reports of paramyxovirus-like nuclear inclusions identical to those of Paget's disease in non-Paget bone disorders have all been restricted to typical osteoclasts. In contrast, our nuclear inclusion-bearing giant cells have to be considered as foreign body giant cells, as indicated by their documented phagocytosis of oxalate crystals, and in agreement with the current view of their nature (Gherardi et al. 1980b; Benhamou et al. 1987). Osteoclasts and inflammatory giant cells are two distinct and separate cell types. Both belong to the monocyte-macrophage system, but their lineages diverge early after commitment of the precursor haemopoietic stem cell (Chambers 1985; Nijweide et al. 1986; Nijweide et al. 1990). The presence of abundant TRAP activity in our oxalate-induced giant cells should not mislead us into regarding them as osteoclasts, since the occurrence of TRAP activity in cells other than osteoclasts and especially in activated macrophages is now firmly established (Bianco et al. 1987, 1988). Rather, the occurrence of extremely high levels of TRAP in oxalotic tissue can be taken as a further instance of a non-osteoclast cell type endowed with high levels of the enzyme. One can anticipate from our data that very high levels of serum TRAP unrelated to bone resorption may occur in patients with oxalosis, a notion to be kept in mind

in view of the widespread use of TRAP measurements for assessment of bone turnover.

TRATPase has recently been claimed to represent a more reliable cytochemical marker of osteoclasts (Andersson and Marks 1989). We found that the vast majority of our oxalate-phagocytosing giant cells were negative, whereas all osteoclasts were positive. However, a few giant cells were positive. This can be interpreted in two ways: either a few osteoclasts participate in the formation of oxalate-induced granulomas or TRATPase can in turn be expressed in non-osteoclastic giant cells under certain circumstances. We favour the second explanation for two reasons: firstly, the TRATPase-positive cells were engaged in active crystal phagocytosis, that is to say they behave functionally as inflammatory giant cells; secondly, there is proof that the enzyme can be immunologically detected in macrophages (Andersson et al. 1986), which means that it is actually commonly expressed in such cells, although maybe at levels below the detection threshold of cytochemistry in steady-state, unstimulated macrophages.

The morphology of the virus-like inclusions in our case was clearly superimposable on that of typical pagetic inclusions and deserves little comment in itself. However, the admixture we observed of typical filaments with non-filamentous, electron dense material is worthy of note, since this material is morphologically reminiscent of nucleolar pars fibrillaris. This feature can also be observed in pagetic osteoclasts, although it is less popular in the literature. Although no dynamic interpretation can safely be made from static images, it is worth mentioning how the variable relative proportions of nucleolar-like material and virus-like particles could be depicting a sequence of maturational events in the formation of the nuclear inclusions. The observation of a close association of both components of the inclusion with structures resembling nucleolar fibrillary centres is also worthy of note. Taken together, these observations seem to indicate nucleoli as the potential site of formation of virus-like nuclear inclusions.

If non-osteoclastic giant cells in a non-Paget bone disorder contain virus-like particles indistinguishable from those of Paget's disease, what is the meaning of virus-like inclusion in both Paget and non-Paget bone disorders, and what remains of the "slow virus" hypothesis of the pathogenesis of Paget's disease? Before attempting to answer these questions, the independent lines of evidence for the occurrence of a viral infection in Paget's disease should be mentioned: i.e. the demonstration of paramyxovirus antigens in Paget's osteoclasts (Rebel et al. 1980a; Mills et al. 1981, 1984; Basle et al. 1985; Mills and Singer 1987); the demonstration of paramyxovirus RNA in pagetic bone tissue by in situ hybridization (Basle et al. 1986; Gordon et al. 1991); and the expression of paramyxovirus antigens in cells cultured from pagetic bone (Mills et al. 1980, 1985). These data indicate that viral infection actually takes place in pagetic bone together with the occurrence of virus-like inclusions. However, two facts are important. First, the viral RNA in situ is demonstrated in a variety of mononuclear cells (Basle et al. 1986; Kahn 1990); second, the cells expressing viral antigens in culture are also mononuclear cells (Mills et al. 1985), not osteoclasts. Taken together, these data provide evidence of paramyxovirus infection (viral RNA and viral antigens) in mononuclear cells from the bone/bone marrow organ besides osteoclasts. However, nuclear inclusions have never been demonstrated in mononuclear cells, and are restricted to osteoclasts and to non-osteoclast giant cells, as we have shown here.

Putting together these data with our results, we speculate that the occurrence of paramyxovirus-like inclusions, both in osteoclasts and giant cell, both in Paget's disease and non-Paget disorders, may represent an epiphenomenon of fusion of latently infected precursors, under a variety of conditions, and regardless of any pathogenic involvement of the viral infection in the bone disorders. Due to the widespread prevalence of paramyxovirus infection, mononuclear cells, including precursors of osteoclasts and giant cells, would commonly bear a latent infection. This would result in new bursts of viral replication and the appearance of nuclear inclusion only in the permissive environment provided by giant cells, whatever the nature of the giant cells and the stimuli to their formation.

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