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Ultrastructural Evidence of Myofibroblasts in Pseudomalignant Myositis Ossificans

C. Povýšil[1] and Z. Matějovský[2]

[1] 2nd Institute of Pathology (Head: Prof. Dr. J. Dobiáš, DrSc.) and
[2] 1st Clinic of Orthopaedic Surgery (Head: Doc. Dr. E. Eis, CSc.),
Faculty of General Medicine, Charles' University, Prague, Czechoslovakia

Summary. Seven cases of pseudomalignant ossifying myositis with a typical clinical symptomatology have been reported. None of the cases had experienced an injury. All the lesions were intramuscular and all of them showed a zonal arrangement. Electron microscopy in three cases allowed the demonstration of cells showing morphological features of myofibroblasts and monocytic cells of the macrophage type. These previously unreported features together with the zonal pattern of the lesions indicate their reparative nature.

Key words: Pseudomalignant ossifying myositis – Ultrastructure – Myofibroblasts – Macrophages – Pathogenesis.

Introduction

Pseudomalignant ossifying myositis is a non-neoplastic osteoplastic lesion affecting soft tissues (Ackerman, 1958). Previous reports have concentrated on the clinical symptomatology and histological diagnosis (Angervall et al., 1969; Gilmer et al., 1959; Lagier et al., 1975; Paterson, 1970; Rosemeyer, 1972), and ultrastructural observations on only one case have been published (Caulet et al., 1969). In view of this we thought it useful to report the electron microscopic findings obtained in 3 of the 7 cases of our series. In the central cellular areas of pseudomalignant ossifying myositis we identified cells identical with the myofibroblasts of granulation tissue which have apparently not been previously described in this connection. Despite the fact that this new finding does not explain the histogenesis of pseudomalignant ossifying myositis, it might indicate (together with the finding of macrophages and the typical stratified pattern) its relation to reparative processes.

For offprints contact: Dr. C. Povýšil, IInd Department of Pathology, Charles' University, Prague 2, U nemocnice 4, Czechoslovakia

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Material and Method

In all cases the tissue obtained by surgical excision was fixed in 10% neutral formalin for the purpose of routine histological examination. Samples from the peripheral, and the central areas were excised from larger lesions and, after decalcification they were embedded in paraffin. Smaller lesions were processed in toto in a similar way. Histological sections were stained with haematoxylin and eosin, Masson's trichrome, and impregnated for the demonstration of reticulin fibres according to Gomori.

Tissue samples for electron microscopy were obtained at operation in cases No. 3 to 5, fixed in glutaraldehyde and processed as reported in our previous paper (Povýšil et al., 1977). Semithin as well as ultrathin sections were obtained in a similar way. The sections were examined under a Tesla BS 500 electron microscope.

Clinical Data

The series presented here comprises 4 males and 3 females aged 11 to 65 years. In three patients the lesion was located in the muscles of the upper extremities, in four the site of the lesion were the lower extremities (Table 1). No history of injury or other complaint preceding the development of the lesion proper had been recorded. In all cases the presenting sign was spontaneous pain in the appropriate area followed by diffuse swelling within a few weeks. Later a smaller, very firm mass was noted at the same site. With the regression of oedema the pain became milder. Roentgenologically, no changes were visible during the early stages of the disease. In contrast, ovoid, incompletely ossified areas, unassociated with bone, were observed in the soft tissues of all the cases during the subsequent stages. There was negligible ossification in the central areas of the lesions. Patient No. 3 was subjected to a repeated X-ray examinations during the period of 6 weeks. Bone formation was seen to proceed from the periphery to the centre of the lesion. Patient No. 7 had been admitted because of intractable pain. Two weeks after the onset of this disease no changes were seen on the X-ray films of the affected area. Ten days later, however, there was a clearly ossified focus within m. gluteus medius.

In all the cases the lesions were removed in toto. The largest of them measured $7 \times 5 \times 4$ cm. The only exception was patient No. 3, in whom a biopsy specimen was taken at the stage of incomplete ossification for the purpose of differential diagnosis, and the rest of the lesion was removed 14 days later. At present all the patients are in good health, with a complete recovery of the function of the affected limb.

Table 1. Clinical data of 7 patients with pseudomalignant myositis ossificans

Case	Name	Sex	Age	Localisation	Anamnesis in months	Fever	Pain	Size (cm)	Follow-up in years	ELMI
1	V.S.	F	11	Vastus lat.	3	+	+	$4 \times 3 \times 3$	20	−
2	M.R.	F	56	Flex. carpi rad.	2	−	+	$6 \times 4 \times 4$	10	−
3	J.K.	M	12	Rectus fem.	2	+	+	$7 \times 5 \times 4$	2	+
4	M.S.	M	21	Quadriceps fem.	2	+	+	$3{,}5 \times 2 \times 2$	2	+
5	F.K.	M	65	Brachioradialis	4	−	+	$3 \times 2 \times 1{,}5$	1	+
6	N.H.	F	40	Flex. carpi rad.	3	−	+	$3 \times 2 \times 1$	0,45	−
7	S.J.	M	14	Glutaeus medius	1	+	+	$3 \times 2{,}5 \times 2$	0,5	−

ELMI- Electron microscopic examination

Results

Histological Examination. Five cases (Cases No. 1–3, 5 and 7) showed all the three zones characteristic of pseudomalignant ossifying myositis. The peripheral parts of the lesions were composed of spicules of lamellar bone not infrequently lined by osteoblasts and limiting the whole lesion from the surrounding muscles (Fig. 1). In the intermediate zone there were ribbons of lamellar osteoid with osteoblastic rims (Fig. 2) and, in addition, type 2 osteoid (Fig. 6) of Lagier et al. (1975). There were also densely cellular bands with occasional focal osteoid formation (Fig. 3). In such cases the central parts of the lesions were composed of cellular and vascular connective tissue (Fig. 4) developing in places tiny osteoid islets so that the pattern occasionally resembled that of an osteosarcoma. However, neither conspicuous cellular abnormalities nor mitoses were recorded in our cases. Evidence against the neoplastic nature of the lesions lay in their zonal pattern and the absence of mitoses.

In cases 4 and 6 the major part of the lesions was occupied by osseous tissue, ribbons of osteoid of both types and the previously described cords of cellular tissue. In the centre there were occasional areas of hypocellular, partly hyalinized connective tissue.

The muscles in the immediate neighbourhood of the lesions were frequently atrophic, showing oedema of the interstitium and round cell infiltration around the vessels. In case 3 some areas of the muscle were replaced by loose connective tissue of myxoid appearance, wherein occasional atrophic muscle fibres were demonstrated.

Electron Microscopic Examination. The tissues available for electron microscopical studies included those of the intermediate and the central zones only. The ribbons of lamellar osteoid were composed of bundles containing regularly oriented collagen fibrils showing a 640 Å periodicity. At their periphery there were continuous rims of osteoblasts (Figs. 5 and 7) with numerous processes from the cytoplasmic membrane. The cytoplasm of the osteoblasts contained a strongly developed rough endoplasmic reticulum and large aggregates of glycogen particles (Fig. 7) in addition to the organelles usually present.

In the trabeculae of type 2 osteoid (Fig. 6) as well as in the cellular cords (Fig. 3) the most conspicuous findings were dense, elongated or polygonal cells showing a Golgi zone in the vicinity of the nuclei and a striking granular endoplasmic reticulum (Fig. 9). Such cells resembled most preosteoblasts and osteoblasts. Admixed with the dense cells, there were fairly numerous light cells (Figs. 8 and 10) containing abundant free ribosomes, mitochondria, dense bodies of uneven size showing characteristics of phagolysosomes and a moderately developed granular endoplasmic reticulum. At the periphery, their cytoplasmic membrane was undulated to produce tiny digit-like processes. Such elements most frequently resembled monocytes or macrophages of intermediate size, but in other instances they showed features of preosteoclasts (Fig. 11). Multinucleate osteoclasts were fairly frequent within the cords. The intercellular substance consisted of amorphous material of intermediate density with numerous irregu-

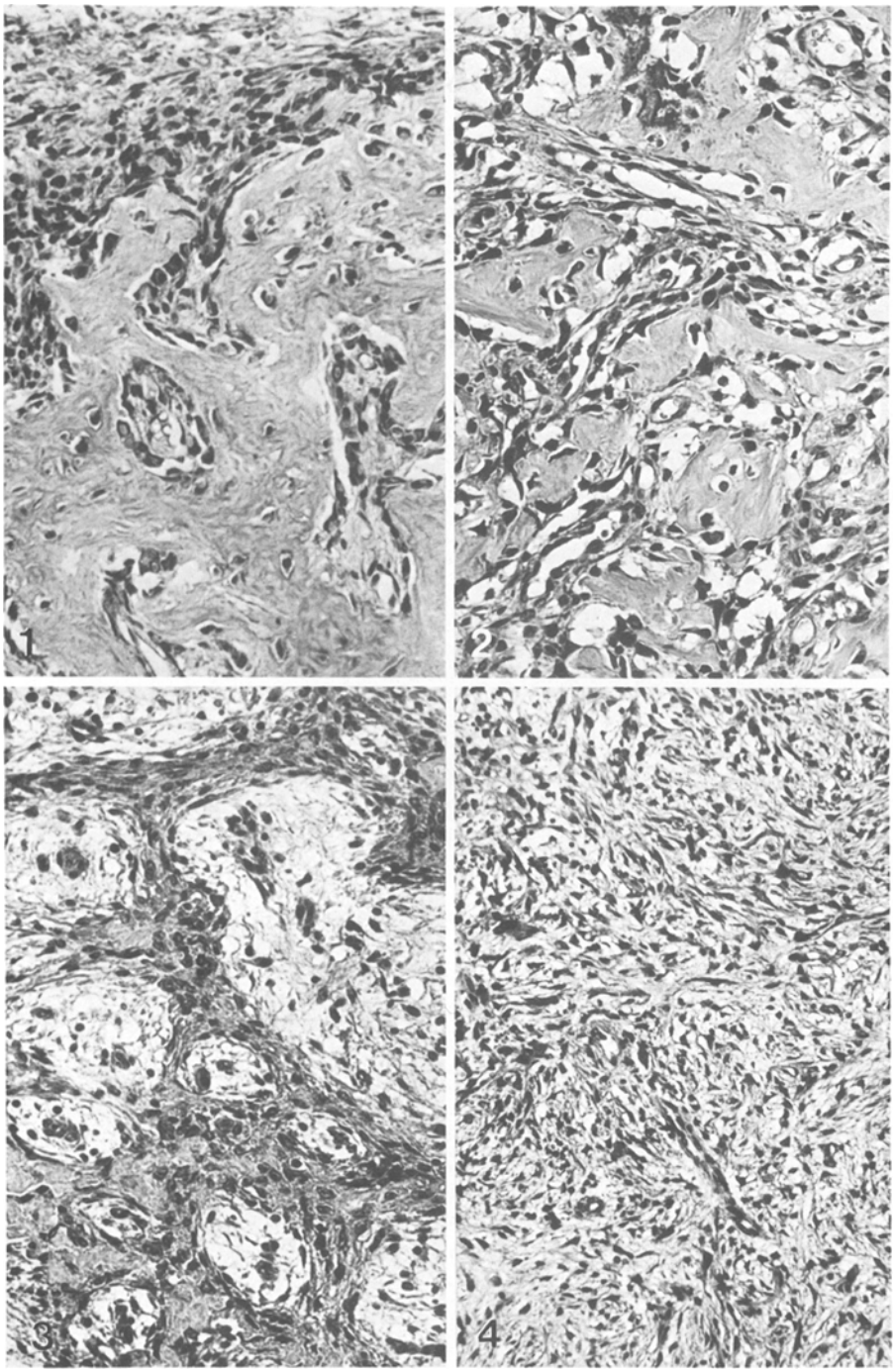


Fig. 1. Peripheral zone of the lesion composed of trabeculae of lamellar bone lined with osteoblasts. Haematoxylin and eosin, ×150

Fig. 2. Intermediate zone comprising ribbons of osteoid with interposed cellular connective tissue. Haematoxylin and eosin, ×150

Fig. 3. Central zone with cellular cords with interposed loose vascular connective tissue. Haematoxylin and eosin, ×150

Fig. 4. Cell-rich vascular connective tissue of the central zone. Haematoxylin and eosin, ×150

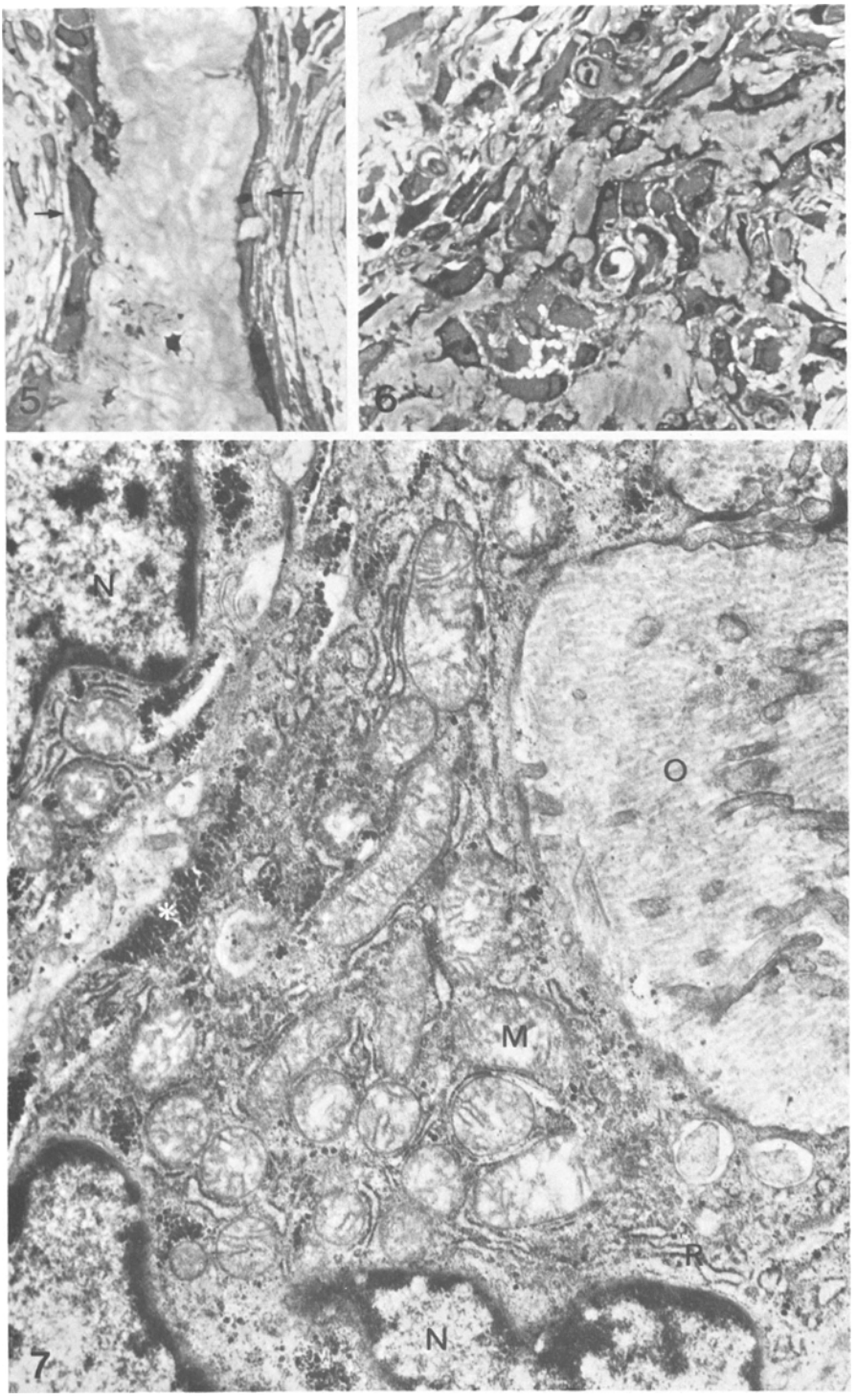


Fig. 5. Osteoid trabeculae with osteoblastic rims (↗). Semithin section, Azur C, ×620

Fig. 6. Lagier's type II osteoid trabecule. Semithin section Azur C, ×620

Fig. 7. An osteoblast at the periphery of an osteoid trabecule (*O*). The cytoplasm contains mitochondria (*M*), granular endoplasmic reticulum (*R*) and small glycogen aggregations (*). *N*-nucleus. ×18,000

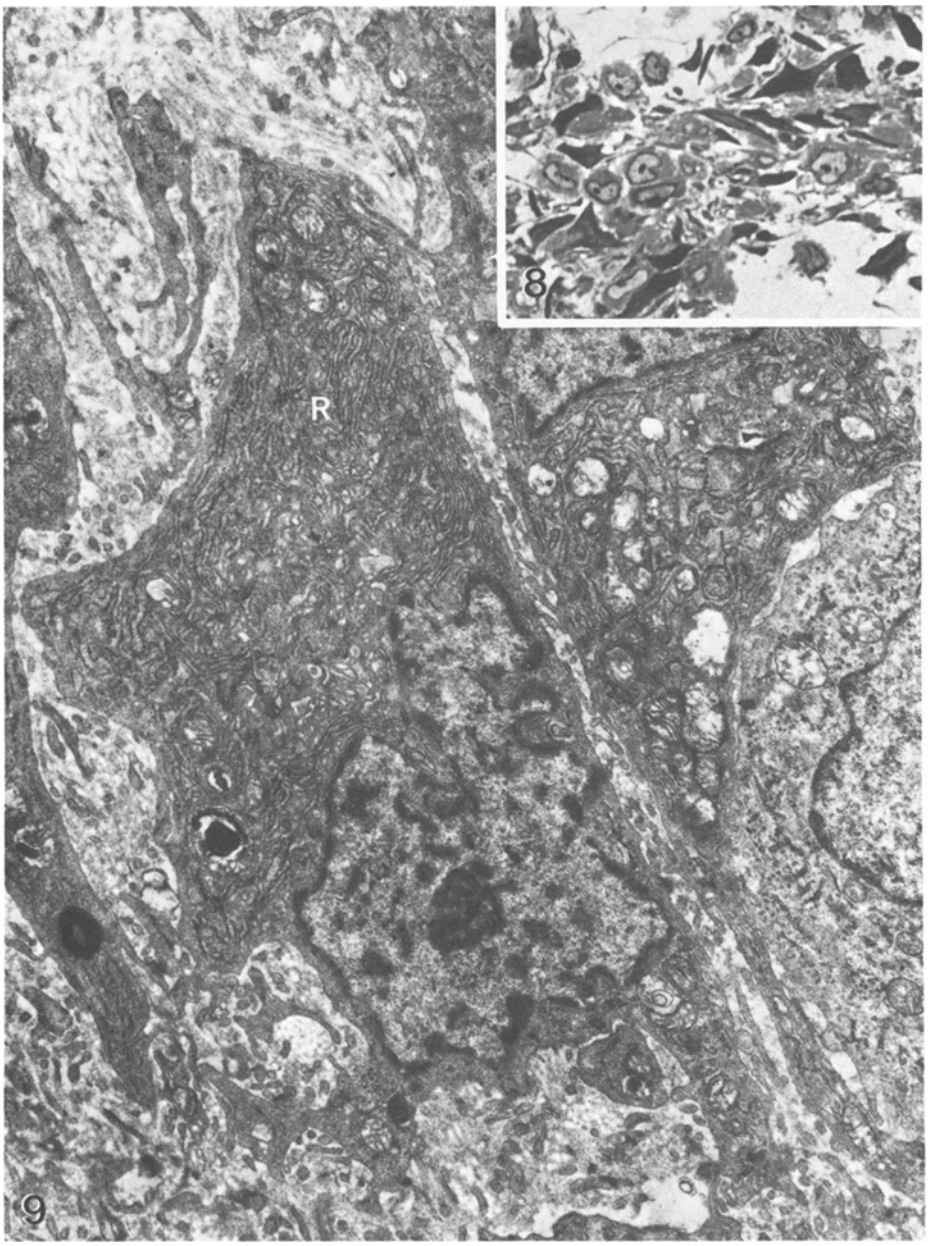
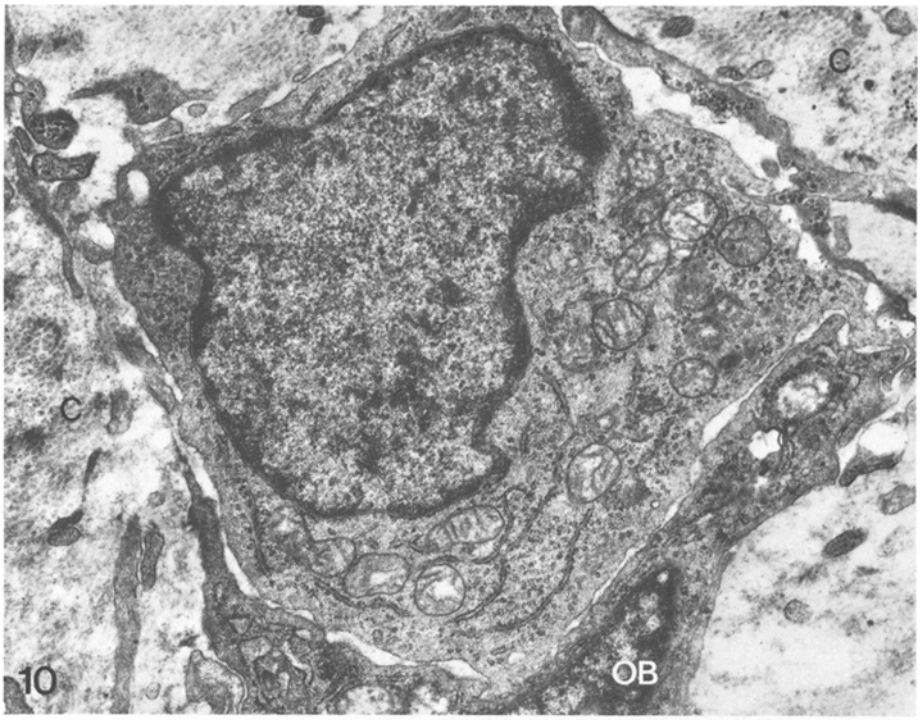


Fig. 8. The so-called cellular cord as visualized in a semithin section. The cord contains dark cells of fibroblastic or osteoblastic type and oval monocytic cells. Azur C, ×620

Fig. 9. Osteoblast-like cells showing a conspicuous granular endoplasmic reticulum (*R*) in one of the so-called cellular cords of the central zone of the lesion. ×16,000



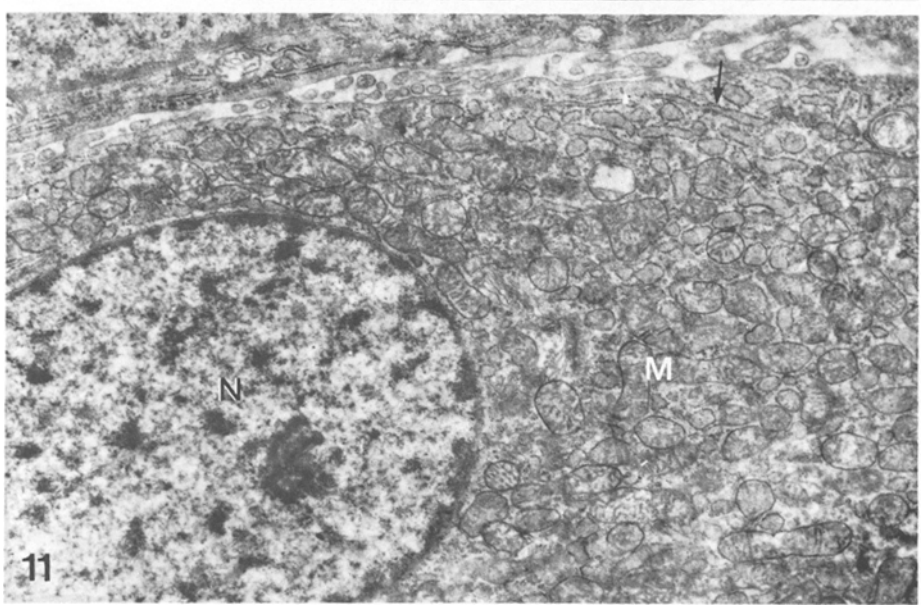


Fig. 10. A smaller monocytic cell of the so-called cellular cord. In its close vicinity there is a part of the body of an osteoblasts (*OB*) and collagen bundles (*C*). ×18,000

Fig. 11. Preosteoclast with numerous mitochondria (*M*), and a granular endoplasmic reticulum (↗). *N*-nucleus. ×13,000

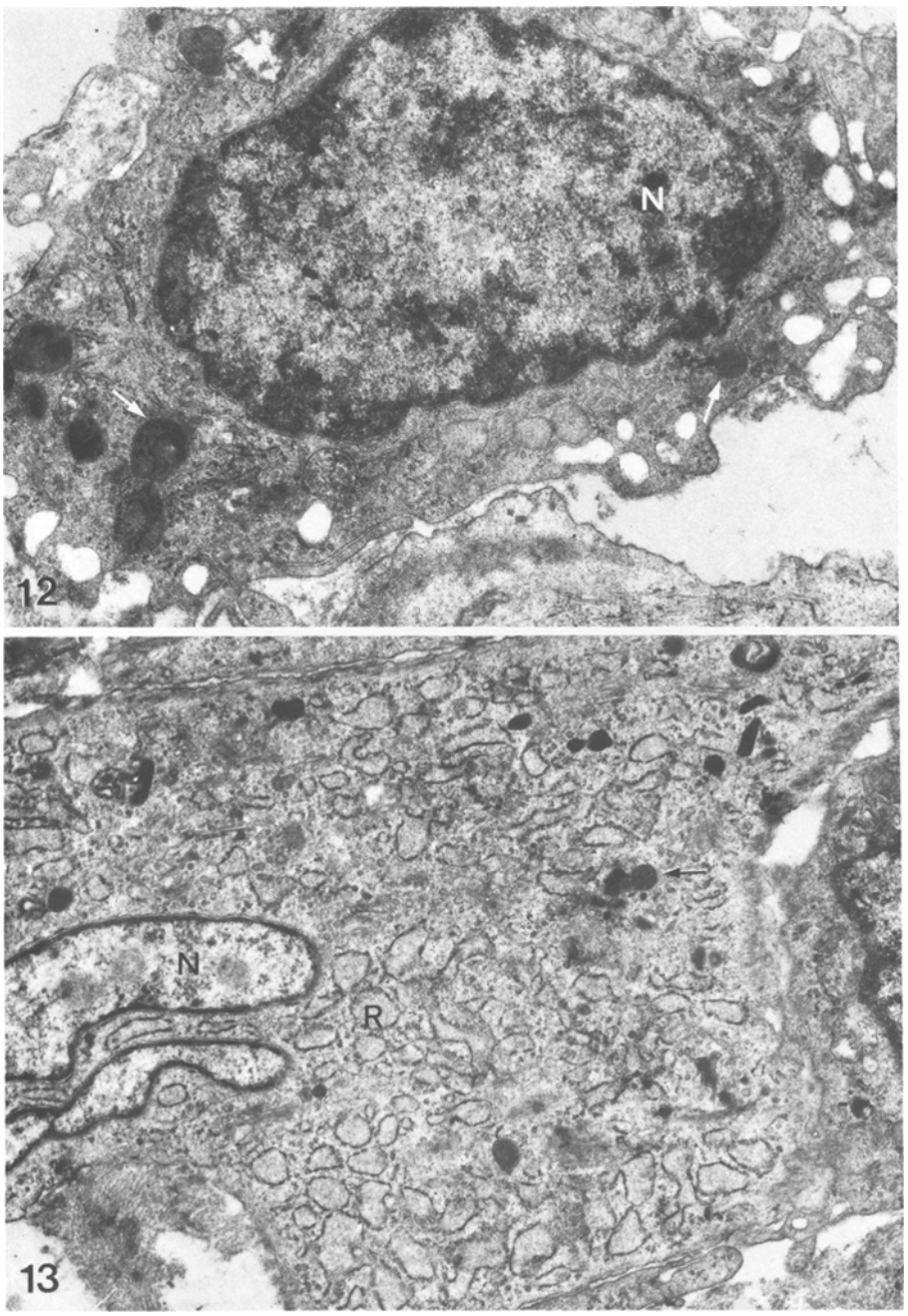


Fig. 12. A macrophage from the cellular tissue of the central zone with phagolysosomes (↗). N-nucleus. ×15,000

Fig. 13. Fibroblast from the central cellular area showing a conspicuous dilatation of the granular endoplasmic reticulum (*R*) and dense bodies (↗). Dilated cisternae of the granular endoplasmic reticulum contain amorphous material of medium density. *N*-nucleus. ×18,000

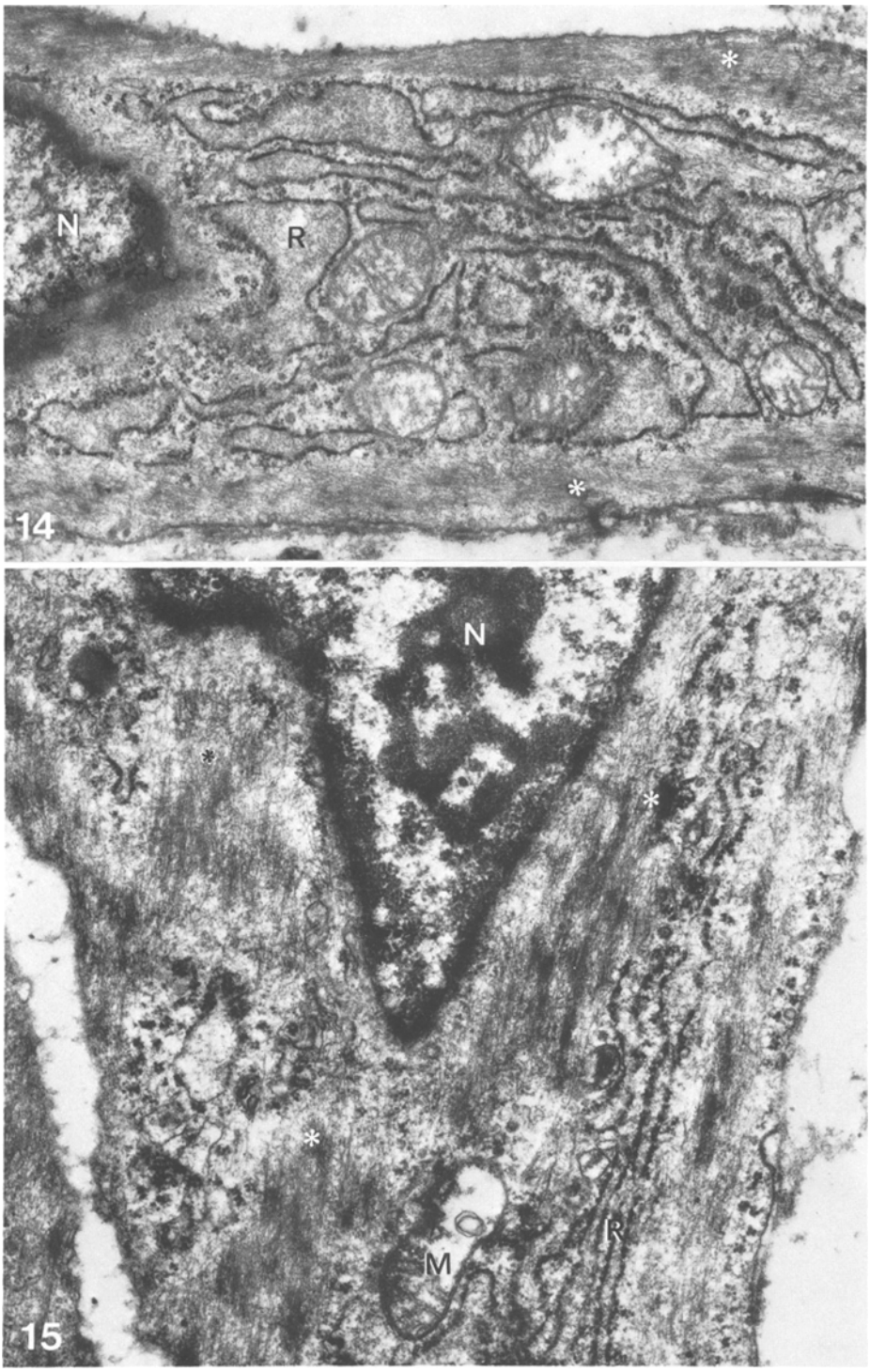


Fig. 14. A myofibroblast of the central zone with a well-developed endoplasmic reticulum (*R*) and bundles of myofilaments (*) paralleling the cytoplasmic membrane. *N*-nucleus. ×24,000

Fig. 15. A myofibroblast of the central zone containing bundles of myofilaments (*) showing occasional dense zones. *R*-granular endoplasmic reticulum, *M*-mitochondrion, *N*-nucleus. ×40,000

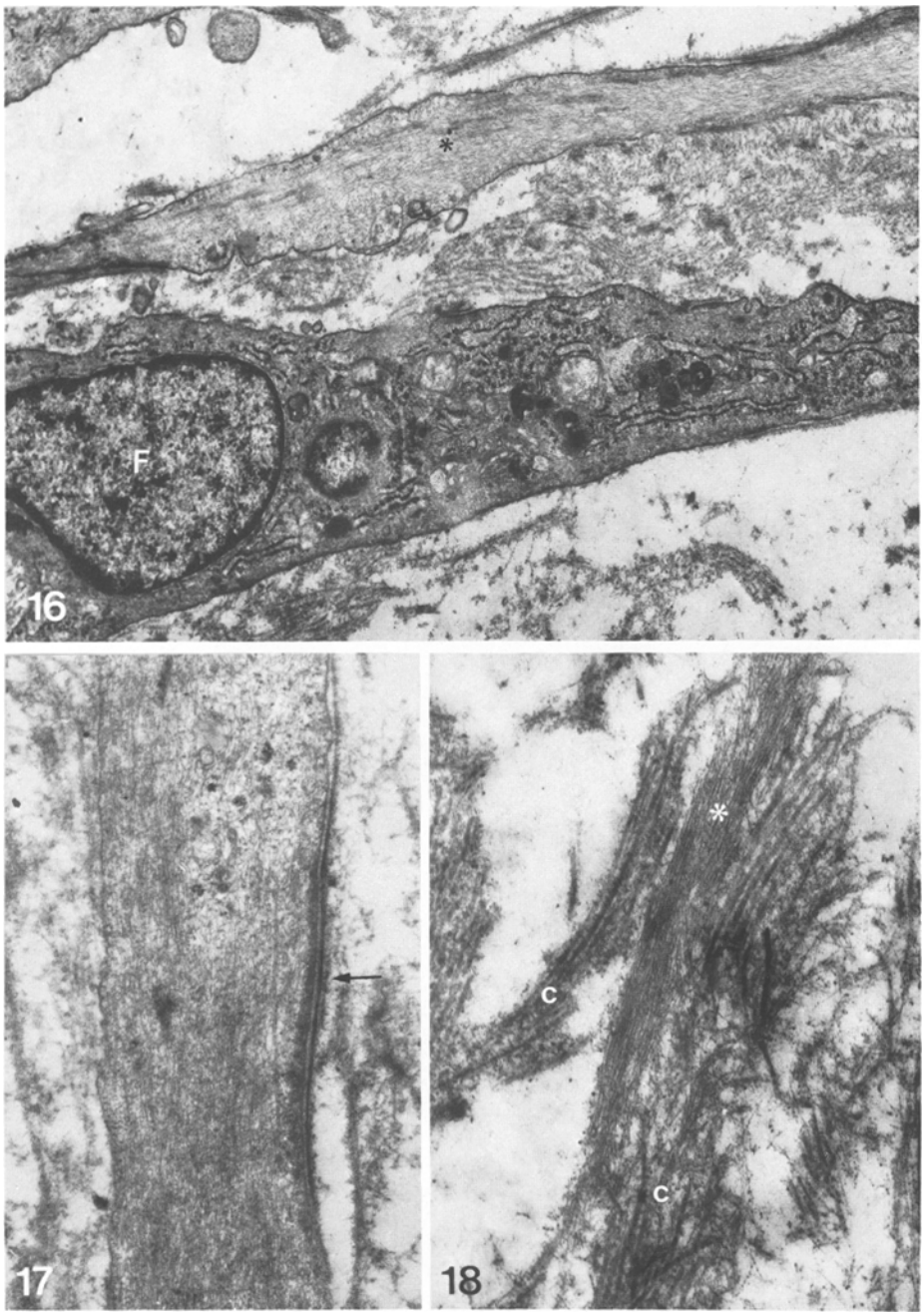


Fig. 16. The central cellular zone. There is a process of a myofibroblast containing myofibrils (*) in the vicinity of a cell showing morphological features of fibroblast (*F*). ×18,000

Fig. 17. A process of a myofibroblast with a basement membrane (↗) in a close proximity to the cytoplasmic membrane. ×24,000

Fig. 18. A bundle of fine microfilaments (*) between immature collagen fibres (*C*) within the intercellular substance of the central core of the lesion. ×30,000

larly oriented collagen-type fibres frequently lacking appreciable periodicity. On other occasions small foci of typical osteoid were found.

Besides ocassional bundles of collagen fibers the loose vascular tissue between the osteoid trabeculae contained monocytic cells. In addition, there were elongated cells interconnected with desmosomes; such cells exhibited some features characteristic of myofibroblasts. Besides a well developed granular endoplasmic reticulum, their cytoplasm contained bundles of fine fibrils similar to those found in the cells of the central zone. No basement membranes were revealed however.

The central cellular area was available for electron microscopy in case 3 only. Besides monocytic cells (Fig. 12), and fibroblasts (Figs. 13 and 16) it contained elongated cells of variable size showing the characteristics of myofibroblasts, with long, narrow cytoplasmic processes (Figs. 14, 15 and 16). Such cells contained ovoid nuclei and, in their cytoplasm, granular endoplasmic reticulum, bundles of microfilaments, single lipid droplets and dense bodies (Figs. 14, 15 and 16). The bundles or myofibrils were most frequently found in close proximity to the cytoplasmic membrane (Fig. 14), which occasionally developed pinocytic vacuoles. Less frequently, small groups of such filaments were situated amidst cell organelles (Fig. 15). In some instances darker zones could be identified in the bundles (Fig. 15). In the close vicinity of the cytoplasmic membrane of such cells, interconnected with rare desmosomes, a slight formation of the basement membrane was frequently demonstrated (Fig. 17). Intercellular spaces contained amorphous material of intermediate density and tiny bundles of immature collagen fibres and groups of fine fibrils (Fig. 18). Capillaries with a well developed basement membrane were rather frequent and showed no abnormalities.

Discussion

All the cases presented fulfil the generally adopted diagnostic criteria of pseudomalignant ossifying myositis. The clinical as well as the radiological features were quite characteristic. The zonal pattern with trabeculae of mature bone at the periphery and central cellular areas was found in nearly all cases. In two cases the difference between the central and peripheral areas was not marked and this was attributed to the age and size of the lesion.

The results of the analysis of the present series seem to support that view because in those two cases the lesions were smaller and the history longer when compared with the other cases which showed cellular cores lacking signs of osteoplasia. The repeated radiological examinations carried out in some of our cases indicated clearly that ossification proceeded from the periphery towards the centre of the lesion. Therefore one can assume that if the lesions were treated in a conservative manner, they would undergo ossification in toto giving rise to a lesion predominantly composed of lamellar cancellous bone. Our observations include three cases not included in the present series, which might represent terminal stages of an intramuscular localized osteoplastic process of the type discussed here. The features supporting such a relation include, in particular, a similar clinical symptomatology and radiological findings.

The routine diagnosis of pseudomalignant ossifying myositis in lesions totally removed surgically and thus allowing the recognition of their zonal pattern is straight forward. In contrast, it may be extremely difficult in small biopsy specimens which permit no adequate topographic orientation. In such cases the false diagnosis of malignancy can be avoided by comparing the morphological with the radiological findings and by taking a biopsy which includes the different layers of the lesion. The absence of mitosis and marked cellular atypicality usually facilitates the differential diagnosis. Despite these facts, however, the lesion may on occasions be difficult to differentiate from parosteal osteosarcoma.

Until recently, the ultrastructure of pseudomalignant ossifying myositis has been studied in only one case (Caulet et al., 1969). In that report the authors have focused their attention upon the process of ossification. In contrast to the findings presented here the above authors observed collagen fibres with abnormally low periodicity. Our own material comprises 3 cases. In all of them there were variable numbers of cells, uneven in size, mutually interconnected with desmosomes and showing morphological features of myofibroblasts. Such cells were the main cell type in the core of the lesion as observed in case No. 3. Their cytoplasm contained granular endoplasmic reticulum, bundles of regularly oriented myofilaments with occasional electron dense zones. The cytoplasmic membrane immediately neighbouring a rudimentary basement membrane was seen to develop pinocytotic vacuoles. Similar cells were also observed between the osteoid trabeculae even in such cases where only samples containing cellular cords have been available for study. Among the cells of the central connective tissue zone there were also monocytic cells which could be identified particularly by their lysosomal apparatus. Their numerous phagosomes did not contain any structures which could have indicated the origin of the substances ingested. The monocytic cells frequently showing features of preosteoclasts were also regularly present in the so-called cellular cords, where they accompanied mature osteoclasts.

Fibroblastic cells exhibiting features of smooth muscle cells have been described for the first time by Oshea (1970) in the rat ovary and by Moss et al. (1970) in the chicken aorta. The term myofibroblasts was used by Majno et al. (1971) and Gabbiani et al. (1972) who had observed similar cells in granulation tissue. The relationship between myofibroblasts and smooth muscle cells has been demonstrated by Hitchell et al. (1971) using an immunofluorescent technique. Myofibroblasts have been recorded in human granulation tissue (Ryan et al., 1974), in Dupuytren's disease (Gabbiani et al., 1972; Gokel et al., 1977), in nodular fasciitis (Wirman, 1976), in circumscribed fibromatosis (Feiner et al., 1976), in regenerating tendons (Postacchini et al., 1977) and in several malignant mesenchymal tumours (Churg et al., 1977). The study of the life cycle of myofibroblasts showed that such cells occur in only one phase of the course of Morbus Dupuytren (Gokel et al., 1977) or of a healing wound (Rudolph et al., 1977). In the pseudomalignant ossifying myositis, too, the proliferation of myofibroblasts is only transitory, occurring only during the earliest stages of the process. During the later stages osteoblasts occur at the periphery of the foci, which ultimately become the predominant cell type. It is extremely difficult

to assess the origin of osteoblasts on the basis of the present findings alone, because the problem has not been completely solved even in other sites such as bone (Pritchard, 1972). It has been most frequently suggested that the osteoblasts originate from proliferating connective tissue cells situated, in particular, in the vicinity of vessels (Pritchard, 1972; Göthlin et al., 1973). In this context, some authorities have suggested that fibroblasts, chondroblasts and osteoblasts may develop from one common stem cell (Pritchard, 1972). The myofibroblasts considered as fibroblasts showing some differentiation towards smooth muscle cells (Ryan et al., 1974), might also bear a close histogenetic relation to osteoblasts. At the present state of knowledge, however, the problem remains unsolved. It is also uncertain whether or not myofibroblasts occur in all the conditions associated with osteoplasia. Studies concerning the ultrastructure of osseous callus (Aho, 1966; Göthlin et al., 1970) or fibrodysplasia (myositis) ossificans progressiva (Maxwell et al., 1977) do not mention myofibroblasts at all. It should be pointed out, however, that some authors of the above papers (Göthlin et al., 1970; Maxwell et al., 1977) did recognize microfilaments within the cytoplasm of some fibroblasts.

The findings presented here indicate that myofibroblasts play a significant role in the pathogenesis of pseudomalignant ossifying myositis. This, on the one hand, might indicate some relationship between the lesion and reparative processes and, on the other hand, the possibility of a relation to some members of the fibromatosis group including nodular fasciitis. The central, nonossified parts of pseudomalignant ossifying myositis resemble, to a certain degree, the findings as recored in some pseudosarcomatous proliferative processes of soft tissues which at time may also undergo ossification (Dahl et al., 1977). The clinical course and the general topography of such lesions, even of the focally ossifying ones, differ slightly from the former ones. In particular, there is an absence of zonal arrangement. The reported data on ultrastructural findings also differ from those obtained in our cases. Not a single paper devoted to the ultrastructure of various fibromatoses including nodular fasciitis has mentioned the presence of monocytic cells of the macrophagic type (Feiner et al., 1976; Wirman, 1976; Gokel et al., 1977). We arrived at similar conclusions in one of our own unpublished case of fibromatosis of the scapular region that had been subjected to electron microscopical examination.

Under such conditions it seems probable that the foci of pseudomalignant ossifying myositis are virtually composed of granulation tissue that had originated during reparation of undefined regressive changes in voluntary muscles. Besides the findings of myofibroblasts and of phagocytic monocytoid cells such a concept can be supported by the fact that in pseudomalignant ossifying myositis the cores strongly resemble granulation tissue and, above all, by the zonal arrangement of the foci, particularly characteristic of the entity under discussion. Ultimately, such a concept would be in accord with the views of those authorities who thought that the condition might be associated with injury (Rosemeyer, 1972). We, like others authors (Angervall et al., 1969; Jeffreys et al., 1966; Lagier et al., 1975; Paterson, 1970) were unable to obtain a history of trauma in the cases studied. This, does not, however, exclude the possibility of repeated small injuries. Moreover, the presumed reparative process may represent a reac-

tion to other regressive changes such as those produced by inflammation, local ischaemia, etc.

It is evident from the preceding discussion that the pathogenesis of pseudomalignant ossifying myositis cannot be explained merely by the demonstration of myofibroblasts. Attempts at producing the lesion experimentally have remained unsuccessful. No material from the initial stages of the condition has been presently available and thus the problem awaits its solution. However in our opinion, some evidence has been gathered in support of the reparative nature of the condition. The presence of macrophages is believed to indicate histogenetic differences between pseudomalignant ossifying myositis and the lesions of the fibromatosis group including nodular fasciitis. The whole problem obviously requires a detailed analysis and a comparison of the two above conditions at the ultrastructural level. At present very few cases have been examined electron microscopically. So-called pseudomalignant ossifying myositis is a clinico-pathologic entity of obscure etiology, the development of which is associated with the proliferation of myofibroblasts and the presence of phagocytic monocytic cells. Whether these new findings can be used as an aid in the differential diagnosis between the entity discussed here and some true neoplasms, particularly the parosteal and extraosteal osteosarcoma, requires further verification.

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