Eur. Radiol. 8, 800–806 (1998)

European
Radiology

Original article

The SAPHO syndrome: defining the radiologic spectrum of diseases comprising the syndrome

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Received 1 April 1997; Revision received 5 August 1997; Accepted 2 October 1997

Abstract. The objective of our study was to clarify the radiologic spectrum of disease entities belonging to the SAPHO syndrome (SAPHO being an acronym for synovitis, acne, pustulosis, hyperostosis, and osteitis). A retrospective analysis of radiologic data was undertaken to determine the relationship of the osteoarthritic changes seen in palmoplantar pustulosis (PPP, $n = 179$), acne ($n = 3$), psoriasis vulgaris (PsV, $n = 355$), generalized pustular psoriasis (GPP, $n = 25$), and chronic recurrent multifocal osteomyelitis (CRMO, $n = 4$). Osseous changes of PPP, acne, and CRMO overlap each other; 7 PPP, 2 acne, and 3 CRMO patients manifested stenocostoclavicular hyperostosis as well as hyperostosis of the spine, pelvis, and/or femur. These findings were not seen in either PsV or GPP patients. Thirteen PsV and 4 GPP patients had peripheral arthritis and/or symmetrical sacroiliitis, which were not observed in the PPP, acne, and CRMO patients. The PPP, acne, and CRMO patients may be grouped as belonging to the single disease entity, namely SAPHO syndrome. Our findings do not support the inclusion of PsV and GPP in the spectrum of this syndrome.

Key words: Arthritis – Bone diseases – Hyperostosis – Psoriasis – Skin diseases

Introduction

The term SAPHO syndrome has been coined to describe diseases that manifest sterile inflammatory bone lesions together with skin eruptions, SAPHO being an acronym for the following conditions: synovitis, acne, pustulosis, hyperostosis, and osteitis [1–4]. The SAPHO syndrome groups together the following osteo-articular lesions that have been described as separate medical entities: chronic recurrent multifocal osteomyelitis (CRMO) [5, 6], pustulotic arthro-osteitis (PAO) [7–9], and arthro-osteitis associated with a follicular occlusive triad (FOT) [10–12].

Kahn and Kahn have formalized the diagnostic criteria for the SAPHO syndrome (Table 1) [3]. The diseases included are sterile osteitis associated with psoriasis vulgaris (PsV), generalized pustular psoriasis (GPP), and arthritis associated with GPP, in addition to palmoplantar pustulosis (PPP) and severe acne [3]. The criteria also include chronic recurrent multifocal osteomyelitis (CRMO) with or without skin disease. However, there is disagreement among dermatologists as to the relationship between PPP and PsV, some maintaining that PPP is distinct from PsV due to differing histologic and clinical features [13–15]. Furthermore, the results of clinical study and human leukocyte antigen (HLA) typing suggest that PPP and acne are distinct from PsV [12, 16–21]. Therefore, whether PsV and GPP are a part of the spectrum of this syndrome has yet to be definitively resolved.

Although some studies have focused on the radiologic findings in specific diseases comprising the SAPHO syndrome [11, 17, 22–25], the radiologic spectrum of the SAPHO syndrome has yet to be fully investigated. Thus, the purpose of this study has been to describe the radiographic features of PPP, acne, PsV, GPP, and CRMO, and to investigate the osteo-articular changes that occur in these conditions, so as to clarify the radiologic spectrum of this syndrome.

Materials and methods

A computer search was conducted of the medical records and radiologic data of patients treated for PPP, PsV, and GPP at Jichi Medical School (Japan), their diagnoses having been made by senior dermatologists. There were 179 cases of PPP, 355 cases of PsV, and 25 cases of GPP that were handled between 1976 and 1995. The author (H. S.) retrospectively reviewed all the radiologic exams of each patient with full knowledge of the dermatologic

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Table 1. Current criteria for the SAPHO syndrome. Any of the three presentations is sufficient for a diagnosis. (From [3])

Chronic recurrent multifocal osteomyelitis (CRMO)
Usually sterile
Spine may be involved
With or without skin condition
Acute, subacute, or chronic arthritis associated with any of the following:
Palmoplantar pustulosis (PPP)
Pustular psoriasis (GPP)
Severe acne
Any sterile[a] osteitis[b] associated with any of the following:
PPP
GPP
Psoriasis vulgaris (psoriasis)
Severe acne

[a] Or with presence of *P. acnes*
[b] One localization is sufficient, including spondylodiscitis

diagnosis. In addition, records of 3 patients with acne and 4 patients with chronic recurrent multifocal osteomyelitis (CRMO) or SCCH, but without skin disease, were obtained from the files of this department and reviewed.

Hence, the radiologic exams of 64 patients (31 males and 33 females) constituted the basis of this study, and the ages when the skin or orthopedic condition first was manifested ranged from 14 to 58 years (mean 41 years). In addition, the findings of bone scintigraphy were available for 44 patients, and CT scans of the sternoclavicular joint and the pelvis were available for 7 and 2 patients, respectively. Finally, the inferior venacavographic exam of 1 PPP patient was also reviewed.

From the radiologic data, findings of the following aspects were investigated: (a) evidence of involvement of the anterior chest wall; (b) the presence of hyperostosis of the spine, pelvis, and/or long bones; (c) signs of sacroiliitis; and (d) indications of peripheral arthritis.

Cases that showed anterior chest wall involvement were further reviewed for two characteristics: the presence of hyperostosis of the clavicle, sternum, and/or ribs, and evidence of arthritis of the manubriosternal and sternoclavicular joints. The radiologic criteria for hyperostosis of the anterior chest wall included evidence of diffuse sclerosis in the sternum, clavicle, or ribs. Furthermore, diffuse tracer uptake into these bones during bone scintigraphy was considered to indicate hyperostosis as well. The radiologic criteria for arthritis of the anterior chest wall included the presence of erosive defects in the manubriosternal joint on plain radiography and/or a localized tracer uptake into the manubriosternal and/or sternoclavicular joints on bone scintigraphy, but focal tracer uptake limited to only the costosternal joint was not included.

Hyperostosis of the spine, pelvis, and long bones was considered present when evidence of a focal or diffuse sclerosis with or without periosteal new bone formation was seen radiographically. Hyperostosis of the sternum, ribs, and clavicle corresponds to the radiologic diagnosis of sternocostoclavicular hyperostosis (SCCH), whereas hyperostosis of the spine, pelvis, and long bones corresponds to the radiologic diagnosis of CRMO. Furthermore, sacroiliitis was considered present when erosion, joint-space narrowing, sclerosis, and/or ankylosis were seen radiographically.

Bone biopsies were performed in 1 PPP patient, 2 CRMO patients with no skin disease, and 1 acne patient. Finally, all pathologic specimens (microscopic slides) were reviewed by a pathologist (T. F.).

Results

Incidence

This radiologic review revealed that 40 PPP patients (22% of 179 cases), 13 PsV patients (4% of 355 cases), and 4 GPP patients (16% of 25 cases) showed osseous changes. It was noted that the PsV patients never developed PPP, and vice versa, and that all 4 GPP patients had a preexisting PsV before their pustular episodes. The provocative factors in 2 GPP patients were an infection ($n = 1$) and complications from steroid administration ($n = 1$), but no provocative factor was identified in the other 2 GPP patients. The radiologic findings for each skin condition and CRMO are summarized in Table 2.

PPP/acne/CRMO features

Sternocostoclavicular hyperostosis was seen in 18 PPP patients. Seven of them manifested hyperostosis in the axial and/or peripheral skeletons: 1 of the spine and the femur, 1 of the spine and pelvis (Fig. 1), and 5 of the spine

Table 2. Radiologic features of each skin condition and chronic recurrent multifocal osteomyelitis. PPP palmoplantar pustulosis; PsV psoriasis vulgaris; GPP generalized pustulotic psoriasis

	Hyperostosis[a]	SCCH	Sacroiliitis		Arthritis	
			Unilateral	Bilateral	Chest wall	Peripheral
PPP ($n = 40$)	8	18	3	0	38	0
Acne ($n = 2$)	0	2	0	0	0	0
PPP/acne ($n = 1$)	1	1	0	0	0	0
CRMO[b] ($n = 4$)	3	3	0	1[c]	0	0
PsV ($n = 13$)	0	0	0	2	2	11
GPP ($n = 4$)	0	0	0	1	4	3

[a] Hyperostosis of the spine, pelvis, and/or long bones
[b] Chronic recurrent multifocal osteomyelitis without skin disease
[c] Bilateral, but asymmetric

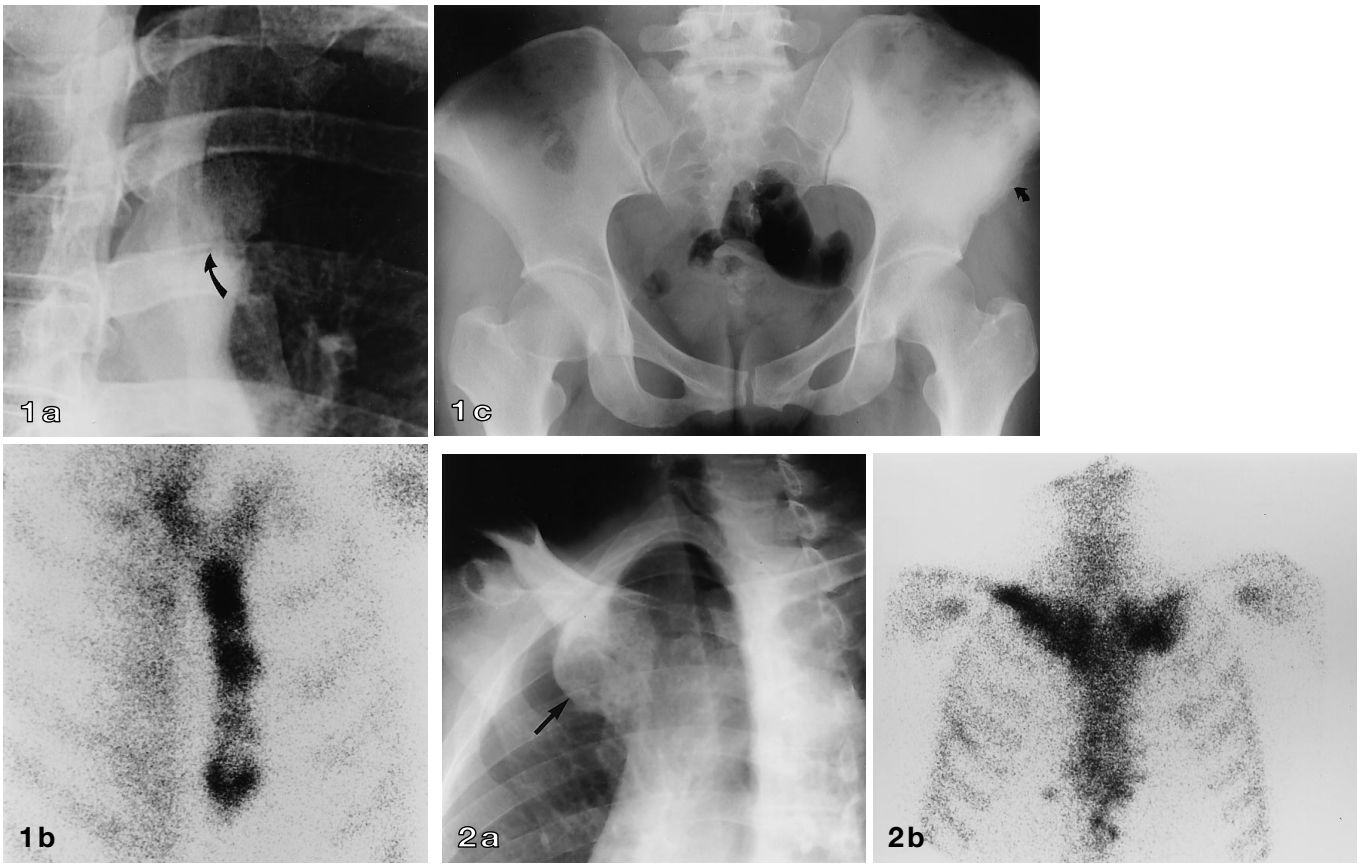

Fig. 1a–c. A 31-year-old woman with PPP. **a** Left posteroanterior oblique view of the sternum shows irregularities and sclerosis of the manubriosternal joint *(arrow)*. **b** Left anterior oblique projection of this bone scintigraph shows increased tracer uptake in the sternum. However, no increased activity is seen in the manubrium, costosternal joints, and clavicle. While there appears to be an erosion in the manubriosternal joint on plain radiography, the lesion is limited to the sternal body. **c** Anteroposterior radiography of the pelvis shows diffuse sclerosis of the left iliac bone. Fluffy periosteal new bone formation is seen along the iliac wing *(arrow)*. The sacroiliac joints appear normal

Fig. 2a, b. A 62-year-old man with acne pustulosa. He was diagnosed with PPP 20 years earlier, although it was completely cured at the time of this radiologic examination. **a** Left posteroanterior oblique view of the right sternoclavicular joint shows hyperostosis of the right clavicle and sternum *(arrow)*. **b** Bone scintigram shows an increased uptake in the sternum, clavicles, and first rib and sternoclavicular joints

only. One PPP patient had hyperostosis of the spine without SCCH. Two acne patients also had SCCH. There was 1 patient with SCCH who had acne pustulosa but also had developed PPP 20 years earlier (Fig. 2). Three CRMO patients had both SCCH and hyperostosis of the spine and long bones. Three PPP patients showed evidence of sacroiliitis, which was unilateral. In one of these PPP patients, a CT scan revealed soft tissue swelling adjacent to the sacroiliac joint (Fig. 3).

During the follow-up period, 6 patients with hyperostosis of the spine underwent radiography two times or more. The radiographs showed the development of a bony bridge in the spine (Fig. 4). On subsequent radiologic inspection, the progression of this ossification was indicative of new periosteal bone formation rather than syndesmophytosis.

PsV/GPP features

Of the 13 PsV patients, 2 demonstrated an increased tracer uptake localized to the sternoclavicular joint. Of the 4 GPP patients, 3 showed an increased tracer uptake in the manubriosternal and/or sternoclavicular joints, whereas the remaining patient showed erosion and periosteal bone formation in the costoclavicular joint (Fig. 5 a). No PsV or GPP patient manifested SCCH. Arthritis of the peripheral joints was noted in 11 PsV patients and 3 GPP patients (Fig. 5 b). Predominantly distal interphalangeal joint involvement was seen in 3 patients, a mutilating arthritis in 1 patient, symmetrical polyarthritis in 2 patients, and asymmetrical oligoarthritis in 8 patients. Symmetrical sacroiliitis was identified in 2 PsV patients and 1 GPP patient (Fig. 5 c).

Pathological findings

The pathological findings were similar in all 4 patients, i. e., infiltration of neutrophils, lymphocytes, and plasma cells, fibrosis and a reactive formation of new bone. In two of these patients, significant plasma cell infiltration was noted (Fig. 6). The findings were nonspecific but consistent with the diagnosis of chronic osteomyelitis.

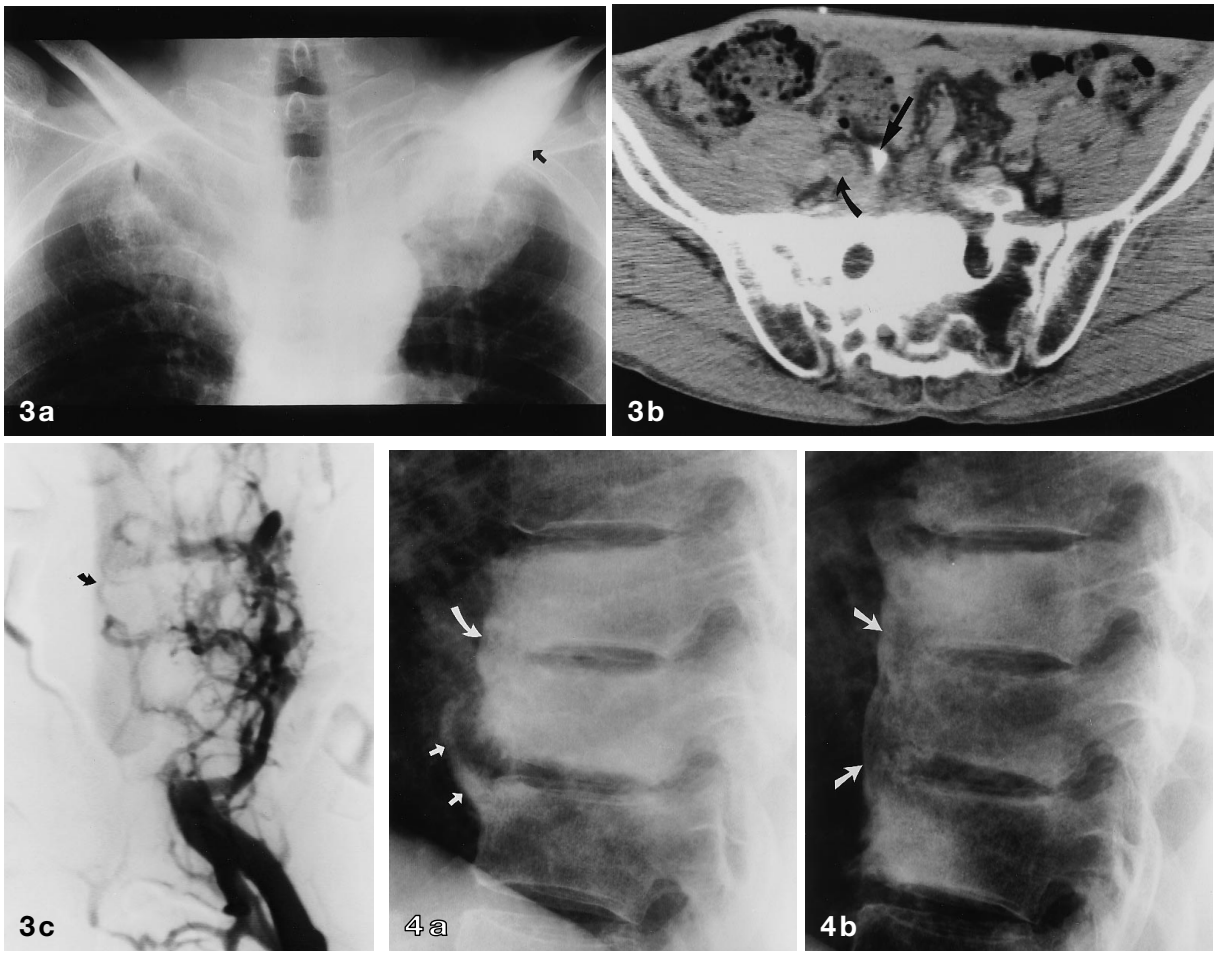

Fig. 3a–c. A 53-year-old man with PPP. **a** Posteroanterior radiograph of the chest shows hyperostosis (SCCH) of the anterior chest wall. Note the extensive periosteal reaction in the left clavicle *(arrow)*. **b** Computed tomograph of the sacroiliac joints shows unilateral sacroiliitis. A soft tissue mass has displaced the right common iliac artery *(arrow)*, and the right common iliac vein is thrombosed *(curved arrow)*. **c** Inferior venacavogram injected through the left femoral vein reveals complete obstruction of the inferior vena cava (IVC). The proximal portion of the IVC is faintly opacified *(arrow)*

Fig. 4a–b. A 44-year-old PPP woman with a complaint of low back pain but with no evidence of anterior chest wall lesion. **a** A 1984 lateral view of the thoracic spine shows tongue-like new bone formation extending superiorly from the upper corner of the tenth vertebral body *(small arrows)*. The eighth and ninth spines show diffuse sclerosis and new bone formation anterior to the vertebral bodies *(large arrow)*. **b** In this photo taken 6 years later, the tongue-like new bone formation merges with the ossification of the ninth vertebral body *(arrows)*. Diffuse sclerosis of the ninth spine has become less prominent

No microbiologic study of these pathologic samples was performed.

Venn diagram

Using all available data, a Venn diagram was constructed based on the presence or absence of hyperostosis or arthritis in the sternocostoclavicular region, the presence or absence of hyperostosis in the spine and/or peripheral skeleton, and the patients' skin diseases (Fig. 7). According to the diagram, hyperostosis was found to be a radiologic feature that linked the PPP, acne, and CRMO patients. Furthermore, although anterior chest wall involvement was noted in PsV and GPP patients, this consisted of arthritis of the manubriosternal and costoclavicular joints, whereas hyperostosis similar to that seen in the PPP, acne, and CRMO patients was not present in these patients.

Discussion

The criteria for the SAPHO syndrome include PsV and GPP among the skin conditions (Table 1). The rationale for establishing the SAPHO syndrome is that the unusual bone involvement manifested is the common denominator among the four skin diseases, either by its radiologic appearance or pathologic features [4]. The full acceptance of the SAPHO syndrome as an unique entity may depend in part on whether the osteo-articular lesions common to PPP, FOT, and CRMO are also seen in PsV and GPP.

Our study suggests that the distinctive radiologic feature that characterized osteo-articular changes in PPP/acne/CRMO patients was hyperostosis. The radiologic

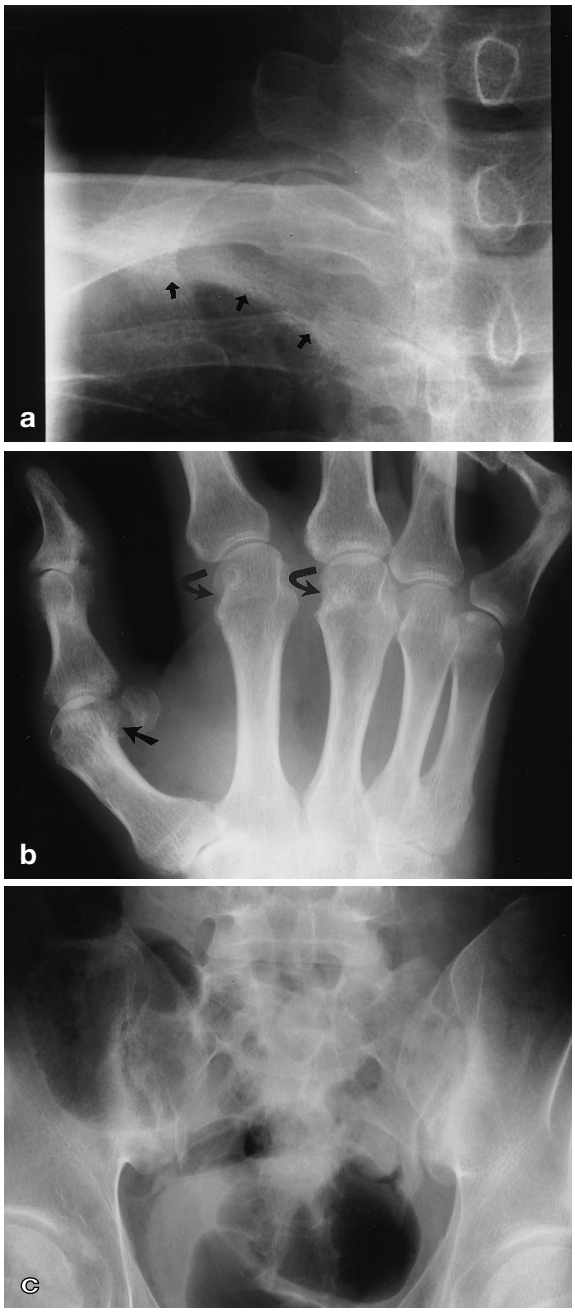

Fig. 5a–c. A 37-year-old man with GPP. **a** A close-up anteroposterior view of the cervical spine shows erosion in the right costoclavicular joint, and a fine, linear periosteal reaction in the clavicle *(arrows)*. **b** An oblique posteroanterior radiographic view of the right hand shows marginal erosion and joint space narrowing from the first to third metacarpophalangeal joints and the interphalangeal joint of the first finger *(arrows)*. **c** An anteroposterior radiographic view of the pelvis reveals symmetric sacroiliitis

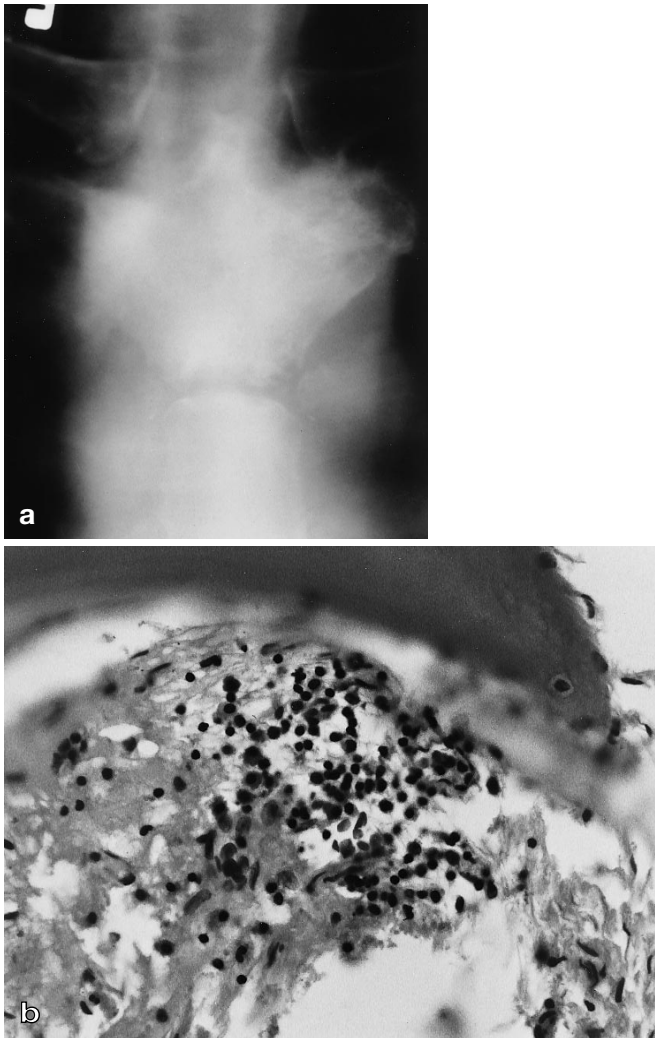

Fig. 6a, b. A 50-year-old woman with swelling and anterior chest wall pain. **a** An anteroposterior tomograph of the sternum shows diffuse sclerosis of the manubrium. **b** This enlargement of a pathologic specimen obtained from the manubrium shows a cluster of plasma cells and reactive new bone formation. (Hematoxylin and eosin stain, original magnification × 100)

and pathologic hyperostosis findings in the involved bones are indistinguishable from those of osteomyelitis. These same findings related to hyperostosis have been reported in previous studies [8, 11]. Furthermore, bacteriologic data have indicated that hyperostosis seen in acne cases is indeed osteomyelitis [7]. Although the etiology of the bone changes observed in these disease entities remains speculative, these findings suggest that the etiology is basically an inflammatory process that originates in the bone marrow.

Osteo-articular lesion in the sternocostoclavicular region is seen as characteristic of psoriatic arthritis, and among the representative radiologic features in PsV cases is erosive, inflammatory arthritis of the manubriosternal [26] and sternoclavicular joints [27]. Increased tracer activity in the sternocostoclavicular joint is seen in patients manifesting PsV [23, 28], and PsV patients with anterior chest wall involvement may be classified as a subgroup of psoriatic arthritis [28, 29]. However, extensive meta-analyses revealed that hyperostotic changes occurring in patients manifesting both PPP and PsV were probably related to the coincidental presence of PPP [24]. In fact, in Vaele et al.'s series, 2 SAPHO patients among 100 patients with psoriatic arthropathy had PPP [29]. The results of our study also suggest that hyperostotic abnormalities, such as SCCH and hyperosto-

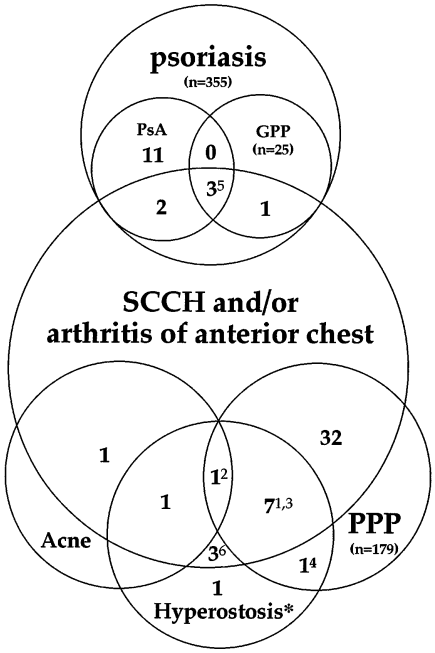

Fig. 7. A Venn diagram showing relationships among the cases. PPP and acne are linked by a case that manifested both skin conditions. PPP, acne, and CRMO are linked by the cases manifesting hyperostosis. The *number* in each defined area indicates the total number of each disease category. The *number in parentheses* indicates the total number of patients with the specified skin conditions. *Superscript* indicates the figure number in the text. *Asterisk* indicates the spine and peripheral skeleton. *SCCH* sternocostoclavicular hyperostosis; *PsA* psoriatic arthropathy; *GPP* generalized pustular psoriasis; *PPP* palmoplantar pustulosis

sis of the spine, pelvis, and long bones, do not occur in patients with PsV only.

The relationship of the SAPHO syndrome and seronegative spondyloarthropathy is the subject of ongoing debate. Although several investigators have speculated about the possible linkage of the SAPHO syndrome with seronegative spondyloarthropathy [2–4, 9, 17], we found that the radiologic manifestations of PPP, acne, and CRMO are distinct from seronegative spondyloarthropathy in several aspects.

Firstly, signs of syndesmophytosis, which characterize radiologic manifestations of seronegative spondyloarthropathy, were not observed in the PPP and acne patients. While the radiographic appearance of pervertebral ossification may initially simulate a syndesmophytic appearance associated with a seronegative spondyloarthropathy, the progression of this ossification on subsequent radiologic inspection was found to be indicative of new periosteal bone formation (Fig. 2). Secondly, the sacroiliitis identified in 3 of the 4 PPP cases was entirely unilateral, and though sacroiliitis in patients with a seronegative spondyloarthropathy may or may not be symmetric, unilateral involvement is exceptional. For these reasons we have concluded that osseous changes due to PPP, acne, and CRMO are radiologically distinguishable from osseous changes due to PsV and GPP as seronegative spondyloarthropathies.

Dihlmann and Dihlmann coined the term "acquired hyperostosis syndrome" (AHS) to designate patients with chest wall hyperostosis [30]. They categorized AHS into the complete, incomplete, and possible form. In complete AHS, SCCH is associated with axial and/or peripheral hyperostosis and with psoriasiform or acneform dermatosis. Seven PPP and 2 acne patients in our series who manifested SCCH in addition to hyperostosis of the axial and peripheral skeletons corresponded to the complete AHS patients of the Dihlmann.

The practical significance of this study may be questioned. However, the radiologic classification shown in this study may well have a genetic basis, and it is hoped that with the development of more sophisticated molecular genetic techniques, a precise relationship among these cutaneous and osteo-articular disorders will be identified. Meanwhile, we believe that the relationship of cutaneous and osteo-articular disorders that this investigation has identified will help practicing radiologists in interpreting radiologic examinations of patients with unusual osteo-arthriticular changes.

To conclude, patients who manifest SCCH and/or hyperostosis of the spine, pelvis, and peripheral skeleton with or without PPP and hyperostosis associated with acne can be classified as belonging to the SAPHO syndrome. However, the results of this radiologic study do not support the inclusion of PsV and GPP in the spectrum of this syndrome.

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