Possible role of plasminogen activator content of the palmar nodules in recurrence of Dupuytren's contracture

Increased amounts of plasminogen activator enzymes were found in the large Dupuytren's nodules in the so-called active phase of the disease. A prospective study in 15 patients who had operations investigated possible relationships between fibrinolytic capacity of the palmar nodules (assessed by the fibrin plate method) and the recurrence of contracture. There were substantial analogies and suggestive connections with the results of previous electron microscopic studies. Combined with the presence of myofibroblasts, the high increase of plasminogen activator enzymes in the fascial nodules may be regarded as a predictive marker for possible recurrence after surgical treatment of Dupuytren's contracture. (J HAND SURG 1987;12A:1017-9.)

Giovanni Merlo, M.D., F.I.C.S., Gian Paolo Ambroggio, M.D., Aldo Mosca, M.D., *and* Elisa Oberto, M.D., *Turin, Italy*

In 1972 Gabbiani and Majno[1] first described unusual fibroblasts (myofibroblasts) in the palmar fascia of patients with Dupuytren's contracture. Several other investigators have stated that the only location of these cells was in the nodules of the aponeurosis[2, 3] or in the overlying palmar skin.[4, 5] All of these authors believed that the nodules play a primary role in the production of contracture through the smooth muscle-like properties of myofibroblasts. In addition, Gelberman et al.[3] observed an interesting connection between the presence of myofibroblasts in the palmar nodules and the recurrence of the disease after surgical treatment. These cells were found in the nodules of the resected aponeurosis of all three patients in their series who had a recurrence. They concluded that the presence of myofibroblasts in the resected palmar fascia of patients with Dupuytren's contracture is a marker of disease activity and that the resection of aponeurosis during periods of myofibroblast activity may be followed by recurrence in higher number of patients than would be expected. Metabolic activity of the myofibroblasts, with well-developed rough endoplasmic reticulum, Golgi apparatus, microfilaments with numerous electron-dense bodies, and indented nuclei that suggest active contraction, have indeed been shown and reported by Vande Berg et al.[5]

In our recent biochemical study[6] of the pathogenesis of Dupuytren's contracture we found a remarkable decrease or even complete lack of fibrinolytic capacity of the palmar tissue and presence of fibrin/fibrinogen in those areas of the aponeurosis where early small nodules were forming. There were considerable amounts of plasminogen activator enzymes in the large nodules of the evolutionary phase of the disease. We concluded that a decrease of fibrinolytic capacity probably allows the deposition of fibrin in the palmar aponeurosis and the formation and enlargement of nodules by progressive adhesion of fibroblasts to the polymerizing fibrin. The high fibrinolytic activity of the large nodules results from the "modulation" of many fibroblasts into contractile myofibroblasts and therefore could be considered as a biochemical sign of evolution of contracture. It has been observed that when fibroblasts undergo transformation they synthesize, like stimulated macrophages, very high amounts of plasminogen activators.[7]

Compared with former studies, our results suggest certain correlations between the electron microscope

From the Institute of Surgical Pathology, University of Turin, and the Division of Plastic and Reconstructive Surgery, Trauma Center, Turin, Italy.

Research was supported by a grant from the Ministry of Education.

Received for publication Aug. 18, 1986; accepted in revised form April 13, 1987.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Reprint requests: Giovanni Merlo, M.D., Via Vittorio Veneto 14, 10017-Montanaro/Turin, Italy.

Table I. Relationship between duration of disease, age of patients, presence of other fasciitis, increased fibrinolytic capacity of the fascial nodules, and recurrence after operation to treat Dupuytren's contracture

Duration of contracture (yr)	*Patients (no.)*	*Average age (yr)*	*Other fasciitis* (no.)*	*Recurrence (no.)*	*Increased fibrinolytic capacity of the nodules (no.)*
0-2	2	38	0	1	2
3-7	7	54	3	0	3
8-12	5	68	3	1	2
>12	1	72	1	0	1
Total	15		7	2	8

*Other hand, foot, or penis.

and the biochemical data. A prospective study was therefore carried out in 15 patients who had operations to treat Dupuytren's contracture, to investigate possible connections between the fibrinolytic capacity of the nodular tissue and the recurrence of disease after surgical treatment.

Materials and methods

Fibrinolytic capacity of the palmar fascia was assessed in 14 men and one woman patient; ages ranged from 37 to 74 years. Operations were performed with the patient under general anesthesia to treat Dupuytren's contracture. The average duration of disease was 6 years (range of 2 to 13 years). Eight patients had bilateral disease and Peyronie's syndrome was present in one of them. Specimens were taken from nodules that were often tightly linked with the overlying skin and from the seemingly uninvolved areas of each aponeurosis. Fibrinolytic capacity was assessed by the fibrin plate technique[8] and expressed as mm^2 of lysis area per milligram of defatted wet tissue.[6] Increased plasminogen activator content of the nodule was recorded as a positive difference between its fibrinolytic capacity and that of the surrounding apparently uninvolved tissue.

Since the majority of recurrences occur within the first few postoperative months,[9, 11] our patients were followed-up for a minimum of 3 years, with an average follow-up of 41 months. Frequent follow-up visits allowed close examination for recurrence of fasciitis.

Results

During 52 months of follow-up two true recurrences were noted at 24 and 30 months after operation. According to Gelberman et al.,[3] a true recurrence is defined as "the appearance of new fascial nodules or bands, determined by appearance and palpation, in an area where fasciectomy had been previously performed." Duration of disease averaged 5 years and 6 months in the patients with recurrence. No relationship was identified between the age of patients, duration and severity of contracture, bilateral incidence, presence of Peyronie's disease, and recurrence of fasciitis (Table I). Increase of fibrinolytic capacity ranged from 8% to +184% in the nodules of eight of 15 patients.

Comparison of biochemical data with the clinical course revealed some interesting findings. Of seven patients who lacked increased fibrinolytic capacity in the nodules, none had a recurrence. The incidence of recurrence in patients with increased plasminogen activator content was two of eight. Patients with significant increase (+170 and +184) of specific fibrinolytic enzyme content had a recurrence.

Discussion

Recurrence of deformity has been noted over a period as long as 10 years after operation to treat Dupuytren's contracture.[10, 12] The pattern has been well described by several investigators.[9, 10] Previous theories of the basic pathogenesis suggested that the disease has a definable chronological pattern, marked by repeated periods of waxing and waning, with predictable stages of development.[13, 15] The so-called "active phase" is mostly identified with the nodular thickening of the fascia.[15, 16] Efforts to find a common denominator among patients with recurrent fasciitis were unsuccessful for a long time, but the finding of myofibroblasts in the fascial nodules seemed to explain the mechanisms of clinical recurrence. Thus the presence of these cells was proposed as a marker of disease activity in Dupuytren's contracture,[3] although recurrence was observed in only three of seven cases with myofibroblasts in the nodules of the resected aponeurosis.

Studies of granulating wounds in animals[14, 17] and

electron microscopic research in man[5] indicated a defined life cycle of these cells. This leads us to think that the myofibroblasts were in a particularly active phase in those three cases. Thus reliable signs of an active state of the myofibroblasts could identify patients with higher risk of recurrence better than the mere presence of these cells in the fascial nodules.

This work has shown true recurrence of disease in only two of eight patients with increased plasminogen activator content in the nodules, but only in those with the highest fibrinolytic enzyme content.

Fibroblasts are known to have the capacity to increase the release of plasminogen activator enzymes when particular conditions occur[18] or when they incur a transformation process.[7] Then if one considers that myofibroblasts are nothing but a temporary and reversible modification ("modulation") of fibroblasts substantial analogies and likely connections seem to exist between the results of our work and the electron microscopic study of Gelberman et al.[3] Recurrences occurred in both series of patients only when there were myofibroblasts in the nodules and, especially, only when the nodules had a very high increase of plasminogen activator content. We propose that the probability of recurrence after operation correlates in some measure with an active state of the myofibroblasts in the palmar nodules at the time of the surgical treatment of disease. The high fibrinolytic capacity of these cells at that time also may have a part in the onset and development of recurrence.

REFERENCES

1. Gabbiani G, Majno G. Dupuytren's contracture: Fibroblast contraction? An ultrastructural study. Am J Pathol 1972;66:131-46.
2. Hueston JT, Hurley JC, Wittingham S. The contracting fibroblast as a clue to Dupuytren's contracture. Hand 1976;8:10-12.
3. Gelberman RH, Amiel D, Rudolph RM, Vance RM. Dupuytren's contracture. An electron microscopic, biochemical and clinical correlative study. J Bone Joint Surg [Am] 1980;62:425-32.
4. James WD, Odom RB. The role of the myofibroblast in Dupuytren's contracture. Arch Dermatol 1980;116: 807-11.
5. Vande Berg JS, Rudolph R, Gelberman R, Woodward MR. Ultrastructural relationship of skin to nodule and cord in Dupuytren's contracture. Plast Reconstr Surg 1982;69:835-44.
6. Merlo G, Ambroggio GP, Castagna B, Mosca A, Oberto E. Fibrin/fibrinogen and and fibrinolytic activity of the palmar fascia in Dupuytren's contracture. J HAND SURG 1986;11B:55-7.
7. Unkeless JC, Gordon S, Reich E. Secretion of plasminogen activator by stimulated macrophages. J Exp Med 1974;139:834-50.
8. Astrup T, Mullertz S. The fibrin plate method for extimating fibrinolytic activity. Arch Biochem 1952;40: 346-51.
9. Hueston JT. Digital Wolfe grafts in recurrent Dupuytren's contracture. Plast Reconstr Surg 1962;29:342-4.
10. Millesi H. The clinical and morphological course of Dupuytren's disease. In: Maladie de Dupuytren. Paris: Expansion Scientifique, 1966:47-60.
11. Tubiana R. Les conceptions actuelles du traitement chirurgical de la maladie de Dupuytren. In: Orthopédie et traumatologie. Conférences d'enseignement. Paris: Expansion Scientifique, 1967:7-21.
12. Hakstian RW. Late results of extensive fasciectomy. In: Maladie de Dupuytren. Paris: Expansion Scientifique, 1966:123-7.
13. Luch JV. Dupuytren's contracture. A new concept of the pathogenesis correlated with surgical management. J Bone Joint Surg [Am] 1959;41:635-64.
14. Gokel JM, Hübner G. Occurrence of myofibroblast in the different phases of Morbus Dupuytren (Dupuytren's contracture). Beitr Pathol 1977;161:166-75.
15. Chiu HF, Mc Farlane RM. Pathogenesis of Dupuytren's contracture. A correlative clinical-pathological study. J HAND SURG 1978;3B:1-10.
16. Hamamoto H, Ueba Y, Sudo Y, Sanada H, Yamamuro T, Takeda T: Dupuytren's contracture. Morphological and biochemical changes in palmar aponeurosis. Hand 1982;14:237-47.
17. Gabbiani G, Hirschel BJ, Ryan GB, Staktov PR, Majno G. Granulation tissue as a contractile organ. A study of structure and function. J Exp Med 1972;135: 719-34.
18. Crutchley DJ, Connan LB, Maynard JR. Stimulation of fibrinolytic activity in human skin fibroblasts by prostaglandins E_1, E_2, and I_2. J Pharmacol Exp Ther 1982;222:544-9.