Chapter 103

Fibrosing diseases: Diabetic Stiff Hand Syndrome, Dupuytren's Contracture, Palmar and Plantar Fasciitis, Retroperitoneal Fibrosis, and Peyronie's Disease

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Fibrosis is a complex reactive process usually resulting from an inflammatory insult to normal tissue. The end result of the fibrotic process is the replacement of normal tissue architecture by a proliferation of macromolecules referred to as the extracellular matrix (ECM). Although fibrosis is essential to the normal repair mechanism in damaged tissue, it may interfere with normal tissue function, especially if the process is overly exuberant or inappropriate. Diseases characterized by excessive or inappropriate fibrosis are shown in Table 103.1.

**TABLE 103.1. Fibrosing diseases**

<table>
<thead>
<tr>
<th>Skin and musculoskeletal system</th>
<th>Sclerosing cholangitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive systemic sclerosis</td>
<td>Esophageal stricture</td>
</tr>
<tr>
<td>Morphea</td>
<td>Collagenous colitis</td>
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<tr>
<td>Graft-host reaction</td>
<td>Mesenteric fibrosis</td>
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<tr>
<td>Diabetic stiff-hand syndrome</td>
<td>Oral submucous fibrosis</td>
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<tr>
<td>Dupuytren's contracture</td>
<td>Diffuse pancreatic fibrosis</td>
</tr>
<tr>
<td>Aponeurotic plantar fibrosis</td>
<td>Inflammatory fibroid polyp of the gastrointestinal tract</td>
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<tr>
<td>Knuckle pads (Garrod's nodules)</td>
<td>Sclerosing peritonitis</td>
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<tr>
<td>Plantar fasciitis</td>
<td>Genitourinary</td>
</tr>
<tr>
<td>Keloids</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Idiopathic fibrosing cervicitis (neck)</td>
<td>Nephrosclerosis</td>
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<tr>
<td>Focal myositis</td>
<td>Interstitial cystitis</td>
</tr>
<tr>
<td>Lungs</td>
<td>Peyronie's disease</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>Renal inflammatory pseudotumor</td>
</tr>
<tr>
<td>Chronic pleural reaction</td>
<td>Other</td>
</tr>
<tr>
<td>Peribronchial fibrosis</td>
<td>Pseudotumor</td>
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<tr>
<td>Cardiovascular</td>
<td>Calcifying fibrous pseudotumor</td>
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<tr>
<td>Constrictive pericarditis</td>
<td>Retroperitoneal fibrosis</td>
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<tr>
<td>Atherosclerotic plaques</td>
<td>Riedel's struma</td>
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<tr>
<td>Intimal proliferation</td>
<td>Cancer, especially sclerosing large cell lymphoma</td>
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<tr>
<td>Inflammatory abdominal aneurysm</td>
<td>Sjögren's syndrome</td>
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<tr>
<td>Chronic fibrosing periaortitis</td>
<td>Systemic idiopathic fibrosis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Multifocal idiopathic fibrosis</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>Polyfibromatosis</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Inflammatory myofibroblastic tumor</td>
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</table>

PATHOGENESIS OF FIBROSIS

The same processes responsible for normal tissue repair likewise result in the pathologic findings seen in the fibrosing syndromes. However, in the latter, the processes continue unchecked and may result in tissue or organ dysfunction (1,2,3). Normal wound healing has been characterized as progressing through four distinct phases: tissue injury, followed by a local inflammatory response, proliferation of the ECM, and tissue remodeling (Table 103.2). The hallmark of fibrosis is the increased production or decreased turnover of ECM molecules. Central to this process is the activation of fibroblasts, resulting in fibroblast proliferation, differentiation, and production of increased quantities of ECM. Fibroblast activation is heavily regulated; numerous cytokines, cellular adhesion molecules, and other inflammatory mediators have been implicated in this process. Neutrophil-derived mediators include interleukin-1α (IL-1α) and IL-1β, interferon-α (IFN-α), IFN-β, IFN-γ, transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), leukotriene-B4 (LTB4), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNFα), and intracellular adhesion molecule-1 (ICAM-1) (4). Macrophage-derived factors including free oxygen radicals, H2O2, NO, TGF-β, PDGF, fibronectin, TNF-α, insulin-like growth factor (ILGF), and prostaglandin-E2 (PGE2) have also been shown to modulate the structure of ECM (5). Mast cell mediators including IL-4, IL-13, tryptase, and endothelin-1 play an active role in the fibrotic process (6). Other growth factors including oncostatin M (OSM), tissue inhibitor of matrix metalloproteinase (TIMP), and connective tissue growth factor (CTGF) affect fibroblast function and collagen production (7).

<table>
<thead>
<tr>
<th>Table 103.2. The normal healing process</th>
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<tbody>
<tr>
<td><strong>Phase 1</strong></td>
</tr>
<tr>
<td>Tissue injury</td>
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<tr>
<td>Exposure of hidden proteins</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Platelet activation</td>
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<tr>
<td>Release of mediators</td>
</tr>
<tr>
<td>0</td>
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<tr>
<td>Coagulation</td>
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<tr>
<td>Release of chemoattractants</td>
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<tr>
<td>0–2</td>
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<tr>
<td><strong>Phase 2</strong></td>
</tr>
<tr>
<td>Secondary inflammation</td>
</tr>
<tr>
<td>Neutrophils and eosinophils</td>
</tr>
<tr>
<td>1–4</td>
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<tr>
<td>Monocytes and macrophages</td>
</tr>
<tr>
<td>2–6</td>
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<tr>
<td><strong>Phase 3</strong></td>
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<tr>
<td>Tissue proliferation</td>
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<tr>
<td>Fibroblast migration</td>
</tr>
<tr>
<td>1–7</td>
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<tr>
<td>Vascular ingrowth</td>
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<tr>
<td>2–10</td>
</tr>
<tr>
<td>Collagen secretion</td>
</tr>
<tr>
<td>2–21</td>
</tr>
<tr>
<td>Myofibroblast differentiation</td>
</tr>
<tr>
<td>7–72</td>
</tr>
<tr>
<td><strong>Phase 4</strong></td>
</tr>
<tr>
<td>Tissue remodeling</td>
</tr>
<tr>
<td>Modification by proteases</td>
</tr>
<tr>
<td>3–21</td>
</tr>
<tr>
<td>Collagen cross-linking</td>
</tr>
<tr>
<td>7–72</td>
</tr>
<tr>
<td>Contraction</td>
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<td>21–72</td>
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</tbody>
</table>

Of the cytokines and growth factors implicated in the pathogenesis of fibrosing diseases, clear evidence has emerged implicating a key role for TGF-β in these disorders (8). TGF-β, a 25-kd homodimeric polypeptide cytokine in a superfamily of dimeric polypeptides that includes bone morphogenic protein and activins, regulates a wide variety of cellular responses. Virtually all human cells produce and have receptors to TGF-β. Its role in cellular proliferation and differentiation, fibrogenesis, and wound repair has been described; additionally, multiple other biologic processes such as normal development and apoptosis are influenced by TGF-β. Three isoforms of TGF-β have been identified; each is highly conserved and encoded by a distinct gene. Binding affinity for TGF-β receptors and tissue expression differs for each of the isoforms, and genetic deletion of individual isoforms results in different phenotypes in a mouse model (9).

TGF-β is secreted as an inactive precursor molecule and stored in the ECM through covalent bonds with latent TGF-β-binding protein (LTBP), which prevents binding to its cellular receptors. Activation of TGF-β is achieved through its cleavage from LTBP by extracellular enzymes including thrombospondin-1, plasmin, and various proteases (10). Following activation, TGF-β directly affects ECM production by stimulating collagen production, angiogenesis, cytokine production, proteolytic enzyme inhibitors, and fibroblast chemotaxis and differentiation (9). Active TGF-β is stored in intracellular platelet granules, and the release of platelet-activated TGF-β appears to be a crucial step in the initiation of tissue wound repair. TGF-β, in turn, stimulates its own production, resulting in sustained TGF-β secretion and activation (11). It remains unclear why tissue damage may result in pathologic fibrosis rather than the usual self-limited healing process (12).

The biologic effects of TGF-β are mediated through its binding to one of three cell membrane receptors (types I, II, and III). Types I and II are serine-threonine protein kinases expressed on nearly all cell types. Type III receptors are nonsignaling receptors that bind TGF-β and transfer it to the type II receptor. TGF-β may bind directly to either type
III or type II receptors. Once activated by TGF-β, type II receptors bind and phosphorylate type I receptors, which activate downstream signaling pathways. Type I receptors are unable to bind TGF-β alone, and type II receptors are unable to initiate downstream signaling in the absence of type I receptors. It is believed that the type I receptor mediates specific cellular responses to TGF-β, whereas the type II receptor determines ligand specificity (13). Activation of the type I receptor, in turn, initiates intracellular signaling to the cellular nucleus through the phosphorylation of intracellular transcription factors referred to as Smads. The Smads include a family of at least 10 proteins that directly influence cell-specific gene transcription in response to TGF-β signaling (14); they are further categorized into different classes that may either facilitate or inhibit TGF-β-mediated signal transduction (15). In addition to the Smad pathway, TGF-β has also been shown to activate intracellular signaling through the mitogen-activated and stress-activated protein kinase systems (16).

Connective tissue growth factor (CTGF), a cysteine-rich peptide member of the CCN family of growth factors, has also been shown to play a prominent role in tissue repair and fibrosis (17). CTGF is induced by TGF-β (17) or thrombin (18) and is inhibited by TNF-α (19). CTGF stimulates fibroblast proliferation, chemotaxis, and differentiation as well as collagen and fibronectin synthesis. The receptors mediating the effects of CTGF and the intracellular signaling mechanism of CTGF remain unknown (20). The induction of CTGF synthesis by TGF-β and the similarity of responses elicited by the two growth factors suggest that the effects of TGF-β may be mediated by CTGF (21).

DUPUYTREN'S CONTRACTURE

Pathology and Biochemistry

First described in a case report by Plater in 1614 and later more fully described by Dupuytren's in 1831 (22), Dupuytren contracture is characterized by fibrotic thickening of the palmar fascia, resulting in flexion contracture of the fingers (23). Plantar fibromatosis, histologically identical to Dupuytren's contracture, may result in similar deformities in the lower extremity (24). Systemic idiopathic fibrosis, multifocal idiopathic fibrosis, and polyfibromatosis are severe fibrotic syndromes that may be associated with a similar thickening of the palmar fascia (25).

Three stages of progression have been described in Dupuytren's contracture (26): stage I, the presence of a fibrous nodule without digital contracture; stage II, contracture with fascial thickening and nodular enlargement; and advanced stage III, with joint contracture, rigid fascial cords and nodules, and muscle atrophy.

The early stage is histologically characterized by fibroblast proliferation; as the condition progresses and contracture appears, myofibroblast differentiation is prominent. Additionally, the active phase of the disease process is marked by significantly increased production of several cytokines, including BFGF, TGF-β, PDGF, IL-1α, and IL-1β. Although the major collagen type in normal palmar fascia is type I, several studies have shown an increase in type III collagen deposition in Dupuytren's contracture (27). The myofibroblasts in Dupuytren's contracture also produce fibronectin, laminin, tenascin, and type IV collagen (28). Myofibroblast apoptosis appears to be the hallmark of stage III disease, and the lesions of the contracture consist mainly of type I collagen (29).

Etiology

Despite a wealth of observational and experimental data, the cause of Dupuytren's contracture remains unknown. A strong association exists between genetic predisposition, coexisting disease states, and the development of this condition (Table 103.3). The influence of heredity is demonstrated by the significant geographic variation in disease prevalence among different populations: up to 30% of Northern European men over the age of 65 years are affected; a similar prevalence is seen in Australia, whereas the disorder appears to be uncommon in Africa and Asia (30). Although middle-aged men are more frequently affected than women, Dupuytren's contracture becomes increasingly prevalent in women after the age of 75 years (31). Children are uncommonly affected (32). Some studies have suggested an autosomal dominant with incomplete penetration mode of inheritance, whereas others favor autosomal recessive inheritance (30).

TABLE 103.3. Associations with Dupuytren’s contracture

<table>
<thead>
<tr>
<th>Intrinsic associations</th>
<th>Disease associations</th>
<th>Extrinsic associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>Diabetes mellitus</td>
<td>Palmar injury</td>
</tr>
<tr>
<td>Northern European descent</td>
<td>Epilepsy</td>
<td>Vibration injury (white-finger disease)</td>
</tr>
<tr>
<td>Increasing age</td>
<td>Plantar fascitis</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Family history</td>
<td>Peyronie disease</td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Chromosomal abnormalities</td>
<td>Plantar fibrosis (Ledderhose's disease)</td>
<td>Anticonvulsant therapy</td>
</tr>
<tr>
<td>HLA-DR3</td>
<td>Knuckle pads (Garrod's nodules)</td>
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<td></td>
<td>Carpal tunnel syndrome</td>
<td></td>
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<td></td>
<td>Trigger finger</td>
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<td></td>
<td>Rheumatoid arthritis</td>
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<td></td>
<td>Eosinophilic fascitis</td>
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<tr>
<td></td>
<td>Hyperlipidemia</td>
<td></td>
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<tr>
<td></td>
<td>Human immunodeficiency virus</td>
<td></td>
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<tr>
<td></td>
<td>Extrinsic associations</td>
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<tr>
<td></td>
<td>Palmar injury</td>
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<tr>
<td></td>
<td>Vibration injury (white-finger disease)</td>
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<tr>
<td></td>
<td>Alcoholism</td>
<td></td>
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<tr>
<td></td>
<td>Cigarette smoking</td>
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</table>
A correlation between alcoholism and Dupuytren contracture has been noted in many studies, but nonalcoholic liver disease does not appear to be closely associated with the disorder. An association between epilepsy and Dupuytren's contracture exists and appears to correlate with the duration of the seizure disorder; it has been suggested that anticonvulsant therapy, rather than the epilepsy alone, may be the most important factor. The frequency of Dupuytren's contracture is increased in patients with both type 1 and type 2 diabetes mellitus (DM) and correlates with patient age and duration of diabetes. Smokers may have as much as a threefold increased risk for developing Dupuytren contracture as compared with nonsmokers (31). An association with human immunodeficiency virus (HIV) infection has been suggested (33) and may be a consequence of antiretroviral therapy (34). An increased prevalence of human leukocyte antigen (HLA)-DR3 haplotype A1 B8 has been observed in patients with Dupuytren's contracture (30), raising the possibility of an autoimmune etiology. There does not appear to be a clear association between occupation and the risk for developing Dupuytren's contracture, although repeated vibration exposure may be associated with this disorder (35).

**Clinical Findings**

Dupuytren's contracture begins with a nodular thickening in the palmar or digital fascia, with associated overlying dimpling of the skin. Initially, patients may complain of tenderness over the affected area or a limitation in mobility of the associated finger. Unlike the nodules seen in association with flexor tenosynovitis, the nodule of Dupuytren's contracture does not move in concert with flexion of the tendon. Fibrotic cords then form and extend into the fascia of the affected finger, resulting in a progressive flexion deformity (Figs. 103.1 and Figs. 103.2). There is no predilection for the dominant or nondominant hand (36), and the condition may be bilateral. The fourth finger is most commonly affected; the fifth, first, third, and second fingers in decreasing frequency may also be involved (37). Involvement of the first or second fingers can be particularly disabling and may progress rapidly, especially in the younger patient (38).

![Fig. 103.1. Dupuytren's contracture. This is an early stage of Dupuytren's contracture characterized by a puckering of the skin and the presence of a nodular thickening of the palmar fascia. The contracture of the fourth metacarpophalangeal joint is in an incipient stage but should progress with time. Similar lesions may be present in the plantar fascia (plantar fibromatosis).](image1)

![Fig. 103.2. Dupuytren's contracture. This magnetic resonance imaging (MRI) scan of the same patient as in Figure 103.1 demonstrates the invading mass of connective tissue extending along the palmar fascia into the adjoining structures. The contractile mass of tissue has enmeshed itself around the flexor digitorum profundus and superficialis tendons and exerts traction, resulting in an angular deformity of the tendon and a clinical contracture.](image2)

The differential diagnosis of Dupuytren's contracture includes occupational skin thickening, spastic digital deformities such as those seen in cerebral palsy, and joint contractures from chronic immobilization or disuse. Rare soft tissue malignancies such as epithelioid sarcoma may mimic the clinical findings seen in Dupuytren's contracture. The history and physical findings usually suffice to exclude these other conditions; in the event of clinical uncertainty, magnetic resonance imaging (MRI) of the involved structures may be a valuable diagnostic tool (37).
Therapy

No systemic medication has proved consistently beneficial in the treatment of Dupuytren's contracture. Splinting and range-of-motion exercises may provide palliative benefit for patients with early symptoms of the disease. Preliminary results using skeletal traction with external fixator devices have shown clinical improvement in the degree of contracture (39). Irradiation, ultrasound, dimethylsulfoxide, vitamin E, and allopurinol have not been shown to be effective (40). One patient reportedly improved after treatment with colchicine (41). Intralesional triamcinolone injections have been shown to cause regression of nodules in Dupuytren's contracture, although multiple injections are required, and one half of patients experience reactivation of the disease (42). Intralesional IFN-γ was shown to be beneficial in a small pilot study (43), and promising results were seen in a series of phase II trials using intralesional collagenase (44).

Surgery has been the most commonly used form of therapy for Dupuytren's contracture and is usually considered in patients with disabling contractures. The complication rate of the surgical treatment of Dupuytren's contracture has been reported to be as high as 19% (45) and includes neurovascular injury, hematoma, skin necrosis, infection, flexion contracture, and reflex sympathetic dystrophy (RSD). Several surgical procedures are employed, including nodule excision, regional fasciectomy, and dermatofasciectomy with skin grafting. Long-term (10-year) results of surgical therapy for Dupuytren's contracture show high rates of disease recurrence (47%) and extension (79%) (46).

SYNDROME OF LIMITED JOINT MOBILITY

Definition and Clinical Findings

The syndrome of limited joint mobility (SLJM), also known as diabetic stiff hand syndrome, diabetic cheiroarthropathy, or diabetic waxy skin, is characterized by stiffness of the metacarpophalangeal (MCP), interphalangeal (IP), and wrist joints in patients with DM. Originally described as a complication of type 1 DM (47), SLJM has subsequently been recognized as a common early complication of both type 1 and type 2 DM (48). Up to 50% of type 1 diabetic patients and 75% of type 2 diabetic patients may be affected at some point during the course of the disease (48). Several studies have been unable to uncover a correlation between the development of SLJM and the level of glycemic control, and there is conflicting evidence to suggest a relationship of SLJM with the duration of DM (49, 50, 51, 52, 53, 54, 55, 56, 57, 58).

SLJM usually begins with joint stiffness in the fifth finger and progresses radially. The joint is not directly involved; limitation in mobility is attributed to abnormal collagen thickening in the periarticular tissue (49). Inability to extend the digit is the usual clinical finding; the limitation is usually painless and mildly disabling, although flexion contractures may occur in long-standing disease and may impair hand mobility. Some evidence suggests that joint contracture in SLJM is a result of tenosynovitis from involvement of the musculotendinous apparatus in the finger. The “prayer sign” may be present, demonstrating the failure of palmar approximation due to contractures of the small joints of the hand (Fig. 103.3). Large joints, including the shoulders, elbows, and ankles, may also be involved. Involvement of the cervical spine has been described as complicating endotracheal intubation (59), and foot involvement may contribute to lower extremity diabetic complications (51). A restrictive pulmonary disease has been associated with SLJM, but it is unclear whether this is attributable to thoracic joint limitation (52) or a systemic
alteration in collagen structure (53). Autoantibodies are not present in isolated SLJM, and systemic markers of inflammation are not elevated. SLJM is a marker for other diabetes-related complications, and an association between SLJM and microvascular disease (retinopathy, nephropathy) in men and macrovascular disease in women has been demonstrated (54) (Table 103.4).

### TABLE 103.4. Diabetic complications involving the upper extremity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Typical joints involved</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome of limited joint mobility</td>
<td>MCP, PIP, wrists, other joints</td>
<td>Decreased range of motion of the small joints.</td>
</tr>
<tr>
<td>Diabetic sclerodactyly</td>
<td>Distal digits, but may extend to entire hand</td>
<td>Thinned, waxy skin</td>
</tr>
<tr>
<td>Reflex sympathetic dystrophy (RSD)</td>
<td>Contracture and edema of the entire hand, occasionally entire Arm</td>
<td>More often bilateral (42%) than in other conditions (5%) Bone scan is positive</td>
</tr>
<tr>
<td>Adhesive capsulitis</td>
<td>Contracture of shoulder</td>
<td>Often associated with RSD or bicipital or superspinatus tenosynovitis</td>
</tr>
<tr>
<td>Dupuytren contracture</td>
<td>3rd, 4th, and 5th MCP and PIP contractures</td>
<td>Palpably thickened palmar fascia, dimpling of skin, associated with plantar fibromatosis</td>
</tr>
<tr>
<td>Flexor tenosynovitis</td>
<td>Any digit, but especially 2nd, 3rd, and 4th digits</td>
<td>Presence of painful trigger finger, thickened tendon sheath, nodule on tendon in area of pulley</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>MCP and PIP contractures</td>
<td>Prominent pain, wasting of thenar musculature, positive Tinel's and Phelan's sign. Slowed nerve conduction</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>Variable contractures</td>
<td>Dysesthesias, pain, loss or proprioception and fine touch. Abnormal nerve conduction delayed</td>
</tr>
<tr>
<td>Aseptic necrosis of humoral head</td>
<td>Shoulder contractures</td>
<td>Pain, loss of motion, radiographic changes delayed</td>
</tr>
</tbody>
</table>

MCP, Metacarpophalangeal joint; PIP, proximal interphalangeal joint; RSD, reflex sympathetic dystrophy.

SLJM is usually readily differentiated from other causes of joint contracture in the diabetic patient. As noted previously, Dupuytren contracture is common in DM but does not generally follow the same pattern of digital involvement; furthermore, SLJM is not associated with the formation of palmar nodules. Carpal tunnel syndrome may lead to joint contracture due to atrophy of the intrinsic hand muscles, which is not a characteristic of SLJM (60). RSD associated with frozen shoulder may be seen in DM, but the associated muscle atrophy, vasomotor, and sudomotor changes seen in RSD are not a part of SLJM.

### Pathology

Skin biopsy specimens in SLJM show active fibroblasts with extensive fibrosis and abnormal amounts of collagen (48, 61). Abnormal collagen cross-linking and glycosylation are seen and may be attributed to nonenzymatic glycosylation (55), a common finding in DM. Abnormal collagen cross-linking inhibits collagenase-induced collagen degradation, leading to further collagen accumulation (56). Additionally, insulin has been suggested to act as a growth factor for collagen production (57). Other theories include fibroblast-induced collagen and glycosaminoglycan synthesis resulting from decreased local oxygen tension as a result of microangiopathy (58) and increased collagen hydration associated with polyol accumulation (59).
Treatment

No specific form of therapy has emerged as the treatment of choice for SLJM. Tight control of serum glucose may improve skin thickening (62). Range-of-motion exercises maintain hand mobility, but do not affect joint contractures. Corticosteroid injection of affected tendon sheaths has been suggested for symptomatic relief (60). Observational data have noted some improvement after treatment with aldose reductase inhibitors, but this remains experimental (63).

PLANTAR FASCIITIS

Pain in the heel or over the plantar surface of the foot is a frequent musculoskeletal complaint. Plantar fasciitis, a syndrome of inflammation and pain involving the plantar fascia and its insertion at the medial calcaneus, is the most common cause of heel pain (64). The plantar fascia is a fibrous aponeurosis that provides static support to the longitudinal arch of the foot. Repetitive or excessive loads to the foot may lead to inflammation, degeneration, and fibrosis of the fascia (65). Running, jumping, improper footwear, and abnormal loading such as with obesity or sudden changes in athletic training may be causative factors. Altered gait mechanics, resulting from pes planus or pes cavus, abnormal subtalar motion, or inadequate foot dorsiflexion or plantarflexion further contribute excessive loading stress to the plantar fascia (66).

Pathology

Histopathology of plantar fasciitis includes collagen degeneration (67), chronic inflammation (68), and localized fibrosis and granulomatous changes (65). Some investigators have questioned the role of chronic inflammatory changes in the pathogenesis of plantar fasciitis, suggesting instead that chronic degeneration of tendon collagenous fibers is the more likely etiology (69, 70). However, localized inflammation at the origin of the plantar fascia extending to the periosteum may be demonstrated by triple-phase bone scan (66). Plain radiographs often demonstrate a calcific spur projecting from the calcaneal tuberosity (Fig. 103.4), but this finding is not specific for plantar fasciitis and is not implicated as the cause of the observed symptoms (71).

FIG. 103.4. Plantar fasciitis. This patient was a long-distance runner who continued to run despite severe calcaneal pain secondary to plantar fasciitis. A large calcaneal hyperostosis extends anteriorly, following the plantar fascia. The patient responded to 8 months of abstinence from long-distance running and eventually was able to resume running at reduced distances with the use of antipronator running shoes.

Diagnosis

Examination usually reveals a point of maximal tenderness to palpation over the anteromedial calcaneus. The pain is generally worst immediately upon arising in the morning or after periods of inactivity. Other causes of heel pain should be excluded (Table 103.5), and care should be taken to evaluate for a systemic inflammatory disease or other conditions that may be associated with plantar fascitis (Table 103.6). Gait mechanics and footwear should be assessed, and the patient should be questioned about overuse or other causes of abnormal loading on the foot. Further diagnostic testing is usually not necessary; however, bone scintigraphy (72), ultrasound (73), and MRI (74) may be used as an adjunct to diagnosis.

<table>
<thead>
<tr>
<th>TABLE 103.5. Intrinsic causes of heel pain</th>
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<tbody>
<tr>
<td><strong>Disorder</strong></td>
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</tr>
<tr>
<td>Plantar fasciitis</td>
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<tr>
<td>Achilles tendon</td>
</tr>
<tr>
<td>Tenosynovitis</td>
</tr>
<tr>
<td>Tendinitis</td>
</tr>
<tr>
<td>Subcutaneous bursitis</td>
</tr>
<tr>
<td>Rupture</td>
</tr>
<tr>
<td>Flexor hallucis longus</td>
</tr>
<tr>
<td>Tendinitis or tenosynovitis</td>
</tr>
<tr>
<td>Tibialis posterior</td>
</tr>
<tr>
<td>Tendinitis or tenosynovitis</td>
</tr>
<tr>
<td>Calcaneus</td>
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<tr>
<td>Apophysitis</td>
</tr>
<tr>
<td>Fracture</td>
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<tr>
<td>Periostitis</td>
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<tr>
<td>Erosion</td>
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<tr>
<td>Osteomyelitis</td>
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<tr>
<td>Ostosis</td>
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<tr>
<td>Tarsal tunnel syndrome</td>
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</table>
### Therapy

Conservative therapy remains the cornerstone of treatment. The time to symptom resolution may be prolonged, often 6 to 18 months (67). Rest and unloading of the foot has been described as the single most effective therapy (75). Correction of exacerbating factors to include decreasing weight-bearing load and intensity of activity and ensuring proper footwear are of utmost importance.

Strengthening and stretching exercises, focused on the intrinsic foot muscles and Achilles tendon, may be beneficial (76). Arch supports, custom orthotics, and heel cups are useful in some patients; over-the-counter or prefabricated orthotics may be preferable to custom-made orthoses (77). Splinting of the foot at night to allow passive dorsiflexion has been beneficial in some patients (78). Local therapy with ice packs may afford some relief, and systemic nonsteroidal antiinflammatory drugs (NSAIDs) have been employed with some success (75). Iontophoresis may improve symptoms early in the course of treatment, but offers no long-term advantages (79). Corticosteroid injection of the plantar fascia, with or without ultrasound guidance, is associated with a significant rate of success (80), but is also associated with the risks for plantar fascia rupture and fat pad atrophy. Rupture of the plantar fascia may occur in up to 10% of patients treated with corticosteroid injection (81), suggesting that this form of therapy should be reserved for recalcitrant cases. Other forms of local therapy for plantar fasciitis include extracorporeal shock wave lithotripsy, which has shown some effectiveness in uncontrolled studies (82, 83), and laser irradiation, which was not effective in one controlled trial (84). Surgical intervention may be considered when all forms of conservative therapy have failed. Open fasciectomy (85), percutaneous fasciotomy (86), and radiofrequency lesioning (87) show success rates of 83% to 92% in relief of symptoms. However, plantar fasciotomy may impair the arch-supporting function of the plantar fascia and increase the instability of the foot (87).

### RETROPERITONEAL FIBROSIS

Retroperitoneal fibrosis (RF) is a relatively rare disease for which the true incidence and prevalence are unknown (88, 89, 90). It was first described in the French literature by Alberran in the 1800s, before the first description in the English literature by Ormond after the turn of the century. RF is often referred to as Ormond disease owing to his early, albeit not first, description of the disease. Based on the number of cases diagnosed on a yearly basis in case series, the prevalence is less than 1 in 10,000 (91, 92). There are, however, likely a much larger number of cases that are clinically inapparent or go undiagnosed because of the protean manifestations of the disease.

RF is misnamed, leading to some of the confusion regarding its treatment and prognosis (93). Although fibrosis is a component of the disease, it is a late component. The retroperitoneal mass early on and at the leading edge is highly inflammatory. Although fibrosis is a characteristic finding, the term fibrosis often indicates inappropriately to the treating physician that it is a difficult-to-treat disease. In contrast, most patients respond well to therapy with shrinking of the mass (92).

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### Epidemiology

Idiopathic RF is a disease that can occur at any age, although the peak incidence is 40 to 60 years of age. Cases have been described in children as young as 2 years and in adults older than 80 years (94). This wide spectrum of age onset challenges many of the theories about the pathogenesis of disease (93).

Males are affected more than females (2:1 ratio), likely owing to the higher incidence of atherosclerotic disease that often accompanies and likely plays a role in RF (89). There is no reported ethnic predisposition or apparent genetic component, although there are case reports of identical twins both developing RF and affected siblings with disease (95, 96). There have been no reported clusters of cases or geographic maldistribution (i.e., more cases in the north than the south) (97).

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**TABLE 103.6. Conditions associated with plantar fasciitis**

<table>
<thead>
<tr>
<th>Inflammatory conditions</th>
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<tbody>
<tr>
<td>Reiter's syndrome</td>
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<tr>
<td>Ankylosing spondylitis</td>
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<tr>
<td>Psoriatic arthritis</td>
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<tr>
<td>Intestinal arthropathies</td>
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<tr>
<td>Behçet's disease</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Structural abnormality</td>
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<tr>
<td>Pes valgus</td>
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<tr>
<td>Increased pronation</td>
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<tr>
<td>Flexible “flat foot”</td>
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<tr>
<td>Overuse</td>
</tr>
<tr>
<td>Long-distance running</td>
</tr>
<tr>
<td>Prolonged walking or standing</td>
</tr>
<tr>
<td>Aerobic dance</td>
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<tr>
<td>Other</td>
</tr>
<tr>
<td>Poor footwear</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Gout</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Calcaneal spurs</td>
</tr>
<tr>
<td>Dupuytren's contracture</td>
</tr>
<tr>
<td>Achilles tendinitis</td>
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<tr>
<td>Metabolic bone disease</td>
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**Therapy**

Conservative therapy remains the cornerstone of treatment. The time to symptom resolution may be prolonged, often 6 to 18 months (67). Rest and unloading of the foot has been described as the single most effective therapy (75). Correction of exacerbating factors to include decreasing weight-bearing load and intensity of activity and ensuring proper footwear are of utmost importance.

Strengthening and stretching exercises, focused on the intrinsic foot muscles and Achilles tendon, may be beneficial (76). Arch supports, custom orthotics, and heel cups are useful in some patients; over-the-counter or prefabricated orthotics may be preferable to custom-made orthoses (77). Splinting of the foot at night to allow passive dorsiflexion has been beneficial in some patients (78). Local therapy with ice packs may afford some relief, and systemic nonsteroidal antiinflammatory drugs (NSAIDs) have been employed with some success (75). Iontophoresis may improve symptoms early in the course of treatment, but offers no long-term advantages (79). Corticosteroid injection of the plantar fascia, with or without ultrasound guidance, is associated with a significant rate of success (80), but is also associated with the risks for plantar fascia rupture and fat pad atrophy. Rupture of the plantar fascia may occur in up to 10% of patients treated with corticosteroid injection (81), suggesting that this form of therapy should be reserved for recalcitrant cases. Other forms of local therapy for plantar fasciitis include extracorporeal shock wave lithotripsy, which has shown some effectiveness in uncontrolled studies (82, 83), and laser irradiation, which was not effective in one controlled trial (84).

Surgical intervention may be considered when all forms of conservative therapy have failed. Open fasciectomy (85), percutaneous fasciotomy (86), and radiofrequency lesioning (87) show success rates of 83% to 92% in relief of symptoms. However, plantar fasciotomy may impair the arch-supporting function of the plantar fascia and increase the instability of the foot (87).
The overall incidence appears to be increasing, likely because of the enhanced diagnostic capabilities of computed tomography (CT) and MRI (98, 99). A major predisposition to developing RF is an abdominal aortic aneurysm. RF is noted in up to 10% to 15% of abdominal aortic aneurysms at the time of surgical resection (100).

Clinical Signs and Symptoms

One of the challenges in diagnosing RF is the lack of characteristic signs or symptoms. Most of the time, the presenting symptoms are nonspecific (101) (Table 103.7). Vague back, flank, or abdominal pain is the primary symptom at presentation (102). The pain is usually described as dull, aching, and constant. The pain is not normally exacerbated by movement. Less common presenting symptoms are claudication, hematuria, weight loss, malaise, nausea, vomiting, oliguria, and peripheral edema (89, 92, 101). Some of these symptoms are due to the development of uremia resulting from ureteral obstruction (103).

<table>
<thead>
<tr>
<th>TABLE 103.7. Signs and symptoms of retroperitoneal fibrosis</th>
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<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Flank pain</td>
</tr>
<tr>
<td>Malaise</td>
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<tr>
<td>Abdominal pain</td>
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</table>

The physical exam is usually unrevealing. The most common findings are an abdominal or rectal mass (5% to 10%), lower extremity edema (secondary to extrinsic venous compression), hepatomegaly, scrotal edema, abdominal bruits, and costovertebral angle tenderness (101, 103). These latter findings are present in less than 5% of cases. Because of the lack of specific signs and symptoms, there is, on average, a 3- to 4-month delay from onset of symptoms to diagnosis, but the diagnostic lag time may be up to 1 year (104). It is highly likely the disease process is ongoing for weeks to months before onset of symptoms.

Laboratory Findings

The laboratory findings in RF are also nonspecific. Inflammatory measures are usually increased [i.e., (ESR) sedimentation rate erythrocyte and C-reactive protein (CRP)] (92). Renal insufficiency (e.g., elevated blood urea nitrogen or creatinine) is present at the time of diagnosis in almost one half of cases due to ureteral obstruction by the mass (105). Most serologic tests in RF are negative unless the RF is associated with a collagen vascular disease such as vasculitis or systemic lupus erythematosus (SLE) (92, 106). Thus, finding a positive antineutrophil cytoplasmic antibody (ANCA) or antineutrophil cytoplasmic antibody (ANCA) in a patient with RF should prompt a search for an associated vasculitis or other connective tissue disease (107, 108). A decrease in the ESR and CRP with treatment is usually associated with response to treatment; however, radiologic studies are almost always required to assess fully the response to treatment.

Radiographic Findings

Radiologic studies are the most reliable methodology for the diagnosis of RF and for assessing response to treatment (98, 99). Many times, the initial study done in the workup of RF patients is a renal ultrasound. This test is usually performed as part of the evaluation of a patient presenting with acute renal failure. The ultrasound reveals evidence of bilateral ureteral obstruction and oftentimes evidence of a mass as well (100).

The advent of CT and MRI has limited the utility of the intravenous pyelogram and retrograde ureterogram. When done as part of the workup, these tests demonstrate deviation of the ureters medially with obstruction usually in the area where the ureters cross the iliac arteries. The medial deviation of the ureters seems counterintuitive because normally a mass that begins around the aorta would push the ureters laterally (101). Although not definitively proved, it is believed that the mass envelops the ureters and then recedes over time; as it progresses from inflammatory to fibrotic, the ureters are pulled medially.

CT and MRI are now the preferred diagnostic tools in RF (98, 99). Frequently, an MRI or CT is done for evaluation of nonspecific abdominal or back pain, and the mass is serendipitously discovered. Workup of an ill-defined pelvic or abdominal mass or a palpable pulsatile abdominal mass may also reveal an unexpected finding of a retroperitoneal mass. The findings of MRI or CT in RF are a homogeneous retroperitoneal mass surrounding the aorta primarily below the takeoff of the renal arteries (Fig. 103.5). The mass follows the iliac arteries after the bifurcation. Rarely, the mass can involve only one or the other iliac artery. The mass can progress cephalad and surround the aorta into the chest and mediastinum (109). The mass rarely extends more than 4 to 5 cm lateral to the aorta. It will also rarely extend anteriorly or posteriorly, although cases of extension anteriorly into the small bowel mesentery and posteriorly into the spine are reported. Isolated cases of fibrosis involving the ovarian vessels, the spermatic vessels, pancreas, spleen, pericardium, pleura, uterus, cervix, and lungs are reported (93). If the mass surrounds or invades the kidneys or liver or is present in one of the above rare locations, an alternate diagnosis should be considered (110). For the most part, CT and MRI are of sufficient sensitivity to differentiate lymphomas, sarcomas, and infectious masses from RF. Radiographic studies alone should not be depended on in cases with atypical features such as nodularity, associated lymphadenopathy, or unusual location (111). In these cases, biopsy,
likely by an open surgical procedure, is required for diagnosis.

**FIG. 103.5. Retroperitoneal fibrosis.** A tumor-like periaortic mass of homogeneous reactive fibrosis pulls the ureters medially in this contrasted computed tomography scan of the abdomen and retroperitoneum in a patient with retroperitoneal fibrosis.

**Pathology**

As mentioned in the introduction, the pathologic appearance of RF differs significantly from what its name implies (88,112). The microscopic appearance ranges from inflammatory to noninflammatory in the same mass (92,113). It is rare for there not to be a significant inflammatory component to the mass (113). This has led some investigators to propose changing the name from RF to inflammatory aortitis. The central core is often fibrotic, with the advancing edge being the most inflammatory. The areas of fibrosis are composed of collagen bundles, usually with inflammatory cells intermingled. The inflammatory infiltrate is composed of macrophages, lymphocytes, plasma cells, and occasional eosinophils (113,114,115). The lymphocytic infiltrate is a polyclonal collection of both T and B lymphocytes (113,115). The macrophages are usually lipid laden, similar to those found in atherosclerotic plaques. Immunofluorescence studies of the mass reveal deposits of immunoglobulin G (IgG) in the periaortic region most prominent within the aortic wall and atherosclerotic plaques (116). Ten percent of cases have evidence of frank vasculitis, with medium-sized artery inflammation and fibroid necrosis (108).

**Differential Diagnosis**

The differential diagnosis of RF is limited. More than 75% of cases are idiopathic. Once medications are ruled out (see later), the primary differential diagnosis is malignancy versus infection (110). The primary malignancies that cause retroperitoneal masses are lymphomas and sarcomas. As noted in the radiographic section, lymphomas and sarcomas can be differentiated in most instances from idiopathic RF by the location of the mass, the spread of the mass, or the presence of associated lymphadenopathy.

Infections rarely cause RF. The infectious agents most commonly found are actinomyces and mycobacterial organisms (89). Infections of the fallopian tubes and ovaries can spread into the retroperitoneal area, leading to a fibrotic reaction. Other etiologic factors implicated in RF include local irradiation, ureteral rupture, and retroperitoneal bleed (117).

Unfortunately, pathologic confirmation requires an open procedure in most instances. The reaction of the retroperitoneum to most insults is fibrosis. Thus, a thin-needle biopsy of the mass may reveal only reactive fibrosis. A needle biopsy that reveals only fibrosis does not rule out malignancy or infection (118). A positive biopsy, obviously, is diagnostic. In the case of a negative needle biopsy, to exclude infection or malignancy fully, an open biopsy is required. Laparoscopic biopsy with direct visualization can be a compromise between needle biopsy and an open procedure, although the latter is more definitive (119,120). Often, an open procedure is needed to relieve obstruction, as outlined in the treatment section. When such a procedure is necessary, multiple biopsy samples from multiple sites should be taken (106).

There are other rare diseases that can cause RF. Erdheim Chester syndrome, which is a non-Langerhans cell histiocytic disease, can have as one of its manifestations a retroperitoneal mass (96,121). Erdheim Chester syndrome is characterized by diabetes insipidus and long bone osteosclerosis (122). The retroperitoneal mass in Erdheim Chester syndrome typically is invasive, infiltrating into the
kidney and up the biliary tract into the liver. It is characterized pathologically by foam-laden histiocytes infiltrating the fibrotic tissue.

A disease related to RF is idiopathic fibrosclerosis. This disease is characterized by fibrotic masses outside of the retroperitoneal space. Orbital pseudotumor, Reidel thyroiditis, mediastinal fibrosis, and fibrotic arthropathy are areas of involvement in fibrosclerosis (123 ).

Cases of drug-induced RF are unusual because the use of methysergide has decreased for the treatment of migraine headaches. Other medications reported rarely to cause RF include B-blockers, methyldopa, hydralazine, certain analgesics, and ergot alkaloids (92, 124 ).

RF may occur in patients with other collagen vascular diseases. The co-occurrence of RF with scleroderma, SLE, polyarteritis nodosa, Wegener's granulomatosis, ankylosing spondylitis, uveitis, and Crohn's disease is rare but supports the theory that RF is, at least in some cases, an immunologically mediated autoimmune disease (125, 126, 127 ).

**Pathogenesis**

The pathogenesis of RF is unclear, and causes remain speculative. As stated earlier, the lack of family history suggests a minimal genetic contribution, whereas the lack of case clustering makes an environmental cause seem less likely. The constant feature of the disease is its periarterial location. Early investigators, such as Mitchinson (88 ), suggested that RF is a reaction to materials leaking through the aortic or arterial wall. The possible link between most of the medications associated with RF is that they are vasoactive, perhaps enhancing such a leak. Others, such as hydralazine, are associated with autoimmune phenomena such as drug-induced SLE, suggesting a more autoimmune pathogenesis.

A more recent and appealing pathogenic mechanism, to this author, has been proposed by Parums and colleagues, who have done the most extensive pathologic assessment of the disease to date (93 ). They propose that RF is part of a continuum of the immune response of atherosclerosis. The underlying aortoimmune reaction is the production of “autoantibodies” to the ceroid component of atherosclerotic plaques. Ceroid is basically a mixture of protein and oxidized low-density lipoprotein (LDL). In one report, 100% of patients with RF had antibodies to ceroid in their serum. Although this 100% association is impressive, more than 50% of age-matched controls also had anticeroid antibodies (128 ). Thus, although anticeroid antibodies may be required for development of RF, their presence does not induce disease in most elderly patients.

As part of this continuum of effects, in response to atherosclerosis, plaque formation, and plaque rupture, antibodies to the ceroid component of the plaque are deposited. In pathologic studies of atherosclerosis, plaques often contain deposited IgG (116 ). In certain individuals, this deposition of IgG leads to an immune response with infiltrating lipid-laden macrophages. Indeed, most atherosclerotic plaques contain lipid-laden macrophages. Rupture of the plaque allows easier and more access of serum antibodies to the antigenic components of the plaque. After antibody deposition, there follows an infiltration of inflammatory cells, including B cells and T cells, that is polyclonal in nature. This aortitis is clinically evident in a small percentage of individuals and may play some role in the development of abdominal aortic aneurysms.

Therapeutic Approach

Once drug and traumatic etiologies are ruled out, the first decision to be made in the approach to the patient with a retroperitoneal mass is whether to undertake biopsy of the mass (100, 132 ). With improved urologic techniques, urinary drainage can almost always be accomplished through retrograde or percutaneous ureteral stent placement. If this ureteral drainage cannot be accomplished, open or laparoscopic freeing of the ureters is required. During the procedure to free the ureters, numerous biopsy specimens should be obtained from multiple areas of the mass.

If ureteral drainage is obtained without a surgical procedure, then determining whether to biopsy is usually based on the appearance of the mass on CT or MRI. As stated earlier, improved CT and MRI techniques allow differentiation of idiopathic RF from that due to infection or malignancy in most instances. When there is uncertainty, percutaneous needle biopsies can be performed through CT or ultrasound guidance. Needle biopsies may reveal tumor or infection; however, most of the time, they reveal nonspecific inflammation or fibrosis (118 ). As a result of sampling error, if the biopsy results are nonspecific, neither tumor nor infection is ruled out. Thus, unless there are specific suspicious areas on CT or MRI, random needle biopsies are usually not warranted. Although biopsies obtained through an open surgical procedure are useful, their utility should be considered in the overall context of the patient's health and ability to undergo a serious operation. If a biopsy was not done initially, if the patient is unresponsive to therapy, performing a biopsy is usually indicated. Biopsy characteristics are not predicative of response to therapy and thus should not serve as rationale for performing a biopsy (93 ).

Surgical therapy is necessary if anatomic obstruction of the ureters, vena cava, or lymphatics cannot be relieved with medical treatment. The surgical procedure is ureterolysis that involves freeing up the ureters, lateralization of the ureters, and wrapping them in omentum to prevent reobstruction (119, 130, 131 ). This is a difficult operation, with 25% serious morbidity and significant mortality. One of the
more serious complications is the development of a ureteral leak (117). Because most patients with RF have significant comorbidities, including hypertension, diabetes, and atherosclerotic disease, careful assessment of the patient's ability to undergo the surgery is necessary. Laparoscopic approaches are feasible; however, they are extremely tedious, requiring up to 4 hours to free each ureter (120). For this reason, an open procedure remains the primary surgical approach. There is some controversy about whether adjunctive medical therapy is necessary once a surgical procedure is done to free the ureters (134). Because of the small numbers of patients, no true randomized study is available to answer this question. In our experience, patients who received surgical therapy and then no medical therapy had a high incidence of relapse requiring additional surgery or medical therapy (92). Those individuals who received medical therapy after surgical therapy had fewer relapses and complications. Most of the other studies indicate that medical therapy is warranted after ureterolysis, although one study found no benefit to adding prednisone to surgical therapy (134). Another complicating factor in assessing response to treatment in RF is that there are some patients who spontaneously remit despite no therapy (103,105). The exact number or percentage of these spontaneous remissions is difficult to ascertain, again owing to the small numbers of patients at each center. Such spontaneous remissions should be considered when reviewing small case reports of success with a given pharmacologic agent or surgical approach.

Patients with abdominal aortic aneurysms and a surrounding retroperitoneal mass should, if they are able to, undergo repair of the aneurysm if it is of sufficient size to warrant surgical intervention (131,135). The aneurysm is not protected from rupture by the mass; if anything, aneurysms associated with RF are more likely to rupture. About 15% of abdominal aortic aneurysms have associated RF. In most instances, the RF will spontaneously resolve when the aneurysm is repaired. In a small number of cases, the RF may "flare" postoperatively, with an increase in mass size and an increase in systemic symptoms, such as fever, malaise, and abdominal pain (93). In these instances, medical therapy is warranted.

The treatment of RF remains anecdotal based on case reports. There are no controlled trials, again owing to the small numbers of patients. Some inferences can be based on patients that refuse therapy or receive surgical therapy alone. Most of these patients experience progressive disease and serve as historical controls. Medical treatment normally consists of corticosteroids at a dose 1 mg/kg per day of prednisone or its equivalent (136,137). The prednisone is then weaned over several months to 10 mg daily and tapered more slowly after that, using a similar regimen as the treatment of giant cell arteritis (92). As with giant cell arteritis, the treatment is continued for a total of 6 to 12 months. Most patients do not relapse after initial therapy, but enough do that patients should be monitored for redevelopment of disease for a number of years after remission (101).

There are a number of case reports of the successful use of tamoxifen for the treatment of RF (138,139). Many of these reports are from the gynecologic literature describing the successful use of tamoxifen to treat desmoid tumors with a fibrotic phenotype (140). In some patients, corticosteroids were coadministered. Because of publication bias, it is unclear how many patients have been unsuccessfully treated with tamoxifen. Our experience with tamoxifen in more than half a dozen patients is disappointing in that all of them progressed while on tamoxifen alone (92). These were patients who were successfully stented, yet for medical or personal reasons did not want to take prednisone. In each instance, once placed on prednisone, the patients responded with a decrease in mass size. The reported effective dose of tamoxifen is 40 mg daily. Patients with hypercoagulable states should not be placed on tamoxifen. A potential mechanism of action of tamoxifen is blocking the oxidation of LDL, which tamoxifen inhibits in the test tube.

Once a remission is obtained with other agents, it is possible tamoxifen is useful in keeping the patient in remission, although again, any such use is purely anecdotal.

A number of immunosuppressive agents have been reported as adjuncts or steroid-sparing agents or for steroid-refractory cases. These agents include methotrexate, azathioprine, cyclophosphamide, and mycophenolate (92,141,142). None of these reports are from controlled trials, and all are anecdotal. They were primarily used in patients refractory to prednisone or in patients who respond to high doses of prednisone but relapse upon tapering. The doses of the agents used are similar to the doses used in rheumatoid arthritis or SLE. The duration of therapy recommended in most reviews is 6 months to 1 year with these agents, similar to the use of prednisone. The length of treatment is, however, also empiric. There is no study that examined the optimum length of therapy.

Because of the protean nonspecific nature of the signs and symptoms of RF, laboratory and radiologic measures must be relied on to gauge response to therapy. If a mass is palpable or the patient has systemic symptoms, these findings can be followed to indicate response to treatment. In most cases, however, it is necessary to monitor ESR or CRP to assess control of inflammation. Although useful, these tests are not entirely reliable as indicators of disease response. Thus, in most cases, it is necessary to perform imaging to assess response (98,101,143). In most cases, this involves either CT or MRI. The mass will usually begin shrinking within a few weeks of institution of therapy if it is going to respond. A reassessment of the mass at 6 weeks is reasonable to assess therapeutic response. If there is no response after 6 to 8 weeks of a particular therapy, then adding on or substituting another treatment is prudent at that time. Follow-up CT or MRI scans can then be performed every 3 to 6 months to assess further the response.
to treatment (99). In most instances, the mass completely disappears or shrinks down to a rind around the aorta.

If the mass appears to have released the ureters by CT or MRI, it is reasonable to not replace the stents when it is time for them to be removed. Normally, stents are replaced every 6 months. In some instances, the ureters do not function normally after stent removal, and ureteral obstruction appears to remain even though the mass is gone (144). In these instances, the stents should be replaced for another 6 months, and then going without the stents can be tried again.

**Prognosis**

In our experience and according to reports in the literature, most patients with RF respond to treatment. If the patient does not respond, then other diagnoses, like infection, malignancy, fibrosclerosis, or Erdheim Chester disease, should be considered. Overall, the 10-year survival rate of patients with RF is less than 70%. Most deaths, however, are due to the accompanying atherosclerotic disease and not to complications of RF. The disease itself is rarely fatal (89,101).

**PEYRONIE'S DISEASE**

Peyronie's disease is an acquired penile deformity that occurs during erection and that develops at a median age of 53 years (145). Although the pathogenesis is unknown, it is believed that in most cases it develops following penile trauma. The primary presenting symptom is painful erection with a noticeable deformity. Most of the time a palpable plaque is present in the penis. Erectile dysfunction often follows the development of Peyronie's disease (146).

**Epidemiology**

The prevalence of clinical disease is about 1.5% in men in their 30s, increasing to 6.5% in men older than 70 years (147). In a study of 100 men with no complaints of Peyronie disease, 22 had palpable penile plaques. The disease is more common in caucasians than African Americans. There appears to be a familial predisposition to disease. Peyronie's disease often develops in patients who also have Dupuytren's contractures or plantar fasciitis, suggesting an overall predisposition to fibrosis (146,148). More advanced lesions contain calcification that can progress to ossification. As in most fibrotic diseases, tissue expression of TGF-β is implicated in the fibrosis of Peyronie's disease. Dysregulation of the ratio of nitric oxide to reactive oxygen species is postulated as another possible pathologic scenario that can lead to fibrosis (149).

**Pathogenesis**

The pathogenesis of Peyronie's disease is unclear, although there is often reported a significant history of penile trauma before development of disease. Thus, Peyronie's disease may be due to aberrant healing of a traumatic lesion. The fibrotic lesion is in the tunica albuginea. Trauma to the penis may result in bleeding into the subtunical spaces or tunical delamination where the septum joins the tunica albuginea. The bleeding is followed by fibrin deposition, fibrosis, and plaque formation. The pathology of the Peyronie plaque is diverse, with some lesions containing significant inflammation and others only fibrotic tissue (149). More advanced lesions contain calcification that can progress to ossification. As in most fibrotic diseases, tissue expression of TGF-β is implicated in the fibrosis of Peyronie's disease. Dysregulation of the ratio of nitric oxide to reactive oxygen species is postulated as another possible pathologic scenario that can lead to fibrosis (149).

**Clinical Features**

The clinical manifestations of Peyronie's disease are usually considered as two triads of symptoms, one occurring early and the other late. The early triad of symptoms consists of a penile nodule or plaque, painful erection, and deformity with erection (149). The lesion becomes less painful over time, presumably because of the resolution of inflammation. The late symptom triad consists of a harder plaque and a stable penile deformity with erection or erectile dysfunction. Physical examination usually reveals a firm nodule or plaque that the patient may not be aware of. The plaque is in most instances on the dorsal side of the penis. The plaque can be documented by ultrasonography, but unless surgical correction is contemplated, further radiographic or vascular evaluation is normally not required (150).

**Therapy**

Therapy of Peyronie's disease can vary from just observation to aggressive surgical débridement and revascularization. A number of therapies are reported in case series to have potential efficacy. These include lithotripsy, orthovoltage radiation, heat therapy, and laser therapy (150,151). A number of medical therapies have been tried, but only a few are of documented efficacy. The most common treatments are potassium aminobenzoate, tamoxifen, acetyl-L-carnitine, colchicine, and vitamin E (152). Colchicine was found to improve symptoms in about 50% of a group of 24 patients. Potassium aminobenzoate is the most used and studied treatment. In a recent analysis of more than 2,500 treated patients, 57% reported improvement (152). A number of case series have reported improvement with tamoxifen, which is used in other fibrotic diseases as well (see retroperitoneal fibrosis section). Acetyl-L-carnitine was compared head to head with tamoxifen in 48 patients over 6 months. In this trial, the patients taking carnitine had a significantly improved outcome compared with those taking tamoxifen. Because of its antioxidant effects, vitamin E has been used to treat Peyronie's disease. The only placebo-controlled trial of vitamin E in Peyronie's disease, however,
Intralesional injections are also frequently prescribed for treatment of Peyronie's disease; these drugs include corticosteroids, interferons, collagenases, and calcium channel blockers. Intralesional corticosteroid injections are probably most useful in the early inflammatory component of disease for pain relief. There is no indication they improve the deformity. Intralesional injections of calcium channel blockers, primarily verapamil, are also frequently administered to patients with Peyronie's disease (153). A number of case reports suggest about a 50% reduction in deformity and pain, whereas most patients reported a significant decrease in disease progression with intralesional calcium channel blockers. Collagenase injections appear to have some efficacy in patients with milder deformities, whereas the benefits of intralesional interferons appear outweighed by the substantial side effects of these agents (153).

Surgical therapy is reserved for patients with severe deformity or erectile dysfunction that negatively affects sexual function. A number of reconstructive techniques have been tried with variable success and significant potential side effects. Penile implantation is indicated only when severe erectile dysfunction is present (150).

REFERENCES


