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Microtubuloreticular Structures in Autoimmune-related Myopathy

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=Abstract=**Microtubuloreticular structures are composed of undulating reticulated microtubules lying within dilated cisternae of rough endoplasmic reticulum, measuring 18-27 nm in diameter. Although these structures occasionally occur in normal mammalian cells, most examples come from the tissues of diseased individuals, particularly from cases of autoimmune disease and viral infection. We have experienced 10 cases of inflammatory myopathy in the last 2 years. Of particular interest was their presence in the pericytes (3 cases), stromal fibroblasts (2 cases) and histiocytes (1 case) as well as in the endothelial cells in 8 cases. Two cases of polymyositis revealed a marked degenerative change without evident microtubuloreticular structures in the capillary endothelial cells. These findings confirm the previous reports that these structures are of considerable diagnostic value for autoimmune-related myopathy when taken in conjunction with other clinicopathological features, and also prove that the pericyte should be included as the target cell of microtubuloreticular structures.**

Key Words: *Microtubuloreticular structure, Inflammatory myopathy, Endothelial cell, Pericyte, Fibroblast, Dermatomyositis, Autoimmune disease*

INTRODUCTION

Microtubuloreticular structures (MTRS) are subcellular membranous complexes found within dilated cisternae of the rough endoplasmic reticulum (RER) or the perinuclear cistern. They consist of 25 nm tubuli which are arranged in intermeshed networks that can measure up to 2 μm across (Grimsley *et al.* 1985; Ghadially 1988). In human tissue, MTRS were first recognized in the glomerular endothelium of patients with systemic lupus erythematosus (Gyorkey *et al.* 1972). Subsequently they were observed in various organs or tissues affected by systemic autoimmune diseases (Norton *et al.* 1970; Gyorkey *et al.* 1972), acquired immune deficiency syndrome (Orenstein *et al.* 1984; Onerheim *et al.* 1984; Sidhu *et al.* 1985), neoplasms (Gyorkey *et al.* 1971) and in lymphoproliferative diseases (Pothier *et al.* 1973; Glick *et al.* 1980; Imamura *et al.* 1981). Banker (1975) protested that the major abnormalities in dermatomyositis were in the walls of the intramuscular blood vessels, more specifically in the endothelial cells of capillaries, arterioles, and veins. Endothelial inclusions consisting of microtubular aggregates were found within the cytoplasm of 76 to 98% of all intramuscular blood vessels (Banker 1975). The detection rate of the inclusions correlated well with the degree of disease activity (Hashimoto *et al.* 1971). The present study describes the occurrence of MTRS in muscles due to inflammatory myopathy, mainly dermatomyositis. The nature of the MTRS and their possible diagnostic significance were discussed.

MATERIALS AND METHODS

All ten patients included in this study had a clinical history and laboratory findings compatible with inflammatory myopathy. Seven cases were der-

Table 1. Clinical summaries of seven cases

Patient No	Age/Sex	Major clinical symptoms	EMG	ANA	LDH	CPK
1	27/F	Malar rash, proximal muscle weakness, progressive myalgia				
2	28/F	Malar rash, joint swelling generalized ache	Myopathy	Positive	395	51
3	54/M	Malar rash, generalized weakness	Myopathy	Negative	213	579
4	23/M	Proximal muscle weakness				
5	31/F	Facial rash, fever, proximal muscle weakness, myalgia	Inflammatory myopathy	Positive	298	114
6	17/F	Skin rash, myalgia, fever, alopecia	Myopathy	Positive	362	27
7	42/F	Polyarthralgia, fever, myalgia multiple joint swelling and limitation of motion	Polymyositis	Positive	485	874

Table 2. Cell types containing MTRS in ten patients studied

Patient No.	Age/Sex	Clinical diagnosis	MTRS seen in			
			Endothelium	Pericyte	Fibroblast	Histiocyte
1	27/F	Dermatomyositis	+	−	−	−
2	28/F	Dermatomyositis	+	−	+	−
3	54/M	Dermatomyositis	+	−	−	−
4	23/M	Dermatomyositis	+	−	−	−
5	31/F	SLE, Dermatomyositis	+	+	−	−
6	31/M	Dermatomyositis	+	+	−	−
7	54/M	Dermatomyositis	+	+	+	+
8	17/F	Dermatomyositis	+	−	−	−
9	42/F	Polymyositis		marked degeneration		
10	22/F	Polymyositis		marked degeneration		

MTRS: microtubuloreticular structure SLE: systemic lupus erythematosus
+: present −: absent

matomyositis, 1 case mixed dermatomyositis and systemic lupus erythematosus and 2 cases polymyositis. Only seven patients only had available clinical data (Table 1). In addition to clinical history, a number of studies were carried out, including electromyography (EMG), fluorescent anti-nuclear antibodies (ANA), serum lactic dehydrogenase (LDH) and creatine phosphokinase (CPK). Five of these patients had malar rash and/or myalgia and four had muscle weakness. All showed an electromyographic finding compatible with myopathy. ANA was positive in four, and LDH was positive in five.

The biopsies muscle were subjected to a histopathological and electron microscopical examinations. For light microscopy, routine hematoxylin and eosin stain were performed. For electron microscopy, the tissue was immediately fixed in 2.5% phosphate buffered glutaraldehyde (pH 7.2-7.4), post-fixed in 1% osmium tetroxide for 2 hours and embedded in Epon mixture. Sections were stained with uranyl acetate and lead citrate and viewed in a Hitachi-600 electron microscope.

RESULTS

Light Microscopy:

Histologic features were similar and revealed

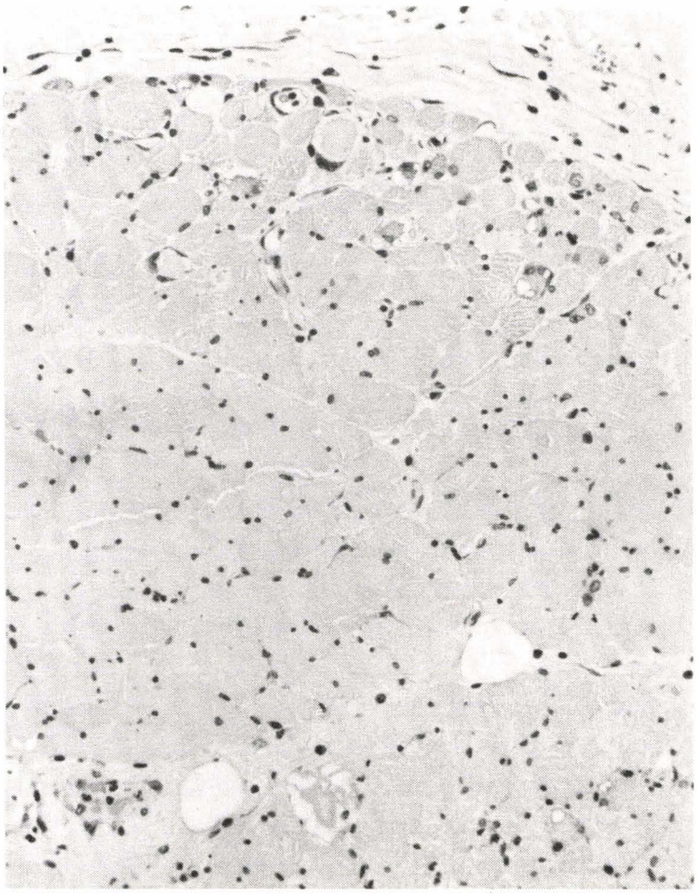

Fig. 1. Perifascicular atrophy and degeneration of myofiber. H&E X100

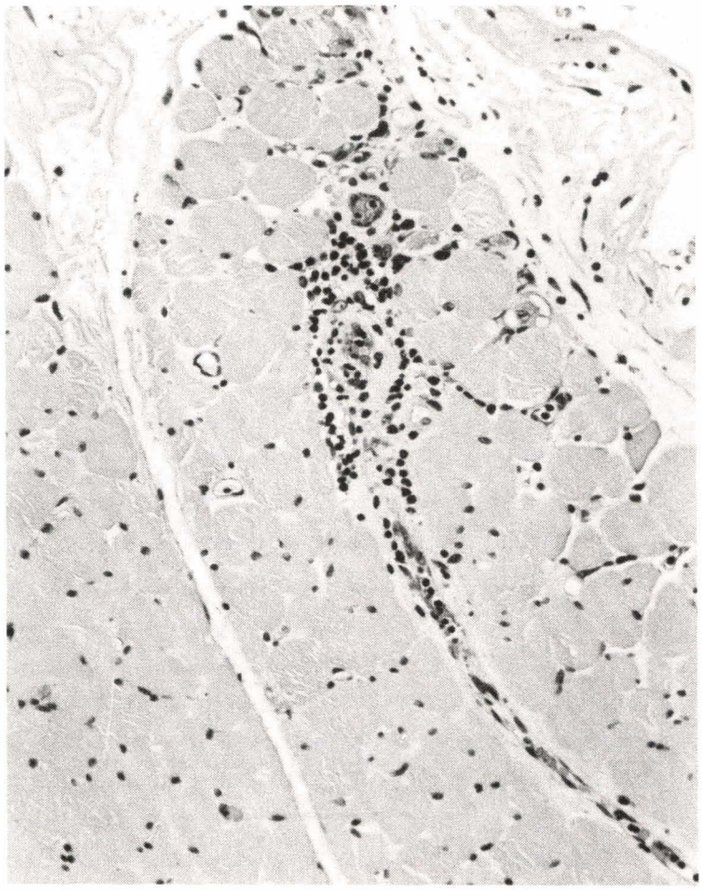

Fig. 2. A focus showing mononuclear cellular infiltration around a small blood vessel. H&E X100

size variation of myofiber in variable degree, interstitial lymphocytic infiltration, interstitial edema, internal nuclei, perifascicular atrophy and scattered degenerating and regenerating fibers (Fig. 1). Two cases were associated with perivasculitis (Fig. 2).

Electron Microscopy:

As shown in Table 2, two cases revealed a marked degenerative change without evident MTRS. The remaining 8 cases contained MTRS in the capillary endothelial cells (Fig. 3 & 4).

MTRS were also infrequently observed in the pericytes (Fig. 5), fibroblasts (Fig. 6) and histiocytes (Fig. 7). These were set within the rough endoplasmic reticulum and perinuclear cistern, and were arranged in an intermeshed network measuring about 20nm in average width. The muscle fibers themselves revealed nonspecific degenerative change as evidenced by loss or disorganization of myofibrils, thick condensation of Z-band like materials, accumulation of lysosomes and glycogen particles (Fig. 8). MTRS were not detected within the myofiber itself.

DISCUSSION

It has been stated that there are two types of MTRS, namely lupus-type and chimpanze hepatitis-type (Ghadially 1988). The lupus-type almost invariably lies within a dilated cistern of the RER or the perinuclear cistern, and chimpanze hepatitis-type lies free in the cytoplasmic matrix. The pathogenesis and nature of MTRS have not been fully clarified. Regarding the mode of formation, they budded from the wall of the rough endoplasmic reticulum or from the nuclear membranes into the cisternae which they eventually filled (Hashimoto *et al.* 1971). Initial speculation concerning the origin of MTRS focused upon an apparent similarity of their intermeshed microtubuli to paramyxovirus nucleocapsids (Gyorkey *et al.* 1971; De Sousa *et al.* 1974). However, the current view is that these may be of cellular derivation (Grimley and Henson 1983). Against the viral hypothesis is; 1. the failure to

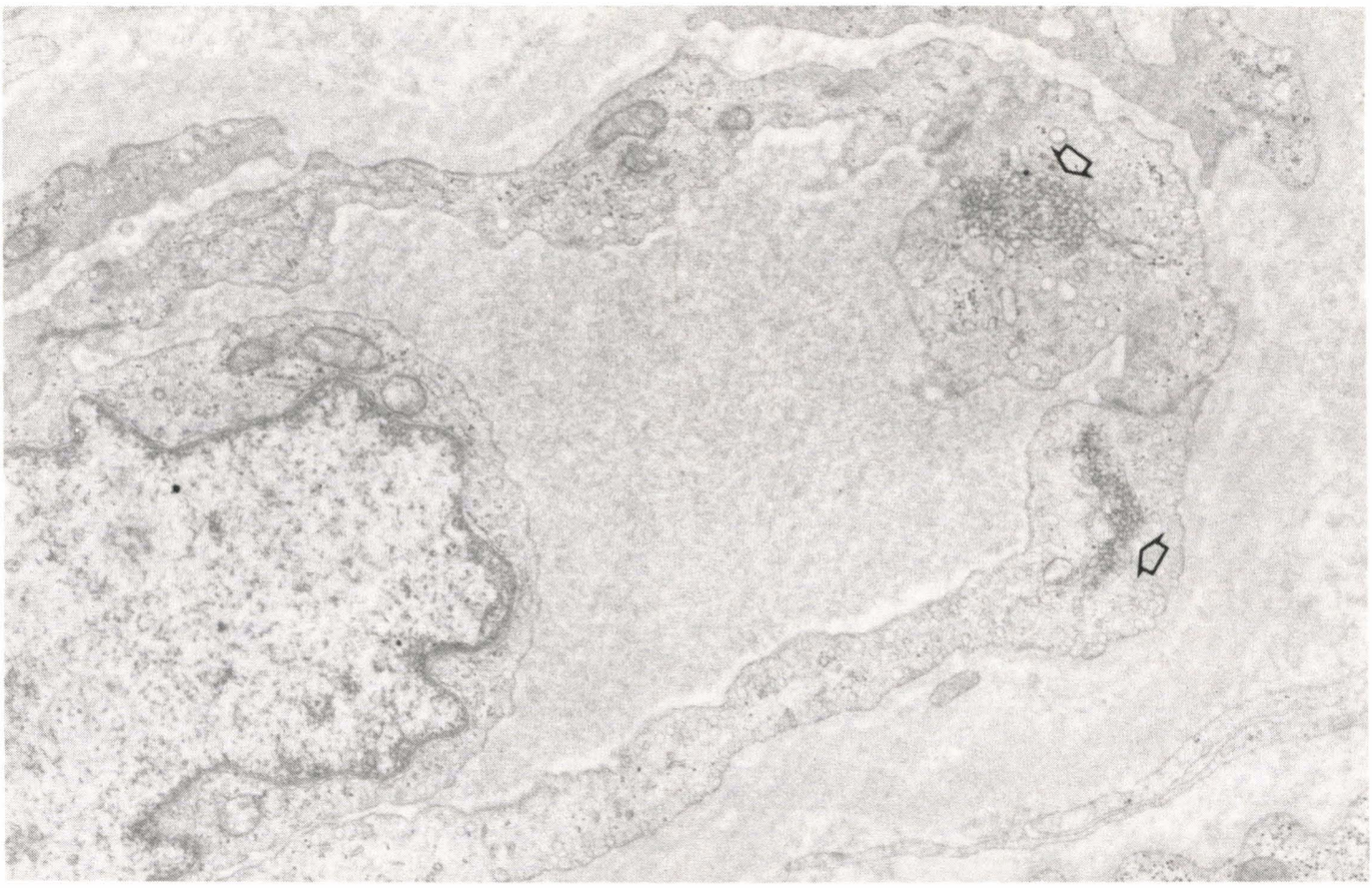

Fig. 3. Microtubuloreticular structure (arrow) set within the RER of the capillary endothelial cells. EM X18,400

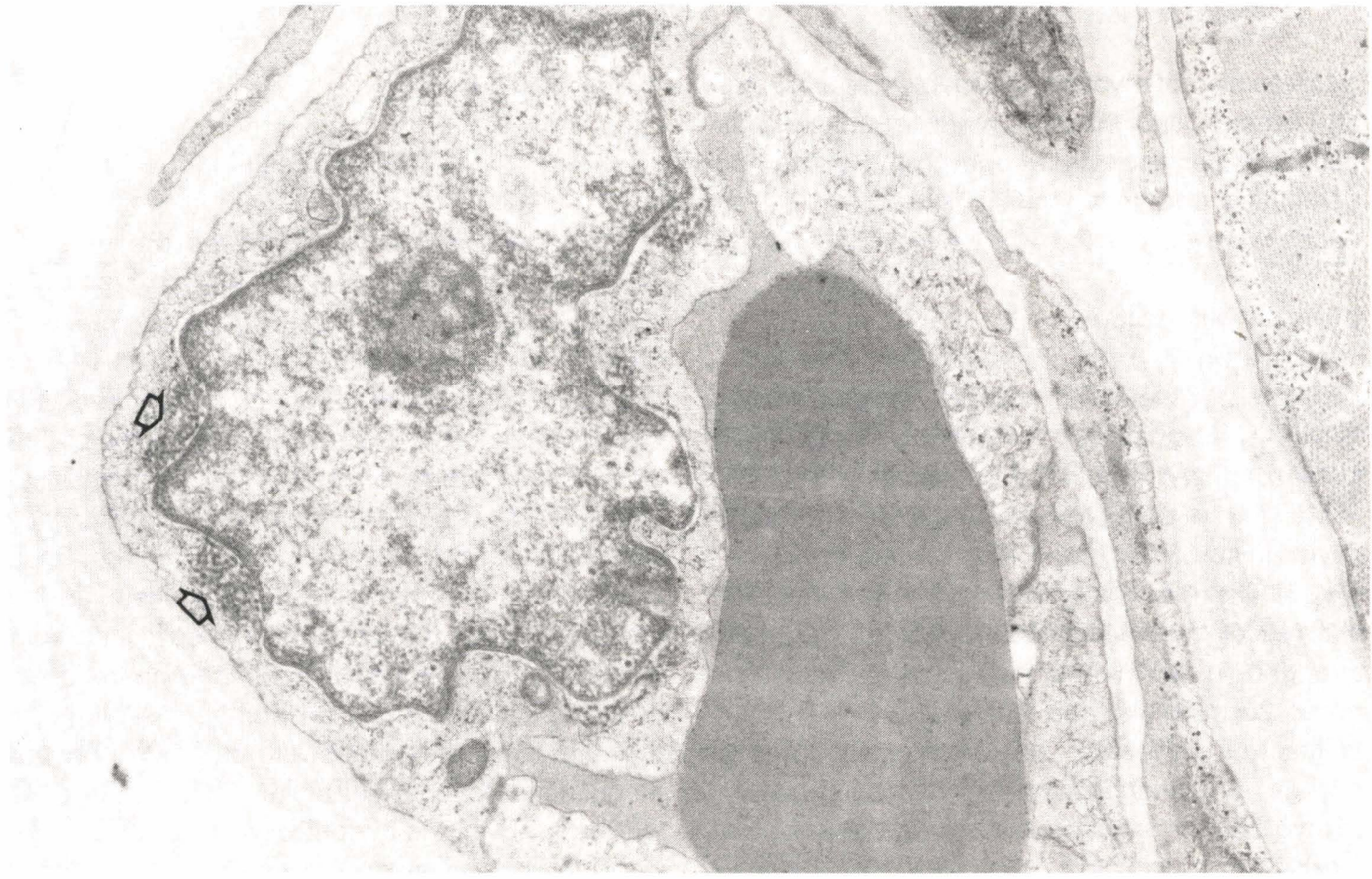

Fig. 4. Microtubuloreticular structure (arrow) set within the perinuclear cistern. EM, X23,000

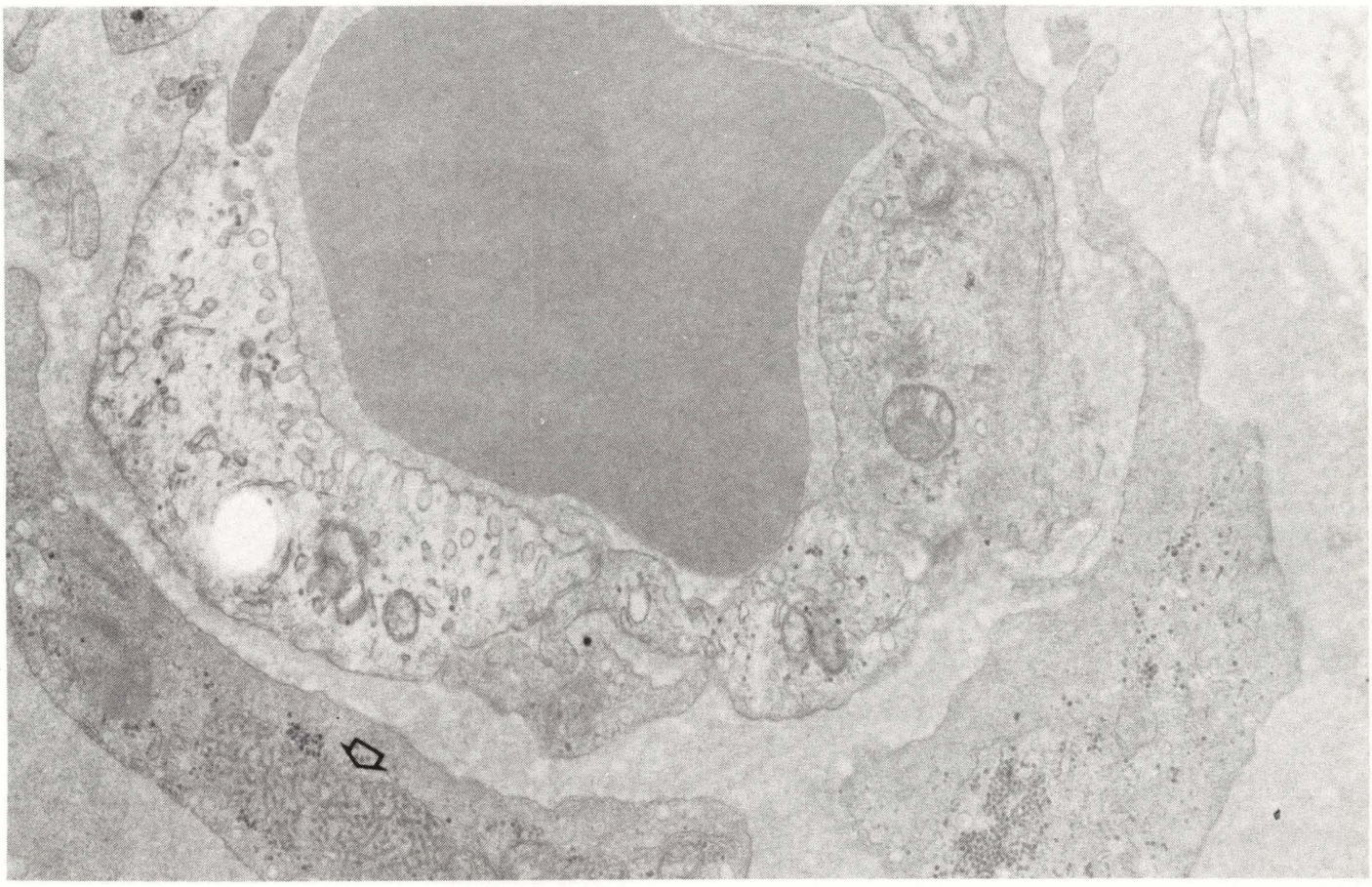

Fig. 5. Microtubuloreticular structure (arrow) in the percyte. EM X27,600

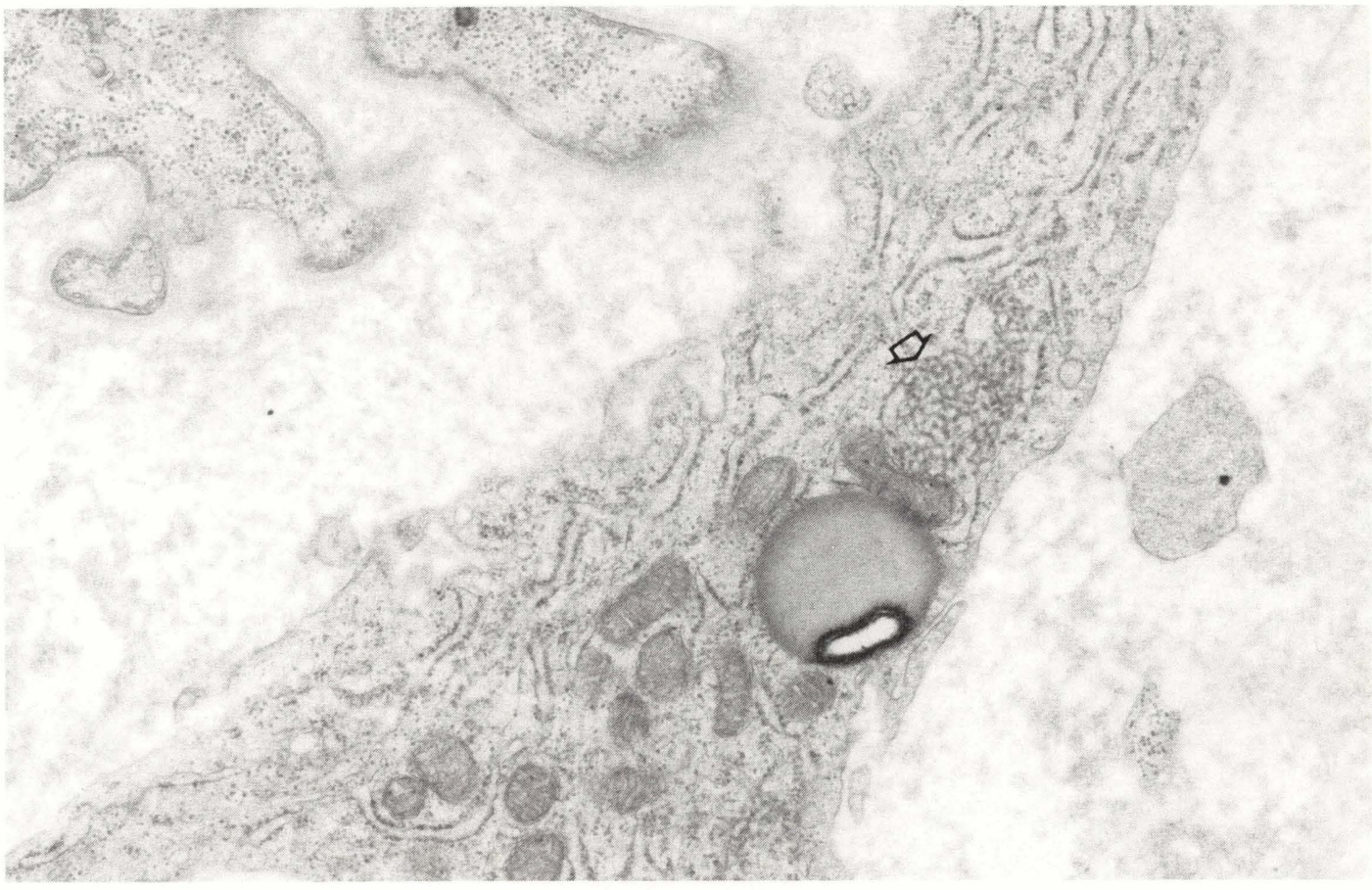

Fig. 6. Microtubuloreticular structure (arrow) in the fibroblast. EM, X27,600

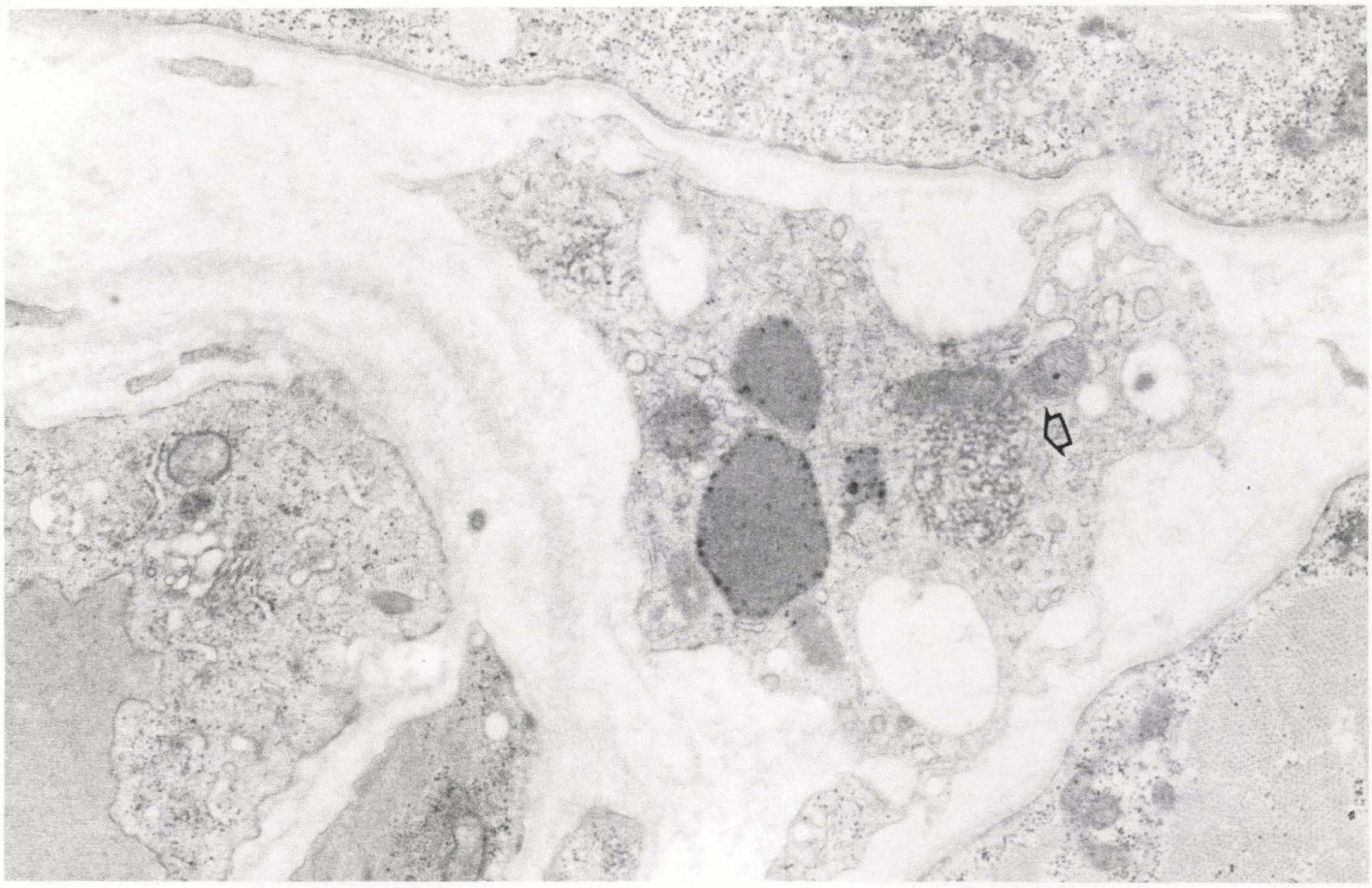

Fig. 7. Microtubuloreticular structure (arrow) in the histiocyte. EM, X23,000

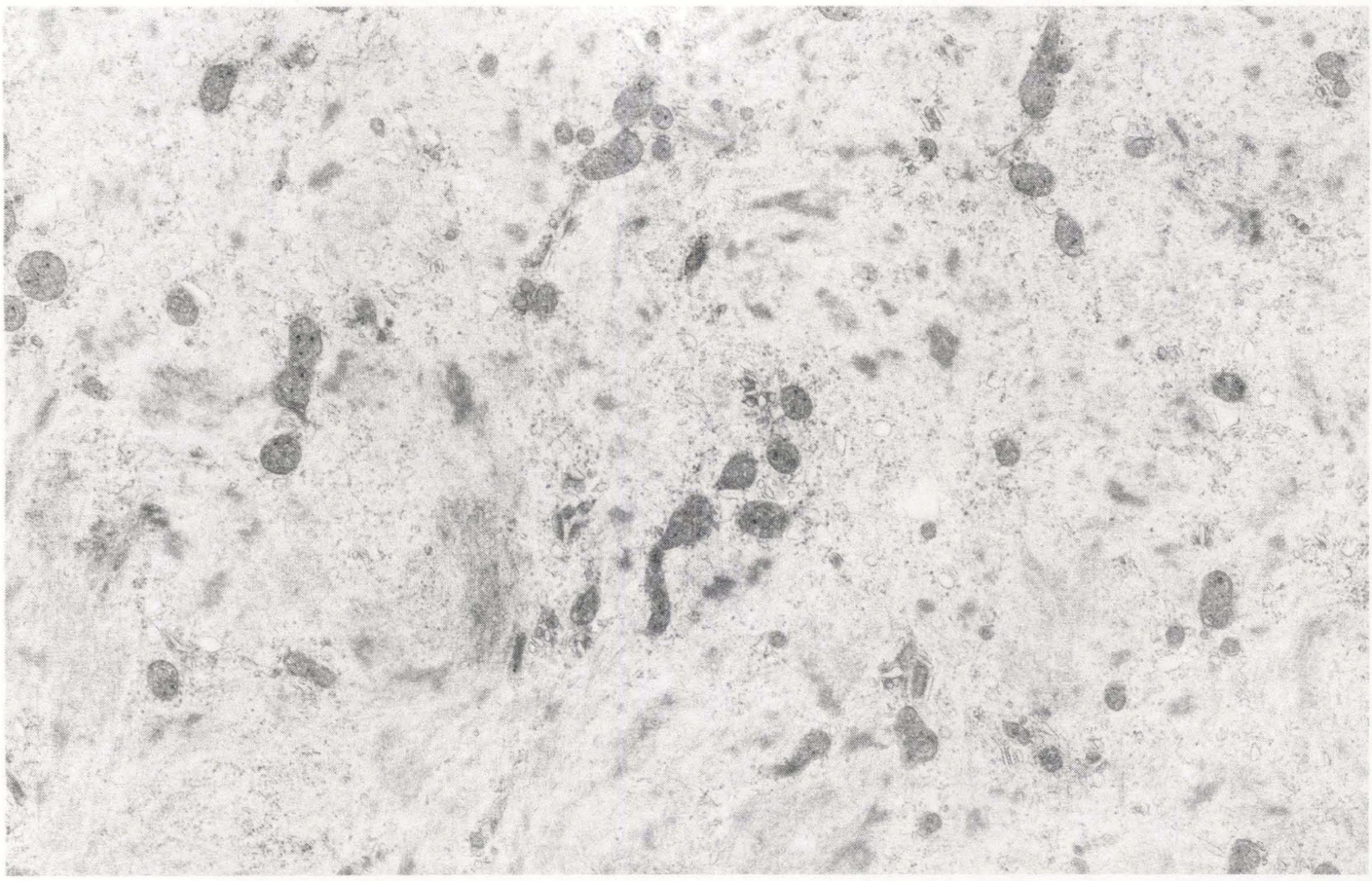

Fig. 8. Loss and disorganization of myofibrils with thick condensations of Z-band like materials. EM, X18,400

isolate the virus from inclusion bearing tissues 2. the paramyxoviruses are somewhat smaller in diameter and occur in the cytoplasm and not in the endoplasmic reticulum (Pincus *et al.* 1970). 3. MTRS do not contain RNA.

Recently several workers have suggested that interferon might be the agent which induces the formation of MTRS. Since patients with systemic lupus erythematosus (SLE) or acquired immune deficiency syndrome (AIDS) exhibit chronically high levels of serum interferon, the role of plasma interferon in the natural pathogenesis of MTRS was anticipated. Grimley *et al.* (1985) described MTRS in the peripheral blood mononuclear cells during cycles of therapy with DNA-recombinant human alpha-interferon. These results together with exogenous alpha-interferon were consistent with the hypothesis that the frequent MTRS observed in the peripheral blood mononuclear cells of patients with SLE or AIDS may be pathogenetically related to the spontaneous and persistent elevations of endogenous alpha-interferon detected.

However, lymphocyte MTRS in cases of chronic SLE persisted without concomitant elevations of serum interferon (Carette *et al.* 1985). And MTRS could not be detected in several homosexual males with elevated serum interferon. This lack of direct correspondence between MTRS detection and serum interferon levels suggested that the duration or intensity of exposure to endogenous interferon may be critical. It is also conceivable that local concentrations of interferon in the reticuloendothelial system or tissues targeted by immune reactions could be more influential in MTRS formation than plasma levels. In dermatomyositis, vascular injury was considered to be the primary event, and both perifascicular atrophy and necrosis may be secondary to ischemia from the vascular lesion (Hashimoto *et al.* 1971; Chou and Miike 1981). Atrophic myofibers displayed a great variety of abnormalities, including subsarcolemmal collection of glycogen particles, Z-disk streamings, loss of myofilaments and rarefaction of sarcomeres. The present study revealed similar histologic features in myofibers. In addition, thick condensation of Z-band like material resembling nemaline rod was also observed. Although the nature of the vascular injury in dermatomyositis is unknown, the principal localization of MTRS in endothelial cells suggests that these structures might have some relation to the vascular injury. Some workers protested that the frequency of MTRS paralleled the degree of disease activity (Norton *et al.* 1970; Hashimoto *et al.* 1971). If the patient had a clinically active and progressive disease, the lesion was histologically active, and the frequency of inclusions was high. In our patients studied, although precise clinical evaluation in terms of grading was not obtained, the patients were admitted to the hospital in at least a clinically active state. It was of note that there were 3 cases in this study that showed MTRS in the pericytes. All of these cases also had MTRS in the endothelium, and one case had MTRS in the fibroblasts and histiocytes as well.

MTRS were observed in various tissues affected by systemic autoimmune diseases, AIDS and neoplasms. However, the cells in which they have been seen include endothelium, fibroblasts, glial cells, lymphoid cells, mononuclear cells, macrophages and tumor cells (Glick *et al.* 1980).

The fact that MTRS have been seen in many different disease states shows that they are neither pathognomonic nor diagnostic of any particular disease. However, frequent presence of these structures in the inflammatory myopathy has shown in the present study and literature that these are of considerable diagnostic value when taken in conjunction with clinical and histopathological features.

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＝국 문 초 록＝

자가면역성 근병증에서의 Microtubuloreticular structure (MTRS)

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권태정 · 박성혜 · 지제근

Microtubuloreticular structure(MTRS)는 직경 18-27 nm의 세망성 미세관(microtubule)으로 구성되며 rough endoplasmic reticulum의 확장된 cisterna에서 발견된다. 이 구조가 비록 정상 포유류 세포에서도 드물게 나타나지만 가장 흔히는 질병 특히 자가면역성 혹은 바이러스 감염증에서 발견되기 때문에 오래전부터 이 MTRS의 성상에 대한 논의가 있어 왔다.

저자들은 지난 2년간 서울대학교병원에서 염증성 근병증을 10예 경험하였다. 이들의 근 생검을 전자현미경으로 검색한 결과 전형적 MTRS가 혈관내피세포에서 8예, 혈관주위세포에서 3예, 간질 섬유모세포에서 2예, 그리고 조직구에서 1예 발견되었다. 이러한 소견을 통하여 MTRS가 염증성 근병증 특히 피부근염에서 피부생검을 하는 경우 그 진단에 중요한 의미를 가지고 있음을 알 수 있었고 또 MTRS는 혈관내피세포 외에도 혈관주위세포, 섬유모세포 혹은 조직구에서도 관찰될 수 있음을 알게 되었다.