A Study of Musculoskeletal Manifestations in 12 Patients with SAPHO Syndrome

Jeff P. Steinhoff, Ana Cilursu, Gerald F. Falasca, Leonardo Guzman, Antonio J. Reginato

Synovium and synovial fluid findings in SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome have not been well characterized, and only a few patients have been described in the Americas. We describe clinical, pathologic, and synovial fluid findings in 12 patients with the SAPHO syndrome: hidradenitis suppurativa (7), acne fulminans or conglobata (3), acneiform folliculitis (1) and palmoplantar pustulosis (1). Routine synovial fluid studies were performed in 6 patients, and light and transmission electron microscopic studies were performed in synovium in 2 patients and in bone in 1.

The most common musculoskeletal manifestations included erosive or nonerosive oligoarthritis involving metacarpal phalangeal (MCP) and metatarsal phalangeal (MTP) joints as seen in 9 patients, sclerosis of the sacroiliac joints as seen in 5 patients, and osteitis pubis as seen in 1. Three patients had signs of skeletal hyperostosis. The patients with acne fulminans and acneiform folliculitis had chronic aseptic multifocal osteomyelitis. Synovial fluid was sterile in 7, mildly inflammatory in 5, and highly inflammatory in 2. Electron microscopic studies of synovium in 2 patients and of bone in 1 were not useful to detect microorganisms. Three African-American patients with hidradenitis suppurativa presented with pyoderma gangrenosum, and 2 of them had leukocytoclastic vasculitis, and a life threatening course unresponsive to antibiotics, corticosteroids and immunosuppressive therapy.

SAPHO in the Americas is most severe in African-Americans with hidradenitis suppurativa, and it presents with heterogeneous musculoskeletal and cutaneous manifestations including erosive polyarthritis or oligoarthritis with nonspecific mild inflammatory fluid. Leukocytoclastic vasculitis and recalcitrant pyoderma gangrenosum were seen in 2 of our patients with the most severe hidradenitis suppurativa. SAPHO syndrome may present with clinical manifestations similar to those seen with seronegative spondyloarthropathies, but it has distinctive cutaneous, radiographic articular, and bone manifestations. Sites of chronic infection need aggressive antibiotic therapy and may need surgical resection. (J Clin Rheumatol 2002;8:13–22)

Key words: SAPHO syndrome, Acneiform folliculitis, Hidradenitis suppurativa, Palmoplantar pustulosis, Acne fulminans, Acne conglobata

Since 1959, there have been over 200 reports of patients afflicted with 2 or more of the heterogeneous combination or related findings now referred to as SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome (1–10). Hidradenitis suppurativa and pyoderma gangrenosum are other skin conditions that may be associated with the syndrome (11–13). Most of the patients with SAPHO syndrome have been described in Japan, Scandinavia, Germany, and France (14–17). Although both the SAPHO syndrome acronym and classification criteria were proposed in 1987 by Chamot et al. (8), these criteria have not been validated in comparison with closely related conditions, particularly seronegative spondyloarthropathies. This syndrome still is under-reported and possibly under-recognized in the Americas, likely because of its chronic and relapsing nature as well as its expanding body of clinical and radiographic manifestations. Musculoskeletal manifestations have been characterized by the presence of acute or chronic synovitis, sacroilitis, monostotic or polyostotic sclerosing bone lesion(s), and sterile osteomyelitis (2, 4, 17–24). In-
formation about radiographic manifestations of peripheral joint and synovial fluid analysis in this condition is scarce (17). Spondyloarthropathies with or without associated inflammatory bowel disease (10) have also been reported in patients with the syndrome, but the human leukocyte antigen (HLA) B-27 has been found in only about 10% of such patients (11–14, 17). Because this syndrome is not commonly observed in the United States, and because there are no validated criteria, patients with features of SAPHO present the potential for misdiagnosis. In this report, we describe a wide spectrum of relapsing, often disfiguring skin involvement, musculoskeletal syndromes, and other systemic manifestations, as well as synovial fluid and pathological findings of patients thought to suffer from SAPHO syndrome.

PATIENTS AND METHODS

Twelve patients with features of SAPHO syndrome have been seen since 1974 at Cooper Hospital University Medical Center, Camden, New Jersey (8 patients), Veterans Administration Medical Center, Philadelphia, Pennsylvania (2 patients), and Salvador Hospital, Santiago, Chile (2 patients). In accordance with the diagnostic classification recommended by Chamot et al. (8) (Table 1), these patients presented with a wide variety of musculoskeletal manifestations, including chronic multifocal sterile osteomyelitis, hyperostosis, and erosive and/or nonerosive peripheral or axial arthropathies associated with hidradenitis suppurativa (patients 1 through 7; Table 2), ulcerative or pustular forms of acne or acne conglobata (patients 2, 5, 8, 9, and 10), acneiform folliculitis (patient 11), and palmar-plantar pustulosis (patient 12; Table 3).

Patients were evaluated using conventional radiographic examination of the peripheral joints, pelvis, and axial skeleton. Arthrocentesis was performed in patients 1, 2, 3, 7, 8, 10, and 11, with synovial fluid analysis performed by standard techniques in addition to culture for bacterial, fungal, and acid-fast bacilli. Search for propionibacterium acnes in aerobic or anaerobic cultures was not performed. Synovial tissue was obtained from the ankle of patient 8 and the wrist of patient 2, and bone and synovium were taken from the left wrist of patient 11. Tissues were fixed in formalin and stained with routine stains. In patients 2 and 11, synovium and bone, respectively, were also fixed in glutaraldehyde (½ strength Karnovsky’s fixative) and processed for transmission electron microscopic studies in accordance with a previously described technique (25). Surgical or punch out skin biopsies were performed in areas of hidradenitis suppurativa (patients 1 through 7), areas of pyoderma gangrenosum (patients 1, 2, and 7), skin lesions with clinical features of vasculitis (patient 1 and 7), and acneiform folliculitis (patient 11). The diagnosis of hidradenitis suppurativa, acne conglobata, ulcerative and pustular acne, acneiform folliculitis, palmar-plantar pustulosis, and pyoderma gangrenosum were performed based on characteristic clinical and pathologic findings (26, 27). Laboratory testing included serum calcium, alkaline phosphatase, hemoglobin, hematocrit, white blood cell count, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and antinuclear antibodies (ANA) in most of the patients. Anticytoplasmic, antカードiolipin antibodies, and HLA-B27 testing was performed in only 4 patients. In patient 11, bone scintigraphy and nuclear magnetic resonance imaging were performed to detect areas of bone involvement associated with areas of clinical apparent cellulitis.

RESULTS

Demographic Features

Eight patients were African-American, 2 were Latin-American, and 2 were Caucasians. Forty-five percent were women. The age at presentation of the articular com-

<table>
<thead>
<tr>
<th>TABLE 1. Diagnostic criteria for SAPHO syndrome</th>
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<tbody>
<tr>
<td>Sterile multifocal chronic osteitis:</td>
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<tr>
<td>Involvement of the chest, spine, pelvis or long bones</td>
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<tr>
<td>Absence of skin lesions</td>
</tr>
<tr>
<td>Acute“ or chronic arthritis” associated with:</td>
</tr>
<tr>
<td>Palmo-plantar pustulosis</td>
</tr>
<tr>
<td>Palmo-plantar pustular psoriasis</td>
</tr>
<tr>
<td>Severe acne</td>
</tr>
<tr>
<td>Hidradenitis suppurativa</td>
</tr>
<tr>
<td>Sterile mono or polyostitis associated with:</td>
</tr>
<tr>
<td>Palmo-plantar pustulosis</td>
</tr>
<tr>
<td>Palmo-plantar pustular psoriasis</td>
</tr>
<tr>
<td>Severe acne</td>
</tr>
<tr>
<td>Hidradenitis suppurativa</td>
</tr>
<tr>
<td>Folliculitis</td>
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</table>

× Pseudo-septic; 
× with periarticular bone involvement; 
× with positive culture for Propionibacterium acnes.
<table>
<thead>
<tr>
<th>#</th>
<th>Patient</th>
<th>Acne Conglobata</th>
<th>Pyoderma Gangrenosum</th>
<th>Hidradenitis Suppurativa</th>
<th>Miscellaneous</th>
<th>Synovitis</th>
<th>X-Ray Findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50yoAW</td>
<td>—</td>
<td>L. Leg</td>
<td>Groin</td>
<td>L. hand pathergy; Bilateral keratitis; Elevated ESR, B-27 negative</td>
<td>R. wrist &amp; ankle; Bilateral 5PIP &amp; DIP</td>
<td>R. SI sclerosis; Erosive: hands; bilateral JSN of 1-5MCP; Feet: JSN of L. 2-4 PIP &amp; R. 3-4 PIP; Cupping of R. 1 MTP and L. 1 DIP</td>
<td>Surgery, HS Prednisone; Cephalexin; Ibuprofen; Acetaminophen</td>
</tr>
<tr>
<td>2</td>
<td>56yoAM</td>
<td>—</td>
<td>GB R. Leg</td>
<td>Groin, Axilla, Neck</td>
<td>Elevated ESR; L. wrist; L. knee</td>
<td>—</td>
<td>Osteopenia; R. 1 MCP sclerosis; Knee sclerosis &amp; JSN</td>
<td>Surgery, HS Colchicine; Indomethacin; Probeneed</td>
</tr>
<tr>
<td>3</td>
<td>33yoAW</td>
<td>—</td>
<td>—</td>
<td>Scalp, Axilla</td>
<td>Elevated ESR; Elbows, neck; L. wrist &amp; PIPS R. 4PIP</td>
<td>—</td>
<td>Periarticular osteopenia of wrists and hands</td>
<td>Surgery, HS Cephalexin, ASA</td>
</tr>
<tr>
<td>4</td>
<td>48yoAM</td>
<td>—</td>
<td>—</td>
<td>Axilla, Groin, Rectum</td>
<td>Elevated ESR; Bilateral MCPs &amp; PIPS</td>
<td>L. iliac hyperostosis; SI sclerosis: L&gt;R; Feet: R. midstalar erosion; Bilateral MTP demineral; R. 1&amp;5 PIP erosion</td>
<td>Surgery, HS Indomethacin</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>34yoCW</td>
<td>—</td>
<td>Axilla</td>
<td>Groin</td>
<td>Elevated ESR; R. second digit-Raynaud’s R. foot hyperesthesia &amp; skin dystrophy; Feet: PIPS &amp; DIPS</td>
<td>—</td>
<td>Hand demineralization; ↑JS of L. SI joint with mild sclerosis</td>
<td>Surgery, HS</td>
</tr>
<tr>
<td>6</td>
<td>46yoAW</td>
<td>—</td>
<td>Groin</td>
<td>—</td>
<td>L. uveitis; Polyclonal gammopathy; Elevated ESR + RF</td>
<td>Bilateral wrist &amp; PIPS R. 4 MCP</td>
<td>Periarticular demineral. of feet and hands; R. SI sclerosis; Spine: Sclerosis of L5,S1</td>
<td>Surgery, HS</td>
</tr>
<tr>
<td>7</td>
<td>38yoAW</td>
<td>Feet Ankles, Hands</td>
<td>Groin, Axilla, Neck</td>
<td>Axillary cellulitis; Polyclonal gammopathy Culture: P. acnes; Elevated ESR, B27 negative</td>
<td>Knees wrists ankles elbows</td>
<td>Feet: hyperostosis; Erosion: L2&amp;5MTP, bilateral cuboid &amp; 1 MTP; Hands: erosion of R.5MCP and R. fifth digit flexion contr.</td>
<td>Surgery, HS Prednisone, Methotrexate, Antibiotics</td>
<td>Colchicine; Indomethacin</td>
</tr>
</tbody>
</table>

A = African-American; ASA = aspirin; C = Caucasian; DIP = distal interphalangeal joint; ESR = erythrocyte sedimentation rate; GB = gall bladder; HS = hidradenitis suppurativa; JSN = joint space narrowing; L = left; M = man; MCP = metacarpal joints; MTP = metatarsal joint; NTP = nitroglycerin paste; R = right; RF = rheumatoid factor; SI = sacroiliac; W = woman.
plaints for the 12 patients ranged from 17 to 63 years of age, with a median age of 45 years (Tables 2 and 3). Patients with hidradenitis, acne, and palmoplantar pustulosis are discussed.

Hidradenitis Suppurativa

Seven of the 12 patients with SAPHO syndrome presented with hidradenitis suppurativa. All eventually required surgery for drainage and/or resection of the sweat glands. Two of these also had acne conglobata. Six were African-American, and 5 were women. The age at presentation of the articular complaints for these 7 patients ranged from 33 to 56 years of age, with a mean age of 43 (Table 2). Groin areas were affected in all 7 patients (Fig. 1A), axillae in 6, perirectum and neck in 2, and breasts in 1. Three African-Americans presented with aggressive pyoderma gangrenosum (Fig. 1B), and life-threatening complications were observed in 3.

Vasculitic manifestations. Patient 1 developed severe hidradenitis suppurativa associated with pyoderma gangrenosum of her thigh, biopsy proven vasculitic lesions on her legs (Fig. 1A), bilateral keratitis, and pathergy. She also presented with groin, vulvar, and perirectal abscesses requiring repeated surgical drainage and extensive resection of her perineal sweat glands and rectum, culminating in a permanent colostomy (Fig. 1A). Her vasculitic lesions and pyoderma gangrenosum did not respond to hyperbaric oxygen, local application of anticholinergics, high-dose and pulse corticosteroid therapy, or cyclophosphamide. She died due to complications of a Gram-negative bacteremia. Patient 2 developed hidradenitis suppurativa of his groin, axillae, and posterior neck, a large right-leg ulcer with features of pyoderma gangrenosum, and an acute abdomen due to acalculous necrotizing cholecystitis, probably caused by a visceral manifestation of pyoderma gangrenosum. His cholecystitis and acute abdomen resolved with corticosteroid therapy. Patient 7 developed extensive pyoderma gangrenosum associated with severe recalcitrant biopsy-proven leukocytoclastic vasculitic lesions of the legs and pyoderma gangrenosum of her hands and feet, which were only partially controlled with antibiotics, methotrexate, dapsone, and cyclosporine.

Musculoskeletal features. Articular manifestations became apparent roughly 1 to 5 years after the hidradenitis suppurativa was diagnosed. Joint involvement, affecting mainly wrists, fingers, and toes (proximal interphalangeal (PIP), MCP, and MTP joints), was seen in 5 patients. Patient 2 presented with a recurrent chronic synovitis of the left wrist that required a synovial biopsy and bacterial cultures to exclude a chronic infectious etiology. Knee involvement was seen in 2

### TABLE 3. Acne, acneiform folliculitis, palmoplantar pustulosis, and SAPHO syndrome

<table>
<thead>
<tr>
<th>#</th>
<th>Patient</th>
<th>Skin Lesion</th>
<th>Miscellaneous</th>
<th>Synovitis</th>
<th>X-Ray Findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>17yoLAM</td>
<td>Acne Fulminans</td>
<td>Fever Elevated ESR, B27(−)</td>
<td>R. ankle</td>
<td>Periostitis, osteolytic. lesion of R. fibula</td>
<td>Tetracycline Drainage</td>
</tr>
<tr>
<td>10</td>
<td>20yoLAM</td>
<td>Acne Fulminans</td>
<td>Fever Elevated ESR, B27(−)</td>
<td>Knees</td>
<td>Bilateral SI erosions</td>
<td>Tetracycline NSAIDs</td>
</tr>
<tr>
<td>11</td>
<td>43yoCM</td>
<td>Acneiform folliculitis</td>
<td>Mouth ulcers cellititis, fever</td>
<td>R. knee</td>
<td>Osteitis (by MRI)</td>
<td>Antibiotics NSAIDs</td>
</tr>
<tr>
<td>12</td>
<td>60 BW</td>
<td>Palmoplantar</td>
<td>Elevated ESR</td>
<td>Dactylitis</td>
<td>Localized demineralization Phalanges</td>
<td>NSAIDs Corticosteroids</td>
</tr>
</tbody>
</table>

A = African-American; ASA = aspirin; C = Caucasian; ESR = erythrocyte sedimentation rate; JS = joint space; JSN = joint space narrowing; LA = Latin-American; M = man; SI = sacroiliac joint; R = right; W = woman.
patients. Four patients had mild intermittent back pain, with morning stiffness lasting less than 30 minutes.

**Radiographic features.** Periarticular demineralization of affected finger joints was seen only in 4 patients. Erosions in hands and feet were seen in 3 patients in association with the most severe hidradenitis suppurativa, and 2 of those patients also had pyoderma gangrenosum. In 2 patients, erosions extended deep into the subchondral bone and had an overhanging edge, although the articular joint space was preserved (Figs. 2A, B). Three patients had unilateral subchondral sclerosis of the sacroiliac joint mainly affecting the iliac bone, and 1 patient had both sacroiliac joints affected with joint space narrowing and subchondral sclerosis. One patient also demonstrated sclerosis and erosive changes of the symphysis pubis.

**Laboratory and pathologic studies.** Clear synovial fluid was obtained from the right knee of 3 patients, which showed normal viscosity and 800–1000 cells/mm³ with 80% mononuclear cells. No crystals were seen, and cultures showed no bacterial growth. Serum protein electrophoresis revealed a polyclonal gammopathy in 2 patients. Synovial biopsy of the left wrist of 1 patient showed diffuse synovial lining cell proliferation, hyper vascularization, few macrophages, and abundant perivascular lymphocytic and plasma cell infiltration (Fig. 3A). Electron micrographs showed synovial cell proliferation, prominent endothelial cells containing dense bodies, and perivascular infiltrates of lymphocytes, monocytes, and plasma cells. No bacteria were seen (Fig. 3B). RF and ANA were negative in all but 1 patient. HLA B-27 testing was performed in 2 patients and was negative. One patient grew *Propionibacterium acnes* from a culture of her pyoderma gangrenosum.

**Management.** The articular manifestations were easily controlled with nonsteroidal anti-inflammatory drugs (NSAIDs), but the pyoderma gangrenosum and vasculitic skin lesions observed in 2 patients were only partially controlled with antibiotics, corticosteroid therapy, and immunosuppressive therapy (Table 2).

**Acne Conglobata, Acne Fulminans, Acneiform Folliculitis, and Palmoplantar Pustulosis**

Six patients presented with severe forms of acne and musculoskeletal manifestations (Tables 2 and 3). Two were African-American, 2 were Latin American, and 2 were Caucasian. Five were men. Two patients also had hidradenitis suppurativa and are included in Table 2.
Acne conglobata. One patient had acne conglobata and developed asymmetric polyarthritis involving his hands, knees, and feet in addition to a progressive erosive cervical spondyloarthritis with osteosclerosis of his cervical vertebrae and his sacroiliac joint (Fig. 4A). Joint erosions were seen in his ulnar styloids and several proximal interphalangeal (PIP) joints. He also developed an aseptic destructive arthropathy of his right second toe PIP joint (Fig. 4B). His acne was partially controlled with tetracycline and his arthritis with indomethacin, but his spondyloarthritis showed progressive erosive radiographic changes. His synovial fluid was mildly inflammatory with 5,000 cells/mm³ with 80% mononuclear cells.

Acne fulminans. One patient presented with ulcerating pustular acne, polyarthralgia, low back pain, high fever, and leukocytosis with radiographic and scintigraphic changes of bilateral sacroiliitis. His acne was controlled with tetracycline, and his articular manifestations subsided with the antibiotic therapy and non-steroidal anti-inflammatory agents.

Another patient also had severe ulcerative acne (Fig. 5A) and presented with acute arthritis of his left ankle, high fever, and leukocytosis. Synovial fluid obtained was cloudy, with 30,000 cells/mm³ with 80% polymorphonuclear cells, negative gram and acid-fast stains, and eventual sterile bacterial cultures. Left ankle radiographs showed a round focal osteolytic area with a periosteal reaction of the distal fibula (Fig. 5B). A biopsy revealed a fibrotic synovium with scarce polymorphonuclear cell infiltrate, necrotic bone fragments, and subsequent sterile bacterial cultures (Fig. 6). His acne responded to antibiotic therapy, but his left ankle synovitis had a very chronic course while receiving antibiotics. It was finally controlled with the administration of indomethacin.

Acneiform folliculitis. Acneiform folliculitis was observed in patient 11, a 43-year-old white man who since age 34 has presented with recurrent attacks of synovitis that mainly involves the right knee and ankles but sometimes migrated to other joints. His attacks were associated with high fevers that lasted 7–10 days. These attacks occurred 2–3 times a year. On these occasions he also presented with periarticular swelling of his thighs, knees, and ankles that was diagnosed as cellulitis. He also had folliculitis of his buttocks and legs since the beginning of his musculoskeletal complaints. Serial bone scans revealed increased uptake in his midtarsal and metatarsal joints, right ankle, right distal radius, left distal third of the ulna, right lateral femoral condyle, and both tibial shafts. MRI of the left distal radius and both femurs showed an abnormally high central marrow signal surrounded by low intensity areas on T1-weighted pulse sequences and opposed signal characteristics on T2-weighted sequences, which

FIGURE 2. (A) Articular erosions (arrow) observed in patient 1. (B) Erosion (arrow) seen in patient 7. Both patients had hidradenitis suppurativa and SAPHO.
was interpreted as possible aseptic bone necrosis.

His most recent episode was characterized by synovitis of his left first and fourth MCP joints and ankles and a cellulitic area over his left lateral malleoli. Bone scan showed increased uptake in his first and second left metacarpal bones and in both ankles, whereas those areas that had shown increased uptake on previous bone scans were fading. About 5 mL of cloudy fluid was aspirated from his right ankle, which showed 5,000 cells/mm³ with 85% lymphocytes and 15% polymorphonuclear cells. No crystals were seen, Gram stain and acid-fast bacterial stain were negative, and subsequent bacterial cultures showed no growth.

A bone biopsy of his left second metacarpal bone showed a low-grade chronic osteomyelitis with reactive fibrosis and new bone formation. Synovium revealed increased fibrosis with areas of neovascularization. Bacterial and mycobacterial cultures showed no growth. Acid fast, Gram, and silver stainings were negative. Electron microscopic studies showed increased osteoclasts with numerous large intracytoplasmic vacuoles. No microorganisms were seen. Laboratory studies showed an ESR of 89 mm/hour, a C-reactive protein of 114 IU. Serum biochemical profile, C3, C4, ANA, RF, anti-streptolysin O (ASO) titers, hepatitis B, hepatitis C, Lyme serologies, cryoglobulin, and rapid plasma regain (RPR) were negative. Enzymatic testing for glucocerebrosidase leukocyte enzymatic activity was normal, and DNA studies for chromosome 16p13 locus for familial Mediterranean fever were uninformative.

Since the beginning of his attacks, the patient noticed erythematous papules and follicular pustules over his shoulders, proximal extremities, and buttocks. Skin biopsies obtained from several of these papules and pustules showed collections of polymorphonuclear cells in the hair follicles forming abscesses. Biopsies obtained from 2 different cellulitic areas showed signs of acute inflammation with perivascular inflammatory infiltrates. Bacterial cultures showed no growth. A variety of nonsteroidal anti-inflammatory agents as well as antibiotics and colchicine failed to control or alter the frequency of his attacks, although all were self-limited. Since 1993, only mild folliculitis has been present, and he has experienced only intermittent episodes of polyarthralgias with occasional polyarthritis, which have been controlled with ibuprofen.

Palmoplantar pustulosis. One patient presented with a 2-month history of painless hyperkeratotic papules on her palms and soles without evidence of skin psoriasis. She also complained of diffuse painful fingers and knees. Hand ra-
diographs showed demineralization of her left second and fifth and right fifth fingers, affecting the proximal and distal phalanges with periosteal thickening. Her articular manifestations failed to improve with nonsteroidal anti-inflammatory agents, and she required a prolonged course of low dose corticosteroids and intensive hand occupational therapy.

DISCUSSION

In assessing our clinical population, we compared the SAPHO manifestations of hidradenitis suppurativa, acne conglobata, palmoplantar pustulosis, acneiform folliculitis, ulceropustular acne, and pyoderma gangrenosum with other reports (5–17). We found that SAPHO associated with hidradenitis suppurativa was not entirely a disease of African-American men as previously suggested by other studies (11, 21). Only 2 of our 7 patients were African-American men, far less than the 85% in earlier studies. There is clearly a high prevalence in the African-American population, but African-American women and Caucasians are also affected.

The musculoskeletal and radiographic changes such as periostitis, hyperostosis, sacroilitis, periarticular demineralization, and spinal disease have been well-documented (11, 13, 16–17) and were present in our patients. The outcome in our patients differs from those described in a recent report from France that included 120 patients with SAPHO syndrome associated with palmoplantar pustulosis (50%), skin psoriasis (25%), severe acne (9%), or even patients without skin lesions (16%) observed in a population mainly formed by European whites (17). All these patients had a benign course without serious or life-threatening clinical or laboratory abnormalities, and most of the patients had a satisfactory response to nonsteroidal anti-inflammatory agents. A minority required administration of second line drugs. There were no deaths. All of our patients with hidradenitis suppurativa underwent extensive surgery to remove areas of hidradenitis and sweats glands, and received antibiotics and nonsteroidal anti-inflammatory agents. The 2 hidradenitis suppurativa patients with associated vasculitis and pyoderma gangrenosum received high doses of corticosteroids, cyclophosphamide, or cyclosporine without significant improvement (27–32) (Table 2). Leukocytoclastic vasculitis in hidradenitis suppurativa is unusual and may be coincidental or related to the persistent infectious agent antigens attacking the sweat glands. In our series, patients with both hidradenitis suppurativa and pyoderma gangrenosum had more aggressive manifestations.

The patients with the most severe hidradenitis suppurativa had more erosive arthropathy than the patients with milder hidradenitis suppurativa (Table 2). Although pyoderma gangrenosum is sometimes associated with rheumatoid arthritis (30), inflammatory bowel disease (33, 34), and various spondyloarthopathies (33, 34), there is only one report of visceral pyoderma gangrenosum (35). Patient 2 is probably the first report of a SAPHO patient with hidradenitis suppurativa complicated with noncalcific acute cholecystitis, possibly due to a visceral manifestation of pyoderma gangrenosum or vasculitis. To our knowledge, patient 1 is also the first report of pathergy associated with hidradenitis suppurativa-SAPHO and pyoderma gangrenosum.

Other less common manifestations, such as concomitant pyoderma gangrenosum, acne conglobata, Raynaud’s phenomenon, sclerodactyly, and ocular manifestations have been previously reported (11, 15, 17) with hidradenitis suppurativa-SAPHO. The histology of the cutaneous and osseous manifestations of SAPHO syndrome have been described previously (3, 17–21, 29). However, there have been no synovial membrane studies.

Our studies of synovium revealed a striking plasma cell infiltrate, few macrophages, and granular dense deposits on electron microscopy that are suggestive of immune complex deposition, possibly in response to bacterial antigen presentation; however, no immunohistochemistry was performed. Immune complex formation could be an important factor in
the synovitis and erosive polyarthritis seen in our patients, but this would require further documentation.

Synovial fluid obtained from 4 patients with hidradenitis suppurativa was mildly inflammatory and showed a predominance of mononuclear cells in 3 and polymorphonuclear cells in 1. Synovial fluid was inflammatory in the patient with acneiform folliculitis and aseptic osteomyelitis of the ankle, as in the patient with acneiform folliculitis, with cell count of 5000 and 30,000/mm$^3$ and a predominance of polymorphonuclear cells or lymphocytes, respectively. No Reiter’s cells were seen. Synovial fluid analysis was important to exclude a septic or crystal induced arthritis, but did not provide any characteristic changes.

Severe forms of acne and musculoskeletal manifestations have also been frequently described (3, 6, 8, 12, 22). One patient with acne conglobata was radiographically afflicted with periarticular bone demineralization, severe erosive spondyloarthropathy, and spinal hyperostosis similar to previous reports of SAPHO syndrome (Fig. 4A). Two patients presented with episodes of acne fulminans consisting of high fevers, leukocytosis, high ESR, and sterile osteolytic lesions in addition to periosteal reactive changes (Fig. 6). Their ages and clinical courses are also similar to previous reports of acne fulminans and SAPHO (12, 16, 22). To our knowledge, patient 11 is the first case of SAPHO syndrome associated with acneiform folliculitis.

Patient 11 was a middle-aged Caucasian man with a chronic, intermittent, occasionally episodic migratory, periartthritis, cellulitis, and synovitis whose clinical manifestations also involved fevers and chills. These symptoms were in addition to chronic folliculitis and acneiform pustules on nonplantar skin regions. Bone biopsies revealed a sterile, low-grade osteitis and periostitis with inflammation and reactive fibrosis. Synovial biopsies demonstrated chronic synovitis, and skin biopsies demonstrated perifollicular abscess formation.

In 4 patients with SAPHO syndrome in this series in whom HLA-B27 was studied, the test was negative. This finding corresponded with other previous studies (11, 12, 15, 17), which may reflect the low frequency of the B27 antigen in African-American patients, although several studies have cited a 5%-10% incidence of HLA-B27 antigen (17, 19, 21).

Most studies, including this one, have found few if any patients who were positive for ANA, although 1 study found 30% of patients with a positive ANA test (21). A novel finding in our series is the polyclonal gammopathy seen in patients 6 and 7 associated with dense plasma cell infiltrates in skin and synovial biopsies (Fig. 3A). Although increased plasma protein concentrations have been documented, only 1 study has cited elevated globulins, and subsequent serum protein electrophoresis proved them to be $\alpha$-globulins (12).

The exact mechanism involved

FIGURE 5. (A) Ulcerating acne was observed in patient 10, who presented with acne fulminans. (B) Left ankle of patient 10 demonstrated periostitis of the distal fibula and a focal osteolytic area (arrow).
in the pathogenesis of SAPHO has yet to be unraveled. There is a
questionable association with HLA-B27 reported throughout the
literature although not confirmed in our series, but this may be owing
to the similarities and crossover between SAPHO and the spondyloar-
thropathies. Maugars et al. found crossover in 7 of 21 SAPHO pa-
nients who simultaneously met the European spondyloarthropathy
classification criteria (20).

The crossover with spondyloar-
thropathies may contribute to the
finding of HLA-B27 in some SAPHO patients, and thus it makes that ge-
netic component less likely overall. However, the existence of an undis-
covered genetic marker subjected to a reactive condition secondary to a
skin infection with a low-virulence bacteria or bacterial product is still
a questionable association with acne fulminans and prominent acromioclavicular joint involve-

The absence of proven disease mech-
nanisms, classification remains diffi-
cult and requires further validation.

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