THE PATHOLOGY OF FROZEN SHOULDER

A DUPUYTREN-LIKE DISEASE

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Of 935 consecutive patients referred with shoulder pain, 50 fitted the criteria for primary frozen shoulder. Twelve patients who failed to improve after conservative treatment and manipulation had excision of the coracohumeral ligament and the rotator interval of the capsule. The specimens were examined histologically, using special stains for collagen. Immunocytochemistry was performed with monoclonal antibodies against leucocyte common antigen (LCA, CD45) and a macrophage/synovial antigen (PGMI, CD68) to assess the inflammatory component, and vimentin and smooth-muscle actin to evaluate fibroblasts and myofibroblasts.

Our histological and immunocytochemical findings show that the pathological process is active fibroblastic proliferation, accompanied by some transformation to a smooth muscle phenotype (myofibroblasts). The fibroblasts lay down collagen which appears as a thick nodular band or fleshy mass.

These appearances are very similar to those in Dupuytren's disease of the hand, with no inflammation and no synovial involvement. The contracture acts as a check-rein against external rotation, causing loss of both active and passive movement.

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The term frozen shoulder was first used by Codman (1934) who described the common features of slow onset, pain near the insertion of the deltoid, inability to sleep on the affected side, painful and restricted elevation and external rotation, and a normal radiological appearance. Lundberg (1969) subdivided the frozen shoulder syndrome into primary or idiopathic cases and those in which the condition was secondary to soft-tissue injury, fracture, arthritis, hemiplegia or any other known cause.

The cause of frozen shoulder remains enigmatic. The original pathological descriptions of Neviaser (1945) and Simmonds (1949) suggested a chronic inflammatory condition, but Lundberg (1969) found no significant number of inflammatory cells. He suggested that the primary pathology was fibrosis and fibroplasia, reporting that the morphology of the contracted tissue was similar to that of Dupuytren's contracture. Kay and Slater (1981) described the histological findings of the shoulder capsule in one diabetic patient and found them to be identical to those seen in fibromatoses such as Dupuytren's disease with none of the inflammatory features described by Neviaser (1945).

Recent arthroscopic studies (Wiley 1991; Uitvlugt et al 1993; Bunker, Lagas and DeFerme 1994) and open surgical exploration (Ozaki et al 1989) have suggested that the main abnormalities in primary frozen shoulder are in the rotator interval and the anterior capsule. Neer et al (1992) suggested that the coracohumeral ligament was contracted and Ozaki et al (1989) stated that release of this ligament was curative.

We therefore decided to excise the coracohumeral ligament in patients who had failed to respond to manipulation under anaesthesia for chronic frozen shoulder, and to subject the excised tissue to histological examination. We aimed to confirm the presence of a contracture and to discover whether it was inflammatory or fibroblastic in nature.

PATIENTS AND METHODS

We studied only primary or idiopathic cases of frozen shoulder, defining the syndrome by Codman's (1934) original criteria, as modified by Zuckerman, Cuomo and Rokito (1994). The criteria for inclusion were insidious onset, true shoulder pain, night pain, painful restriction of

both active and passive elevation to less than 100° and of external rotation to less than one half of normal, and a normal radiological appearance.

Of 935 patients referred to the Exeter Shoulder Clinic, a total of 50 fulfilled these criteria and formed the study group. All 50 were at first treated conservatively by steroid injection and physiotherapy for at least two months. Nine patients improved; the other 41 failed to gain relief and were advised to have a manipulation under anaesthesia.

To exclude any other cause for their symptoms, shoulder arthroscopy was performed before manipulation unless there was a specific contraindication. The 12 patients who failed to improve after manipulation had the surgical release described by Ozaki et al (1989) and the tissue obtained from these patients was used for the histological study.

Patients. The average age of the 50 original patients was 56.1 years; there were 24 women and 26 men. The left and right shoulders were equally involved, with an average duration of symptoms of 15.5 months.

On examination the mean combined elevation was 83.2° with mean external rotation of 9.4°. Twenty-nine patients (58%) had evidence of Dupuytren's contracture in the hand. Twenty-two (44%) were either known to be diabetic or had an elevated fasting blood-sugar level, which was measured in all patients. The mean fasting serum lipid level was also elevated as against a matched control group; this finding is reported separately.

Of the 12 patients requiring surgical release, four were diabetic, one of them being insulin-dependent. Ten had had a previous shoulder arthroscopy. All ten showed scarring and contracture of the tissues at the rotator interval. The infraglenoid recess was found to be less capacious than normal and the capsule was thickened. As reported in all other arthroscopic studies (Wiley 1991; Uitvlugt et al 1993; Hannafin, DiCarlo and Wickiewicz 1994; Esch 1994), there were no adhesions.

Surgical release. We performed open surgical release in 12 patients through a 5 cm oblique skin-crease incision, from the lower border of the clavicle to just below the coracoid process. The deltoid muscle was split in the direction of its fibres and the coracoacromial ligament was exposed and cleaned. This ligament appeared to be normal and was excised to expose the coracohumeral ligament.

In 11 of the 12 cases the coracohumeral ligament appeared to be abnormal; in the other case it looked normal but was histologically abnormal and had the appearance of a nodular fleshy band (Fig. 1) which was inextensible and prevented external rotation. In three patients the band had been partially torn by the previous manipulation. The whole of the rotator interval was grossly thickened making it difficult to define the edges of subscapularis and supraspinatus. The area of the coracohumeral ligament and the rotator interval was excised, using electrocautery because of its considerable vascularity. As large a specimen as possible was taken for histological examination.

In ten patients, this excision of the coracohumeral ligament provided immediate release with external rotation improving from a mean of 5° to a mean of 58°. In two patients there was no improvement; one of these was diabetic with severe Dupuytren's contracture in both hands.

Excision of the coracohumeral ligament creates a hole in the capsule through which the long head of biceps can be seen, but no attempt was made to close the gap. Subcuticular sutures were used to close the wound; all patients were discharged on the first postoperative day to attend for outpatient physiotherapy.

Histological examination. All 12 specimens were examined by one author (PPA) with no prior knowledge of the clinical history or operative findings. Blocks were fixed in 10% buffered formalin, embedded in paraffin wax and sectioned for staining with haematoxylin and eosin, Van Gieson (for collagen type III), and Martius scarlet blue (MSB, for collagen types I and III). Sections were also studied for birefringence under polarised light, and others were prepared for immunocytochemistry by the avidin biotin complex method (Hsu, Raine and Fanger 1981). We used monoclonal antibodies against the following antigens: leucocyte common antigen (LCA, CD45 Dako, cat.no. M701, 1:150 dilution), macrophage and synovial-cell anti-
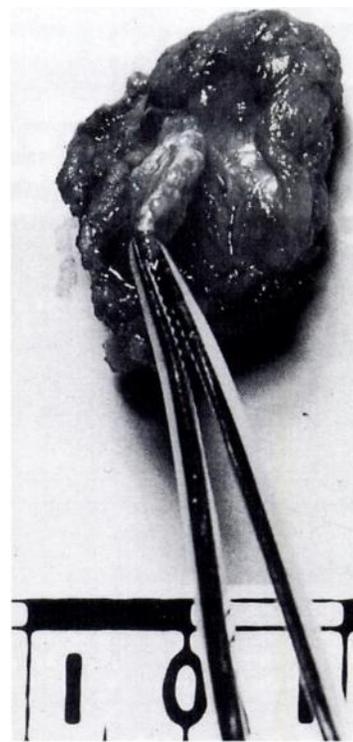

Fig. 1

An operative specimen. The forceps hold the coracoacromial ligament, under which is the excised coracohumeral ligament, altered to nodular fleshy tissue.

Table I. Details of the findings in 12 specimens excised from patients with frozen shoulder

Case	Sex/age (yr)	Mature collagen	Cellularity	Vascularity	Monoclonal antibodies (see text)			
					LCA	Vimentin	PGMI	ASMA
1	F/54	+++ nodular/ laminar	+++ in nodules	+++	+ -	+++	+ -	+
2	M/56	++ nodular/ laminar	+++ in nodules	+++	-	+++	+	++
3	M/52	++ laminar/ nodular	+	+	+ -	+	+ -	+ -
4	M/56	+++ nodular/ laminar	+++ in nodules	+++	+	+++	+	++ -
5	F/50	++ laminar/ nodular	+ scattered	+	-	+	-	-
6	M/50	++ nodular/ laminar	++ in nodules	++	+ -	++	+ -	+ -
7	M/48	+++ laminar/ nodular	+	++	+	++	+	+
8	M/46	+++ laminar/ nodular	++ scattered	+++	-	++	+	++
9	F/55	++ nodular/ laminar	++	++	+ -	++	+	++
10	M/69	++ laminar/ nodular	++	++	-	++	-	+ -
11	F/60	++ laminar/ nodular	++	+	+ -	++	-	+ -
12	M/52	+++ laminar/ nodular	++	+	+	++	-	-

gen (PGMI CD68, Dako cat.no. M876, 1:300 dilution after pretreatment with Trypsin), the common mesenchymal cell intermediate filament vimentin (Dako cat.no. M725, 1:12 dilution) and alpha smooth-muscle actin (Sigma cat.no. A-2547, 1:40 000 dilution after pretreatment with Trypsin). These were used according to the manufacturer's instructions with appropriate negative and positive controls and internal controls in the sections themselves (for example, connective-tissue septa in fat and the smooth-muscle walls of blood vessels). Positive results were visualised by horseradish peroxidase digestion of diaminobenzidine (DAB) after neutralisation of endogenous peroxidase by hydrogen peroxide in alcohol.

For comparative purposes, Dupuytren's tissue excised from the hands of six other patients was similarly treated, sectioned and stained and the same immunocytochemical methods and antibodies applied.

The results are shown in Tables I and II as negative (-), or positive on a semiquantitative scale from +(weak), ++(moderate), or +++(strong) by visual assessment under the microscope.

RESULTS

The histological findings and results of immunocytochemistry in the 12 patients with primary frozen shoulder and six with Dupuytren's contracture of the hand are summarised in Tables I and II.

The blocks of excised tissue from the shoulders measured from 1.0 × 1.0 cm to 5.0 × 3.0 cm (average 2.4 × 1.5 cm). They were either nodular or laminar or showed a mixture of these patterns (Fig. 2). The nodules consisted of fibroblasts intermingled with collagen; cellularity was high or moderate (Fig. 3). The more laminar

Table II. Details of the findings in six cases of Dupuytren's disease

| Case | Sex/age (yr) | Mature collagen | Cellularity | Vascularity | Monoclonal antibodies (see text) | | | |
					LCA	Vimentin	PGMI	ASMA
1	F/35	++ nodular/ laminar	++	+++	+ small aggregates of lymphocytes around periphery	++ particularly in nodules	-	+ in nodule
2	F/62	++ mainly modular	+++	+++	+ - peripheral around vessels	++ in nodules	-	+ -
3	M/40	+++ laminar/ nodular	++	+++	-	+	-	++
4	F/28	++ nodular	++	++	-	++ in nodules	-	+
5	M/73	+++ mainly laminar	+	+	-	+	-	+
6	M/67	+++ nodular/ laminar	+	+++	-	++ in nodules	-	-

areas showed fibroblasts arranged alongside layers or bundles of dense collagen. There was no clear distinction between these two patterns, one merging with the other.

Van Gieson and MSB studies produced identical results, suggesting that most of the collagen laid down was of the 'mature' type III (Fig. 4), and this was confirmed by strong birefringence under polarised light. There was increased vascularity (high or moderate) in seven cases (Fig. 5). We attempted to relate cellularity and vascularity to the 'activity' of the lesion, that is to the duration and severity of symptoms and signs.

The histological appearances of the tissues excised from frozen shoulders and from Dupuytren's contractures of the hand were similar in all respects. The Dupuytren tissue tended to show more strings of nodules and had slightly greater cellularity and vascularity.

The results of immunocytochemistry of shoulder tissue showed that vimentin was strongly expressed by fibroblasts, especially in the nodules (Fig. 6). These cells also expressed alpha smooth-muscle actin in all but two cases, thus displaying a differentiation or a change to a myofibroblastic phenotype (Fig. 7). Leucocytes and macrophages were scanty and were never seen in the nodules or laminae, only on the periphery and usually around small vessels. Synovium was present in seven cases and was either entirely normal or showed minimal papillary infoldings
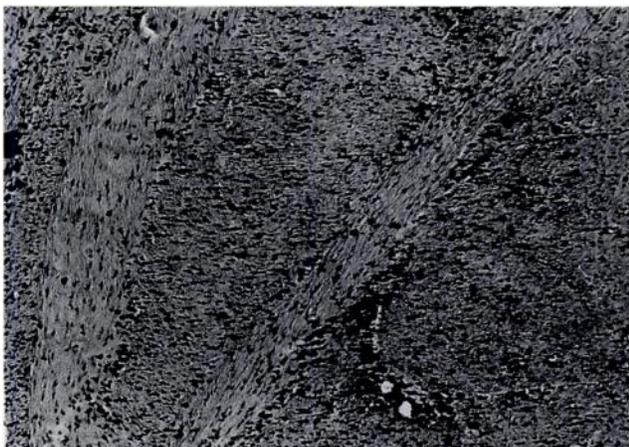

Fig. 2

A low-power view of the nodular/laminar arrangement of the thickened coracohumeral ligament (haematoxylin and eosin ×65).
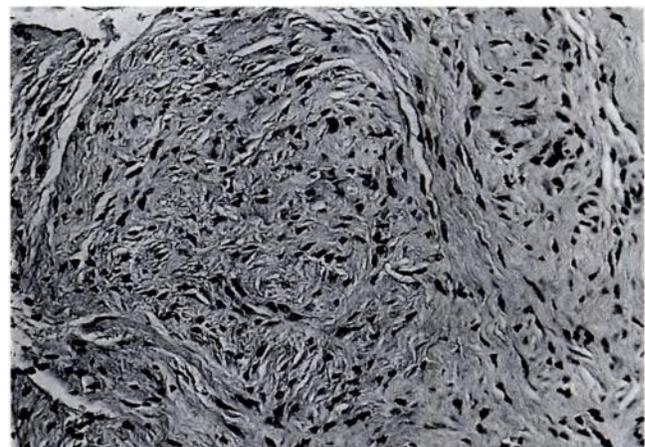

Fig. 3

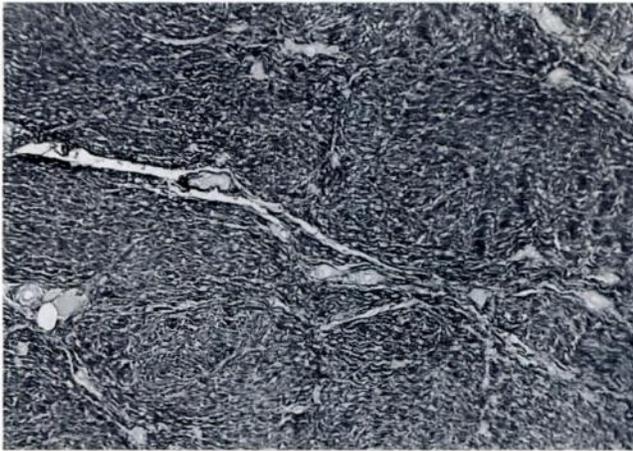A moderately cellular nodule of fibroblasts and collagen (haematoxylin and eosin ×240).
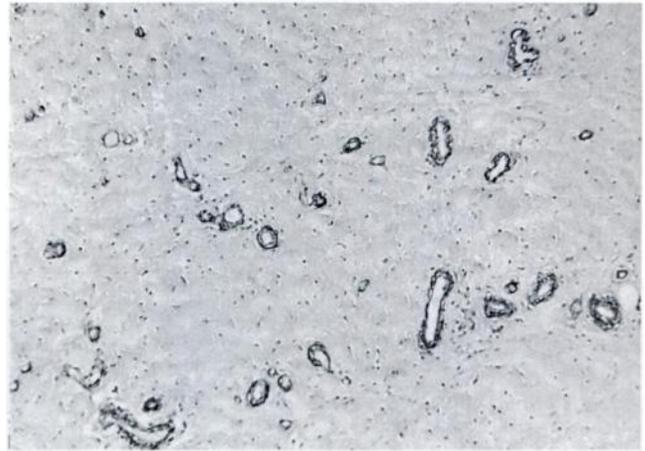
Fig. 4

A dense mass of collagen (Van Gieson ×100).

Fig. 5

Richly vascular area; small arteries are stained for their smooth muscle media by antibody to alpha smooth-muscle actin (immunoperoxidase ×100).
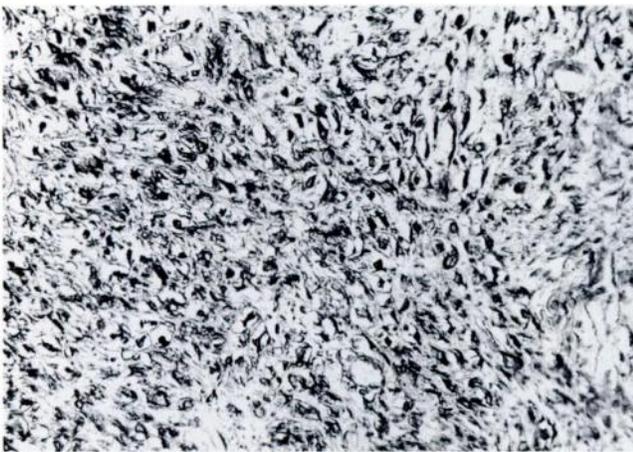

Fig. 6

Strong expression of vimentin by fibroblasts (immunoperoxidase ×240).

Fig. 7

Fibroblasts also express alpha smooth-muscle actin, that is, a myofibroblast phenotype. Note that the blood vessel on the left, as an internal control, shows strong staining of its smooth-muscle coat (immunoperoxidase ×640).

without hyperplasia (Fig. 8).

Our findings have shown that primary frozen shoulder is a fibrosing condition and not an inflammatory one. The general histology and immunocytochemistry were indistinguishable from those seen in Dupuytren's contracture.

DISCUSSION

It is difficult to define primary frozen shoulder (Zuckerman et al 1994). The definition which we used was based on that of Codman (1934) which has been utilised in other major studies. However, the authors had not excluded other causes of shoulder pain and stiffness by routine shoulder arthroscopy. Wiley (1991) reported 150 patients with a presumed diagnosis of frozen shoulder; only 37 had the primary nature confirmed by shoulder arthroscopy. Bayley (personal communication, 1994) found a 50% false-positive clinical diagnosis of frozen shoulder before arthro-
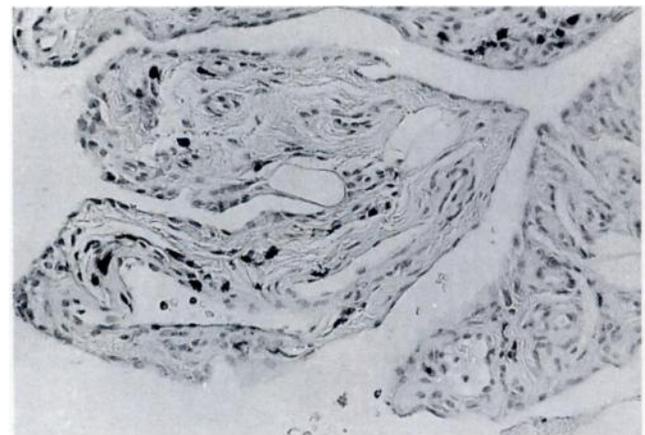

Fig. 8

The synovium shows microscopic papillae but few inflammatory cells. These are stained dark by antibody to leucocyte common antigen (CD 45) (immunoperoxidase ×240).

scopy. Thus, no earlier study of frozen shoulder was tightly controlled by exclusion of other causes by arthroscopy.

In our study secondary causes were excluded and two associations became clear: first, that with Dupuytren's disease and secondly, an association with diabetes. We found Dupuytren's disease of the hand in 58% of our patients. Fisher, Kurtz and Shipley (1986) found a 34% incidence of Dupuytren's contracture in patients with diabetic cheirarthropathy and a 60% incidence in diabetic patients without cheirarthropathy. This shows that Dupuytren's disease is common in diabetics, but we could find no previous study which has linked Dupuytren's disease with frozen shoulder in a tightly controlled group.

The relationship between diabetes and frozen shoulder is well documented (Bridgman 1972; Lequesne et al 1977; Fisher et al 1986; Pal et al 1986). Diabetic patients have a 10% to 20% incidence of frozen shoulder and this rises to 36% in insulin-dependent diabetics. Of patients with bilateral shoulder involvement, 42% are diabetic. Diabetic patients with frozen shoulder often fail to respond to manipulation (Janda and Hawkins 1993). This accounts for the higher incidence of diabetes in our excision and histology group (46%) compared with the 27% in our manipulation group. The patients who had excision and histology were self-selected by failure to benefit from manipulation. It could be argued that the patients from whom tissue was obtained for histology were suffering from diabetic cheirarthropathy.

Diabetic cheirarthropathy was first described by Lundbaek (1957), and is characterised by flexion contracture of the metacarpophalangeal and proximal interphalangeal joints of the fingers, with thickening, induration and a waxy feel to the skin. In severe cases diabetic cheirarthropathy is associated with flexion contractures of the wrists and elbows. None of the patients in our series had signs of diabetic cheirarthropathy on careful examination. The arthroscopic findings were identical in the diabetic and the non-diabetic patients from whom tissue had been obtained for histology. There were also no differences between the open-surgery group and the manipulation group. The histology was identical in diabetic and non-diabetic patients.

The cause of primary frozen shoulder has been uncertain since it was first described by Codman (Bunker 1985). Postulated causes include an autoimmune connective-tissue disorder, recurrent haemarthrosis, reactive arthropathy, crystal arthropathy, infection, trauma, algodystrophy, suprascapular nerve entrapment, and rotator-cuff degeneration. All these have been studied and disproved. The few previous studies of tissue from patients with primary frozen shoulder have suggested either an inflammatory process (Neviaser 1945; Simmonds 1949; DePalma 1952) or a fibromatosis (Lundberg 1969; Kay and Slater 1981; Ozaki et al 1989; Hannafin et al 1994).

Neviaser's study of ten cases in 1945 is often cited. He found thickening and contracture of the capsule with considerable or extensive fibrosis in six cases but interpreted the increased cellularity as due to inflammatory changes. Simmonds (1949) reported four cases which showed dense collagen fibres, much increased vascularity and the presence of histiocytes; he also considered frozen shoulder to be an inflammatory condition. DePalma (1952) explored 32 cases; in some, histological examination showed degeneration of collagen fibres, round-cell infiltration, increased vascularity, thickening of the synovial membrane and evidence of increased fibrosis. He also concluded that the changes were consistent with low-grade inflammation.

All these surgeons found evidence of fibrosis and vascularity, findings which our study has confirmed. We have also shown conclusively that the main cell populations in the lesions are fibroblasts and myofibroblasts; inflammatory cells are either absent or scanty and their presence is probably secondary to the mechanical and functional abnormality. Without the specific identification of cells by immunocytochemistry, it is possible to mistake fibroblasts and myofibroblasts for inflammatory cells.

The early macroscopic descriptions of frozen shoulder cannot be bettered. Neviaser (1945) reported that the thickened and contracted capsule peeled from the humeral head like adhesive plaster from skin. He termed this 'adhesive capsulitis' and is often misquoted as describing adhesions within the joint. No adhesions have been reported in numerous recent arthroscopic studies (Wiley 1991; Uitvlugt et al 1993; Bunker et al 1994). Simmonds (1949) described the rotator cuff as looking "like a vascular leathery hood with no obvious demarcation between the tendons". We now describe the usual demarcation between the tendons as the rotator interval, and his description matches our findings. DePalma (1952) stated that the coracohumeral ligament is "converted into a tough inelastic band of fibrous tissue spanning the interval between the coracoid process and the tuberosities of the humerus. It acts as a powerful check-rein ... division of the coracohumeral ligament allows early restoration of scapulohumeral motion". This accords perfectly with our findings and those of Ozaki (1989) and Neer et al (1992).

Earlier links with Dupuytren's disease were made by Lundberg (1969) who noted that the capsule was compact or dense with an increase in cells which were mainly fibroblasts. He reported the similarity to Dupuytren's tissue, but attributed the idea to Norden (personal communication, 1969). In 1981, Kay and Slater described the histology of one case in a brief letter to the *Lancet* stating that it was similar to that of Dupuytren's disease. Ozaki et al (1989) reported histological findings of fibrosis in some of their 17 cases, but did not study cell type. Hannafin et al (1994) performed arthroscopic biopsies of the capsule in 15 patients, finding diffuse capsular fibroplasia, thickening and contracture, but arthroscopy allows only small biopsies from the periphery of the lesion.

Our biopsies from the coracohumeral ligament and the rotator interval area were indistinguishable from the standard textbook and journal descriptions of Dupuytren's dis-

ease (Gabbiani and Majno 1972; Hueston, Hurley and Whittingham 1976; Chiu and McFarlane 1978) both for general microscopic appearances and for cell types. Inflammation is absent or minimal and the synovium remains inactive.

Conclusions. Primary frozen shoulder is relatively rare, accounting for only 50 (4.7%) of 935 shoulder referrals. Thickening and contracture of the coracohumeral ligament and rotator interval act as a tight check-rein which prevents external rotation. The vascular collagenous tissue has a high cellular content, shown by immunocytochemistry to be mainly fibroblasts and myofibroblasts.

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REFERENCES

Bridgman JF. Periarthritis of the shoulder and diabetes mellitus. *Ann Rheum Dis* 1972;31:69-71.

Bunker TD. Time for a new name for 'frozen shoulder'. *BMJ* 1985; 90:1233-4.

Bunker TD, Lagas K, DeFerme A. Arthroscopy and manipulation in frozen shoulder. *J Bone Joint Surg [Br]* 1994;76-B:Supp 1:53.

Chiu HF, McFarlane RM. Pathogenesis of Dupuytren's contracture: a correlative clinical-pathological study. *J Hand Surg [Am]* 1978; 3:1-10.

Codman EA, ed. Tendinitis of the short rotators. In: *Ruptures of the supraspinatus tendon and other lesions in or about the subacromial bursa.* Boston: Thomas Todd and Co, 1934.

DePalma AF. Loss of scapulohumeral motion (frozen shoulder). *Ann Surg* 1952;135:193-204.

Esch JC. Arthroscopic treatment of resistant primary (idiopathic) frozen shoulder. *J Shoulder Elbow Surg* 1994;3(1):S71.

Fisher L, Kurtz A, Shipley M. Association between cheiroarthropathy and frozen shoulder in patients with insulin-dependent diabetes mellitus. *Br J Rheumatol* 1986;25:141-6.

Gabbiani G, Majno G. Dupuytren's contracture: fibroblast contraction? an ultrastructural study. *Am J Pathol* 1972;66:131-46.

Hannafin JA, DiCarlo EF, Wickiewicz TL. Adhesive capsulitis: capsular fibro-plasia of the glenohumeral joint. *J Shoulder Elbow Surg* 1994;3(1):S5.

Hsu SM, Raine L, Fanger H. Use of avidin-biotin-peroxidase complex (ABC) in immuno-peroxidase techniques: a comparison between ABC and unlabelled antibody (PAP) procedures. *J Histochem Cytochem* 1981;29:577-80.

Hueston JT, Hurley JV, Whittingham S. The contracting fibroblast as a clue to Dupuytren's contracture. *Hand* 1976;8:10-2.

Janda DH, Hawkins RJ. Shoulder manipulation in patients with adhesive capsulitis and diabetes mellitus: a clinical note. *J Shoulder Elbow Surg* 1993;2:36-8.

Kay NR, Slater DN. Fibromatoses and diabetes mellitus. *Lancet* 1981;2(8241):303.

Lequesne M, Dang N, Bensasson M, Mery C. Increased association of diabetes mellitus with capsulitis of the shoulder and shoulder-hand syndrome. *Scand J Rheumatol* 1977;6:53-6.

Lundbaek K. Stiff hands in long term diabeties. *Acta Med Scand* 1957;158:447-51.

Lundberg BJ. The frozen shoulder. *Acta Orthop Scand* 1969;119:1-59.

Neer CS, Satterlee CC, Dalsey RM, Flatow EL. The anatomy and potential effects of contracture of the coracohumeral ligament. *Clin Orthop* 1992;280:182-5.

Neviaser JS. Adhesive capsulitis of the shoulder. *J Bone Joint Surg* 1945;27:211-22.

Ozaki J, Nakagawa Y, Sakurai G, Tamai S. Recalcitrant chronic adhesive capsulitis of the shoulder: role of contracture of the coracohumeral ligament and rotator interval in pathogenesis and treatment. *J Bone Joint Surg [Am]* 1989;71-A:1511-5.

Pal B, Anderson J, Dick WC, Griffiths ID. Limitation of joint mobility and shoulder capsulitis in insulin- and non-insulin-dependent diabetes mellitus. *Br J Rheumatol* 1986;25:147-51.

Simmonds FA. Shoulder pain: with particular reference to the 'frozen' shoulder. *J Bone Joint Surg [Br]* 1949;31-B:426-32.

Uitvlugt G, Detrisac DA, Johnson LL, Austin MD, Johnson C. Arthroscopic observations before and after manipulation of frozen shoulder. *Arthroscopy* 1993;9:181-5.

Wiley AM. Arthroscopic appearance of frozen shoulder. *Arthroscopy* 1991;7:138-43.

Zuckerman JD, Cuomo F, Rokito S. Definition and classification of frozen shoulder: a consensus approach. *J Shoulder Elbow Surg* 1994; 3(1):S72.