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Primary Frozen Shoulder

Global Capsular Stiffness versus Localized Contracture

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Stiffness in primary (idiopathic) frozen shoulders has been attributed to a global fibroplasia of the capsule despite the fact surgical release of the capsule at the rotator interval and of the coracohumeral ligament restores motion in almost all patients. Occurrence of vimentin, a cytocontractile protein known to be present in Dupuytren's contracture and in clubfeet, has been reported in resection specimens of anterior capsular structures. We hypothesized vimentin would occur only in the anterior structures but fibroplasia would occur throughout the capsule. Tissues removed from four patients were stained with antibodies against vimentin, allowing us to confirm its presence in only in anterior capsular structures, supporting our first hypothesis contracture is due to a selective involvement of the anterior capsule. Staining the sections against types I and III collagen permitted the detection of both collagens in the anterior and the posterior capsular structures and thus confirmed our second hypothesis that fibroplasia involves the entire joint capsule. Therefore it seems, in patients with primary frozen shoulder, fibroplasia and contracture are two distinct processes.

Level of Evidence: Level IV, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

In 1934 Codman[6] stated frozen shoulder is "difficult to explain from the point of view of pathology." Not much has changed during the intervening 70 years as we still struggle to explain various aspects of the disease process, particularly the pathophysiology. It has not been explained why a contracture occurs in adduction and internal rotation despite a global capsular fibroplasia. It is surprising, in view of current understanding, surgical release of the coracohumeral ligament and the joint capsule in the area at the rotator interval in patients unresponsive to conservative measures is usually enough to obtain a full range of motion.

Progressive restriction of external rotation and abduction at the level of the glenohumeral articulation is the hallmark of primary frozen shoulder. Surgery performed to release this restriction usually is limited to anterior structures.[4,5,17,19–22,27–29] Generally, the results obtained are satisfactory. From this clinical evidence one must conclude the process of contracture is due to a selective involvement of the capsule and not to the presence of a global synovitis and capsular fibroplasia. The latter changes have been confirmed by many arthroscopic and surgical observations.[10,11,18,23] Some surgeons include the posterior structures in the capsular release, either in instances of loss of internal rotation[1,13,25] or of a global loss of shoulder motion.[14] Harryman et al[11,12] recommend complete capsular release, apparently believing global fibroplasia is responsible for the contracture. Gerber et al[9] add a division of the posterior capsule to the anterior release "if applicable" without stating the criteria for applicability.

Biopsies obtained during the release of contracted anterior structures demonstrate varied and often contradictory pathologic changes. These include a thickened capsule and coracohumeral ligament;[15] compact, cellular, and dense fibrous tissue; presence of mostly fibroblasts and sometimes an increased vascularity as well as an almost unchanged synovial lining;[17] fibrosis, hyalinization, and fibrinoid degeneration[22] and vascular villous synovitis; and mature scar tissue, but little evidence of any active inflammatory cellular process.[3]

Immunohistochemical examination has further helped elucidate the process of contracture.[3,21] A dense matrix of Type III collagen populated with fibroblasts and myofibroblasts has been identified in the capsule at the rotator

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Each author certifies that his or her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
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TABLE 1. Main Histologic Findings in Synovial Tissue

Site of Biopsy	Synovial Cell Layer	Subsynovial Vascularity	Matrix Density	Villi
Posterosuperior	3 cell layers	+++	Reduced	+++
Rotator interval	1 to 2 cell layer	++	Reduced	++
Coracohumeral ligament	1 cell layer	+++	Reduced, thick vessel walls	None
Axillary fold	3+ cell layers	+++	Reduced	+++
Inferior capsule	3+ cell layers	normal	Reduced	None

Synovial vascularity: +++ = hypervascular, ++ = very vascular. Matrix density: reduced = loose connective tissue. Villi: +++ = very villous, ++ = villous

interval.[21] Type III collagen, in contrast with Type I, is not spatially oriented[16] or present in areas of fibroplasia. Bunker and Anthony[3] excised the coracohumeral ligament and the capsule at the rotator interval in 12 patients and found histologic evidence of active fibroblastic proliferation accompanied by some transformation to smooth muscle phenotypes (myofibroblasts), but no synovial involvement. Immunohistochemical investigations also included monoclonal antibodies against the cytocontractile protein vimentin;[3] the authors concluded from this study that "... vimentin, a common mesenchymal cell intermediary filament, was strongly expressed by fibroblasts, especially in the nodules."

We reported vimentin in the contracted spring ligament of seven human fetuses with a severely deformed clubfoot[8] and of 41 postnatal club foot specimens from children aged 6 to 30 months.[24] We therefore wondered whether this protein is also present in the joint capsule of patients with primary frozen shoulder and, if present, whether it is distributed evenly over the entire capsule or limited to the anterior capsular structures.

We hypothesized (1) the cytocontractile protein vimentin would only be present in the anterior structures because their surgical release has repeatedly shown a restoration of glenohumeral motion, and (2) fibroplasia involves the entire joint capsule to an almost identical degree with no preferential involvement of the anterior capsule.

MATERIAL AND METHODS

We prospectively identified four female patients who underwent an arthroscopic release for primary frozen shoulder (Patient 1, 66 years old; Patient 2, 69 years old; Patient 3, 62 years old; and Patient 4, 42 years old). The average duration of symptoms was 12 months. Only Patient 1 had a history of Dupuytren's contracture. The average of forward flexion was 70º (opposite side 180º), of external rotation 10º (opposite side 60º), of abduction 120º (opposite side 180º) and the level of internal rotation L1 (opposite side T8). During surgery a marked synovial reaction of the glenohumeral joint was found and several tissues were obtained after division and partial resection: (1) synovial tissue and capsule from the posterosuperior part of the joint (n = 4); (2) synovial tissue and capsule at the rotator interval (n = 4); (3) tissue from the coracohumeral ligament (n = 4); 4) synovial tissue and capsule from the axillary fold (n = 2); and (5) synovial tissue and inferior capsule in contact with the axillary nerve (n = 1). The resected specimens were preserved for microscopic examination and fixed in 10% neutralized formalin and embedded in paraffin. Seven-micron sections were stained with hematoxylin-eosin and Azan.

To test the first hypothesis of a selective involvement of anterior structures in the process of contracture, monoclonal antibodies against desmin (monoclonal mouse IgG, AM072-5M, BioGenex, San Ramon, CA) and against vimentin (monoclonal mouse IgG, AMO74-5M; BioGenex) were used for immunohistochemical staining. The first step of this two-step process involves the binding of the primary antibody to the antigen, and during the second step the bound antigen is detected by a chromogen. The details of the laboratory procedures have been described.[24] Specimens stained without the primary antibody served as negative controls. We used sections from nodules of Dupuytren's contracture for positive control specimens.

To test the second hypothesis fibroplasia involves the entire capsule to an almost identical degree with no preferential involvement of the anterior capsule, the sections were stained with monoclonal antibodies against Types I and III collagen (Cedar-

TABLE 2. Main Histologic Findings of Extracellular Matrix of Capsule and/or Ligaments

Site of Biopsy	Cellularity, Fibroplasia	Matrix Density	Vascularity	Perivascular Infiltration	Signs of Inflammation
Posterosuperior	++	Slightly reduced	++	No	No
Rotator interval	++	Reduced		No	No
Coracohumeral ligament	+	Reduced	++	Occasional	No
Axillary fold	++	Normal	+	No	No
Inferior capsule	Normal	Normal	Normal	No	No

Cellularity: ++ = much increased, + = increased. Vascularity: ++ = very vascular, + = more vascular than normal

TABLE 3. Vimentin Expression in Synovial Tissue

Site of Biopsy	Expression in Cells	Expression in Endothelial Cells	Perivascular Expression	Matrix
Posterosuperior	++	++	No	No
Rotator interval	++	++	No	+++
Coracohumeral ligament	No	No	No	No
Axillary fold	No	++	No	No
Inferior capsule	+	No	No	No

Expression on cells: ++ = strong expression, + = expression spotty. Perivascular expression: +++ = very strong expression. Matrix: +++ = very strong expression

line Laboratories Ltd, 5516-8th Line, RR #2, Hornby, Ontario, Canada). Details of this technique have been described previously.[13] Dilution for Type I collagen was 1:200 and 1:500 for Type III.

We (HKU) assessed the histologic features using a semiquantitative evaluation (Tables 1–4). The vascularity was graded as follows: hypervascular = +++; very vascular = ++; more vascular than normal = +; or normal. The matrix density was assessed as being reduced, slightly reduced or normal. Presence of synovial villi was graded as being very villous = +++; villous = +; or normal. The cellularity was graded as being much increased = ++; increased = +; or normal. The intensity of vimentin expression rated very strong = +++; strong = ++; spotty = +; or absent.

RESULTS

We found little difference in the histologic findings in the synovial tissue and the extracellular matrix of capsule/ligaments of the posterior and anterior structures (Tables 1, 2). Vimentin expression in synovial and endothelial cells was similar at the level of the posterosuperior site and the rotator interval (Table 3). It was strongly expressed in cells and extracellular matrix of the capsule at the rotator interval (Fig 1) (Table 4), the coracohumeral ligament, and the axillary fold. In positive controls using tissue from the palmar fascia of Dupuytren's contracture, the expression of vimentin in cells and matrix was strong (Fig 2). No expression for vimentin was detected in cells or in the extracellular matrix from posterosuperior capsule specimens (Fig 3). There was no difference in expression at the synovial tissue between these sites. Desmin was not expressed in any section. A marked synovial vascular reaction accompanied by formation of villi was found at all sites, although the intensity varied among different locations (Fig 4).

Presence of fibroplasia was evident at all surgically released sites, and areas of spatially nonaligned Type III collagen containing an increased number of fibroblasts (Figs 5, 6) were separated by strands of spatially aligned Type I collagen containing the typical fibrocytes in nearly normal numbers. The simultaneous presence of Types I and III collagen was similar at all released sites with the exception of the inferior capsule in which little type III collagen was found. Signs of inflammation or perivascular infiltration were not detected in any section.

DISCUSSION

Based on the assumption the contracture in primary frozen shoulder involves the capsule at the rotator interval and the coracohumeral ligament, one study[3] proceeded successfully with a surgical division of only these two structures. Surgical specimens from these sites were stained with monoclonal antibodies against the common intermediate filament vimentin. This protein is present in other processes involving contracture. Brenner et al[2] documented vimentin is strongly expressed in nodules of Dupuytren's contracture. Bunker and Anthony[3] reported a strong expression in fibroblasts of the two divided structures. Although their results clearly show the rotator interval and the coracohumeral ligament are involved in the process of contracture, the absence of biopsies from the posterior capsule limits the value of their study because neither absence nor presence of vimentin in the posterior capsule can be ruled out. We confirmed this study's[2] results in

TABLE 4. Expression of Vimentin in Capsule and/or Ligaments

Site of Biopsy	Cells	Matrix	Endothelial Cells
Posterosuperior	No	No	No
Rotator interval	++	+++	++
Coracohumeral ligament	++	++	No
Axillary fold	++	++	No
Inferior capsule	+	++	No

Expression in cells: ++ = strong expression, + = expression spotty. Expression in matrix: +++ = very strong expression, ++ = strong expression

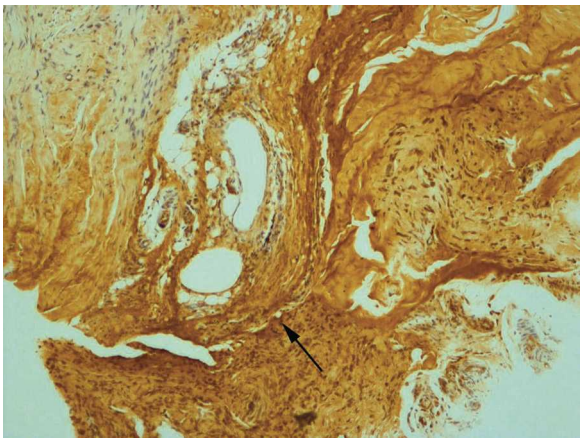

Fig 1. This microphotograph shows a strong but localized expression of vimentin in the capsule at the rotator interval; it is easily recognized by the intensive staining of cells and extracellular matrix (arrow) (stain: vimentin; original magnification, ×100).

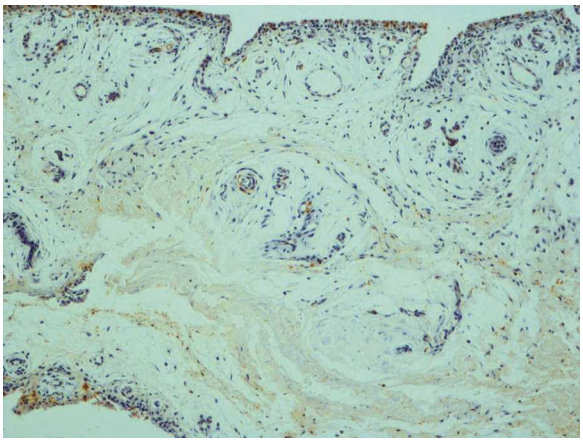

Fig 3. No vimentin expression is detected in this section taken from the vascular posterosuperior capsule (stain: vimentin; original magnification, ×100).

respect to the two anterior structures. We were fortunate to include specimens of the posterosuperior capsule and expose them to monoclonal antibodies against vimentin. Microscopic observations failed to reveal a vimentin expression in the posterosuperior capsule, clearly indicating contracture in primary frozen shoulder does not involve this part of the joint capsule. This selective involvement occurred despite fibroplasia of the entire capsule; therefore, fibroplasia and contracture are different processes and these terms should not be used synonymously.

A limitation of our study is the recruitment of patients who underwent a division of the posterior capsule in addition to a release of anterior structures. We generally proceed only with a division of the contracted anterior structures; however, in four patients we followed the advice of Harryman et al[11] and Harryman and Lazarus[12] to release the posterior capsule. A further limitation is the fact that we used only semiquantitative methods of assessment and made no attempt to ascertain interobserver variability of the scoring system.

We found not only a vimentin expression in cells but also in the matrix. A similar distribution also was seen in

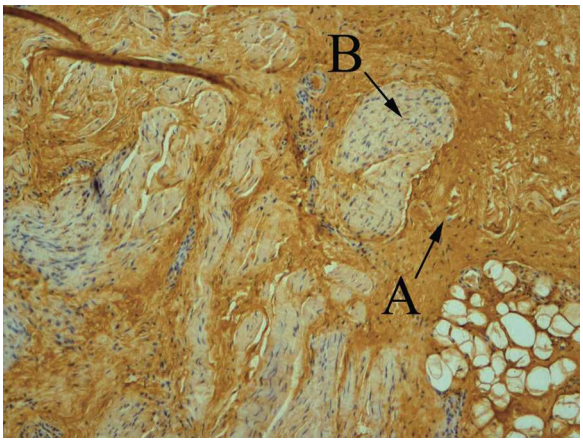

Fig 2. A strong cellular and extracellular expression of vimentin (arrow A) is evident in this positive control specimen using a resection specimen of Dupuytren's contracture. The presence of collagen strands not picking up vimentin probably represents mature collagen of the palmar fascia (arrow B) (stain: vimentin; original magnification, ×100).

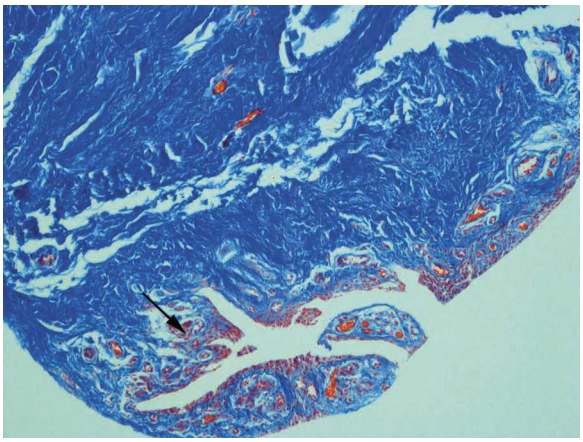

Fig 4. This microphotograph taken from a section of the capsule at the rotator interval shows the hypervascular synovial reaction (arrow) surrounded by dense, loose connective tissue. The loose connective tissue lacks the spatial orientation of its collagen bundles (stain, Azan; original magnification, ×100).

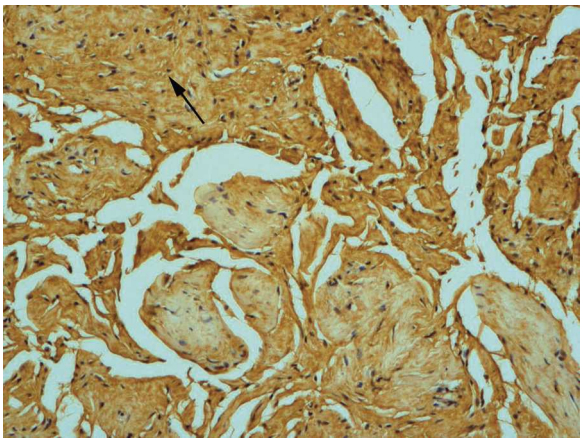

Fig 5. In this section taken from the posterosuperior capsule areas characterized by fibroplasia and increased cellular density show a strong staining for Type III collagen (arrow). They surround unstained islands of spatially aligned collagen containing mostly fibrocytes (stain: type III collagen; original magnification ×200).

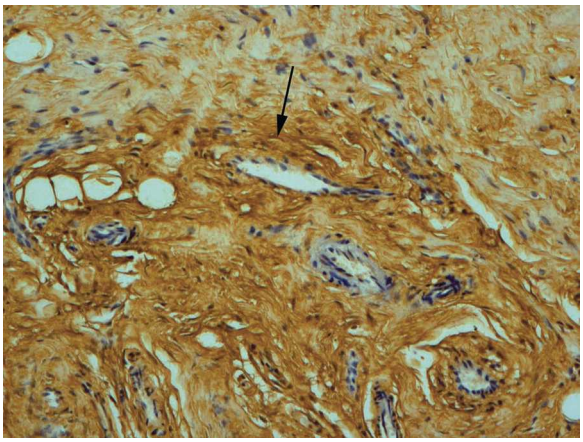

Fig 6. In this microphotograph taken from a section of the capsule at the rotator interval, an area staining strongly for Type III collagen (arrow) borders a site of rather mature collagen that does not pick up the Type III collagen stain (stain: type III collagen; original magnification ×200).

our positive controls using tissue from Dupuytren's contracture.

Absent expression for desmin should be expected as Eyden[7] has shown reactive myofibroblasts lack substantial amounts of desmin. In our investigation of postnatal clubfeet a positive desmin expression was never observed.[24]

The selective expression of vimentin in the anterior structures merits further experimental investigation because our study cannot determine whether the cytocontractile protein vimentin is the cause of the contracture or whether it is elaborated in response to the antalgic position in adduction and internal rotation.

We stained sections of our knee contracture model in rats[26] with vimentin. Preliminary results do not support an assumption of a causal involvement of vimentin in the contracture process but rather an elaboration of this protein in response to immobilization in flexion. A more in-depth study is planned.

The expression of vimentin limited to anterior capsular structures but absent from the posterior capsule confirms our first hypothesis only the anterior parts of the glenohumeral joint capsule, particularly the capsule at the rotator interval and the coracohumeral ligament, are involved in the contracture process in primary frozen shoulder. This study also confirmed our second hypothesis: fibroplasia involves the entire joint capsule to an almost identical degree with no preferential involvement of the anterior capsule.

We conclude the reduced range of motion of the primary frozen shoulder is foremost attributable to a contracture of anterior capsular structures, particularly the coracohumeral ligament and the capsule at the rotator interval as seen by the selective expression of the cytocontractile protein vimentin. This finding confirms the clinical experience division of these structures is usually sufficient to restore the lost range of motion. Another important outcome is the need for a clear distinction between fibroplasia and contracture. Although fibroplasia involves the entire capsule, presence of cytocontractile proteins is limited to the anterior capsular part. Consequently, we deal with a selective involvement of anterior capsular structures in the process of contracture. The data suggest in the absence of a clinically relevant limitation in internal rotation there is no need to perform routinely a posterior capsular release in patients suffering from primary frozen shoulder.

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