extremities, ischemic leg ulcers, digital gangrene, avascular necrosis of bone, retinal artery occlusion leading to painless transient vision loss, renal artery stenosis, and glomerular lesions, as well as infarcts of spleen, pancreas, and adrenals. Libman-Sacks endocarditis consists of very small vegetations, histologically characterized by organized platelet-fibrin microthrombi surrounded by growing fibroblasts and macrophages. Glomerular lesions are manifested with hypertension, mildly elevated serum creatinine levels, proteinuria, and mild hematuria. Histologically, these lesions are characterized in an acute phase by thrombotic microangiopathy involving glomerular capillaries, and in a chronic phase with fibrous intima hyperplasia, fibrous and/or fibrocellular occlusions of arterioles, and focal cortical atrophy (Table 379-2). Premature atherosclerosis has been recognized as a rare feature of APS. Coombs-positive hemolytic anemia and thrombocytopenia are laboratory findings associated with APS. Discontinuation of therapy, major surgery, infection, and trauma may trigger CAPS.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of APS should be seriously considered in cases of thrombosis, cerebral vascular accidents in individuals younger than 55 years of age, or pregnancy morbidity in the presence of livedo reticularis or thrombocytopenia. In these cases, aPL antibodies should be measured. The presence of at least one clinical and one laboratory criterion ensures the diagnosis even in the presence of other causes of thrombophilia. Clinical criteria include: (1) vascular thrombosis defined as one or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ; and (2) pregnancy morbidity, defined as (a) one or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation; (b) one or more premature births of a morphologically normal neonate before the thirty-fourth week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency; or (c) three or more unexplained consecutive spontaneous abortions before the tenth week of gestation. Laboratory criteria include (1) LA, (2) anticardiolipin (aCL), and/or (3) anti-β2GPI antibodies, at intermediate or high titers on two occasions, 12 weeks apart.

Differential diagnosis is based on the exclusion of other inherited or acquired causes of thrombophilia (Chap. 141), Coombs-positive hemolytic anemia (Chap. 129), and thrombocytopenia (Chap. 140). Livedo reticularis with or without a painful ulceration on the lower extremities also may be a manifestation of disorders affecting (1) the vascular wall, such as polyarteritis nodosa, SLE, cryoglobulinemia, and lymphomas; or (2) the vascular lumen, such as myeloproliferative disorders, atherosclerosis, hypercholesterolemia, or other causes of thrombophilia.

TREATMENT ANTIPHOSPHOLIPID SYNDROME

After the first thrombotic event, APS patients should be placed on warfarin for life, aiming to achieve an international normalized ratio (INR) ranging from 2.5 to 3.5, alone or in combination with 80 mg of aspirin daily. Pregnancy morbidity is prevented by a combination of heparin with aspirin 80 mg daily. IV immunoglobulin (IVIg) 400 mg/kg every day for 5 days may also prevent abortions, whereas glucocorticoids are ineffective. Patients with aPL in the absence of any clinical event who are simultaneously positive for aCL, anti-β2GPI, and LA or have SLE are at risk to develop thrombotic events and can be protected by aspirin 80 mg daily.

Some patients with APS and patients with CAPS have recurrent thrombotic events despite appropriate anticoagulation. In these cases, IVIg 400 mg/kg every day for 5 days may be of benefit. Patients with CAPS, who are treated in the intensive care unit, are unable to receive warfarin; in this situation, therapeutic doses of low-molecular-weight heparin should be administered. In cases of heparin-induced thrombocytopenia and thrombosis syndrome, inhibitors of phospholipid-bound activated factor X (FXa), such as fondaparinux 7.5 mg SC daily or rivaroxaban 10 mg PO daily, are effective. The above drugs are administered by fixed doses and do not require close monitoring; their safety during the first trimester of pregnancy has not been clearly established.

380 Rheumatoid Arthritis

Ankoor Shah, E. William St. Clair

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by a symmetric, peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. Because it is a systemic disease, RA may result in a variety of extraarticular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities.

Insights gained by a wealth of basic and clinical research over the past two decades have revolutionized the contemporary paradigms for the diagnosis and management of RA. Serum antibodies to cyclic citrullinated peptides (anti-CCPs) are routinely used along with rheumatoid factor as a biomarker of diagnostic and prognostic significance. Advances in imaging modalities have improved our ability to detect joint inflammation and destruction in RA. The science of RA has taken a major leap forward with the identification of new disease-related genes and further deciphering of the molecular pathways of disease pathogenesis. The relative importance of these different mechanisms has been highlighted by the observed benefits of the new class of highly targeted biologic and small-molecule therapies. Despite these gains, incomplete understanding of the initiating pathogenic pathways of RA remains a sizable barrier to its cure and prevention.

The last two decades have witnessed a remarkable improvement in the outcomes of RA. The historic descriptions of crippling arthritis are currently encountered much less frequently. Much of this progress can be traced to the expanded therapeutic armamentarium and the adoption of early treatment intervention. The shift in treatment strategy dictates a new mind-set for primary care practitioners—namely, one that demands early referral of patients with inflammatory arthritis to a rheumatologist for prompt diagnosis and initiation of therapy. Only then will patients achieve their best outcomes.

CLINICAL FEATURES

The incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases. The presenting symptoms of RA typically result from inflammation of the joints, tendons, and bursae. Patients often complain of early morning joint stiffness lasting more than 1 h that eases with physical activity. The earliest involved joints are typically the small joints of the hands and feet. The initial pattern of joint involvement may be monoarticular, oligoarticular (≤4 joints), or polyarticular (>5 joints), usually in a symmetric distribution. Some patients with inflammatory arthritis will present with too few affected joints to be classified as having RA—so-called undifferentiated inflammatory arthritis. Those with an undifferentiated arthritis who are most likely to be diagnosed later with RA have a higher number of tender and swollen joints, test positive for serum rheumatoid factor (RF) or anti-CCP antibodies, and have higher scores for physical disability.

Once the disease process of RA is established, the wrists, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints stand out as the most frequently involved joints (Fig. 380-1). Distal interphalangeal (DIP) joint involvement may occur in RA, but it usually is a manifestation of coexistent osteoarthritis. Flexor tendon tenosynovitis is a frequent hallmark of RA and leads to decreased range of motion, reduced grip strength, and "trigger" fingers. Progressive destruction of the joints and soft tissues may lead to chronic, irreversible deformities. Ulnar deviation results from subluxation of the MCP joints, with subluxation of the proximal phalanx to the volar side of the hand. Hyperextension of the PIP joint with flexion of the DIP joint ("swan-neck deformity"), flexion of the PIP joint with hyperextension of the DIP joint ("boutonnière deformity"), and subluxation of the first MCP joint with hyperextension of the first interphalangeal (IP) joint ("Z-line