Virchows Arch [Pathol Anat] (1981) 391:301–308

Virchows Archiv A

Light and Electron Microscopic Study of Ear Cartilage in a Case of Relapsing Polychondritis Evolving Under Corticoid Treatment

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Summary. Light and electron microscope studies of the ear cartilage in a patient with relapsing polychondritis (RP) under corticoid treatment are reported. Unilateral auricular deformation evolved without inflammatory episodes and the lesions consisted mainly of marginal erosions filled with fine collagen fibrils and containing degenerating perichondrial cells in their basal parts. Degenerative cells were scattered throughout the perichondrium, but cartilage erosions only occured when numerous cells were affected in a same area. Cartilage outside the eroded zones did not seem to be modified. Cartilage lesions thus appear to be a result of a chondrocyte renewal defect leading to loss of proteoglycans and elastic fibers, with only collagen remaining. These data suggest that inflammation is probably not the initial pathogenic process responsible for cartilage injury in RP, but that a metabolic defect in perichondrial cells might be involved.

Key words: Relapsing polychondritis – Ear cartilage – Marginal erosions – Perichondrial cell degenerescence

Introduction

Relapsing polychondritis (RP) or chronic atrophic polychondritis is a rare disease characterized by episodic inflammation of cartilages (mainly of ear, nose, trachea and bronchi) and peripheral joints. Involved cartilages undergo progressive atrophy resulting in characteristic deformations of the nose and ears and, frequently, in severe respiratory deficiency. The aetiology of RP is unknown. An autoimmune mechanism is probably involved (Dolan et al. 1966; Hughes et al. 1972; Herman and Dennis 1973; Rogers et al. 1973; Rajapakse and Bywaters 1974; Schaul and Schumacher 1975). Depletion of matrix proteoglycans

This work was carried out with a grant from the INSERM, CRL No 79. 1 218 4

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0340-1227/81/0391/0301/$01.60

reported in RP cartilage has been compared with effects of papain (Arkin and Masi 1975) and attributed to abnormal proteolytic activity of chondrocytes (Hashimoto et al. 1977). Our light and electronmicroscope observations of ear cartilage in an RP patient under corticoid treatment whose unilateral auricular cartilage atrophy evolved without inflammation, suggest that the basic disorder affects the function and differenciation of perichondrial cells.

Material and Methods

L.E. a 42 year old man, had been suffering from febrile bronchitic attacks for 10 years, associated 5 years later with episodes of accute polyarthritis, which regressed rapidly under corticotherapy. Dyspnoeic asthmatic crises occurred. Characteristic deformity of the nose (saddle deformation) and right ear (cauliflower aspect with hearing loss) developed progressively. The patient was admitted to the intensive medical care centre with intense dyspnoea. Tracheobronchoscopy revealed diffuse narrowing of the tracheobronchial tree, dyskenesia of the posterior walls of the trachea and primary bronchi which protruded during expiration and coughing, and marked congestion and tickening of the mucosa. The patient recovered with intensive corticoid and antibiotic treatment, but thenceforth required an intra-tracheal cannula (Hautant's cannula) to allow bronchial drainage, and corticotherapy had to be maintained to prevent recurrences. Biological signs consisted in increased sedimentation rate (80/100), hyperleucocytosis (without eosinophilia) but with no notable changes in serum proteins and no evidence of specific inflammation (absence of antistreptolysins, etc...). Immunological investigations revealed anticartilage antibodies against monkey trachea (Prof. Eyquem, Institut Pasteur, Paris) but only weak and even dubious positivity was observed subsequently.

The ear of the recovering RP patient and a normal ear of a 40-year old man in an irreversible coma were biopsied and the samples treated with conventional techniques for electronmicroscopy. Semithin sections stained with PAS-Hemalun, toluidin blue or Weigert's fuschsin-resorcin were studied histologically. A few thin sections were stained with 1% orcein. Nasal cartilage from a previous biopsy was studied solely on paraffin sections.

Results

Light Microscopy. Nose cartilage was almost entirely replaced by fibrous tissue in which remaining cartilage fragments still showed normal metachromasia with toluidine blue.

Ear cartilage had focal erosions appearing as triangular amorphous areas (Fig. 1a–d) bereft of chondrocytes and faintly orthochromatically stained with toluidin blue; only slight and irregular metachromasia remained near the normal matrix and chondrocytes lining the erosions. The eroded zones had no elastic fibers; the matrix elastic network broke off abruptly upon contact with them (Fig. 1a). The perichondrial cell layer was replaced by dispersed or clustered cells whose cytoplasm was full of fine clear vacuoles (Fig. 1c). The more peripheral cells with large vacuoles were obviously degenerating. A few vacuolated cells could be also observed outside the eroded zones, disseminated all along the fibrous perichondrium (Fig. 1e). No signs of perivascular inflammation were noted anywhere.

Most of the RP patient's cartilage did not appear different from that of the normal control. Chondrocytes had normal glycogen contents (Fig. 1d); matrix basophilia was unchanged as was development of the elastic network. However, a few clear lacunae, corresponding to empty capsules, were observed in some areas (Fig. 1f) whereas they were rare in the normal cartilage.

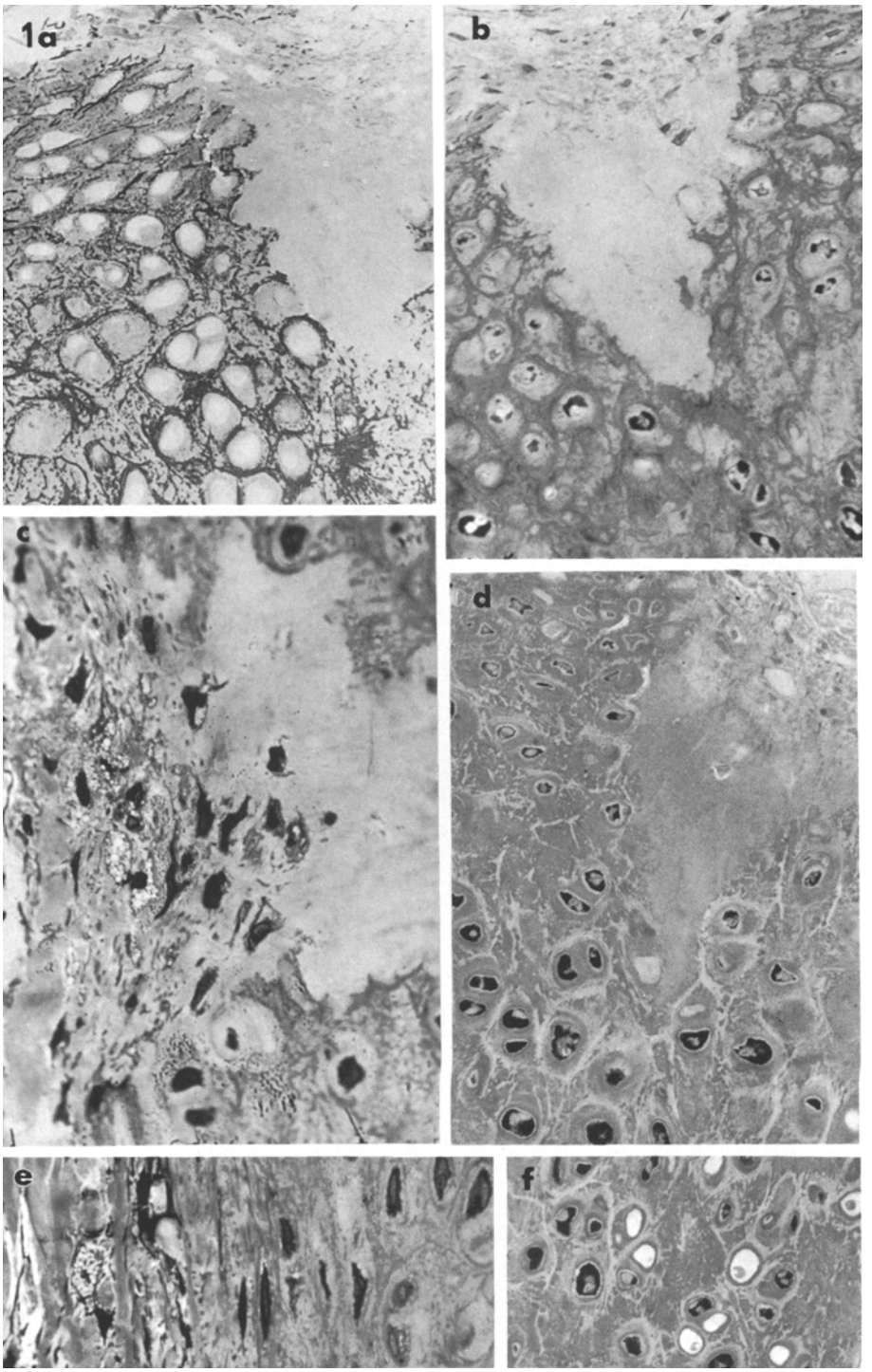

Fig. 1a–f. Semi-thin sections stained with fuchsin-resorcin (**a**), toluidin blue (**b, c, e**), PAS-hemalun (**d, f**). **a–d** eroded zones. Amorphous appearance and lack of chondrocytes and elastic fibers; abrupt interruption of the elastic network (**a**); disorganized perichondrium with vacuolated cells (clearly visible in **c**); normal aspect of cartilage with glycogen-loaded chondrocytes (**d**) outside the eroded zones. **a, b, d,** ×300; **c** ×500 **e** single vacuolated cell in the fibrous perichondrium; ×500. **f** Several clear lacunae (empty capsules) in the deeper cartilage ×200

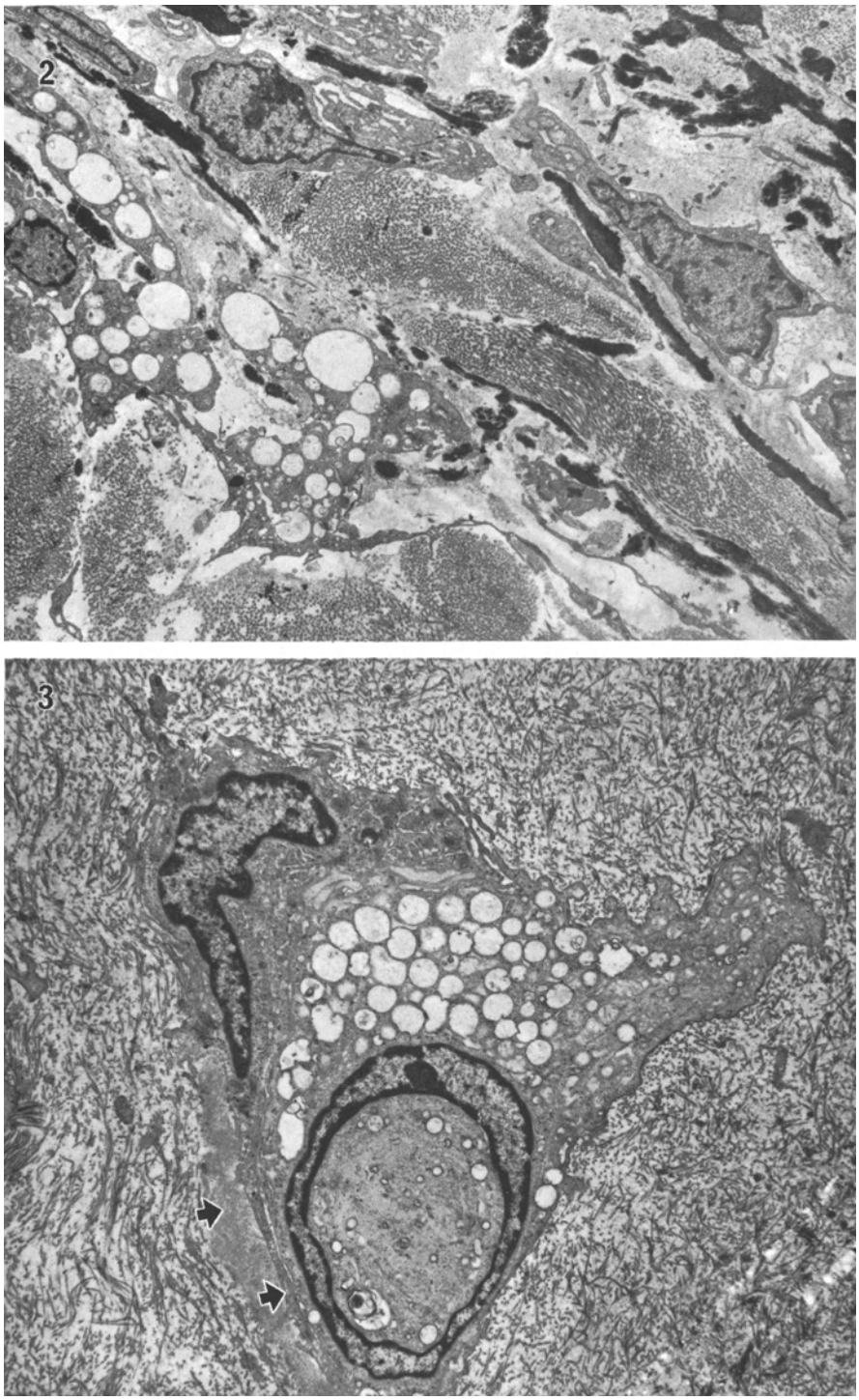

Fig. 2. Orcein-stained thin section. Superficial vacuolated perichondrial cells; normal aspect of the deeper perichondrial cells and elastic fiber network intensely stained with orcein. G $\times$4,500

Fig. 3. Eroded zone containing fine collagen fibrils and a vacuolated cell in contact with an apparently normal cell. Note large intranuclear cytoplasmic invagination containing microfilaments and fragmented ER elements in the vacuolated cell and a dense deposit (probably elastin) (*arrowed*) along the slender extension of the normal cell lining the vacuolated cell (*arrowed*) G $\times$5,600

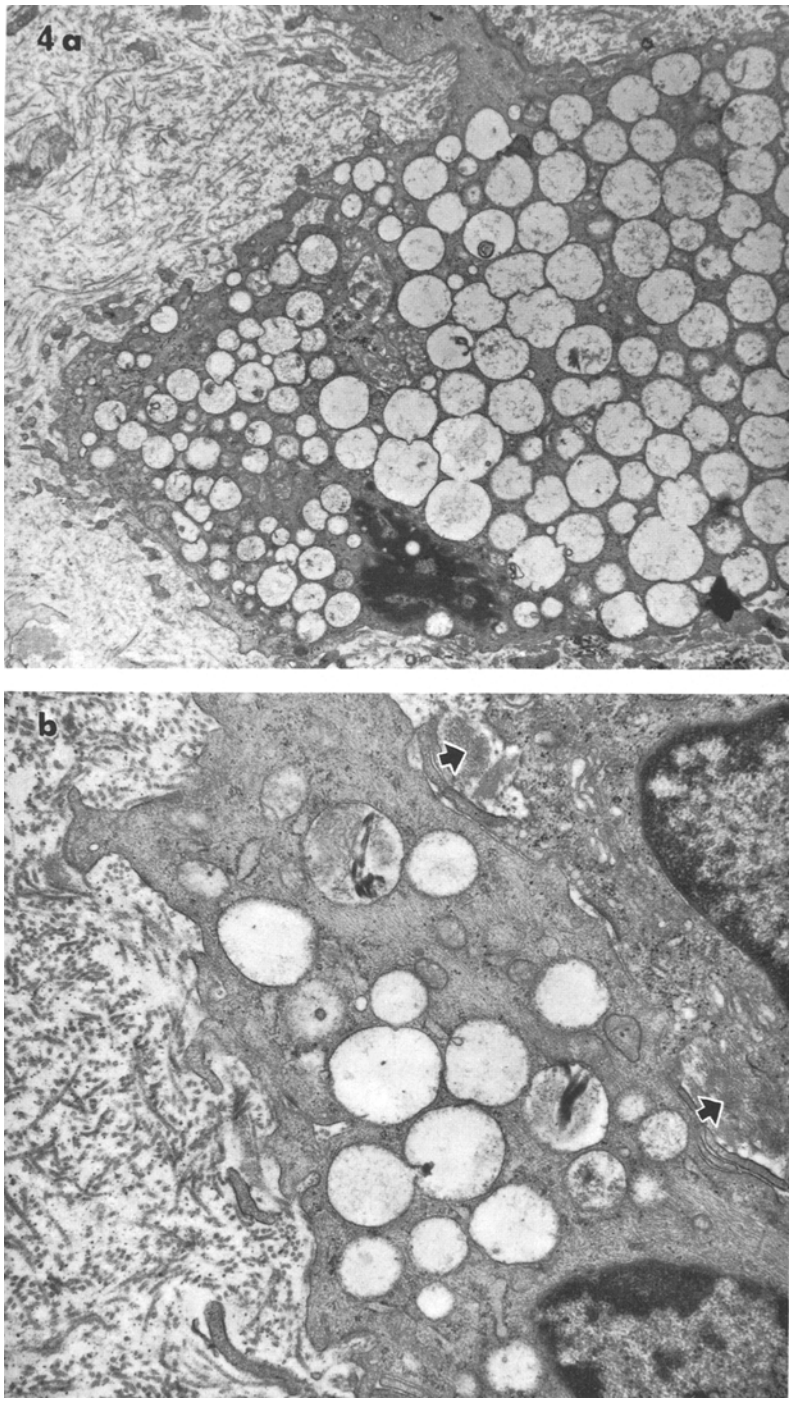

Fig. 4a, b. Vacuolated cells in an eroded zone. Vacuoles of various sizes (**a**) frequently accolated and often protruding into one another. Some contain membraneous debris. Cytoplasm contains abundant microfilaments, a few small recognisable mitochondria and rare rER saccules (**b**). Dense deposits (*arrowed*), indicating elastogenic activity, in contact with a normal cell associated with a vacuolated cell (**b**). Dense accumulation of vacuoles coinciding with nuclear pyknosis (**a**). **a** G $\times 7{,}000$; **b** $\times 15{,}000$

Electron Microscopy. There were no chondrocytic or matrix alterations in contact with the erosive areas which were full of fine collagen fibrils (Fig. 3). At the base of the erosions, vacuolated cells were identified as degenerative perichondrial cells (Fig. 2). Those in contact with the connective-vascular tissue were obviously necrotic as was shown by nuclear pyknosis and disintegration of the cytoplasm which was full of large, confluent vacuoles (Fig. 2). Deeper ones contained numerous microfilaments, rare and small mitochondria and extremely reduced rER and Golgi apparatus (Figs. 3, 4a–b). The vacuoles accumulated in the cytoplasm contained a fine granular substance sometimes with membraneous debris (Fig. 4b). Most of them probably originated through swellings of mitochondria and the loss of their cristae. Alongside such modified cells, were apparently normal cells in contact with which discrete deposits of dense fibrillar material were seen (Figs. 3, 4b), suggesting a feeble elastogenic activity.

Perichondrial cell changes were also seen outside the eroded zones. Often they were but slight, probably indicating the onset of functional deficiency. Progressive depletion of rER and Golgian elements, together with the accumulation of microfilaments seemed, as a rule, to precede vacuolisation.

Outside the eroded zones, no changes were noted in the structure of chondrocytes and matricial tissue nor in the distribution of "proteoglycan granules". A particular concentration of "matrix vesicles" has been reported in RP cartilage (Schaul and Schumacher 1975) and interpreted as evidence of more pronounced catabolic activity of chondrocytes (Hashimoto et al. 1977). These dense vesicles which originate from constrictions at the tips of minute cell processes and tend to agglomerate against mature or young elastic fibers at the periphery of the capsules, were no more abundant in the diseased cartilage than in the normal one.

Discussion

Ear cartilage atrophy in our RP patient seems to be essentially linked with perichondrial abnormalities. Chondrocytes themselves do not seem to be involved either in fibroblastic transformation (Grimaud and Bodelet 1973) or in lytic hyperactivity (Feinerman et al. 1970; Mitchell and Shepard 1972). The replacement of cartilage by a sheet of fine collagen fibrils inside the eroded zones may be related to focal degeneration of perichondrial cells impairing chondrocyte renewal. Rapid depletion of proteoglycans, with their short half life (Silbert 1973), is to be expected under such conditions and RP is in fact known to affect all the classes of proteoglycans in the cartilages involved (Hughes et al. 1972). While little is known on the renewal rates of the various elastic fiber components recent biochemical data do however suggest rapid renewal of newly formed elastin (Hance and Crystal 1975). Local defects in chondrocytes renewal thus could explain the loss of both proteoglycans and elastic fibers while only collagen remains. Cartilage does not seem to be appreciably modified when the degenerescence of scattered perichondrial cells is compensated for by differenciation of neighbouring cells. The severity of RP cartilage lesions thus appears to depend largely on the extension of perichondrial abnormalities. Disruption and fragmentation of cartilage can result from expansion and fusion

of eroded areas, which probably occurred in the nose cartilage of the same patient.

Fibrous erosions can also be privileged sites for invading inflammatory elements, including capillaries, as has often been reported in RP cartilage (Ishihara et al. 1973). Peripheral erosions might also give rise to the diffusion of antigenic factors from the cartilage, capable of inducing further immunological disorders responsible for cartilage and extra-cartilage inflammations. Anticartilage antibodies are not always found, and, above all, do not appear to be specific to RP (Hughes et al. 1972), Humoral or cell-mediated immunity (Herman and Dennis 1973; Rajapaske and Bywaters 1974) demonstrated in RP patients, might simply accompany cartilage destruction without being the cause of the disease. Extra-cartilaginous injuries (vasculitis, episcleritis, iritis, etc...) reported in RP patients (see review Hughes et al. 1972) could thus be accounted for as too could similarities between RP and collagen diseases such as Systemic Lupus Erythematosus where autoimmunity is known to play an important role.

Why perichondrial cells degenerate is not clear. RP mainly affects fibro-elastic-cartilage, but aneurysmal lesions (in particular aortic), reported in this disease suggest that non-chondrocytic elastogenic cells might be also affected. A congenital metabolic defect of perichondrial cells in involved cartilage can be envisaged. RP would thus be related to mesenchymal disgenesis affecting specialized mesenchymal cells, eg. keratocytes in Macular dystrophy of the cornea. However, a toxic effect of humoral factors, such as immunoglobin, which, although they do not diffuse freely in unmodified cartilage (Maroudas 1970), could chronically affect the perichondrium, cannot be ruled out. A viral etiology would perhaps best explain both cell changes and immunological pertubations. A link between chronic viral infection and immunological trouble appears highly probable, for example, in Systemic Lupus Erythematosus which, like other collagenosis-type diseases, can occur with RP.

Acknowledgements. The authors are grateful to Miss G. Haller and Mr. B. Peltre for their technical assistance.

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Accepted December 5, 1980