Clinical and Cellular Effects of Colchicine in Fibromatosis

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The proliferating cells in fibromatoses are myofibroblasts that produce abundant stromal collagen and contain intracellular native and widely spaced collagen fibers. To assess the clinical and cellular effects of colchicine in such tumors, this drug was administered to three patients, one with musculoaponeurotic desmoid fibromatosis, one with Dupuytren's palmar fibromatosis, and one with Peyronie's disease. All three patients had an excellent clinical response, with reduction of tumor size and improvement of contracture. Two cases were studied ultrastructurally; the main cellular changes detected were collapse of the rough endoplasmic reticulum cisternae, reduction of myofilaments, and disappearance of intracellular widely spaced collagen. The findings from this study indicate another probable application for colchicine and support the concept that collagen fibers can be formed intracellularly. *Cancer* 1992; 69:2478–2483.

The fibromatoses are a heterogeneous group of proliferative disorders of fibroblasts that infiltrate surrounding tissues but do not give rise to distant metastases. A common feature is the production of abundant stromal collagen. Electron microscopic studies of fibromatoses have shown that the proliferating cells are fibroblasts or myofibroblasts[1,2] and they may contain intracellular collagen fibrils.[3,4] Collagen fibrils normally are constructed within the extracellular space from precursor molecules secreted by the cells.[5,6] The presence of mature fibrils within the cytoplasm is consequently an abnormal event, but it has been seen occasionally in fibroblastic neoplasms and other soft tissue tumors. The underlying mechanism is controversial. Some authors postulate that it is an expression of the phagocytosis-degradation phenomenon,[3,7–9] whereas others believe that it represents an aberrant secretion process with intracellular polymerization of the collagen precursors.[10–13] The significance of intracellular collagen fibrils in cells of the fibromatoses is unclear, and their presence could reflect an abnormality in collagen synthesis.

Certain drugs, including colchicine and vinblastine, modify the secretory functions of cells by damaging microtubules.[14–17] Hypothetically, administration of these drugs to patients with fibromatoses might alter the process of collagen formation to a degree that could be manifested clinically and detected ultrastructurally. To investigate this possibility, colchicine was administered to three patients with different forms of fibromatosis. One had musculoaponeurotic fibromatosis (desmoid tumor), one had palmar fibromatosis (Dupuytren's contracture), and one had penile fibromatosis (Peyronie's disease). The clinical responses were evaluated, and two cases were studied ultrastructurally.

Case Reports

Case 1

Two years before admission, a 30-year-old woman became aware of a swelling in her right buttock. It increased in size rapidly and was painful. After 1 year she received homeopathic treatment and three cycles of chemotherapy without improvement. At the time of admission, a poorly defined mass estimated as 19 cm in greatest dimension involved the entire right gluteal and hip region, severely limiting movement at the hip joint. A biopsy showed an aggressive fibromatosis in its cellular phase. Treatment with 3 mg/d of colchicine was started, and in 3 weeks the tumor was 40% smaller and well circumscribed. It was no longer painful, and

Presented in part at the XIII European Congress of Pathology, Ljubljana, Yugoslavia, September 1–6, 1991.

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The authors thank Dr. Bruce MacKay for reviewing the manuscript; Drs. Ruy Perez Tamayo and Jorge Albores-Saavedra for their valuable opinions; and Nery Rocha for technical assistance in ultrastructural examination.

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Accepted for publication August 15, 1991.

normal walking was possible. Wide local excision was performed 2 weeks later, and microscopic evaluation of the resected specimen confirmed the diagnosis of aggressive fibromatosis (desmoid tumor). A maintenance dose of 1 mg/d of colchicine was given for 6 months. Two years after surgery, there is no evidence of recurrence.

Case 2

A firm nodule in the center of the right palm of a 21-year-old woman increased in size over a 2-year period until it was 7 × 7 cm, progressively limiting movement of the fingers because of severe contracture. The clinical diagnosis of palmar fibromatosis (Dupuytren's contracture) was confirmed by biopsy. Treatment with 3 mg/d of colchicine was initiated.

By the seventh day, there was subjective reduction in the size of the tumor, and 1 week later movement of the fingers was improved considerably. Two weeks after this, opposition of the thumb was possible without discomfort. Treatment was continued with 1 mg/d of colchicine. Three months later, there was only a mild residual functional deficit, and the nodule measured 2 × 2 cm. The tumor was excised for histologic and ultrastructural study. A 1 mg/d maintenance dose of colchicine was instituted. Two years later, the patient is in clinical remission with no detectable tumor.

Case 3

Six months before admission, a 47-year-old man noticed angulation of the midportion of his penile shaft, which increased rapidly to 45 degrees. There was intense pain with erection and total sexual dysfunction. He was seen by a urologist, who documented a 2.5 × 2.0 cm indurated area in the corpora cavernosa and made the clinical diagnosis of penile fibromatosis (Peyronie's disease). Without histologic confirmation, treatment with 3 mg/d of colchicine was started; the dose was reduced subsequently to 2 mg and then 1 mg because of toxicity. By the time a cumulative dose of 20 mg had been administered, the penile angulation had diminished by approximately 40%, pain had disappeared, and induration no longer could be detected. The patient received 2 mg/d of colchicine for 2 more months without additional clinical improvement. Two years after treatment, the induration and pain have not recurred; the patient still has a 20-degree angulation

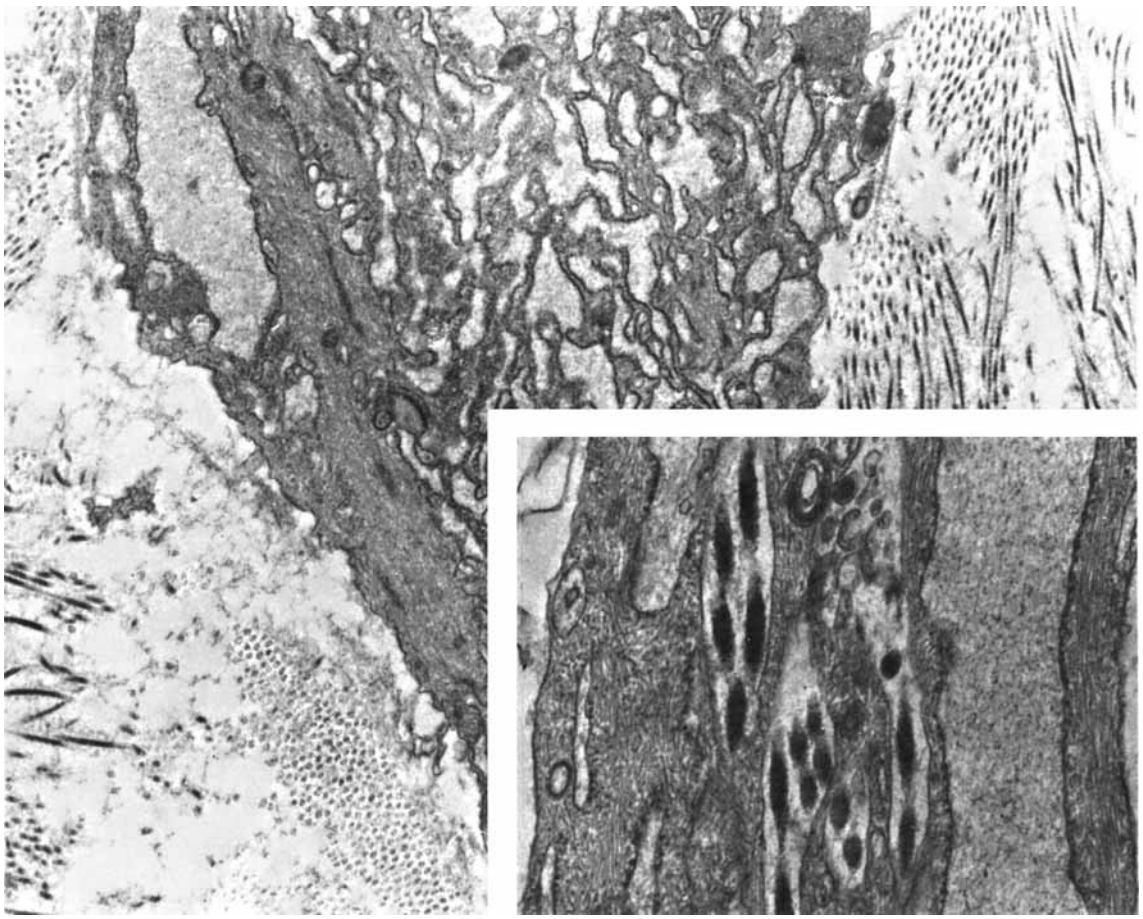

Figure 1. Ultrastructure of musculoaponeurotic fibromatosis before treatment with colchicine. The myofibroblasts contain abundant cytoplasm with RER cisternae and peripheral myofilaments. Collagen fibers with native periodicity are seen within cytoplasmic vesicles (*inset*) and in the extracellular space (uranyl acetate and lead citrate, original magnification ×4400; *Inset*: original magnification ×12,000).

and only mild sexual dysfunction. A biopsy was not performed in this patient.

Microscopic Findings

Conventional paraffin sections stained with hematoxylin and eosin were available from Cases 1 and 2 for review. Both tumors were composed of nodules of plump, spindle-shaped cells surrounded by bands of dense fibrous tissue. The cells were cytologically bland, and mitotic figures were fewer than 1/20 high-power fields. The tumor in the first patient, an aggressive fibromatosis (desmoid tumor), was infiltrating adjacent skeletal muscle extensively.

In Cases 1 and 2, ultrastructural examination was performed before and after colchicine treatment. On the initial biopsy specimen of both cases, the proliferating cells had abundant cytoplasm with multiple extensions that contained many dilated cisternae of rough endoplasmic reticulum (RER) and slender peripheral bundles of smooth muscle myofilaments. Many intracytoplasmic vesicles contained collagen fibers of native periodicity (Fig. 1). Fibrous long-spacing (FLS) collagen was present within a number of RER cisternae; it consisted of widely spaced collagen fibers with a periodicity of 1000 A, which merged with granular material having an identical periodicity (Fig. 2). FLS collagen was not identified within the extracellular space.

A comparative analysis was performed with the use of a planimeter on electron micrographs of specimens from Cases 1 and 2 before and after treatment to provide an assessment of the changes that occurred.

The main ultrastructural changes found after treatment with colchicine were reduction of the total cellular area, diminished number of cells with dilated RER, diminished proportion of myofibroblasts, and disappearance of the FLS collagen. The cells had retraction and thinning of their cytoplasmic extensions (Fig. 3).

Discussion

Studies of collagen secretion and fibrogenesis have demonstrated that the precursor molecule, procollagen, is synthesized in the RER of the fibroblasts, and then it goes through transitional elements of RER to the Golgi apparatus. Later it is transported in vesicles to the cell surface, where it is converted to collagen by the enzymatic action of procollagen peptidase.[18]

Under normal conditions, the cells do not store procollagen or collagen fibers in their cytoplasm; however, it has been demonstrated that in actively remodeling connective tissue the myofibroblasts have collagen fibers in cytoplasmic vesicles.[19–21]

The presence of intracellular collagen is typical of fibromatoses,[3,12] although it occasionally has been de-

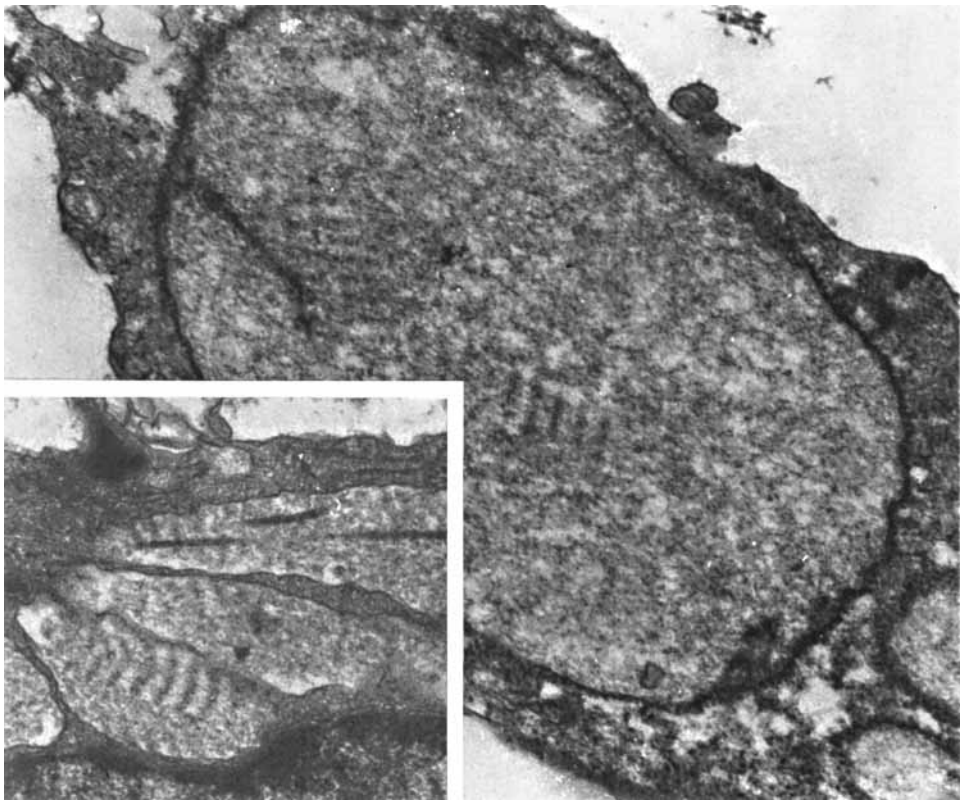

Figure 2. FLS collagen within dilated RER before treatment with colchicine. (*Inset*) The granular material is arranged in bands with a periodicity of 1000 A in continuity with fibers (uranyl acetate and lead citrate, original magnification ×20,000).

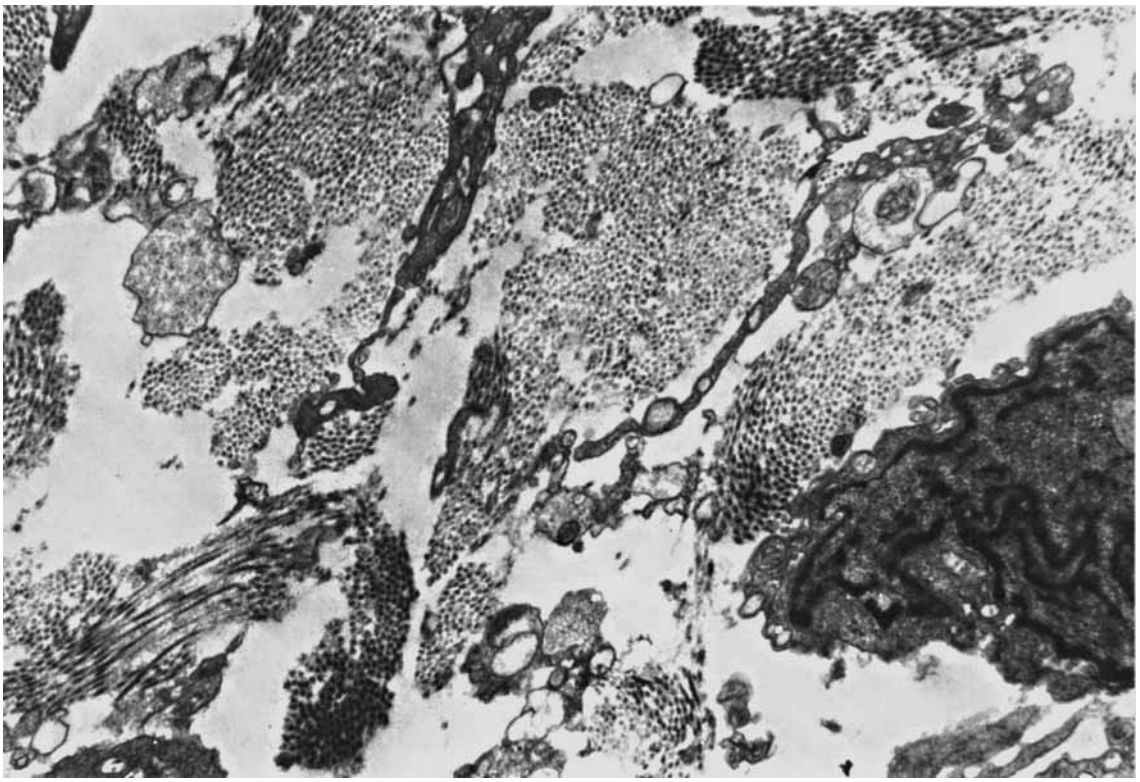

Figure 3. After treatment with colchicine, the fibroblasts became small, with slender cytoplasmic extensions and collapsed RER cisternae. No FLS bodies were seen, and myofilaments were greatly reduced (uranyl acetate and lead citrate, original magnification ×3000).

scribed in other mesenchymal tumors[22] and inflammatory conditions.[4,23,24]

The origin of intracellular collagen remains controversial. Some authors postulate that the fibers are phagocytized for degradation,[7,19-21,25,26] whereas others support the concept of intracellular polymerization of fibers. In 21 specimens of Dupuytren's contracture, Gokel and Hubner[12] found intracellular FLS collagen bodies within cisternae of RER. This observation indicates that the vacuoles and FLS collagen are not section artifacts or invaginations of the cellular surface. It also eliminates the possibility of phagocytosis or degradation within vacuoles. They demonstrated FLS collagen merging with periodically arranged granular material identical to that we saw.

Structures similar to FLS collagen originally were described *in vitro* by Schmitt *et al.*[27] in connective tissue extracts. According to Gross,[28] FLS collagen is formed when tropocollagen molecules are arranged randomly in antiparallel fashion. These structures or "spindle bodies" were described within fibroblasts of several tissues by Movat and Fernando.[29] Their collagenous nature was demonstrated by Fernandez-Madrid *et al.*,[13] who observed massive induction of FLS collagen in chick embryo fibroblasts with the administration of a single dose of colchicine. Their findings suggest that it represents the first step of autophilia of collagen products when the secretion process is blocked. This could be an amplification of the normal process.[30-32] After colchicine administration, we found decreased FLS collagen instead of massive induction. This apparent discrepancy may result from the use of colchicine for a long time, with possible modification of the morphologic expression of collagen fibrogenesis and autophagocytosis.

It is interesting that myofibroblasts decreased in size, their RER collapsed, and they lost the myofibrils. These findings probably explain the clinical effects of tumor size reduction and contracture suppression in our cases. If colchicine inhibits the contractile properties, it could be possible to achieve clinical effects in other conditions characterized by pathologic contracture, such as third-degree burns, rheumatic valvulopathy, peritoneal adhesions, and deforming scars.

To date, the treatment of choice for fibromatoses is surgery, with poor results and frequent recurrences. Other treatments, such as radiation therapy[33] and chemotherapy,[34] have low effectiveness and high morbidity. In isolated cases, good results have been reported with hormones[35,36] and antiinflammatory drugs.[37-39] Colchicine has not been used in fibromatosis. It is an inexpensive, relatively safe drug, and it has been effective in many inflammatory and fibrosing diseases.[40-52]

However, its intimal mechanism of action remains an enigma.

We believe that our results are promising, but additional studies are needed to confirm the clinical and morphologic effects obtained in our three patients and to determine the type and stage of fibromatosis in which colchicine could be effective.

Addendum

We have treated seven more patients with colchicine: three patients with musculoaponeurotic fibromatosis (tumor reduction of 50% in one patient; the other two have recent cases); one patient with palmar fibromatosis (90% reduction with total functional improvement, lost to follow-up); two patients with keloid scars (no recurrence after surgical excision); and one patient with a painful fracture callus of metacarpal bones (100% functional improvement after 1 week of treatment). However, the follow-up periods are still insufficient for valid conclusions to be drawn.

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