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Muscle Changes in Rheumatoid Arthritis

A Review of the Literature with a Study of 100 Cases

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Summary. Muscle changes were studied in biopsy material obtained from 100 patients suffering from classical rheumatoid arthritis. The abnormalities consisted of denervation atrophy of type II muscle fibres, degenerative changes in the sarcoplasm including presence of nemaline rods, and changes within the interstitium: namely perivascular nodular myositis, lymphocytic accumulations, different stages of vasculitis and abnormalities within the intramuscular nerves and muscle spindles. The muscles examined were always severely affected. It is considered that the simultaneous presence of these abnormalities is suggestive of rheumatoid arthritis. The importance of histochemical studies is emphasized. The literature concerning muscle changes in rheumatoid arthritis is reviewed.

Key words: Rheumatoid arthritis — Muscle changes.

Introduction

The changes present in striated muscles in rheumatoid arthritis have been recognised both clinically and pathologically. Muscle wasting and weakness, as clinical signs of muscle atrophy associated with "chronic inflammation of the joints" were recognised by Sir James Paget as long ago as 1873. Many authors considered that muscle atrophy in rheumatoid arthritis is due to inactivity (Hollander, 1966). Ropes et al. (1958) reported a number of cases of rheumatoid arthritis in which muscle atrophy and weakness were the first clinical manifestations of the disease. Morrison et al. (1947) using electromyo-

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graphy observed marked changes in the muscles consistent with denervation. These changes were found even in the very early stages of rheumatoid arthritis. These authors concluded that in rheumatoid arthritis muscle changes might be due to a direct involvement of the neuromuscular system.

The pathological changes affect the contractile elements, as well as the interstitium.

The most common histological findings in rheumatoid arthritis are the pronounced muscle atrophy and nodular myositis. Curtis and Pollard (1940) were the first to note the presence and to describe the histology of nodular myositis. Although it was considered subsequently to be specific by some authors (Steiner et al., 1946; De Forest et al., 1947). Sokoloff et al. (1950) found this lesion in only 56% of patients suffering from rheumatoid arthritis.

Muscle has a relatively limited range of histological changes in reaction to disease (Bethlem, 1970) and most of these changes are not specific. Because of this, diagnosis can not be made on the basis of a single histological feature, but is based on the presence of a combination of different types of changes. In view of this a study was undertaken to examine the presence of different types of muscular changes and their possible diagnostic value, and to study the possible factors concerned with their pathogenesis in classical rheumatoid arthritis.

Material and Methods

The present study has been carried out on biopsy material, obtained from 100 patients suffering from rheumatoid arthritis. Muscle biopsies, frequently from several muscles were taken during operations involving the wrist in 44 cases, the elbows in 32 cases, the knees in 29 cases, the feet in 24 cases, the hips in 17 cases and the hands in 16 cases. The muscle biopsies were taken under general anaesthesia or nerve block. The muscles biopsied were – depending on the operation – the extensor carpi ulnaris, extensor digitorum communis, extensor carpi radialis longus et brevis, vastus medialis, extensor digitorum brevis, gluteus maximus and extensor digiti quinti. Biopsies were taken also from the deltoid muscle and from the biceps brachialis. More than 300 muscle specimens were studied. All the patients were considered to have classical rheumatoid arthritis. The age of patients varied from 36 to 76 years, with an average age of 57.1 years. The duration of rheumatoid arthritis varied from 4 months to 44 years, with a mean duration of 11.6 years. As controls we examined 50 muscle specimens obtained at operation from patients known to be unaffected by rheumatoid arthritis, and from autopsies of 20 patients with an average age of 50.0 years, who had died from unrelated diseases. In all these cases corresponding muscles were examined.

For light microscopy formol fixation and paraffin embedding were used. Numerous transverse and longitudinal sections were cut from each of the muscle specimens and stained with haematoxylin and eosin, van Gieson's and Masson-Goldner's trichrome stains, and impregnated by Gomori's silver method.

For electron microscopy fresh tissue was fixed in glutaraldehyde, post-fixed in osmium tetroxide and dehydrated in acetone. The sections were cut on an LKB ultratome. They were embedded in Epon 812, stained by uranyl acetate and lead citrate, and studied with a Philips 300 electron microscope.

The semi-thin sections 1 μ in thickness were stained with Löffler's toluidine-blue and by the PAS method.

For histochemical studies fresh frozen tissue was used. It was sectioned and stained using NADH-tetrazolium oxydoreductase, myofibrillar ATPase, alpha-glucan-phosphorylase, and the PAS method in order to study the appearances of the type I and type II muscle fibres.

Results

In all the muscle biopsies taken from patients suffering from rheumatoid arthritis, abnormal findings were present. There was no material difference according to the muscle studied. The abnormalities observed can be summarised as follows:

1. Changes in the Diameter and Structure of the Muscle Fibres

The most common and the most pronounced abnormality of the contractile elements was atrophy of the muscle fibres. In transverse sections groups of muscle fibres appeared thin, and often angular. These small fibres contained hyperchromatic and pyknotic nuclei, frequently forming clumps, clusters and chains. Haphazardly swollen, and degenerating muscle fibres were also present, showing the appearances of hyaline degeneration (Fig. 1). In longitudinal sections the marked variation in width was also evident, and in semi-thin sections collections of rod-like structures could be observed within the muscle fibres, mainly in the subsarcolemmal zones. In these areas there was an increase in vesicular nuclei with prominent nucleoli. Changes in the muscle fibres were common and in places they showed disintegration into collections of floccular eosinophilic material.

The ultrastructural changes in the muscle fibres were in accordance with those seen by light microscopy. On cross section centrally placed, swollen nuclei and splitting of the myofibrils were common findings. On longitudinal section the abnormalities of the Z bands were pronounced. Their central areas appeared to be disrupted, and the Z bands showed zig-zag formations. Typical nemaline rods were detected in some of the muscle specimens (Fig. 2).

The histochemical examination revealed that all the atrophic, thin and damaged muscle fibres were type II fibres. The appearances of the "slow" type I fibres could be considered within normal limits. The small, angular, hypotrophic fibres showed very pronounced enzyme activity. The alpha-glucan-phosphorylase activity of the type II fibres was also very marked but somewhat uneven (Fig. 3).

2. Changes in the Interstitial Tissue Including the Presence of Cellular Infiltration

Among the abnormalities affecting the connective tissue component, oedematous swelling and presence of fibrinoid material were often seen, involving mainly the endo- and perimysium. There was no relationship between these changes and other abnormalities found in the muscle. Cellular infiltration in the interstitium was found in 61 cases. The most common type of infiltration was the perivascular nodular myositis. It consisted of perivascular cuffing by lymphocytes and plasma cells, mainly around small arteries and arterioles.

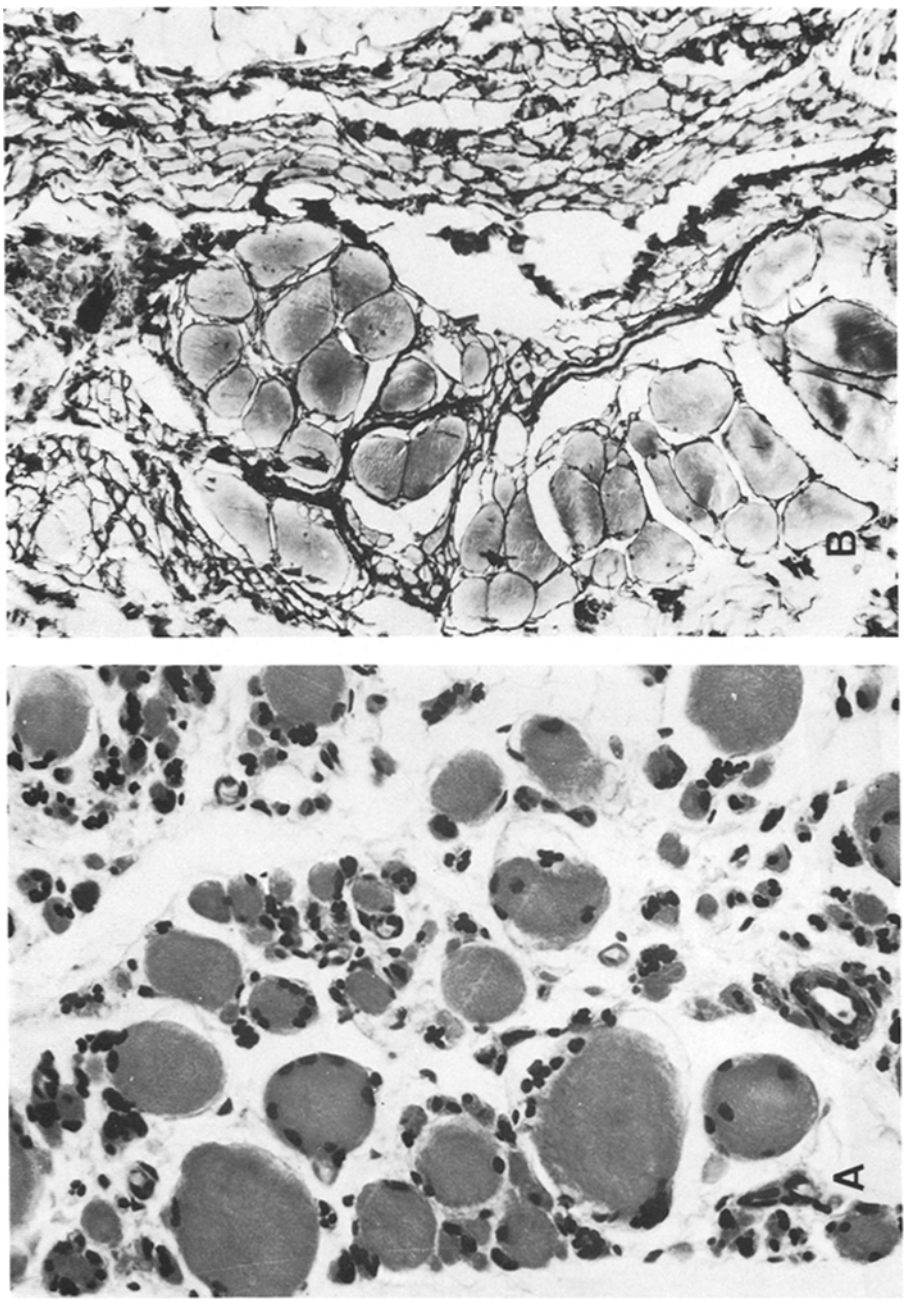

Fig. 1. A Muscle fibres showing atrophic changes and homogenisation of the sarcoplasm. The sarcolemmal nuclei are prominent. There is evidence of hyaline degeneration and vacuolisation of the larger fibres. (HE ×360). **B** Cross section. Silver impregnation showing the difference in size between muscle fibres. The atrophic muscle fibres are situated at the periphery. (Gomori's silver impregnation, ×140)

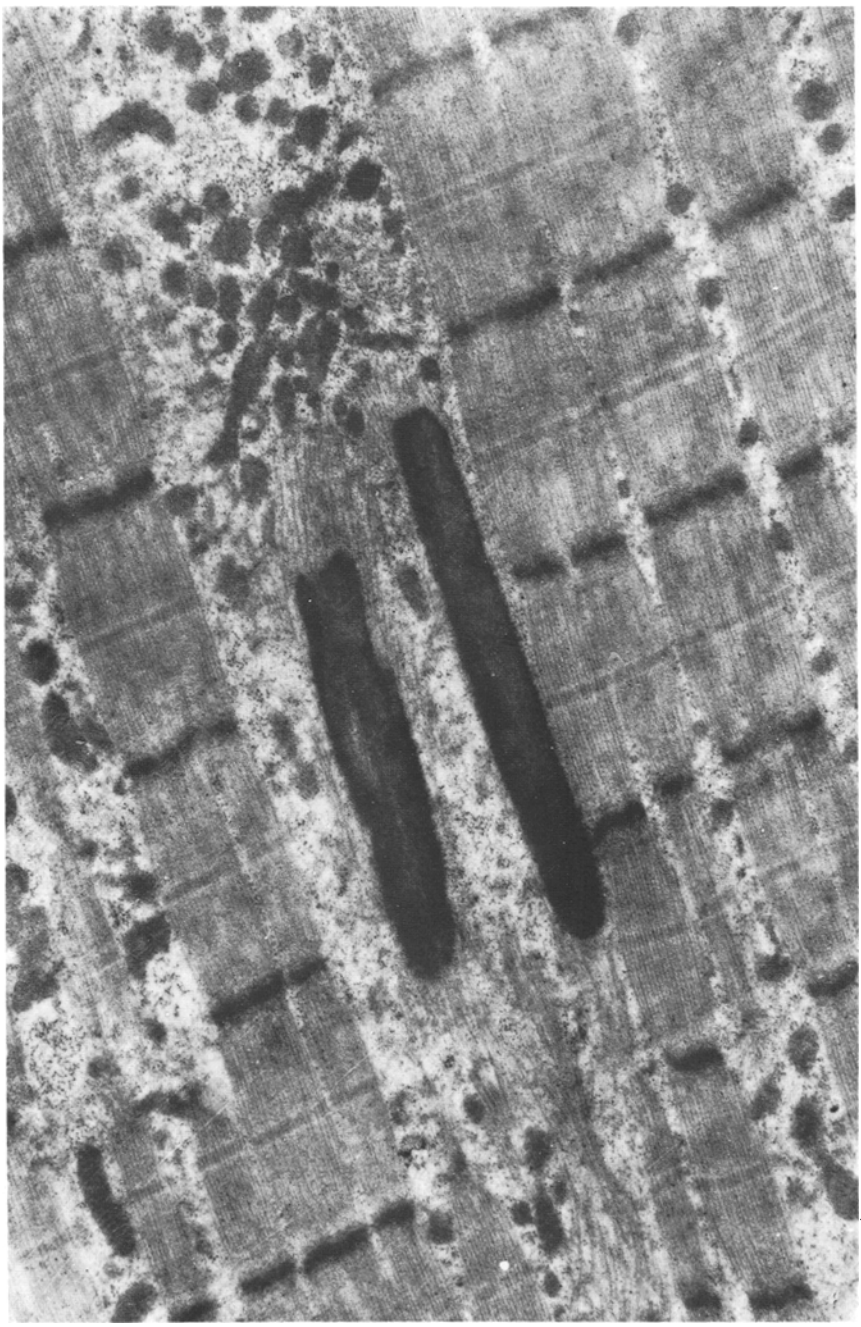

Fig. 2. On the left side the individual myofibrils appear narrowed. The intermyofibrillar space is markedly widened and contains glycogen particles and mitochondria. On the right side two myofibrils show focal degeneration. Two typical nemaline rods sectioned longitudinally are present. (Electron micrograph. ×50,000)

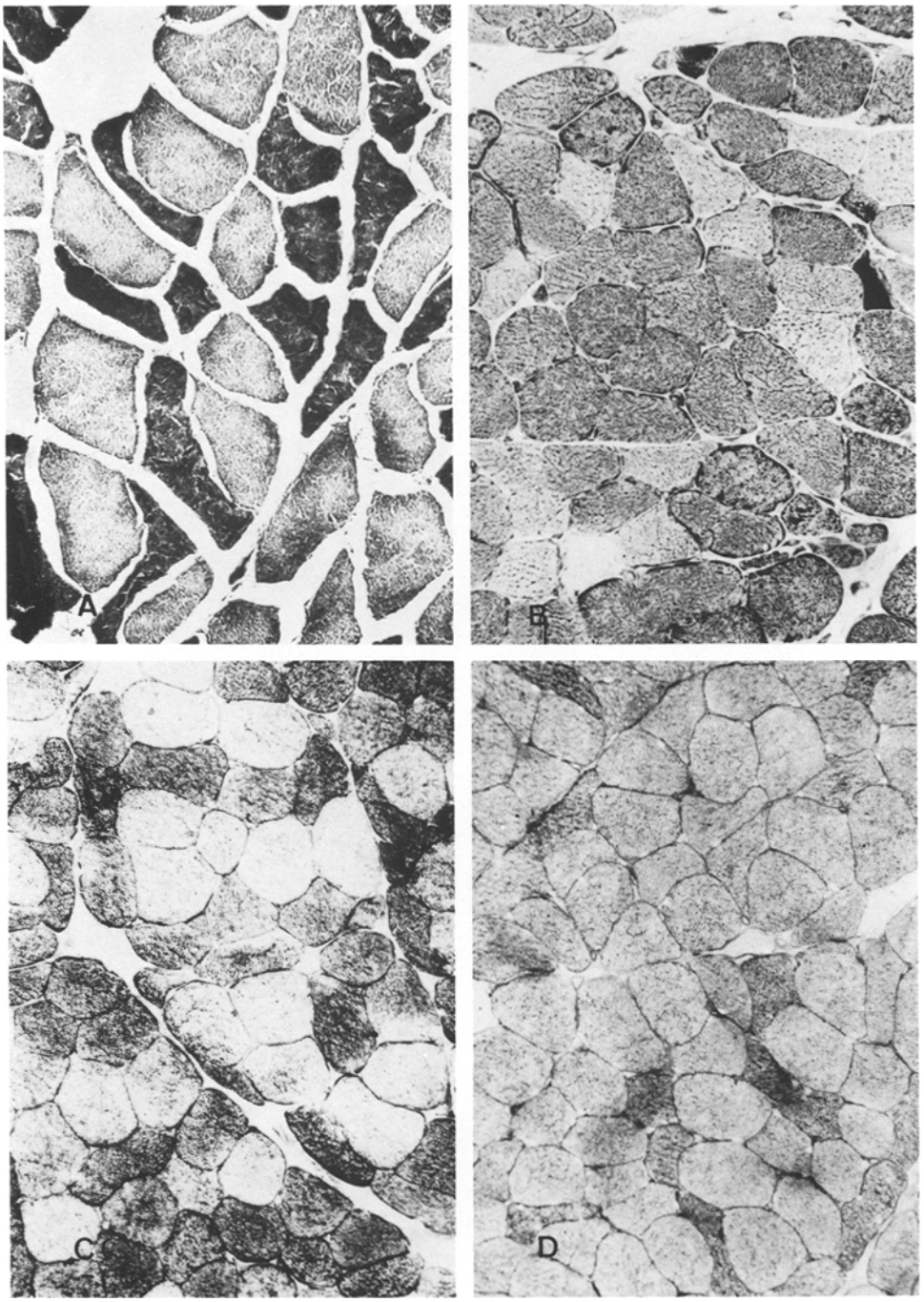

Fig. 3. **A** Myofibrillar ATP-ase reaction showing pronounced enzyme activity in all the atrophic fibres demonstrating that they are type II muscle fibres. (×240). **B** NADH-tetrazolium-reductase reaction showing normal appearances of the type I fibres. (×220). **C** Variation in alpha-glucan-phosphorylase activity in type II muscle fibres. (×220). **D** PAS reaction for glycogen showing that the small, atrophic, angulated muscle fibres containing glycogen are type II fibres. (×220)

This type of lesion was always multiple. Cellular infiltrates composed of lymphocytes and plasma cells were also found elsewhere and they showed the histological picture of lymphocytic accumulation. In these cases large collections of round cells were found also within the muscle fibres (Fig. 4).

3. Changes in the Blood Vessels within the Striated Muscle

Histologically these changes were found in the peri- and epimysium and consisted of acute, subacute and chronic vasculitis. The size of the affected blood vessels was fairly constant and varied from large arterioles to small arteries. The various stages of arteritis were usually present within the same specimen. The acute arteritis was always exudative, with marked oedematous swelling of the vessel walls, and marked infiltration by lymphocytes, plasma cells, leucocytes and occasionally eosinophils. Although this was mainly seen in the adventitia and media, the endothelial lining of the vessels was also swollen and prominent. In the subacute stage the involved arterioles and arteries showed fibroblastic proliferation, while the inflammatory elements were still present. The chronic vasculitis manifested itself by a marked thickening of the vessel wall and fibrosis of the media and adventitia. In 20 cases there was also evidence of phlebitis, which appeared to be acute and necrotizing (Fig. 5).

4. Changes in the Intramuscular Nerve Branches

The small nerve bundles found in the muscles showed two types of abnormality. There was an increased amount of connective tissue within the endo- and perineurium; degenerative changes, which varied in intensity and were consistent with Wallerian degeneration of the nerves, were also present.

5. Changes in the Muscle Spindles

46 muscle spindles were found in the muscle biopsies examined. Only 8 of the spindles could be considered within normal limits. The abnormalities seen in the muscle spindles in patients with rheumatoid arthritis have been described previously (Magyar et al., 1973). These changes can be summarised as follows: a) Marked thickening of the connective tissue capsule of the spindle. b) Narrowing, or even disappearance of the periaxial space of the spindle due to capsular thickening and proliferation of the intracapsular connective tissue. c) Damage to the fibrous septa within the periaxial space. d) Decrease in number of the intrafusal muscle fibres. e) Degenerative changes within the intrafusal muscle fibres. f) Thickening of the walls and narrowing of the lumina of the blood vessels supplying the muscle spindles and g) Damage to the innervation of the muscle spindles.

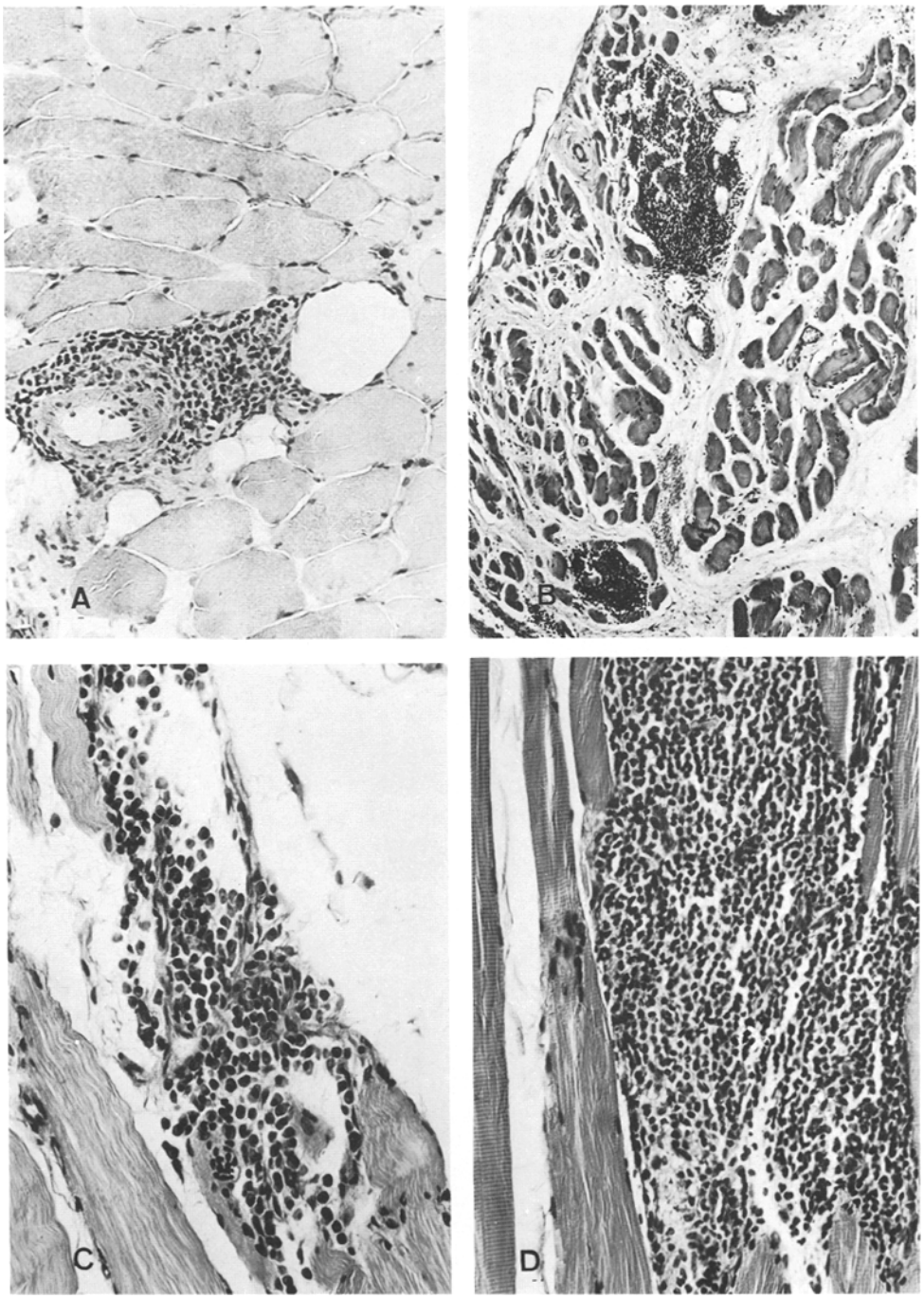

Fig. 4. **A** Typical perivascular nodular myositis. (HE, ×200). **B** Marked interstitial oedema and multiple foci of nodular myositis can be seen. (HE, ×60). **C** A collection of plasma cells within the muscle, replacing the muscle fibres. (HE, ×360). **D** Large intramuscular lymphocytic accumulation. (HE, ×200)

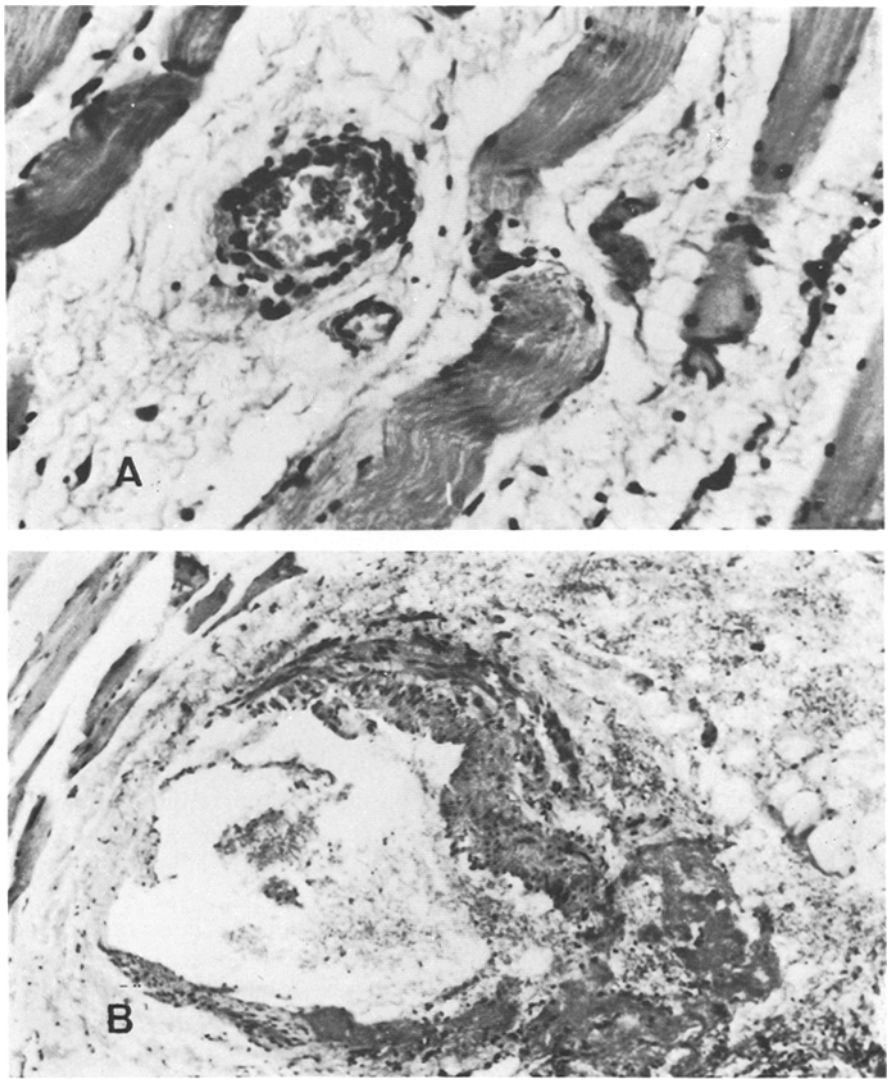

Fig. 5. **A** Small artery within the oedematous interstitial tissue showing the acute stage of vasculitis. (HE, ×360). **B** Acute necrotizing phlebitis present within the perimysium. (HE, ×140)

Discussion

The results of the present study show that in rheumatoid arthritis abnormalities affecting striated muscle are very common. These abnormalities manifest themselves as atrophy of type II fibres, degeneration of sarcoplasm, including presence of nemaline rods, interstitial oedema and different types of inflammatory infiltration. The intramuscular blood vessels and nerves are always affected and there is involvement of muscle spindles.

Muscle wasting is a well known feature in patients with rheumatoid arthritis. In view of the histological pattern of the muscle atrophy seen in this disease we agree with the authors, who consider the muscle atrophy as neurogenic (Morrison et al., 1974; Yates, 1963; Hartmann, 1965; Haslock et al., 1970). Groups of angular fibres with small diameter are seen either adjacent to groups of fibres with normal diameter or are situated at the periphery of the fascicles. This is characteristic of the neurogenic origin of the muscle atrophy. The pronounced enzyme activity (although frequently varying in intensity) seen within the atrophied fibres, and the more evenly spread uniform activity seen in the non-atrophic fibres are also suggestive of neurogenic origin (Bethlem, 1970). According to our observations all the atrophied muscle fibres were type II fibres. This fact corresponds with the presence of nemaline rods found both by light and by electron microscopy (Adams, 1975). Nemaline rods can be found in different kinds of unrelated neuromuscular disorders, and their presence in myopathies associated with collagen diseases has also been reported (Rewcastle and Humphrey, 1965; Engel, A.G. 1966; Engel, W.K. 1967; Cape et al., 1970; Jerusalem, 1971).

We have found marked cellular infiltration, both nodular myositis and lymphocytic accumulations in the muscle specimens in 61% of the cases examined. This frequency is similar to that reported by Sokoloff et al. (1950). Beneke (1972) discussed the possible interpretation of the presence of nodular myositis and lymphocytic accumulation in rheumatoid arthritis and concluded that it is possible that cellular infiltration may be a morphological manifestation of special local auto-immune reaction against muscle proteins. In one of our cases reported separately (Magyar et al., 1974) a very marked plasma cell myositis was found, which may support this possibility. Our findings show that neither the atrophic changes, nor the focal inflammation could be correlated with the duration, or activity of the rheumatoid arthritis, and these findings appear to be independent of the mode of therapy used.

The differential diagnosis between polymyositis and muscle changes associated with rheumatoid arthritis may be difficult, as variation in diameter of the muscle fibres and presence of cellular infiltration may be found in cases of polymyositis of different origin. The extent of the structural changes shows marked variability and differs from case to case both in rheumatoid arthritis and in polymyositis. In cases of polymyositis necrosis of muscle fibres often occurs, and the cellular infiltrate in the endomysium is found especially around the necrotic fibres. While perivascular inflammatory infiltration is a common finding in both conditions, presence of large lymphocytic accumulations is in favour of rheumatoid arthritis.

Arteritis in skeletal muscles in rheumatoid arthritis has been first described by Sokoloff et al. (1951), and studied in detail by Radnai (1953, 1969) and Cruickshank (1954). The pathogenesis of the vasculitis observed in cases of rheumatoid arthritis was discussed recently by Fassbender (1976), who emphasized the immunological aspects. Although inflammation of the venules in the rheumatoid synovial tissue, including nodular and visceral lesions, is well known (Kulka, 1966), necrotizing phlebitis in the skeletal muscle has not been described. In our material necrotizing phlebitis was observed in 20% of the muscles

examined. Vascular changes present in the muscle tissue, and the consequent ischemia may also play an important part in the pathogenesis of the muscle atrophy and lead to further changes in the muscle.

Focal lesions in the peripheral nerves in rheumatoid arthritis are considered to occur in association with the vascular changes (Radnai, 1953). Chamberlain and Bruckner (1970) found evidence of severe denervation in cases of rheumatoid arthritis presenting with neuropathy.

The changes found in the muscle spindles were always marked. In our opinion they were probably due to the generalised vasculitis, which may cause denervation and chronic hypoxia of the extra- and intrafusal muscle fibres (Magyar et al., 1973).

It is considered that any one of these abnormalities would by itself be of little diagnostic value in rheumatoid arthritis. Our observations show that the simultaneous presence of changes, like muscle atrophy of neurogenic origin, degenerative changes in the sarcoplasm, nodular myositis, lymphocytic accumulation, different stages of vasculitis and abnormalities within the nerves and muscle spindles are suggestive of rheumatoid arthritis. We would like to emphasize the importance of histochemical studies to demonstrate the presence of isolated atrophy of type II muscle fibres.

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