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ORIGINAL ARTICLE

L. Panico · U. Passeretti · N. De Rosa · A. D'Antonio
G. De Rosa

Giant cell reparative granuloma of the distal skeletal bones

A report of five cases with immunohistochemical findings

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Abstract Giant cell reparative granuloma (GCRG) is a reactive bone lesion that most often involves the jaws. However, occasional cases of GCRG in the distal extremities have been reported, to which we add five cases. All the patients were young to middle-aged adults and had sharply bordered, lytic lesions. Histologically, all the lesions had areas of osteoclast-like giant cells and osteoblast mantled osteoid. Two of the cases had foci of osteoclast-like giant cells lining vascular spaces. In extragnathic locations, GCRG may simulate other osteolytic giant cells lesions such as giant cell tumour of bone and aneurysmal bone cyst (AnBC). Immunohistochemically, all cases showed positive staining of the stromal spindle cells for vimentin and actin, and of the osteoclast-like giant cells for CD68, vimentin and leucocyte common antigen. GCRG is a benign lesion and conservative therapy is curative. As GCRG may have histological features which resemble AnBC it may be considered to be the solid variant of AnBC.

Key words Giant cell reparative granuloma
Solid aneurysmal bone cyst · Immunohistochemistry

Introduction

Giant cell reparative granuloma (GCRG) is a reactive bone lesion that usually arises in the jaw [2, 10, 12]. Outside this location, GCRG also has been described in the small tubular bones of the hands and feet [1, 4, 5, 6, 7, 10, 14], where it was initially called "giant cell reaction" [1]. Despite the reported extragnathic cases, this lesion continues to be under-recognized by many pathologists.

The importance of identifying this lesions resides in avoiding the diagnosis of other lesions that can arise in the same sites; namely, giant cell tumour of bone (GCT), sarcomas containing giant cells and aneurysmal bone cyst (AnBC). Whereas a conservative therapeutic approach is curative for GCRG of the distal extremities, it may not be appropriate for other lesions. The pathogenesis of GCRG is unclear. It shows overlapping histological features with the classic and solid variants of AnBC [3, 12, 13], and probably has to be regarded as the solid variant of AnBC. We report five additional cases in which immunohistochemical study of the lesions was performed. The relationship between GCRG and AnBC is discussed.

L. Panico · N. De Rosa · A. D'Antonio · G. De Rosa (✉)
Institute of Pathology, University of Naples, via Sergio Pansini 5, I-80131 Naples, Italy

U. Passeretti
Division of Hand Surgery, University of Naples, Naples, Italy

Materials and methods

Five cases of GCRG of the distal extremities were obtained from the files of the University of Naples. All specimens were formalin-fixed and paraffin embedded. They were stained with haematoxylin and eosin, the haematoxylin-van Gieson method, and periodic acid-Schiff technique with and without diastase predigestion.

Immunohistochemical studies were performed using the avidin-biotin-peroxidase complex procedure (Vectastain ABC Elite, Vector Laboratories) with monoclonal antibodies to actin (Dakopatts, Denmark, 1:50 dilution), vimentin (Dakopatts, 1:25 dilution), leucocyte common antigen (LCA; Dakopatts, 1:200 dilution), CD68 (Dakopatts, 1:100 dilution) and polyclonal antibody to α_1-antitrypsin (AAT; Dakopatts, 1:50 dilution). Positive controls were represented by sections of archival tissue known to contain the determinants of interest; all study cases were labelled with ABC after substitution of nonimmune mouse ascites fluid for primary antibodies. The latter preparations served as negative controls.

Results

The clinical features are summarised in Table 1. Three of the patients with GCRG were male and two were female. All were young to middle-aged adults (range 16–41 years) and had normal serum levels of calcium, phosphorus and alkaline phosphatase. Three of the lesions arose in the foot and two occurred in the hand. Two GCRG were resected completely (cases 1 and 5), followed by disease-free survivals of 30 and 65 months respectively.

Table 1 Clinical findings and follow-up of giant cell reparative granuloma (*FOD* free of disease)

Case	Age (years)	Sex	Site	Therapy	Follow-up
1	41	Male	Left 5th metacarpal	Resection	FOD; 65 months
2	16	Male	Left 1st hand phalanx	Curettage	Recurrence; 8 months
				Recurettage	FOD; 27 months
3	17	Male	Right 2nd metatarsal	Curettage	FOD; 33 months
4	31	Female	Right 1st metatarsal	Curettage	FOD; 32 months
5	34	Female	Right 1st foot phalanx	Resection	FOD; 30 months

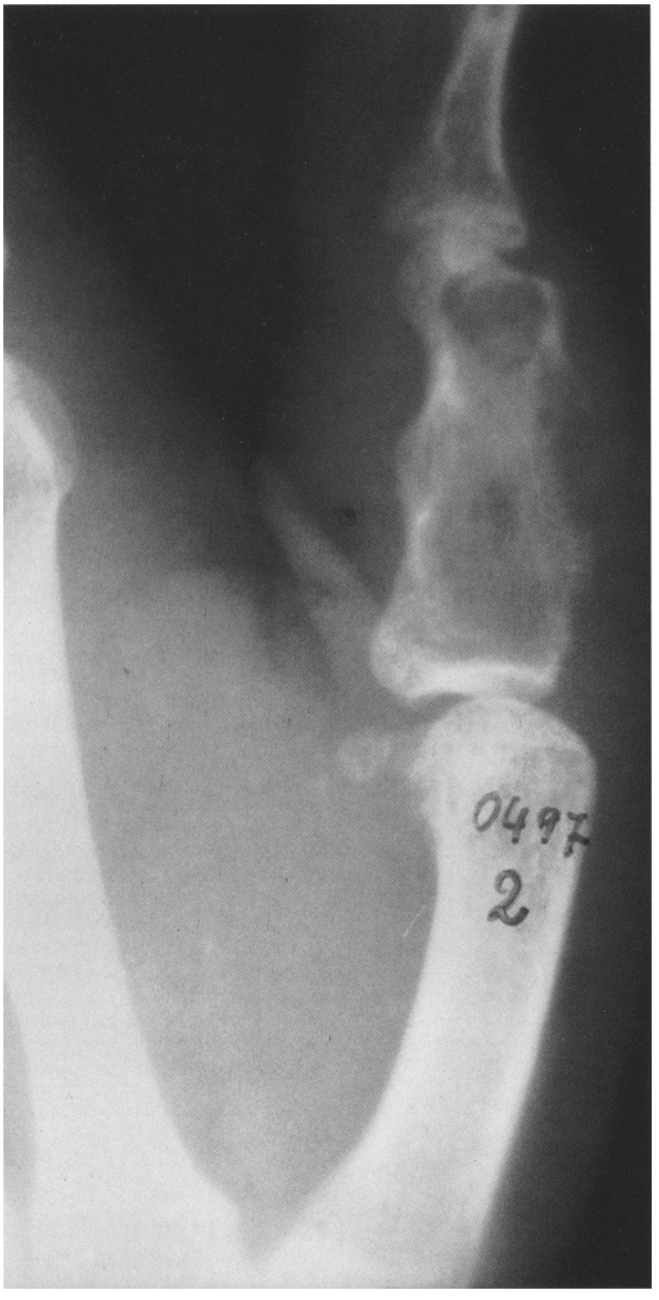


Fig. 1 Roentgenogram, case 2. Sharply circumscribed, wide, osteolytic defect in the left first hand phalanx. The cortex is thinned and interrupted, with incomplete periosteal reaction on the dorsal surface. The osteolytic defect shares internal septation

The other three lesions were treated with curettage. Two of the latter three patients (cases 3 and 4) were free of disease 33 and 32 months after therapy respective. The third individual (case 2) developed a recurrence 8 months after the initial curettage. He was again treated with this procedure and has remained disease-free subsequently for 27 months.

All of the lesions were rounded osteolytic defects on radiography with sharp borders (Fig. 1). There was expansion of the affected bones in cases 1 and 2. The overlying bony cortex was thinned in cases 1, 2 and 5. Cortical interruption was observed in cases 1 and 2, with an incomplete thin rim on the dorsal surface of the lesion. In addition, case 2 had an internally multiloculated radiographic appearance. No intralesional calcifications nor pathological fractures were observed.

The curettage specimens in cases 2, 3 and 4 were grey to white with areas of haemorrhage. Surgical resection in cases 1 and 5 yielded well-circumscribed, white, firm, focally-haemorrhagic lesions that did not involve contiguous articular cartilage.

Microscopically, all of the lesions had a fibrous stroma containing numerous, focally aggregated, osteoclast-like giant cells and foci wherein osteoblasts mantled osteoid trabecula (Fig. 2). The multinucleated osteclast-like giant cells contained bland, oval nuclei with small nucleoli. In cases 2 and 5 they lined irregular, aneurysmal-like, vascular spaces (Fig. 3). Mitotic figures were rare, averaging 1 per 10 high power (×400) fields. Necrosis was not observed.

The lesional matrix contained areas of haemorrhage in all cases and was composed of bland to slightly hyperchromatic spindle cells with minimal to moderate amounts of amphophilic cytoplasm. They were arranged in a storiform pattern in cases 1 and 3 (Fig. 4a). Cases 2 and 5 demonstrated the presence of myxoid matrical changes (Fig. 4b). Three lesions (cases 2, 4 and 5) contained foci of lymphocytic inflammation within the stroma.

Immunohistochemical studies were performed on four specimens from three cases (cases 1, 2, 4 and the recurrence specimen). In all cases the antibody to vimentin stained the spindled stromal and osteoclast-like giant cells strongly and diffusely (Fig. 5a). The fusiform cells were also labelled with antibodies to actin, whereas the osteoclast-like giant cells were negative for this reagent (Fig. 5b). In all cases the giant cells showed a strong, cy-

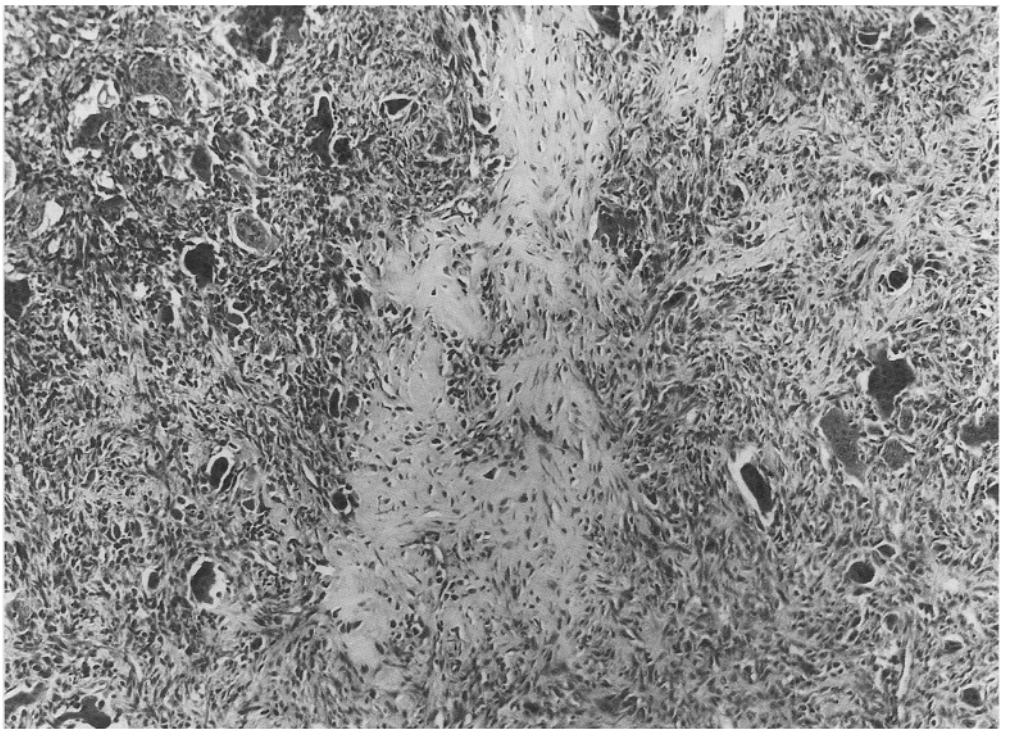


Fig. 2 Trabecula of osteoblastic rimmed osteoid and clusters of osteoclast-like giant cells. Case 2 first curettage; haematoxylin and eosin, ×106

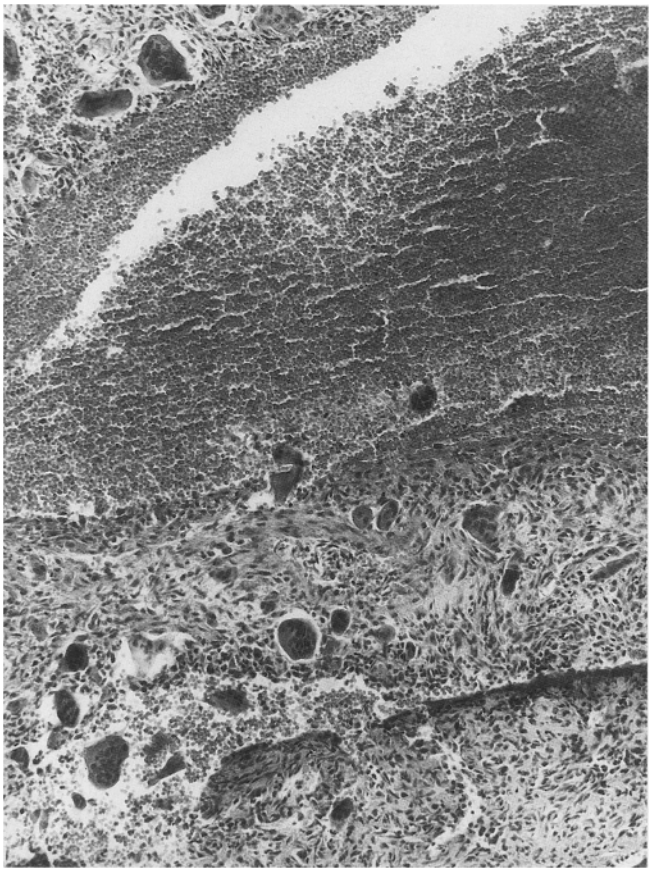


Fig. 3 Aneurysmal-like, blood filled vascular spaces lined by osteoclast-like giant cells. Case 2 recurrence; haematoxylin and eosin, ×106

toplasmic, positive stain for CD68 (Fig. 5c) and a strong membrane stain for LCA (Fig. 5d). The spindle cells did not react with these markers; however, an occasional stain was detectable, for CD68, in mononuclear dendritic reticular cells. In the recurrence specimen a weak positive stain was observed for AAT in the osteoclast-like giant cells, but not in the stromal spindle cells. All negative and positive controls stained appropriately.

Discussion

The initial description of GCRG in the small tubular bones of the hands or feet appeared in the first edition of the Armed Forces Institute of Pathology bone tumor fascicle [1]. Occasional additional reports, comprised of either single cases or small series have followed [4, 5, 6, 7]. The largest studies were those by Wold et al. [14], consisting of 30 cases; 27 of which were seen in consultation, and by Ratner and Dorfman [10] consisting of 20 cases diagnosed between 1966 and 1987, attesting to the relative rarity of GCRG in this site.

The correct diagnosis of this lesion is important because a conservative approach is sufficient, even in cases that recur. This premise is supported by treatment results in case 2 in this series and by other reports [2, 5, 10, 14]. The clinical and radiological features of GCRG are relatively nonspecific. Other lesions that may simulate it radiographically and histologically include the "brown tumours" of hyperparathyroidism [4, 5, 6, 7, 10], sarcomas that contain numerous osteoclast-like giant cells, GCT and AnBC [2, 4, 5, 10, 14]. Lesions of hyperparathyroid osteopathy may con-

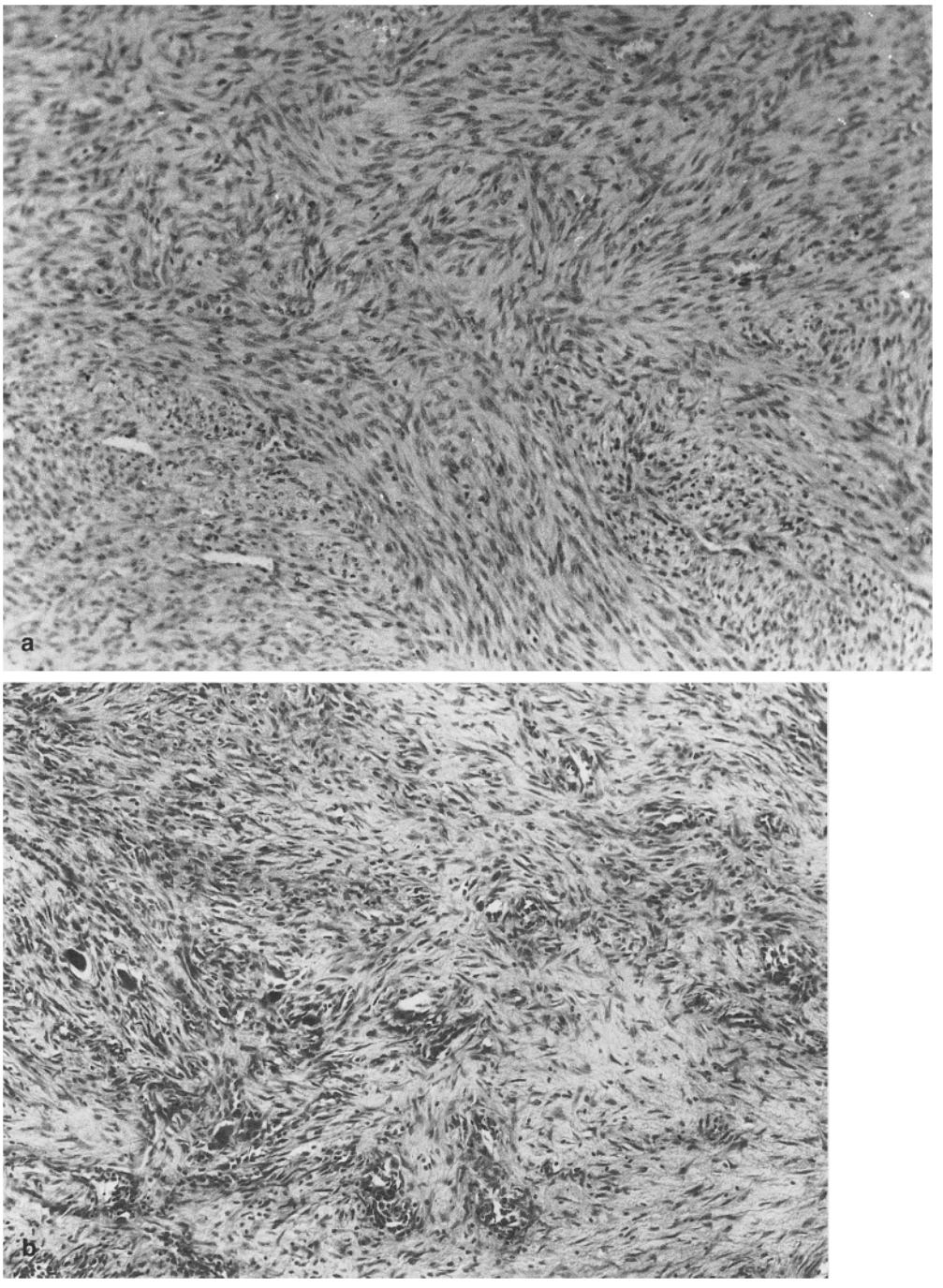
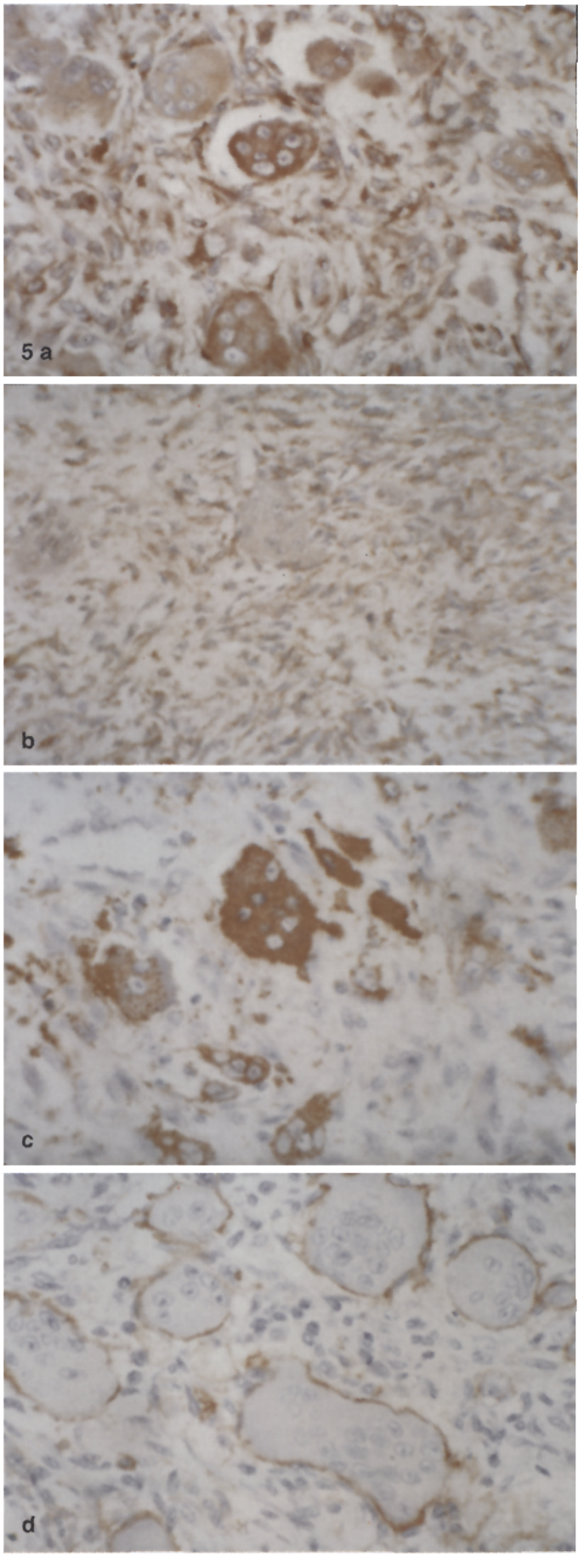


Fig. 4 a Cellular fascicles of spindle cells forming a storiform pattern. Case 1; haematoxylin and eosin, ×106. **b** Storiform pattern of spindle cells with a myxoid stroma. Case 5; haematoxylin and eosin, ×106

tain areas that are identical to GCT and GCRG; however, they are always accompanied by elevations in the levels of serum calcium, phosphorus and alkaline phosphatase. The absence of cytological atypia and radiographic circumscription are the primary criteria which distinguish GCRG from sarcomas. Microscopically, GCRG must also be separated from other benign, giant cell-containing, bone lesions; namely, nonossifying fibroma (NOF), fibrous dysplasia, osteoblastoma, chondroblastoma and chondromyxoid fibroma [6]. Aside from having occasional foci featuring the presence of osteoclast-like giant cells, all of the latter four lesions have other distinctive histological features that separate them from GCRG [6]. The differential diagnosis of NOF is probably not justified. NOF usually involves long bones, but can also affect the jaw bones, especially in patients with the Jaffe-Campanacci syndrome [9]. The radiological differences between NOF and GCRG are apparent, because the distinctive longitudinal appearance of NOF, in its long bone locations, is due to lesional growth modelling from the affected bone: this feature is absent in NOF of the jaw, which show a rounded shape, like GCRG [9]. The histological features of NOF are indis-



tinguishable from GCRG, even though the former, in its late phase, more frequently shares foam cells [9]. It is likely that these two lesions are only two definitions of the same entity [9].

As stated above, the major differential diagnostic alternatives to GCRG of the small tubular bones of the hands and feet are GCT and AnBC [2, 4, 5, 10, 14]. GCT has been reported in the distal extremities albeit rarely [2, 4, 10, 14]. In these instances, the distinction between this neoplasm and GCRG could be difficult both radiologically [5, 10, 14] and histologically [2, 4, 5, 10, 14]. Microscopically, GCRG lacks foci of necrosis [2], has more fibrous stroma [2, 4, 5, 10] when compared with GCT, has clustered rather than dispersed osteoclast-like giant cells [2, 5, 10, 14] and shows foci wherein there is osteoblastic rimming of trabecular osteoid [2, 5, 6, 10, 14].

AnBC preferentially involves the long tubular bones [3, 8, 11, 13]. Its solid variant was initially described in the vertebrae and periorbital bones [12] and subsequently has been reported also in the sites in which the classic AnBC is encountered [3, 13]. The overall incidence of the solid AnBC is, however, quite low, amounting to 15 of 200 cases of aneurysmal bone cyst (7.5%) in the series reported by Bertoni et al. [3] and to approximately 5% (8/163) of the cases described by Vergel De Dios et al. [13]. Histologically GCRG and solid and classic AnBC have many identical features. Indeed, small biopsies of GCRG could be easily mistaken for classic AnBC because of the presence of blood filled, cystic, vascular spaces. These may be separated by thin fibrous septa which contain foci of osteoclast-like giant cells, foamy histiocytes and stromal haemorrhage. Therefore, it is not unreasonable to regard these lesions as morphologically related, with only quantitative histological differences, or as the same entity with distinct definitions in the different anatomic sites of origin. These overlapping microscopic features may lead one to suggest a common histogenesis. AnBC and its variants are currently viewed as reactive processes featuring intraosseous haemorrhage [4, 5, 6, 7, 8, 10, 11], resembling the changes seen in areas of fracture callous formation [6, 14]. The aetiology of such haemorrhage is unclear [4, 6, 8, 11, 14]; local haemodynamic changes, possibly due to other coexisting bone lesions [6, 8, 11], may produce the haemorrhage and, then, the osteoclastic "reparative" reaction that is typical of all three lesions. Our immunohistochemical findings seem to confirm the reactive nature of GCRG, because the expression of both vimentin and actin in the stromal spindle cells can be considered to be a marker of myofibroblastic phenotype. Such a lesion, then, has to be regarded as reactive, just like AnBC. The quantitative histological differences of the solid and cystic compo-

Fig. 5 a Positivity in both spindle cells and osteoclast-like giant cells for vimentin. Immunoperoxidase, ×400. **b** Positivity of the spindle cells for actin. Immunoperoxidase, ×400. **c** Osteoclast-like giant cells show cytoplasmic stain to CD68. Immunoperoxidase, ×400. **d** Membrane stain of the osteoclast-like giant cells for leucocyte common antigen. Immunoperoxidase, ×400

nents of the afore-mentioned specific entities could be attributed to undefined local factors that control cellular maturation and the intensity of the proliferative reaction.

Alternatively, one might view GCRG, solid AnBC and classic AnBC as distinct points in a developmental continuum. Any given lesion may originate as a solid fibrohistiocytic/myofibroblastic proliferation, but because of a persistently altered haemodynamic environment, evolve into a classic AnBC. Preferential sites of origin for these lesions would be considered artificial in this context, because a lesion located in the craniofacial area, or in the small bones of the hands or feet, could probably be diagnosed at an earlier stage of the postulated histological spectrum, before evolution to fully-developed AnBC had occurred. Conversely, AnBC is more common in the long bones of the limbs [3, 8, 11, 13], where it conceivably could elude diagnosis until the later stage of the presumed maturation process. This hypothesis could explain a low incidence of AnBC in bones where solid reparative proliferations (GCRG-solid AnBC) are observed frequently.

Further characterization of these lesions, especially with regard, to their interrelationship, local growth and maturation will be necessary before their pathogenesis is determined.

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