279 No 239

J Oral Pathol Med 1999; 28: 456–64
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JOURNAL OF
Oral Pathology&Medicine
ISSN 0904-2512

Primary chronic osteomyelitis associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome)

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Eyrich GKH, Harder C, Sailer HF, Langenegger T, Bruder E, Michel BA: Primary chronic osteomyelitis associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome). J Oral Pathol Med 1999; 28: 456–64.
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Diffuse sclerosing osteomyelitis may indicate the mandibular localisation of the SAPHO syndrome. Twelve patients with diffuse sclerosis of the mandible were examined for symptoms of the SAPHO syndrome. Nine patients were found to have primary chronic osteomyelitis and eight of these represented a SAPHO syndrome. Results in this series support the hypothesis of an association between primary chronic osteomyelitis and the SAPHO syndrome.

Key words: mandibular osteomyelitis; SAPHO syndrome

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Accepted for publication July 3, 1999

Osteomyelitis of the mandible is defined as an inflammation of the mandibular cortical and cancellous bone. Acute osteomyelitis is commonly caused by bacterial invasion from a contagious focus. Most frequent sources are odontogenic foci, periodontal diseases and pulpal infection, extraction wounds or infected fractures. Osteomyelitis may also appear as a nonsuppurative chronic inflammation of unknown aetiology. A small number of cases of mandibular chronic osteomyelitis are granulomatous osteomyelitis, which is related to tuberculosis or tertiary syphilis.

The literature related to chronic osteomyelitis is confusing. Different disease processes have been designated under one term in some instances, whereas several terms have been designated to lesions that represent the same entity in other instances (1). The variety of classification systems takes into account multiple characteristics such as physiology, pathogenesis, localisation, radiological or clinical appearance and clinical course. The radiological appearance of chronic osteomyelitis may be sclerotic, radiolucent or mixed. Diffuse sclerosing osteomyelitis (DSO) has been chosen to describe the radiologic appearance of the process (Fig. 1). The arbitrary time limit of 1 month is used to separate acute from chronic osteomyelitis (2). The term DSO includes similar entities such as primary chronic osteomyelitis (PCO), chronic tendoperiostitis (1, 3), secondary chronic osteomyelitis and juvenile chronic osteomyelitis (JCO, Garrè's osteomyelitis).

The term primary chronic osteomyelitis (PCO) describes a long-standing, radiologically diffuse sclerosing disease process of unknown aetiology, which involves the cancellous bone. The characteristic morphological findings consist of an extensive periosteal reaction and cortical thickening (Fig. 2), massive thickening of trabeculae, and marrow fibrosis in cancellous bone (Fig. 3). Inflammatory infiltrate is scarce, though foci of dense aggregates of plasma cells (Fig. 4) may be observed occasionally. The absence of pus, fistulae or sequestration is characteristic. The course of the disease lacks an acute state and is therefore considered primarily to be chronic. Periods of onset may last from 3 days to several weeks. The patient usually presents with a limitation of mouth opening, swelling of the cheek, lymphadenopathy and severe pain.

Juvenile chronic osteomyelitis (Garrè's osteomyelitis) usually peaks in puberty and is characterised by voluminous expansion of the mandibular body, periosteal apposition of bone and a mixed sclerosing-lytic appearance of the cancellous bone. The clinical picture resembles PCO, sharing the lack of pus formation, fistulae or sequestration. Therefore, JCO may be considered as a subtype of PCO.

Patients with tendoperiostitis (TP) usually present with a history of parafunctional complaints. Palpation of the temporal, masseter, medial pterygoid, and the digastric muscles reveals tenderness in one or more muscles (4). Radiographically, diffuse sclerosis of the cortical plate and marrow is observed. Pus formation and sequestration are absent.

Secondary chronic osteomyelitis develops from an acute bacterial invasion of the bone with formation of fistulae and possible sequestration. Clinically and radiographically, a broad spectrum ranging from an aggressive osteolytic putrefactive phase to a dry osteosclerotic phase may be observed.

Florid osseous dysplasia (FOD) is radiographically described as sclerosing opaque and dense masses. The bone changes are often adjacent to the apices of the roots of the teeth. Signs of in-

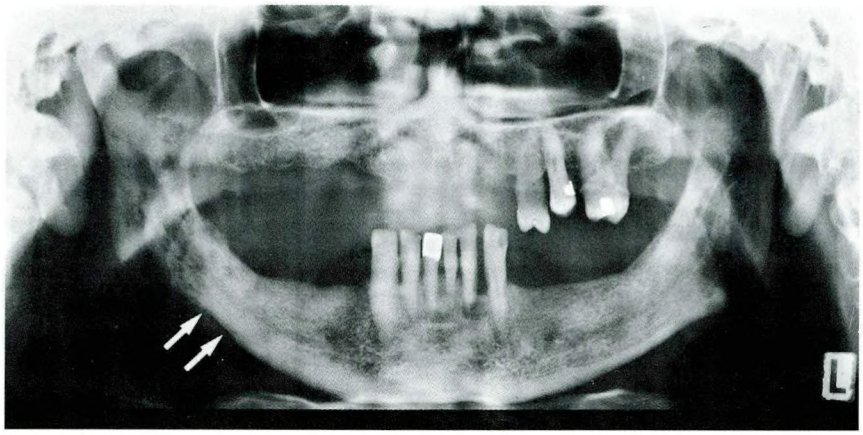


Fig. 1. An orthopantomogram showing typical sclerosis (arrows) involving cortical and cancellous bone of the right mandibular body (patient 9). The mandibular left second incisor shows a periapical radiolucency and interdental vertical loss of bone due to periodontal infection.

flammation may be present. Some cases of FOD occur in two phases. In the first phase, asymptomatic sclerotic masses develop. In the second phase, inflammation is superimposed (5). It may be very difficult to distinguish FOD from periapical cemental dysplasia (PCD), though the clinical course of FOD shows limited growth potential compared to PCD and does not produce pain. However, bony sclerosis may extend from a localised periapical process to a regional lesion. While there may be histological similarity between the two lesions, they are distinct clinical entities and do not usually become more widespread. PCD most commonly occurs in middle-aged women and is localised to the anterior mandibular teeth. The affected teeth always respond positively to vitality tests. This lesion presents with three typical distinct stages: osteolytic stage, cementoblastic stage and inactive stage (6).

An enostosis or compact island of bone can also be observed as an opaque dense sclerotic area. This may derive from an inflammatory processes following trauma (7). An enostosis or bony island may also result from focal ischemia or infarction (e.g., sickle cell disease) (8).

In 1986, CHAMOT *et al.* (9) described a syndrome associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome). Usually the medical history or examination reveals palmoplantar pustulosis (Fig. 5), pustular or plain psoriasis, and acne or hidradenitis suppurativa. Radiological and scintigraphic findings identify the

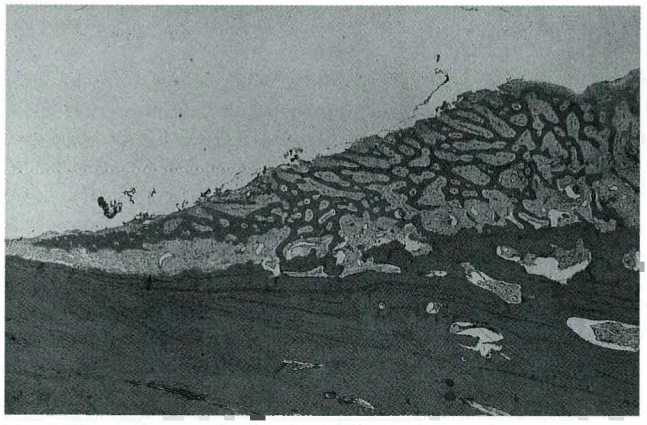


Fig. 2. Photomicrograph of patient 5 illustrating cortical sclerosis and massive periosteal reaction typical of primary chronic mandibular osteomyelitis. (H&E, ×15)

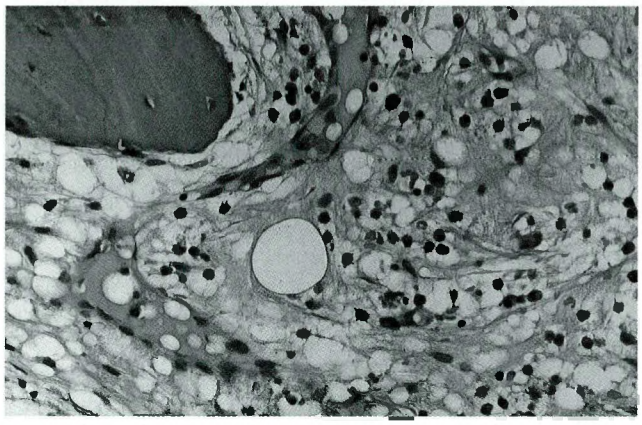


Fig. 4. Photomicrograph of bone from patient 2 showing an inflammatory infiltrate with some denser aggregates of plasma cells. (H&E, ×250)

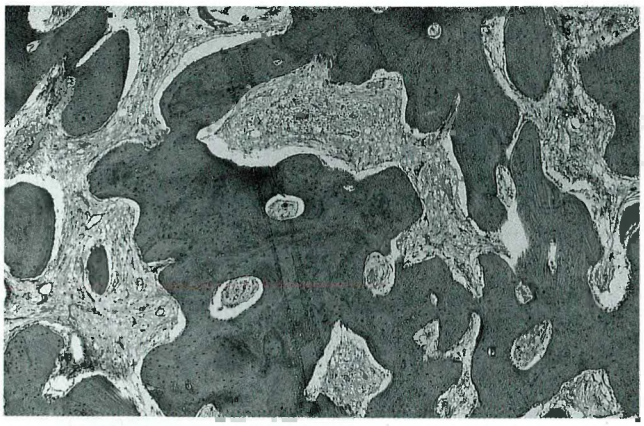


Fig. 3. Photomicrograph of cancellous bone showing massive thickening of trabeculae and marrow fibrosis (patient 2). (H&E, ×32)



Fig. 5. Typical plantar pustulosis (patient 9).



Fig. 6. Scintigraphic imaging demonstrating a significant enhancement of the right mandibular body and the chest wall (patient 9).

anterior chest wall (especially the sternoclavicular joint) as the most prevalent location for the hyperostosis (Fig. 6). Joint involvement may also be noted. In addition to reports from other authors (10, 11), KAHN *et al.* (12) have presented the largest series of 7 patients with mandibular involvement out of 85 cases of SAPHO syndrome. It has been finally concluded that diffuse sclerosing osteomyelitis may represent the mandibular localisation of SAPHO syndrome (12).

In a prospective cohort evaluation, patients with diffuse sclerosing osteomyelitis (DSO) were examined for the type of mandibular chronic sclerosing osteomyelitis and for SAPHO syndrome.

Material and methods

Within a period of 1 year all patients with diffuse sclerosing osteomyelitis (DSO) of the mandible and clinical signs of an acute inflammation (edema of the cheek, limitation of mouth opening, tenderness to palpation and severe pain) were prospectively assessed for concise diagnosis of their mandibular osteomyelitis. The diagnosis of DSO was based on clinical and radiographical findings. If available, medical history, clinical examination, computed tomography of the mandible, skeletal scintigraphy and biopsy specimens were included.

Subsequently, all patients with DSO were examined for symptoms of SAPHO syndrome. Routine immunological and haematological tests were performed with standard methods. Laboratory testing included complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, protein- and immuno-electrophoresis including IgG-subclasses, complement factors, immune complexes, rheumatoid factors, antinuclear antibodies, anti-DNA antibodies, C-(PR3)-ANCA, cardiolipin antibodies, routine chemistry and serological testing for antibodies against rubella, adenoviruses, Coxsackie-B virus, Epstein–Barr virus (EBV), herpes viruses, salivary gland tissue, parvovirus B19, picornavirus, hepatitis viruses B/C, cytomegalovirus, *Chlamydia, Borrelia burgdorferi, Brucella, Campylobacter, Salmonella, Yersinia, Shigella, Treponema pallidum, Neisseria gonorrhoeae* and *Mycoplasma pneumoniae.*

Medical records from the time of the patient's first visit were reviewed. In addition to MDP ^{99m}technetium bone scan (locating increased bone vascularity or osteoblastic activity) and routine radiographs of suspected bone lesions, computed tomography was performed on some patients. The diagnosis of SAPHO syndrome was accepted if the patient met the criteria, such as acute, subacute, chronic arthritis or any extramandibular osteitis, osteomyelitis with scintigraphic enhancement (especially of the sternoclavicular joint and the anterior chest wall), and skin lesions (palmoplantar pustulosis, pustular psoriasis, psoriasis vulgaris, severe acne).

Results

All 12 patients satisfied the selection basis for DSO. However, only nine patients (patients 2–10) met the diagnostic criteria for PCO. All patients were treated at the Department of Maxillofacial Surgery, University Hospital, Zurich and were referred for complete rheumatologic evaluation to the Department of Rheumatology, University Hospital, Zurich. The mean age of the patients was 47.5 years, with a range from 14 to 67 years. There were four men (33%) and eight women (67%). Follow-up periods from disease onset ranged from 3 to 30 years (Table 1).

Case 2

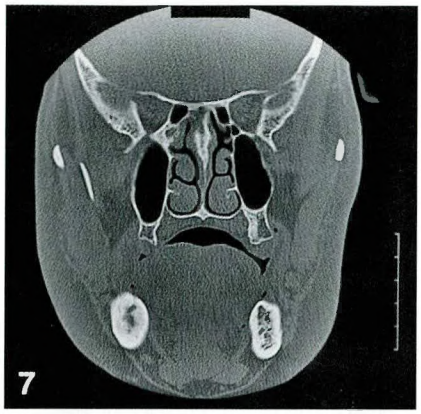
A 41-year-old woman with primary chronic sclerosing osteomyelitis and SAPHO syndrome was referred. The first symptoms of osteomyelitis were detected 20 years ago. After repeated decortication, she received hyperbaric oxygen therapy, a resection of the vertical ramus and reconstruction with a costal graft. Mild acne was observed in puberty. Physical examination revealed no pustulosis. Control CT scans revealed involvement of the transplanted graft. The patient presented with sternoclavicular hyperostosis showing slight scintigraphic enhancement and tenderness to palpation. Antibiotics were effective while on medication. Nonsteroidal anti-inflammatory drugs (NSAIDs) provided partial relief with reduction of pain and swelling during acute exacerbations.

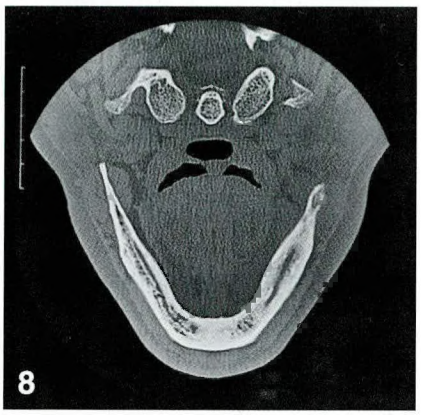
Case 3

A 33-year-old woman, the sister of case 10, had enostosis in the molar region, periapical cemental dysplasia (PCD) with vital teeth in the symphysial region of the mandible, palmoplantar pustulosis, humeral sclerosing osteomyelitis and sternoclavicular hyperostosis; she was re-examined. The patient had undergone 16 operative procedures of the humerus including biopsies, decortications, debridements and insertions

Table 1. Demographic data and diagnoses of all patients (including all 12 patients with DSO)

Case number	Sex	Age at examination (yr)	Duration in years (osteomyelitis)	SAPHO syndrome	Type of mandibular sclerosis
1	F	43	3	No	SCO
2	F	41	21	Yes	PCO
3	F	33	21	Yes	Enostosis and PCD of the mandible; PCO of the humerus
4	F	59	6	Yes	PCO
5	F	39	30	Yes	PCO
6	M	14	3	No	PCO (JCO)
7	F	50	7	Yes	PCO
8	M	64	8	Yes	PCO
9	M	69	4	Yes	PCO
10	F	38	24	Yes	PCO
11	M	57	3	No	TP
12	M	63	3	No	SCO





Figs. 7 & 8. Coronal and axial CT-scans of the mandibular molar region showing sclerotic changes (patient 9).

of gentamycin beads. Mild acne was observed during adolescence. Scintigraphy showed increased uptake in the humerus and the sternoclavicular joints. Occlusal splint therapy led to partial relief. Long-term medication with antibiotics did not cure the disease, but provided partial relief of symptoms while on medication. NSAID led to partial relief.

Case 4

A 59-year-old woman had primary chronic sclerosing osteomyelitis of the mandible and SAPHO syndrome. The orofacial complaints of the patient were suspected to be a myofacial pain syndrome caused by insufficient jaw positioning of the edentulous mandible. The history revealed that one year before splinting and myofeedback therapy, the endodontically treated lower canines had been removed. The patient presented with a palmoplantar psoriasis and a unilateral prominent sternoclavicular joint as well as synovitis of the first metacarpophalangeal joint of both hands. The medical history revealed no periods of pustulosis. Scintigraphic enhancement was found in the mandible, sternoclavicular joints and in both wrists. A revision and decortication of the mandibular lesion along with hyperbaric oxygen therapy were applied. Antibiotics were effective while on medication. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 5

A 39-year-old woman was diagnosed with primary chronic sclerosing osteomyelitis of the mandible since childhood and SAPHO syndrome. Decortication, bimaxillary osteotomies (for secondary asymmetry) and hyperbaric oxygen therapy were performed over the 30-year duration of the disease. Acne had been present in adolescence. Clinical examination revealed a palmar pustulosis and synovitis of both elbows. Both sternoclavicular joints were clinically prominent and showed scintigraphic enhancement. Antibiotics were effective. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 6

A 14-year-old boy had juvenile primary mixed sclerosing-lytic osteomyelitis of the mandible. Before referring the patient to the maxillofacial department, the suspected differential diagnosis included juvenile parotitis, fibrous dysplasia and osteosarcoma. Mild acne was observed. Scintigraphically, slight enhancement of both sternoclavicular joints was noted. Microbiologic cultures revealed *Streptococcus sanguis, Veilonellae* and *Actinomyces* species. A transient C4-deficiency was documented after surgical decortication. After long-term antibiotic medication, laboratory testing showed normal C3 and C4 levels. Repeated decorticationes along with hyperbaric oxygen therapy were performed. Antibiotics were effective while on medication. NSAIDs were ineffective. Since antibiotic medication was aborted, 9 months ago, no more symptoms have been noted. Finally, CT-scans demonstrated complete recovery with restoration of the bony structure.

Case 7

A 50-year-old woman was diagnosed with primary chronic osteomyelitis and SAPHO syndrome. Her orofacial complaints were initially suspected to indicate a myofacial pain syndrome. After 1 year of treatment, pain relief could not be achieved and the third molar was considered as a causative factor. After tooth extraction, her symptoms increased. On physical examination, the patient presented with sternoclavicular hyperostosis, polysynovitis and palmoplantar pustulosis as well as sacroileitis. Decortication along with hyperbaric oxygen therapy was performed. NSAIDs were effective.

Case 8

A 64-year-old man had mandibular primary chronic sclerosing osteomyelitis and SAPHO syndrome. The history revealed plantar pustulosis, especially during summer, and acne lesions in adolescence. Clinical and scintigraphic ex-

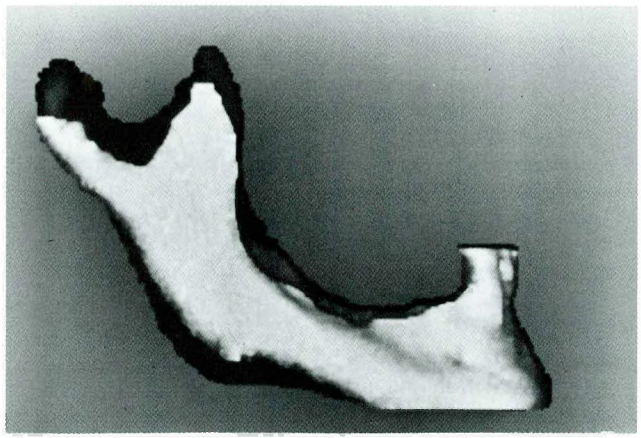


Fig. 9. The lateral aspect of the 3-D (with the software package Gyroview®, ISG Technologies, Toronto, Canada) reconstructed mandible showing deformation of the right mandibular body and condyle (patient 9).

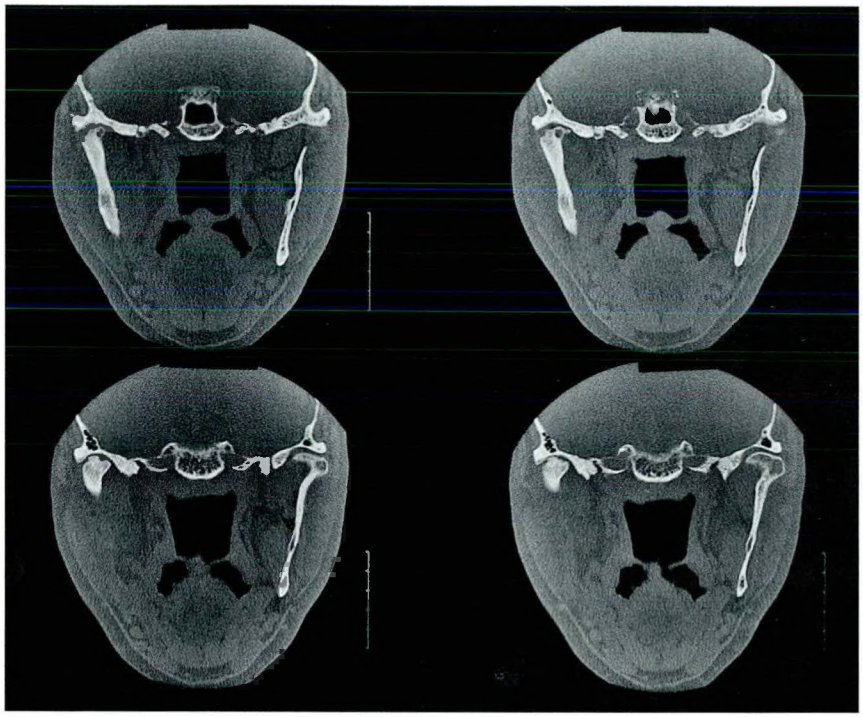


Fig. 10. Coronal CT-scans of the temporomandibular joint revealing osteolytic and cystic destruction of the right condylar head (patient 9).

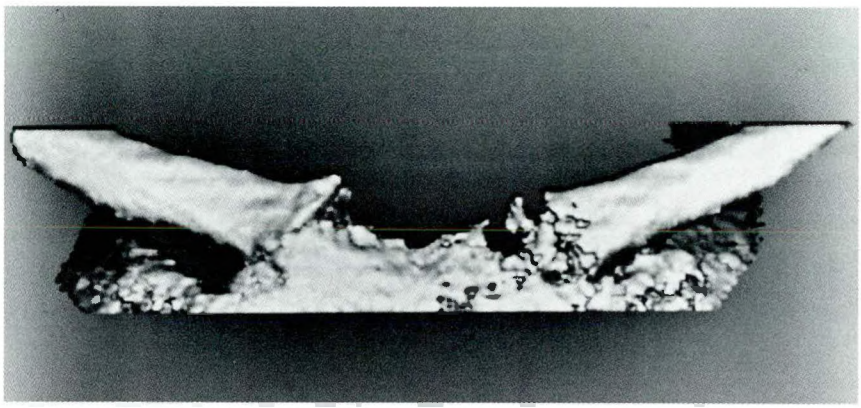


Fig. 11. 3-D CT reconstruction (with the software package Gyroview®, ISG Technologies, Toronto, Canada) of the sternoclavicular joints showing massive destruction of bone on the left and hyperostosis on the right side (patient 9).

amination showed prominent sternoclavicular joints with signs of inflammation. Hyperbaric oxygen therapy was performed. Antibiotics were effective while on medication. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 9

A 69-year-old man with mandibular primary chronic sclerosing osteomyelitis (Figs. 1 & 7–10) of the mandible and SAPHO syndrome was examined. Acne and pustulosis could be observed (Fig. 5). In addition, the patient had hyperostosis on one side and destruction of the sternoclavicular joint (Figs. 11 & 12) on the other side, with impressive scintigraphic enhancement (Fig. 6). Hyperbaric oxygen therapy was performed. Antibiotics were effective while on medication. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 10

A 38-year-old woman, sister of case 3, was examined with mandibular primary chronic sclerosing osteomyelitis and SAPHO syndrome. After repeated revisions, decortications and hyperbaric oxygen therapy, a resection of the ramus and reconstruction with a costal graft were performed. Unfortunately, the disease process recurred in the transplant. The patient had palmoplantar pustulosis and tender sternoclavicular hyperostosis. Scintigraphy clearly showed enhanced uptake in the mandible and slight elevation in the sternoclavicular joint, as well as in the left sacroiliac joint. Antibiotics were ineffective. In spite of good initial response, NSAIDs became ineffective, while glucocorticoids produced immediate relief.

The following text and Tables 1–4 summarise the results of patients 2 to 10 with PCO.

Eight of nine (88.9 %) patients with primary chronic osteomyelitis demonstrated the SAPHO syndrome. The total of 12 patients also included two patients with secondary chronic osteomyelitis and one patient with tendoperiostitis. The duration (before and after diagnosis) since first onset of mandibular osteomyelitis ranged between 3 and 30 years. The patients' ages at examination were between 33 and 69 years, with the exception of patient number 6. Eight of the nine patients with PCO presented with, or reported a history of, skin lesions. In eight of the nine patients with PCO, extra-mandibular scintigraphic enhancement was detected. Surgical intervention was performed in seven patients with PCO and eight patients underwent hyperbaric oxygen therapy. Six patients responded to antibiotic medication.

Table 4 shows laboratory test results for C-reactive protein, ESR (erythro-

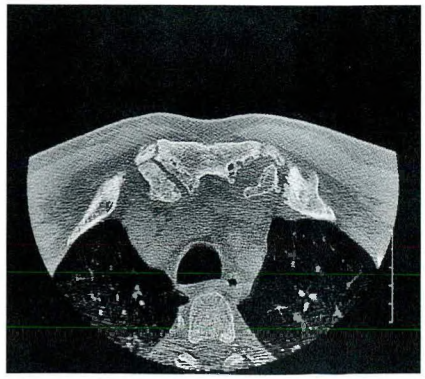


Fig. 12. Axial CT-scan of the chest wall and the sternoclavicular joints are characterised by cystic-osteolytic destructive lesions (patient 9).

Table 2. Diagnostic procedures and results (9 patients with PCO)

Number	SAPHO syndrome	Type of mandibular sclerosis	Skin lesion	CT-scan of the mandible	Scintigraphic enhancement	Biopsy of the mandibular lesion	Microbiology
2	Yes	PCO	Acne (historical)	Yes	Mandible; sternoclavicular	Yes	*Streptococcus; Staphylococcus*
3	Yes	Enostosis and PCD of the mandible; PCO of the humerus	Pustular psoriasis (at examination)	Yes	Mandible; sternoclavicular; humerus	Yes	Coagulase-negative *Staphylococcus*
4	Yes	PCO	No	Yes	Mandible; sternoclavicular	Yes	No
5	Yes	PCO	Pustulosis (at examination); acne (historical)	Yes	Mandible; sternoclavicular; elbows	Yes	Negative
6	No	PCO (JCO)	Acne (at examination)	Yes	Mandible	Yes	*Actinomyces* and *Veilonella* species
7	Yes	PCO	Pustulosis (at examination)	Yes	Mandible; sternoclavicular; sacroiliac	Yes	Negative
8	Yes	PCO	Pustulosis; acne (historical)	Yes	Mandible; sternoclavicular	Yes	*Streptococcus*
9	Yes	PCO	Pustulosis (at examination)	Yes	Mandible; sternoclavicular	No	No
10	Yes	PCO	Pustulosis (at examination)	Yes	Mandible; sternoclavicular; sacroiliac	Yes	*Haemophilus Parainfluenzae; Streptococcus; Actinomyces* and *Veilonella* species

Table 3. Treatment procedures and medications (9 patients with PCO)

Case number	SAPHO syndrome	Type of mandibular sclerosis	Operative treatment	Hyperbaric oxygen therapy (sessions)	Antibiotic effectiveness	NSAIDs effectiveness	Corticoids effectiveness
2	Yes	PCO	Resection (angle, vertical ramus) and reconstruction (costalgraft)	20	Partial: doxicycline clindamycin metronidazole and amoxicillin long-term 6 months	Partial	Not applied
3	Yes	Enostosis and PCD of the mandible PCO of the humerus	Repeated revisions, insertions of gentamycin beads, decortications and biopsies of the humerus	Not applied	Partial: clindamycin rifampicin and ciprofloxacin long-term 27 months	Partial	Not applied
4	Yes	PCO	No	20	Yes: clindamycin	Partial	Not applied
5	Yes	PCO	Decortication; bimaxillary osteotomy	20	Yes: doxicycline clindamycin	Partial	Not applied
6	No	PCO (JCO)	Decortication	60	Yes: metronidazole amoxicillin clarithromycin long-term 24 months	No	Not applied
7	Yes	PCO	Decortication	24	Yes: amoxicillin	Yes	Not applied
8	Yes	PCO	Decortication	60	Yes: doxicycline	Partial	Not applied
9	Yes	PCO	No	30	Yes: clindamycin	Partial	Not applied
10	Yes	PCO	Decortication; resection (angle, vertical ramus) and reconstruction (costalgraft)	124	No: doxicycline metronidazole and amoxicillin long-term 7 months	No	Yes

cyte sedimentation rate) and leucocyte counts as a sensitive indicator of inflammatory processes, such as acute bone inflammation; these were mainly within normal limits. Complement components were decreased in two patients and elevated in one patient. The serum concentrations of IgA, IgM and IgG were elevated in five patients. A dysimmunoglobulinemia was observed in eight patients (including changes in relative distribution of subclasses in seven patients).

Elevated anticardiolipin levels were found in five of nine patients and elevated levels of antinuclear antibodies in eight of nine patients. The frequency of the A2-allele was 78% (7 of 9) in patients with PCO. Serologic testing revealed parvovirus B19 to be the most frequent infectious viral agent (67%, 6 of 9).

Discussion

The term diffuse sclerosing osteomyelitis has been used collectively for different entities and disease stages (1). PCO and SCO, as well as JCO (Garrè), may present as diffuse sclerosing osteo-

Table 4. Laboratory test results (9 patients with PCO)

Patient	2	3	4	5	6	7	8	9	10
ESR	15	36	6	4	6	10	26	13	8
CRP	<3	3	<3	<3	<3	<3	5	18	<3
Leukocytes	3.4	6.2	8.5	10.7	4.8	5.4	7.2	8.9	7.12
Differential white cell count	ly↓	Normal	Normal	Normal	Normal	ly↑	Normal	Normal	Normal
Haemoglobin	11.2	12.8	13.6	13.3	14.6	12.5	12.5	14.4	12.7
Rheumafactors	Negative	Negative	Negative	SP 1:160	Negative	Negative	Negative	Negative	Negative
Dysimmuno-globulinemia	+ IgG↑	+ IgA↑ IgG↑	+	+	Normal	+	+ IgA↑	+ IgA↑ IgE↑	+ IgG↑
IgG-subclasses	SC 1↓ SC 2↑	SC 2↑	SC 1↑ SC 2↓ SC 4↓	SC 1↑ SC 4↑	Normal	SC 4↑	Normal	SC 1↑ SC 2↓	SC 1↓ SC 2↑
Immune complex	Normal	C1q↑ IgG↑	Normal	Normal	Normal	Normal	Normal	C1q↑	Normal
Complement C3	C3↓	Normal	Normal	Normal	C3↓↓	Normal	Normal	Normal	Normal
Complement C4	C4↓	Normal	Normal		Normal	Normal	Normal	Normal	C4↑
Serology	Negative	Parvo B19 IgG	Parvo B19 IgG	Negative	Parvo B19 IgG	Varicella IgG Cytomegalo IgG	Parvo B19 IgG	Parvo B19 IgG	Parvo B19 IgG
Liver enzymes	Normal	Normal	Normal	Normal	Normal	Normal	yGT 84	Normal	Normal
Creatinine	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Glucose	Normal	Normal	Normal	Normal	Normal	7.2	Normal	Normal	Normal
Antinuclear antibodies	Antinuclear 1:80	Antinuclear 1:40	Antinuclear 1:10	Antinuclear 1:80	Normal	Antinuclear 1:40	Antinuclear 1:80	Antinuclear 1:80	Antinuclear 1:160
Anticardiolipin antibodies	Normal	IgG↑	IgG↑	Normal	Normal	Normal	IgG↑ IgA↑	IgG↑	IgM↑
HLA-typing	A24(9), A31(19), B35, B55 (22) DR1 0101–0102/ DRB 0801–0805	A1, A2, B8,B61 (40), DRB1 1601–1601, DRB1 0301	A1, A2, B8, B60 (40) DRB1 1501–1503/DRB 0101–0202 second DRB1 typing failure	A2, Ax, B7, B39 (16) first and second DRB1 typing failure	A2, A68(28), B7, B35, DRB1 0401–04012/ DRB1 0101 DRB1 0701–0702/ DRB1 0101	A26 (10), Ax, B52 (5), B58 (17), DRB1 1501–1503/ DRB5 0101–0202 DRB! 1302/ DRB3 0101–0301	A2, A43, B60 (40), B45 (12), DRB1 0301/ DRB3 0101–0301 DRB1 0901/ DRB3 0101	A2, A26 (10), B44 (12), B58 (17), DRB1 0701–0702/ DRB4 0101, DRB1x	A1, A2, B8,B62 (15), DRB 1301–1306, DRB1 0301

myelitis. Bony sclerosis is a non-specific reaction to any chronic inflammatory process. Clinical course, diagnostic findings and therapeutic response suggest different entities. Moreover, common presentation under the designation DSO complicates evaluation of data.

KAHN *et al.* (12) and SUEI *et al.* (13) offered evidence that suggested DSO to be the mandibular localisation of SAPHO syndrome. In fact, DSO with extramandibular involvement and skin lesions had been described earlier (14). In contradiction to the patient described by FARNAM *et al.* (14), primary chronic osteomyelitis presents a non-putrefactive course. It remains unclear whether SAPHO syndrome might be the predisposing factor for primary chronic osteomyelitis, but the fact that eight of nine patients with primary chronic osteomyelitis of the mandible presented with SAPHO syndrome also supports the hypothesis of an associated disease process. The association of SAPHO syndrome and DSO, and especially with PCO (8 of 9), is noteworthy and appears to support the hypothesis of a common pathologic mechanism.

The great majority of patients with osteomyelitis present abnormal parameters in the immune system (15). The literature expresses contradictory opinions, including a hyperactive, a hypoactive, a cellular exaggerated response or a total impairment of the immune system (15). Complement components were decreased in two of our patients and elevated in one patient. The serum concentrations of IgA, IgM and IgG were elevated in five patients with PCO. A dysimmunoglobulinemia was observed in eight patients with PCO (including changes in relative distribution of subclasses in seven patients). Immunoelectrophoresis failed to reveal increased levels of monoclonal antibodies. MALMSTRÖM *et al.* (15) reported increased concentration levels of IgG, IgA, IgM or IgE in 11 of 15 patients.

The aetiology of SAPHO syndrome and PCO is unknown. One hypothesis advocates an organism of low virulence as a trigger. *Propionibacterium acnes* has been found as the only infectious agent in osteoarticular lesions (12). Beside *Propionibacterium acnes* (16), species of *Actinomyces* and *Eikinella corrodens* have been detected from a large number of biopsy specimens in a prospective study by MARX *et al.* (17). Our series yielded *Actinomyces* species in two of seven cultures. Elevated anticardiolipin levels (5 of 9 tested patients with PCO) support this hypothesis, as they represent immunological stimulation. For example, the antiphospholipid syndrome is associated with vascular thrombosis, skin lesions and persistently elevated levels of antiphospholipid antibodies (18). Anticardiolipin is also suspected to interfere in the arachidonic acid cycle. This might result in decreased prostacyclin production and favour increased platelet adhesiveness and vascular thrombosis (18). PLOTQUIN *et al.* demonstrated elevated PGE (prostaglandin) levels, although PGF (prostacyclin) showed similar quantities in osteomyelitic bone when compared with normal human bone

(19). Medullary vascular thrombosis and vasculopathy (20) have often been mentioned as potential causative factors of mandibular osteomyelitis. BARTKOWSKI *et al.* (21) reported successful treatment of mandibular osteomyelitis with intravenous heparin therapy. However, symptoms only occur in some of the patients with positive anticardiolipin levels; therefore, antibodies may just be markers of the disorder. In contradiction, the offending organism has not been demonstrated in most cases (negative cultures in two of seven specimens). The fact that anticardiolipin antibodies have also been implicated in the development of osteonecrosis, which is often a sclerotic disease in extragnathic bones, and that anticoagulants are able to reduce pain in patients with osteonecrosis, may support the ischemic rather than the infectious character of the disease (22–24). It has to be borne in mind, however, that negative cultures might result from inadequate culturing techniques (17). Genetic factors also have been suspected to play a role in the pathologic scenario (12). In fact, the two sisters (cases 3 and 10), who were evaluated for HLA-typing, revealed common gene loci (A-1, B-8, DR-3; subject of a separate case report). Their haplotype is typically found in autoimmune diseases such as lupus erythematosus and other connective tissue diseases. A higher frequency of the A2 allele [seven of nine patients (78%) with PCO] compared to similar European ethnic groups (21.3% up to 27.8%) was found in our series (25). The fact that antibiotic medication, NSAIDs and corticosteroids can partially alleviate symptoms could be due to the suppression of symptoms but may also support our hypothesis of a microorganism of low virulence. Antibiotic medication may lead to transient partial eradication of the causative microorganism, but cannot prevent recurrence of symptoms. NSAIDs and corticosteroids block the inflammatory cascade on different mediatory levels.

One patient (case 11) of our series, who had a typical myofacial pain syndrome, represents the view that advanced the hypothesis of tendoperiositis (1, 3). Sclerosis in this patient was limited to the mandibular alveolar bone and in addition the patient lacked typical symptoms of acute exacerbations, such as swelling, lymphadenopathy, and typical periodicity. Patients with chronic pain syndromes, such as DSO, often develop secondary myofacial pain. Therefore, treatment with dental splints and myofeedback training may lead to partial relief but can not cure the disease (cases 2, 4 and 7). We agree with MARX (26), who stated that it would seem unlikely to be successful in the face of sclerosis being intramedullary rather than periosteal, and the fact that it occurs in edentulous patients. Also, it would not account for the partial effectiveness of periods of antibiotic medication.

Juvenile chronic osteomyelitis (JCO) may be considered as a rare type of primary chronic osteomyelitis (PCO) and it has also been designated as Garrè's osteomyelitis. Data for case number 6 clearly showed differences in laboratory results, scintigraphic and radiographic findings, while clinical symptoms were almost similar to primary chronic osteomyelitis. We favour the term juvenile chronic osteomyelitis because Garrè did not describe a singular, specific type of osteomyelitis; moreover, he presented 12 different conditions of osteomyelitis in his historical article (27). Hence, we consider JCO as a specific type of PCO, which in later stages may present the typical bony picture of PCO and possibly show development towards SAPHO syndrome.

Open biopsy of the mandibular bone and computed tomography are necessary to establish a precise diagnosis of mandibular osteomyelitis. MARX *et al.* (17) reported consistent microbiologic findings. However, an extraoral approach should be avoided, because possible nerve palsy and scar formation are serious disadvantages, while intraoral biopsies often present contamination. Oral contamination can be excluded when a piece of bone is removed intraorally if an extraoral sterile biopsy (taken by a trepan-bur) is also taken. Only the tip of the cylinder is sent for culturing. Our study incorporated the demands given by MARX (26) for culturing techniques; however, results were inconsistent. Serologic testing revealed parvovirus B19 to be the most frequent infectious viral agent, but positive results may be found in 30–60% of adults (28). Parvovirus B19 infection has been mentioned in association with rheumatic diseases, spherocytosis and bone marrow aplasia (29). MARX (26) also demands PCR-DNA, but preliminary data on four patients in this series still show contradictory results (2 patients with signal overloading, 2 patients with negative results). Tc-scintigraphy is a useful tool for detecting clinically and radiologically silent lesions, especially in extramandibular locations (12).

Because diffuse sclerosing mandibular osteomyelitis responds to treatment inconsistently (30), all treatment options should be applied. Especially in the early stage of the disease, operative procedures such as removal of all necrotic tissue and decortication are usually successful. In addition, hyperbaric oxygen (twice daily sessions at 1.4 atmospheres for 45-min cycles), with at least 20 cycles and long-term antibiotic medication, should always be performed as well. The four patients treated with long-term antibiotic medication showed a decreased frequency of mild symptoms while on medication. Because involvement of reconstructed bone is frequent, resection and second stage reconstruction should be considered carefully in late disease stages. In long-standing refractory chronic osteomyelitis, patients with multiple unsuccessful operative interventions and compromised elderly patients, conservative therapy with NSAIDs or steroids is recommended. Synovitis is most often mild and only rarely destructive. Treatment includes NSAIDs at sufficient dosage levels and, in refractory cases, administration of sulfusalazine. Persistent cases may require administration of methotrexate.

In conclusion, we strongly advocate an association between DSO and SAPHO syndrome. With reference to results from our study and the current literature, we suggest a hypothesis of a microorganism of low virulence functioning as a trigger that causes an exaggerated immune response in genetically predisposed individuals.

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Printed in Denmark by P.J. Schmidt A/S, Vojens

J Oral Pathol Med 1999; 28: 456–64
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JOURNAL OF
Oral Pathology&Medicine
ISSN 0904-2512

Primary chronic osteomyelitis associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome)

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Eyrich GKH, Harder C, Sailer HF, Langenegger T, Bruder E, Michel BA: Primary chronic osteomyelitis associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome). J Oral Pathol Med 1999; 28: 456–64.
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Diffuse sclerosing osteomyelitis may indicate the mandibular localisation of the SAPHO syndrome. Twelve patients with diffuse sclerosis of the mandible were examined for symptoms of the SAPHO syndrome. Nine patients were found to have primary chronic osteomyelitis and eight of these represented a SAPHO syndrome. Results in this series support the hypothesis of an association between primary chronic osteomyelitis and the SAPHO syndrome.

Key words: mandibular osteomyelitis; SAPHO syndrome

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Accepted for publication July 3, 1999

Osteomyelitis of the mandible is defined as an inflammation of the mandibular cortical and cancellous bone. Acute osteomyelitis is commonly caused by bacterial invasion from a contagious focus. Most frequent sources are odontogenic foci, periodontal diseases and pulpal infection, extraction wounds or infected fractures. Osteomyelitis may also appear as a nonsuppurative chronic inflammation of unknown aetiology. A small number of cases of mandibular chronic osteomyelitis are granulomatous osteomyelitis, which is related to tuberculosis or tertiary syphilis.

The literature related to chronic osteomyelitis is confusing. Different disease processes have been designated under one term in some instances, whereas several terms have been designated to lesions that represent the same entity in other instances (1). The variety of classification systems takes into account multiple characteristics such as physiology, pathogenesis, localisation, radiological or clinical appearance and clinical course. The radiological appearance of chronic osteomyelitis may be sclerotic, radiolucent or mixed. Diffuse sclerosing osteomyelitis (DSO) has been chosen to describe the radiologic appearance of the process (Fig. 1). The arbitrary time limit of 1 month is used to separate acute from chronic osteomyelitis (2). The term DSO includes similar entities such as primary chronic osteomyelitis (PCO), chronic tendoperiostitis (1, 3), secondary chronic osteomyelitis and juvenile chronic osteomyelitis (JCO, Garrè's osteomyelitis).

The term primary chronic osteomyelitis (PCO) describes a long-standing, radiologically diffuse sclerosing disease process of unknown aetiology, which involves the cancellous bone. The characteristic morphological findings consist of an extensive periosteal reaction and cortical thickening (Fig. 2), massive thickening of trabeculae, and marrow fibrosis in cancellous bone (Fig. 3). Inflammatory infiltrate is scarce, though foci of dense aggregates of plasma cells (Fig. 4) may be observed occasionally. The absence of pus, fistulae or sequestration is characteristic. The course of the disease lacks an acute state and is therefore considered primarily to be chronic. Periods of onset may last from 3 days to several weeks. The patient usually presents with a limitation of mouth opening, swelling of the cheek, lymphadenopathy and severe pain.

Juvenile chronic osteomyelitis (Garrè's osteomyelitis) usually peaks in puberty and is characterised by voluminous expansion of the mandibular body, periosteal apposition of bone and a mixed sclerosing-lytic appearance of the cancellous bone. The clinical picture resembles PCO, sharing the lack of pus formation, fistulae or sequestration. Therefore, JCO may be considered as a subtype of PCO.

Patients with tendoperiostitis (TP) usually present with a history of parafunctional complaints. Palpation of the temporal, masseter, medial pterygoid, and the digastric muscles reveals tenderness in one or more muscles (4). Radiographically, diffuse sclerosis of the cortical plate and marrow is observed. Pus formation and sequestration are absent.

Secondary chronic osteomyelitis develops from an acute bacterial invasion of the bone with formation of fistulae and possible sequestration. Clinically and radiographically, a broad spectrum ranging from an aggressive osteolytic putrefactive phase to a dry osteosclerotic phase may be observed.

Florid osseous dysplasia (FOD) is radiographically described as sclerosing opaque and dense masses. The bone changes are often adjacent to the apices of the roots of the teeth. Signs of in-

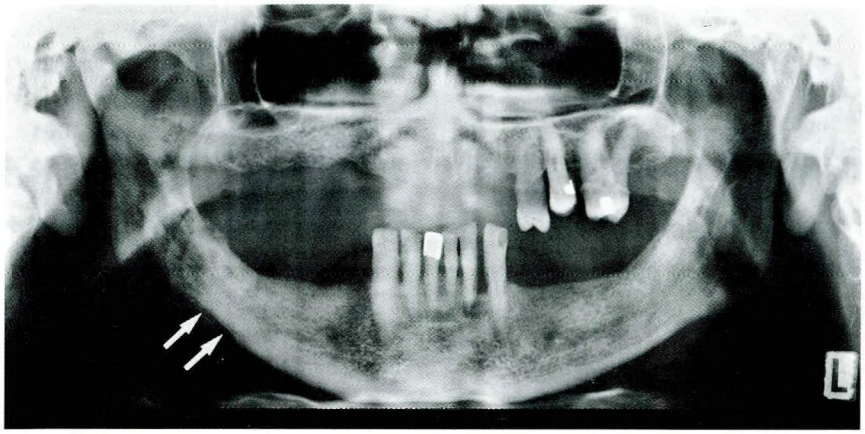


Fig. 1. An orthopantomogram showing typical sclerosis (arrows) involving cortical and cancellous bone of the right mandibular body (patient 9). The mandibular left second incisor shows a periapical radiolucency and interdental vertical loss of bone due to periodontal infection.

flammation may be present. Some cases of FOD occur in two phases. In the first phase, asymptomatic sclerotic masses develop. In the second phase, inflammation is superimposed (5). It may be very difficult to distinguish FOD from periapical cemental dysplasia (PCD), though the clinical course of FOD shows limited growth potential compared to PCD and does not produce pain. However, bony sclerosis may extend from a localised periapical process to a regional lesion. While there may be histological similarity between the two lesions, they are distinct clinical entities and do not usually become more widespread. PCD most commonly occurs in middle-aged women and is localised to the anterior mandibular teeth. The affected teeth always respond positively to vitality tests. This lesion presents with three typical distinct stages: osteolytic stage, cementoblastic stage and inactive stage (6).

An enostosis or compact island of bone can also be observed as an opaque dense sclerotic area. This may derive from an inflammatory processes following trauma (7). An enostosis or bony island may also result from focal ischemia or infarction (e.g., sickle cell disease) (8).

In 1986, CHAMOT *et al.* (9) described a syndrome associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome). Usually the medical history or examination reveals palmoplantar pustulosis (Fig. 5), pustular or plain psoriasis, and acne or hidradenitis suppurativa. Radiological and scintigraphic findings identify the



Fig. 2. Photomicrograph of patient 5 illustrating cortical sclerosis and massive periosteal reaction typical of primary chronic mandibular osteomyelitis. (H&E, ×15)



Fig. 4. Photomicrograph of bone from patient 2 showing an inflammatory infiltrate with some denser aggregates of plasma cells. (H&E, ×250)

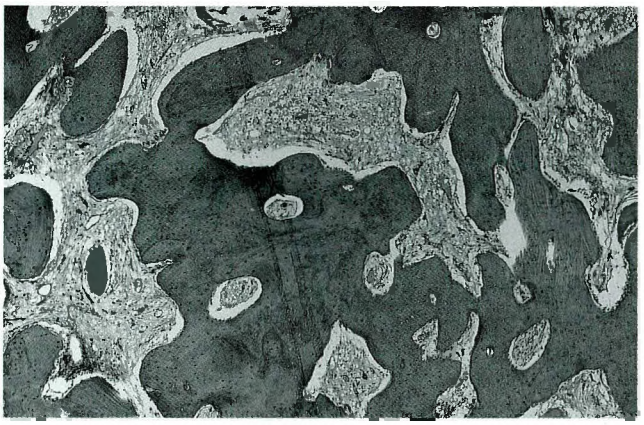


Fig. 3. Photomicrograph of cancellous bone showing massive thickening of trabeculae and marrow fibrosis (patient 2). (H&E, ×32)



Fig. 5. Typical plantar pustulosis (patient 9).



Fig. 6. Scintigraphic imaging demonstrating a significant enhancement of the right mandibular body and the chest wall (patient 9).

anterior chest wall (especially the sternoclavicular joint) as the most prevalent location for the hyperostosis (Fig. 6). Joint involvement may also be noted. In addition to reports from other authors (10, 11), KAHN *et al.* (12) have presented the largest series of 7 patients with mandibular involvement out of 85 cases of SAPHO syndrome. It has been finally concluded that diffuse sclerosing osteomyelitis may represent the mandibular localisation of SAPHO syndrome (12).

In a prospective cohort evaluation, patients with diffuse sclerosing osteomyelitis (DSO) were examined for the type of mandibular chronic sclerosing osteomyelitis and for SAPHO syndrome.

Material and methods

Within a period of 1 year all patients with diffuse sclerosing osteomyelitis (DSO) of the mandible and clinical signs of an acute inflammation (edema of the cheek, limitation of mouth opening, tenderness to palpation and severe pain) were prospectively assessed for concise diagnosis of their mandibular osteomyelitis. The diagnosis of DSO was based on clinical and radiographical findings. If available, medical history, clinical examination, computed tomography of the mandible, skeletal scintigraphy and biopsy specimens were included.

Subsequently, all patients with DSO were examined for symptoms of SAPHO syndrome. Routine immunological and haematological tests were performed with standard methods. Laboratory testing included complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, protein- and immuno-electrophoresis including IgG-subclasses, complement factors, immune complexes, rheumatoid factors, antinuclear antibodies, anti-DNA antibodies, C-(PR3)-ANCA, cardiolipin antibodies, routine chemistry and serological testing for antibodies against rubella, adenoviruses, Coxsackie-B virus, Epstein–Barr virus (EBV), herpes viruses, salivary gland tissue, parvovirus B19, picornavirus, hepatitis viruses B/C, cytomegalovirus, *Chlamydia, Borrelia burgdorferi, Brucella, Campylobacter, Salmonella, Yersinia, Shigella, Treponema pallidum, Neisseria gonorrhoeae* and *Mycoplasma pneumoniae.*

Medical records from the time of the patient's first visit were reviewed. In addition to MDP ^{99m}technetium bone scan (locating increased bone vascularity or osteoblastic activity) and routine radiographs of suspected bone lesions, computed tomography was performed on some patients. The diagnosis of SAPHO syndrome was accepted if the patient met the criteria, such as acute, subacute, chronic arthritis or any extramandibular osteitis, osteomyelitis with scintigraphic enhancement (especially of the sternoclavicular joint and the anterior chest wall), and skin lesions (palmoplantar pustulosis, pustular psoriasis, psoriasis vulgaris, severe acne).

Results

All 12 patients satisfied the selection basis for DSO. However, only nine patients (patients 2–10) met the diagnostic criteria for PCO. All patients were treated at the Department of Maxillofacial Surgery, University Hospital, Zurich and were referred for complete rheumatologic evaluation to the Department of Rheumatology, University Hospital, Zurich. The mean age of the patients was 47.5 years, with a range from 14 to 67 years. There were four men (33%) and eight women (67%). Follow-up periods from disease onset ranged from 3 to 30 years (Table 1).

Case 2

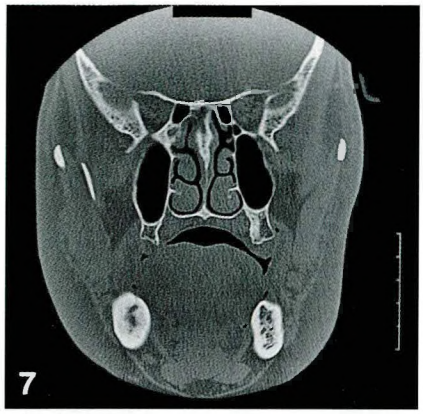
A 41-year-old woman with primary chronic sclerosing osteomyelitis and SAPHO syndrome was referred. The first symptoms of osteomyelitis were detected 20 years ago. After repeated decortication, she received hyperbaric oxygen therapy, a resection of the vertical ramus and reconstruction with a costal graft. Mild acne was observed in puberty. Physical examination revealed no pustulosis. Control CT scans revealed involvement of the transplanted graft. The patient presented with sternoclavicular hyperostosis showing slight scintigraphic enhancement and tenderness to palpation. Antibiotics were effective while on medication. Nonsteroidal anti-inflammatory drugs (NSAIDs) provided partial relief with reduction of pain and swelling during acute exacerbations.

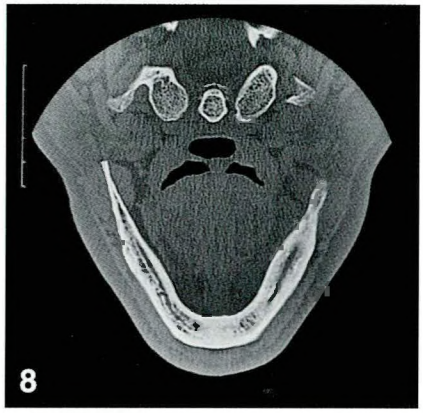
Case 3

A 33-year-old woman, the sister of case 10, had enostosis in the molar region, periapical cemental dysplasia (PCD) with vital teeth in the symphysial region of the mandible, palmoplantar pustulosis, humeral sclerosing osteomyelitis and sternoclavicular hyperostosis; she was re-examined. The patient had undergone 16 operative procedures of the humerus including biopsies, decortications, debridements and insertions

Table 1. Demographic data and diagnoses of all patients (including all 12 patients with DSO)

Case number	Sex	Age at examination (yr)	Duration in years (osteomyelitis)	SAPHO syndrome	Type of mandibular sclerosis
1	F	43	3	No	SCO
2	F	41	21	Yes	PCO
3	F	33	21	Yes	Enostosis and PCD of the mandible; PCO of the humerus
4	F	59	6	Yes	PCO
5	F	39	30	Yes	PCO
6	M	14	3	No	PCO (JCO)
7	F	50	7	Yes	PCO
8	M	64	8	Yes	PCO
9	M	69	4	Yes	PCO
10	F	38	24	Yes	PCO
11	M	57	3	No	TP
12	M	63	3	No	SCO





Figs. 7 & 8. Coronal and axial CT-scans of the mandibular molar region showing sclerotic changes (patient 9).

of gentamycin beads. Mild acne was observed during adolescence. Scintigraphy showed increased uptake in the humerus and the sternoclavicular joints. Occlusal splint therapy led to partial relief. Long-term medication with antibiotics did not cure the disease, but provided partial relief of symptoms while on medication. NSAID led to partial relief.

Case 4

A 59-year-old woman had primary chronic sclerosing osteomyelitis of the mandible and SAPHO syndrome. The orofacial complaints of the patient were suspected to be a myofacial pain syndrome caused by insufficient jaw positioning of the edentulous mandible. The history revealed that one year before splinting and myofeedback therapy, the endodontically treated lower canines had been removed. The patient presented with a palmoplantar psoriasis and a unilateral prominent sternoclavicular joint as well as synovitis of the first metacarpophalangeal joint of both hands. The medical history revealed no periods of pustulosis. Scintigraphic enhancement was found in the mandible, sternoclavicular joints and in both wrists. A revision and decortication of the mandibular lesion along with hyperbaric oxygen therapy were applied. Antibiotics were effective while on medication. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 5

A 39-year-old woman was diagnosed with primary chronic sclerosing osteomyelitis of the mandible since childhood and SAPHO syndrome. Decortication, bimaxillary osteotomies (for secondary asymmetry) and hyperbaric oxygen therapy were performed over the 30-year duration of the disease. Acne had been present in adolescence. Clinical examination revealed a palmar pustulosis and synovitis of both elbows. Both sternoclavicular joints were clinically prominent and showed scintigraphic enhancement. Antibiotics were effective. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 6

A 14-year-old boy had juvenile primary mixed sclerosing-lytic osteomyelitis of the mandible. Before referring the patient to the maxillofacial department, the suspected differential diagnosis included juvenile parotitis, fibrous dysplasia and osteosarcoma. Mild acne was observed. Scintigraphically, slight enhancement of both sternoclavicular joints was noted. Microbiologic cultures revealed *Streptococcus sanguis, Veilonellae* and *Actinomyces* species. A transient C4-deficiency was documented after surgical decortication. After long-term antibiotic medication, laboratory testing showed normal C3 and C4 levels. Repeated decortications along with hyperbaric oxygen therapy were performed. Antibiotics were effective while on medication. NSAIDs were ineffective. Since antibiotic medication was aborted, 9 months ago, no more symptoms have been noted. Finally, CT-scans demonstrated complete recovery with restoration of the bony structure.

Case 7

A 50-year-old woman was diagnosed with primary chronic osteomyelitis and SAPHO syndrome. Her orofacial complaints were initially suspected to indicate a myofacial pain syndrome. After 1 year of treatment, pain relief could not be achieved and the third molar was considered as a causative factor. After tooth extraction, her symptoms increased. On physical examination, the patient presented with sternoclavicular hyperostosis, polysynovitis and palmoplantar pustulosis as well as sacroileitis. Decortication along with hyperbaric oxygen therapy was performed. NSAIDs were effective.

Case 8

A 64-year-old man had mandibular primary chronic sclerosing osteomyelitis and SAPHO syndrome. The history revealed plantar pustulosis, especially during summer, and acne lesions in adolescence. Clinical and scintigraphic ex-

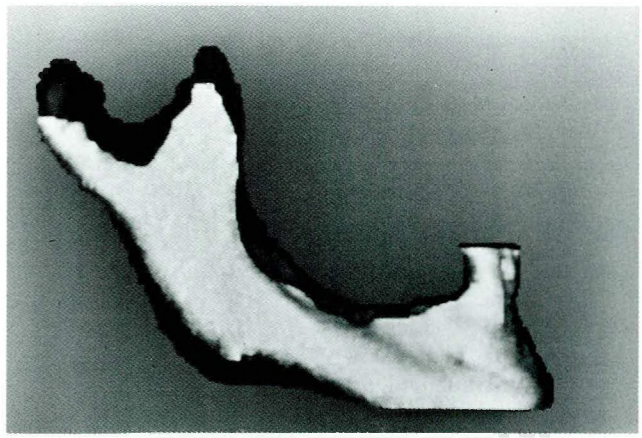


Fig. 9. The lateral aspect of the 3-D (with the software package Gyroview®, ISG Technologies, Toronto, Canada) reconstructed mandible showing deformation of the right mandibular body and condyle (patient 9).



Fig. 10. Coronal CT-scans of the temporomandibular joint revealing osteolytic and cystic destruction of the right condylar head (patient 9).

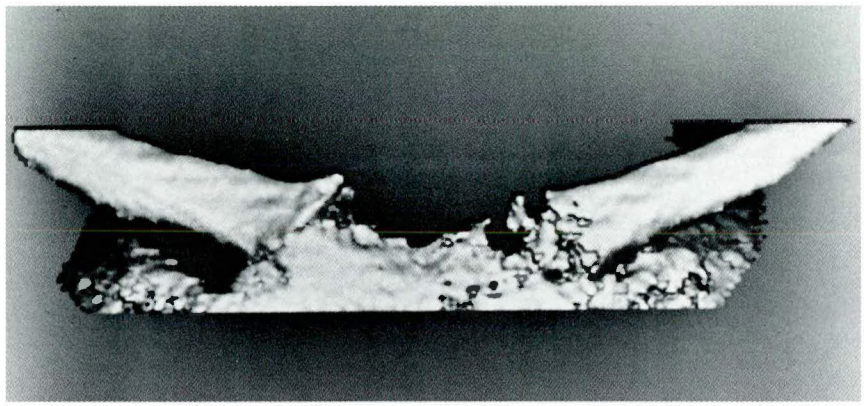


Fig. 11. 3-D CT reconstruction (with the software package Gyroview®, ISG Technologies, Toronto, Canada) of the sternoclavicular joints showing massive destruction of bone on the left and hyperostosis on the right side (patient 9).

amination showed prominent sternoclavicular joints with signs of inflammation. Hyperbaric oxygen therapy was performed. Antibiotics were effective while on medication. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 9

A 69-year-old man with mandibular primary chronic sclerosing osteomyelitis (Figs. 1 & 7–10) of the mandible and SAPHO syndrome was examined. Acne and pustulosis could be observed (Fig. 5). In addition, the patient had hyperostosis on one side and destruction of the sternoclavicular joint (Figs. 11 & 12) on the other side, with impressive scintigraphic enhancement (Fig. 6). Hyperbaric oxygen therapy was performed. Antibiotics were effective while on medication. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 10

A 38-year-old woman, sister of case 3, was examined with mandibular primary chronic sclerosing osteomyelitis and SAPHO syndrome. After repeated revisions, decortications and hyperbaric oxygen therapy, a resection of the ramus and reconstruction with a costal graft were performed. Unfortunately, the disease process recurred in the transplant. The patient had palmoplantar pustulosis and tender sternoclavicular hyperostosis. Scintigraphy clearly showed enhanced uptake in the mandible and slight elevation in the sternoclavicular joint, as well as in the left sacroiliac joint. Antibiotics were ineffective. In spite of good initial response, NSAIDs became ineffective, while glucocorticoids produced immediate relief.

The following text and Tables 1–4 summarise the results of patients 2 to 10 with PCO.

Eight of nine (88.9 %) patients with primary chronic osteomyelitis demonstrated the SAPHO syndrome. The total of 12 patients also included two patients with secondary chronic osteomyelitis and one patient with tendoperiostitis. The duration (before and after diagnosis) since first onset of mandibular osteomyelitis ranged between 3 and 30 years. The patients' ages at examination were between 33 and 69 years, with the exception of patient number 6. Eight of the nine patients with PCO presented with, or reported a history of, skin lesions. In eight of the nine patients with PCO, extra-mandibular scintigraphic enhancement was detected. Surgical intervention was performed in seven patients with PCO and eight patients underwent hyperbaric oxygen therapy. Six patients responded to antibiotic medication.

Table 4 shows laboratory test results for C-reactive protein, ESR (erythro-

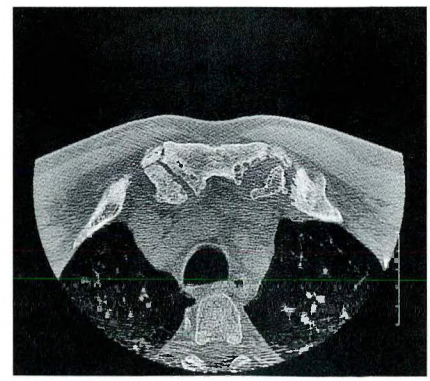


Fig. 12. Axial CT-scan of the chest wall and the sternoclavicular joints are characterised by cystic-osteolytic destructive lesions (patient 9).

Table 2. Diagnostic procedures and results (9 patients with PCO)

Number	SAPHO syndrome	Type of mandibular sclerosis	Skin lesion	CT-scan of the mandible	Scintigraphic enhancement	Biopsy of the mandibular lesion	Microbiology
2	Yes	PCO	Acne (historical)	Yes	Mandible; sternoclavicular	Yes	*Streptococcus; Staphylococcus*
3	Yes	Enostosis and PCD of the mandible; PCO of the humerus	Pustular psoriasis (at examination)	Yes	Mandible; sternoclavicular; humerus	Yes	Coagulase-negative *Staphylococcus*
4	Yes	PCO	No	Yes	Mandible; sternoclavicular	Yes	No
5	Yes	PCO	Pustulosis (at examination); acne (historical)	Yes	Mandible; sternoclavicular; elbows	Yes	Negative
6	No	PCO (JCO)	Acne (at examination)	Yes	Mandible	Yes	*Actinomyces* and *Veilonella* species
7	Yes	PCO	Pustulosis (at examination)	Yes	Mandible; sternoclavicular; sacroiliac	Yes	Negative
8	Yes	PCO	Pustulosis; acne (historical)	Yes	Mandible; sternoclavicular	Yes	*Streptococcus*
9	Yes	PCO	Pustulosis (at examination)	Yes	Mandible; sternoclavicular	No	No
10	Yes	PCO	Pustulosis (at examination)	Yes	Mandible; sternoclavicular; sacroiliac	Yes	*Haemophilus Parainfluenzae; Streptococcus; Actinomyces* and *Veilonella* species

Table 3. Treatment procedures and medications (9 patients with PCO)

Case number	SAPHO syndrome	Type of mandibular sclerosis	Operative treatment	Hyperbaric oxygen therapy (sessions)	Antibiotic effectiveness	NSAIDs effectiveness	Corticoids effectiveness
2	Yes	PCO	Resection (angle, vertical ramus) and reconstruction (costalgraft)	20	Partial: doxicycline clindamycin metronidazole and amoxicillin long-term 6 months	Partial	Not applied
3	Yes	Enostosis and PCD of the mandible PCO of the humerus	Repeated revisions, insertions of gentamycin beads, decortications and biopsies of the humerus	Not applied	Partial: clindamycin rifampicin and ciprofloxacin long-term 27 months	Partial	Not applied
4	Yes	PCO	No	20	Yes: clindamycin	Partial	Not applied
5	Yes	PCO	Decortication; bimaxillary osteotomy	20	Yes: doxicycline clindamycin	Partial	Not applied
6	No	PCO (JCO)	Decortication	60	Yes: metronidazole amoxicillin clarithromycin long-term 24 months	No	Not applied
7	Yes	PCO	Decortication	24	Yes: amoxicillin	Yes	Not applied
8	Yes	PCO	Decortication	60	Yes: doxicycline	Partial	Not applied
9	Yes	PCO	No	30	Yes: clindamycin	Partial	Not applied
10	Yes	PCO	Decortication; resection (angle, vertical ramus) and reconstruction (costalgraft)	124	No: doxicycline metronidazole and amoxicillin long-term 7 months	No	Yes

cyte sedimentation rate) and leucocyte counts as a sensitive indicator of inflammatory processes, such as acute bone inflammation; these were mainly within normal limits. Complement components were decreased in two patients and elevated in one patient. The serum concentrations of IgA, IgM and IgG were elevated in five patients. A dysimmunoglobulinemia was observed in eight patients (including changes in relative distribution of subclasses in seven patients).

Elevated anticardiolipin levels were found in five of nine patients and elevated levels of antinuclear antibodies in eight of nine patients. The frequency of the A2-allele was 78% (7 of 9) in patients with PCO. Serologic testing revealed parvovirus B19 to be the most frequent infectious viral agent (67%, 6 of 9).

Discussion

The term diffuse sclerosing osteomyelitis has been used collectively for different entities and disease stages (1). PCO and SCO, as well as JCO (Garrè), may present as diffuse sclerosing osteo-

Table 4. Laboratory test results (9 patients with PCO)

Patient	2	3	4	5	6	7	8	9	10
ESR	15	36	6	4	6	10	26	13	8
CRP	<3	3	<3	<3	<3	<3	5	18	<3
Leukocytes	3.4	6.2	8.5	10.7	4.8	5.4	7.2	8.9	7.12
Differential white cell count	ly↓	Normal	Normal	Normal	Normal	ly↑	Normal	Normal	Normal
Haemoglobin	11.2	12.8	13.6	13.3	14.6	12.5	12.5	14.4	12.7
Rheumafactors	Negative	Negative	Negative	SP 1:160	Negative	Negative	Negative	Negative	Negative
Dysimmuno-globulinemia	+ IgG↑	+ IgA↑ IgG↑	+	+	Normal	+	+ IgA↑	+ IgA↑ IgE↑	+ IgG↑
IgG-subclasses	SC 1↓ SC 2↑	SC 2↑	SC 1↑ SC 2↓ SC 4↓	SC 1↑ SC 4↑	Normal	SC 4↑	Normal	SC 1↑ SC 2↓	SC 1↓ SC 2↑
Immune complex	Normal	C1q↑ IgG↑	Normal	Normal	Normal	Normal	Normal	C1q↑	Normal
Complement C3	C3↓	Normal	Normal	Normal	C3↓↓	Normal	Normal	Normal	Normal
Complement C4	C4↓	Normal	Normal		Normal	Normal	Normal	Normal	C4↑
Serology	Negative	Parvo B19 IgG	Parvo B19 IgG	Negative	Parvo B19 IgG	Varicella IgG Cytomegalo IgG	Parvo B19 IgG	Parvo B19 IgG	Parvo B19 IgG
Liver enzymes	Normal	Normal	Normal	Normal	Normal	Normal	yGT 84	Normal	Normal
Creatinine	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Glucose	Normal	Normal	Normal	Normal	Normal	7.2	Normal	Normal	Normal
Antinuclear antibodies	Antinuclear 1:80	Antinuclear 1:40	Antinuclear 1:10	Antinuclear 1:80	Normal	Antinuclear 1:40	Antinuclear 1:80	Antinuclear 1:80	Antinuclear 1:160
Anticardiolipin antibodies	Normal	IgG↑	IgG↑	Normal	Normal	Normal	IgG↑ IgA↑	IgG↑	IgM↑
HLA-typing	A24(9), A31(19), B35, B55 (22) DR1 0101–0102/ DRB 0801–0805	A1, A2, B8,B61 (40), DRB1 1601–1601, DRB1 0301	A1, A2, B8, B60 (40) DRB1 1501–1503/DRB 0101–0202 second DRB1 typing failure	A2, Ax, B7, B39 (16) first and second DRB1 typing failure	A2, A68(28), B7, B35, DRB1 0401–04012/ DRB1 0101 DRB1 0701–0702/ DRB1 0101	A26 (10), Ax, B52 (5), B58 (17), DRB1 1501–1503/ DRB5 0101–0202 DRB! 1302/ DRB3 0101–0301	A2, A43, B60 (40), B45 (12), DRB1 0301/ DRB3 0101–0301 DRB1 0901/ DRB3 0101	A2, A26 (10), B44 (12), B58 (17), DRB1 0701–0702/ DRB4 0101, DRB1x	A1, A2, B8,B62 (15), DRB 1301–1306, DRB1 0301

myelitis. Bony sclerosis is a non-specific reaction to any chronic inflammatory process. Clinical course, diagnostic findings and therapeutic response suggest different entities. Moreover, common presentation under the designation DSO complicates evaluation of data.

KAHN *et al.* (12) and SUEI *et al.* (13) offered evidence that suggested DSO to be the mandibular localisation of SAPHO syndrome. In fact, DSO with extramandibular involvement and skin lesions had been described earlier (14). In contradiction to the patient described by FARNAM *et al.* (14), primary chronic osteomyelitis presents a non-putrefactive course. It remains unclear whether SAPHO syndrome might be the predisposing factor for primary chronic osteomyelitis, but the fact that eight of nine patients with primary chronic osteomyelitis of the mandible presented with SAPHO syndrome also supports the hypothesis of an associated disease process. The association of SAPHO syndrome and DSO, and especially with PCO (8 of 9), is noteworthy and appears to support the hypothesis of a common pathologic mechanism.

The great majority of patients with osteomyelitis present abnormal parameters in the immune system (15). The literature expresses contradictory opinions, including a hyperactive, a hypoactive, a cellular exaggerated response or a total impairment of the immune system (15). Complement components were decreased in two of our patients and elevated in one patient. The serum concentrations of IgA, IgM and IgG were elevated in five patients with PCO. A dysimmunoglobulinemia was observed in eight patients with PCO (including changes in relative distribution of subclasses in seven patients). Immunoelectrophoresis failed to reveal increased levels of monoclonal antibodies. MALMSTRÖM *et al.* (15) reported increased concentration levels of IgG, IgA, IgM or IgE in 11 of 15 patients.

The aetiology of SAPHO syndrome and PCO is unknown. One hypothesis advocates an organism of low virulence as a trigger. *Propionibacterium acnes* has been found as the only infectious agent in osteoarticular lesions (12). Beside *Propionibacterium acnes* (16), species of *Actinomyces* and *Eikinella corrodens* have been detected from a large number of biopsy specimens in a prospective study by MARX *et al.* (17). Our series yielded *Actinomyces* species in two of seven cultures. Elevated anticardiolipin levels (5 of 9 tested patients with PCO) support this hypothesis, as they represent immunological stimulation. For example, the antiphospholipid syndrome is associated with vascular thrombosis, skin lesions and persistently elevated levels of antiphospholipid antibodies (18). Anticardiolipin is also suspected to interfere in the arachidonic acid cycle. This might result in decreased prostacyclin production and favour increased platelet adhesiveness and vascular thrombosis (18). PLOTQUIN *et al.* demonstrated elevated PGE (prostaglandin) levels, although PGF (prostacyclin) showed similar quantities in osteomyelitic bone when compared with normal human bone

(19). Medullary vascular thrombosis and vasculopathy (20) have often been mentioned as potential causative factors of mandibular osteomyelitis. BARTKOWSKI *et al.* (21) reported successful treatment of mandibular osteomyelitis with intravenous heparin therapy. However, symptoms only occur in some of the patients with positive anticardiolipin levels; therefore, antibodies may just be markers of the disorder. In contradiction, the offending organism has not been demonstrated in most cases (negative cultures in two of seven specimens). The fact that anticardiolipin antibodies have also been implicated in the development of osteonecrosis, which is often a sclerotic disease in extragnathic bones, and that anticoagulants are able to reduce pain in patients with osteonecrosis, may support the ischemic rather than the infectious character of the disease (22–24). It has to be borne in mind, however, that negative cultures might result from inadequate culturing techniques (17). Genetic factors also have been suspected to play a role in the pathologic scenario (12). In fact, the two sisters (cases 3 and 10), who were evaluated for HLA-typing, revealed common gene loci (A-1, B-8, DR-3; subject of a separate case report). Their haplotype is typically found in autoimmune diseases such as lupus erythematosus and other connective tissue diseases. A higher frequency of the A2 allele [seven of nine patients (78%) with PCO] compared to similar European ethnic groups (21.3% up to 27.8%) was found in our series (25). The fact that antibiotic medication, NSAIDs and corticosteroids can partially alleviate symptoms could be due to the suppression of symptoms but may also support our hypothesis of a microorganism of low virulence. Antibiotic medication may lead to transient partial eradication of the causative microorganism, but cannot prevent recurrence of symptoms. NSAIDs and corticosteroids block the inflammatory cascade on different mediatory levels.

One patient (case 11) of our series, who had a typical myofacial pain syndrome, represents the view that advanced the hypothesis of tendoperiositis (1, 3). Sclerosis in this patient was limited to the mandibular alveolar bone and in addition the patient lacked typical symptoms of acute exacerbations, such as swelling, lymphadenopathy, and typical periodicity. Patients with chronic pain syndromes, such as DSO, often develop secondary myofacial pain. Therefore, treatment with dental splints and myofeedback training may lead to partial relief but can not cure the disease (cases 2, 4 and 7). We agree with MARX (26), who stated that it would seem unlikely to be successful in the face of sclerosis being intramedullary rather than periosteal, and the fact that it occurs in edentulous patients. Also, it would not account for the partial effectiveness of periods of antibiotic medication.

Juvenile chronic osteomyelitis (JCO) may be considered as a rare type of primary chronic osteomyelitis (PCO) and it has also been designated as Garrè's osteomyelitis. Data for case number 6 clearly showed differences in laboratory results, scintigraphic and radiographic findings, while clinical symptoms were almost similar to primary chronic osteomyelitis. We favour the term juvenile chronic osteomyelitis because Garrè did not describe a singular, specific type of osteomyelitis; moreover, he presented 12 different conditions of osteomyelitis in his historical article (27). Hence, we consider JCO as a specific type of PCO, which in later stages may present the typical bony picture of PCO and possibly show development towards SAPHO syndrome.

Open biopsy of the mandibular bone and computed tomography are necessary to establish a precise diagnosis of mandibular osteomyelitis. MARX *et al.* (17) reported consistent microbiologic findings. However, an extraoral approach should be avoided, because possible nerve palsy and scar formation are serious disadvantages, while intraoral biopsies often present contamination. Oral contamination can be excluded when a piece of bone is removed intraorally if an extraoral sterile biopsy (taken by a trepan-bur) is also taken. Only the tip of the cylinder is sent for culturing. Our study incorporated the demands given by MARX (26) for culturing techniques; however, results were inconsistent. Serologic testing revealed parvovirus B19 to be the most frequent infectious viral agent, but positive results may be found in 30–60% of adults (28). Parvovirus B19 infection has been mentioned in association with rheumatic diseases, spherocytosis and bone marrow aplasia (29). MARX (26) also demands PCR-DNA, but preliminary data on four patients in this series still show contradictory results (2 patients with signal overloading, 2 patients with negative results). Tc-scintigraphy is a useful tool for detecting clinically and radiologically silent lesions, especially in extramandibular locations (12).

Because diffuse sclerosing mandibular osteomyelitis responds to treatment inconsistently (30), all treatment options should be applied. Especially in the early stage of the disease, operative procedures such as removal of all necrotic tissue and decortication are usually successful. In addition, hyperbaric oxygen (twice daily sessions at 1.4 atmospheres for 45-min cycles), with at least 20 cycles and long-term antibiotic medication, should always be performed as well. The four patients treated with long-term antibiotic medication showed a decreased frequency of mild symptoms while on medication. Because involvement of reconstructed bone is frequent, resection and second stage reconstruction should be considered carefully in late disease stages. In long-standing refractory chronic osteomyelitis, patients with multiple unsuccessful operative interventions and compromised elderly patients, conservative therapy with NSAIDs or steroids is recommended. Synovitis is most often mild and only rarely destructive. Treatment includes NSAIDs at sufficient dosage levels and, in refractory cases, administration of sulfusalazine. Persistent cases may require administration of methotrexate.

In conclusion, we strongly advocate an association between DSO and SAPHO syndrome. With reference to results from our study and the current literature, we suggest a hypothesis of a microorganism of low virulence functioning as a trigger that causes an exaggerated immune response in genetically predisposed individuals.

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Printed in Denmark by P.J.Schmidt A/S, Vojens

J Oral Pathol Med 1999; 28: 456–64
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JOURNAL OF
Oral Pathology&Medicine
ISSN 0904-2512

Primary chronic osteomyelitis associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome)

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Eyrich GKH, Harder C, Sailer HF, Langenegger T, Bruder E, Michel BA: Primary chronic osteomyelitis associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome). J Oral Pathol Med 1999; 28: 456–64.
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Diffuse sclerosing osteomyelitis may indicate the mandibular localisation of the SAPHO syndrome. Twelve patients with diffuse sclerosis of the mandible were examined for symptoms of the SAPHO syndrome. Nine patients were found to have primary chronic osteomyelitis and eight of these represented a SAPHO syndrome. Results in this series support the hypothesis of an association between primary chronic osteomyelitis and the SAPHO syndrome.

Key words: mandibular osteomyelitis; SAPHO syndrome

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Accepted for publication July 3, 1999

Osteomyelitis of the mandible is defined as an inflammation of the mandibular cortical and cancellous bone. Acute osteomyelitis is commonly caused by bacterial invasion from a contagious focus. Most frequent sources are odontogenic foci, periodontal diseases and pulpal infection, extraction wounds or infected fractures. Osteomyelitis may also appear as a nonsuppurative chronic inflammation of unknown aetiology. A small number of cases of mandibular chronic osteomyelitis are granulomatous osteomyelitis, which is related to tuberculosis or tertiary syphilis.

The literature related to chronic osteomyelitis is confusing. Different disease processes have been designated under one term in some instances, whereas several terms have been designated to lesions that represent the same entity in other instances (1). The variety of classification systems takes into account multiple characteristics such as physiology, pathogenesis, localisation, radiological or clinical appearance and clinical course. The radiological appearance of chronic osteomyelitis may be sclerotic, radiolucent or mixed. Diffuse sclerosing osteomyelitis (DSO) has been chosen to describe the radiologic appearance of the process (Fig. 1). The arbitrary time limit of 1 month is used to separate acute from chronic osteomyelitis (2). The term DSO includes similar entities such as primary chronic osteomyelitis (PCO), chronic tendoperiostitis (1, 3), secondary chronic osteomyelitis and juvenile chronic osteomyelitis (JCO, Garrè's osteomyelitis).

The term primary chronic osteomyelitis (PCO) describes a long-standing, radiologically diffuse sclerosing disease process of unknown aetiology, which involves the cancellous bone. The characteristic morphological findings consist of an extensive periosteal reaction and cortical thickening (Fig. 2), massive thickening of trabeculae, and marrow fibrosis in cancellous bone (Fig. 3). Inflammatory infiltrate is scarce, though foci of dense aggregates of plasma cells (Fig. 4) may be observed occasionally. The absence of pus, fistulae or sequestration is characteristic. The course of the disease lacks an acute state and is therefore considered primarily to be chronic. Periods of onset may last from 3 days to several weeks. The patient usually presents with a limitation of mouth opening, swelling of the cheek, lymphadenopathy and severe pain.

Juvenile chronic osteomyelitis (Garrè's osteomyelitis) usually peaks in puberty and is characterised by voluminous expansion of the mandibular body, periosteal apposition of bone and a mixed sclerosing-lytic appearance of the cancellous bone. The clinical picture resembles PCO, sharing the lack of pus formation, fistulae or sequestration. Therefore, JCO may be considered as a subtype of PCO.

Patients with tendoperiostitis (TP) usually present with a history of parafunctional complaints. Palpation of the temporal, masseter, medial pterygoid, and the digastric muscles reveals tenderness in one or more muscles (4). Radiographically, diffuse sclerosis of the cortical plate and marrow is observed. Pus formation and sequestration are absent.

Secondary chronic osteomyelitis develops from an acute bacterial invasion of the bone with formation of fistulae and possible sequestration. Clinically and radiographically, a broad spectrum ranging from an aggressive osteolytic putrefactive phase to a dry osteosclerotic phase may be observed.

Florid osseous dysplasia (FOD) is radiographically described as sclerosing opaque and dense masses. The bone changes are often adjacent to the apices of the roots of the teeth. Signs of in-

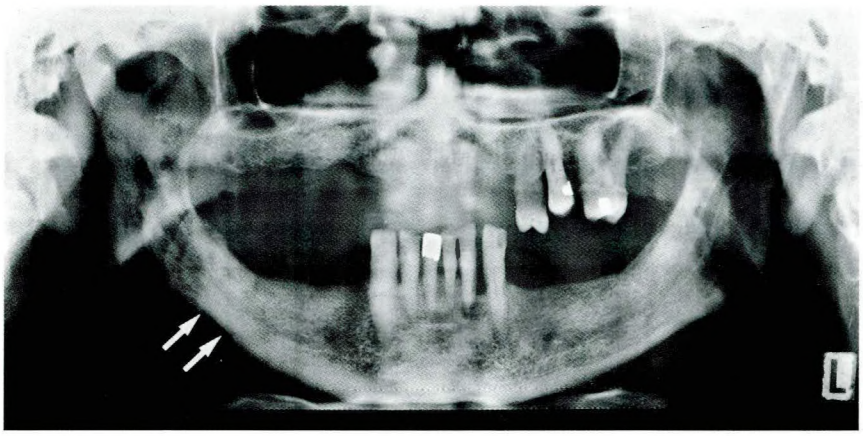


Fig. 1. An orthopantomogram showing typical sclerosis (arrows) involving cortical and cancellous bone of the right mandibular body (patient 9). The mandibular left second incisor shows a periapical radiolucency and interdental vertical loss of bone due to periodontal infection.

flammation may be present. Some cases of FOD occur in two phases. In the first phase, asymptomatic sclerotic masses develop. In the second phase, inflammation is superimposed (5). It may be very difficult to distinguish FOD from periapical cemental dysplasia (PCD), though the clinical course of FOD shows limited growth potential compared to PCD and does not produce pain. However, bony sclerosis may extend from a localised periapical process to a regional lesion. While there may be histological similarity between the two lesions, they are distinct clinical entities and do not usually become more widespread. PCD most commonly occurs in middle-aged women and is localised to the anterior mandibular teeth. The affected teeth always respond positively to vitality tests. This lesion presents with three typical distinct stages: osteolytic stage, cementoblastic stage and inactive stage (6).

An enostosis or compact island of bone can also be observed as an opaque dense sclerotic area. This may derive from an inflammatory processes following trauma (7). An enostosis or bony island may also result from focal ischemia or infarction (e.g., sickle cell disease) (8).

In 1986, CHAMOT *et al.* (9) described a syndrome associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome). Usually the medical history or examination reveals palmoplantar pustulosis (Fig. 5), pustular or plain psoriasis, and acne or hidradenitis suppurativa. Radiological and scintigraphic findings identify the



Fig. 2. Photomicrograph of patient 5 illustrating cortical sclerosis and massive periosteal reaction typical of primary chronic mandibular osteomyelitis. (H&E, ×15)

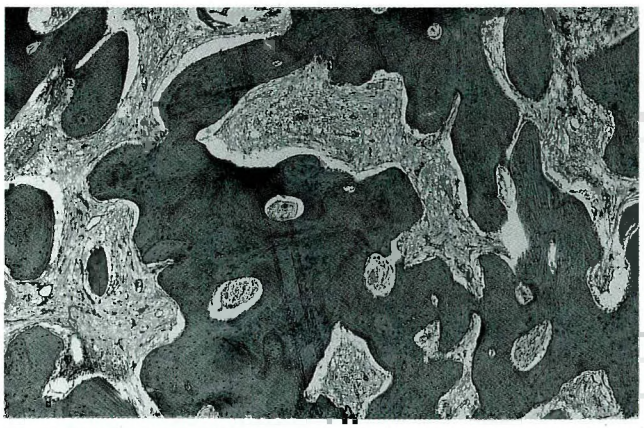


Fig. 3. Photomicrograph of cancellous bone showing massive thickening of trabeculae and marrow fibrosis (patient 2). (H&E, ×32)

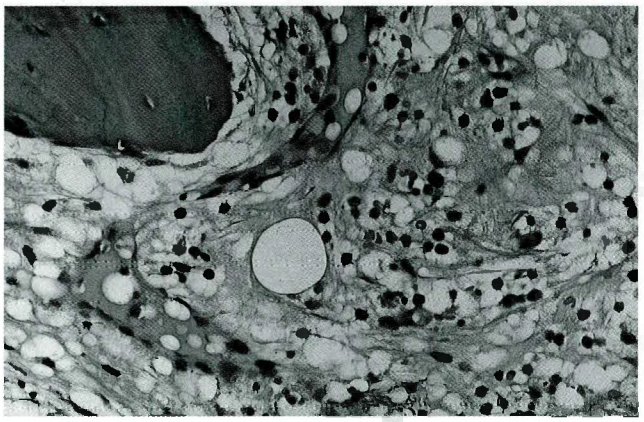


Fig. 4. Photomicrograph of bone from patient 2 showing an inflammatory infiltrate with some denser aggregates of plasma cells. (H&E, ×250)



Fig. 5. Typical plantar pustulosis (patient 9).

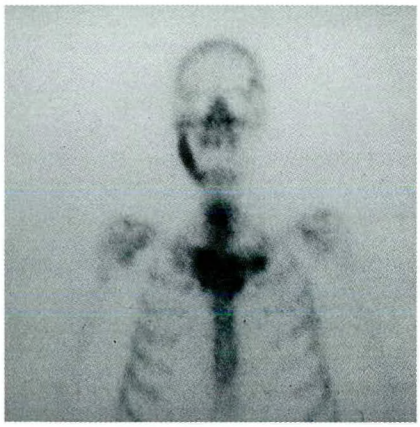


Fig. 6. Scintigraphic imaging demonstrating a significant enhancement of the right mandibular body and the chest wall (patient 9).

anterior chest wall (especially the sternoclavicular joint) as the most prevalent location for the hyperostosis (Fig. 6). Joint involvement may also be noted. In addition to reports from other authors (10, 11), KAHN *et al.* (12) have presented the largest series of 7 patients with mandibular involvement out of 85 cases of SAPHO syndrome. It has been finally concluded that diffuse sclerosing osteomyelitis may represent the mandibular localisation of SAPHO syndrome (12).

In a prospective cohort evaluation, patients with diffuse sclerosing osteomyelitis (DSO) were examined for the type of mandibular chronic sclerosing osteomyelitis and for SAPHO syndrome.

Material and methods

Within a period of 1 year all patients with diffuse sclerosing osteomyelitis (DSO) of the mandible and clinical signs of an acute inflammation (edema of the cheek, limitation of mouth opening, tenderness to palpation and severe pain) were prospectively assessed for concise diagnosis of their mandibular osteomyelitis. The diagnosis of DSO was based on clinical and radiographical findings. If available, medical history, clinical examination, computed tomography of the mandible, skeletal scintigraphy and biopsy specimens were included.

Subsequently, all patients with DSO were examined for symptoms of SAPHO syndrome. Routine immunological and haematological tests were performed with standard methods. Laboratory testing included complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, protein- and immuno-electrophoresis including IgG-subclasses, complement factors, immune complexes, rheumatoid factors, antinuclear antibodies, anti-DNA antibodies, C-(PR3)-ANCA, cardiolipin antibodies, routine chemistry and serological testing for antibodies against rubella, adenoviruses, Coxsackie-B virus, Epstein–Barr virus (EBV), herpes viruses, salivary gland tissue, parvovirus B19, picornavirus, hepatitis viruses B/C, cytomegalovirus, *Chlamydia, Borrelia burgdorferi, Brucella, Campylobacter, Salmonella, Yersinia, Shigella, Treponema pallidum, Neisseria gonorrhoeae* and *Mycoplasma pneumoniae.*

Medical records from the time of the patient's first visit were reviewed. In addition to MDP ^{99m}technetium bone scan (locating increased bone vascularity or osteoblastic activity) and routine radiographs of suspected bone lesions, computed tomography was performed on some patients. The diagnosis of SAPHO syndrome was accepted if the patient met the criteria, such as acute, subacute, chronic arthritis or any extramandibular osteitis, osteomyelitis with scintigraphic enhancement (especially of the sternoclavicular joint and the anterior chest wall), and skin lesions (palmoplantar pustulosis, pustular psoriasis, psoriasis vulgaris, severe acne).

Results

All 12 patients satisfied the selection basis for DSO. However, only nine patients (patients 2–10) met the diagnostic criteria for PCO. All patients were treated at the Department of Maxillofacial Surgery, University Hospital, Zurich and were referred for complete rheumatologic evaluation to the Department of Rheumatology, University Hospital, Zurich. The mean age of the patients was 47.5 years, with a range from 14 to 67 years. There were four men (33%) and eight women (67%). Follow-up periods from disease onset ranged from 3 to 30 years (Table 1).

Case 2

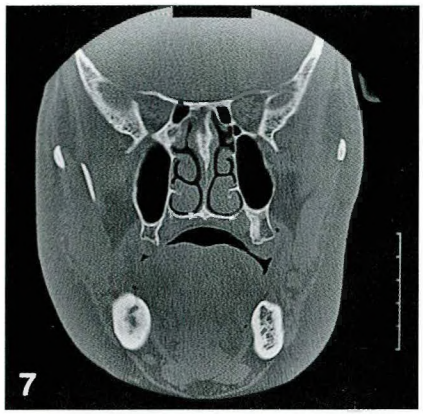
A 41-year-old woman with primary chronic sclerosing osteomyelitis and SAPHO syndrome was referred. The first symptoms of osteomyelitis were detected 20 years ago. After repeated decortication, she received hyperbaric oxygen therapy, a resection of the vertical ramus and reconstruction with a costal graft. Mild acne was observed in puberty. Physical examination revealed no pustulosis. Control CT scans revealed involvement of the transplanted graft. The patient presented with sternoclavicular hyperostosis showing slight scintigraphic enhancement and tenderness to palpation. Antibiotics were effective while on medication. Nonsteroidal anti-inflammatory drugs (NSAIDs) provided partial relief with reduction of pain and swelling during acute exacerbations.

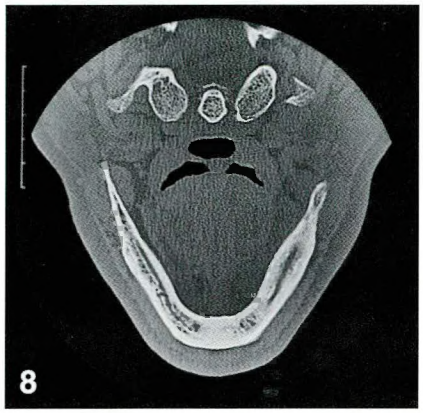
Case 3

A 33-year-old woman, the sister of case 10, had enostosis in the molar region, periapical cemental dysplasia (PCD) with vital teeth in the symphysial region of the mandible, palmoplantar pustulosis, humeral sclerosing osteomyelitis and sternoclavicular hyperostosis; she was re-examined. The patient had undergone 16 operative procedures of the humerus including biopsies, decortications, debridements and insertions

Table 1. Demographic data and diagnoses of all patients (including all 12 patients with DSO)

Case number	Sex	Age at examination (yr)	Duration in years (osteomyelitis)	SAPHO syndrome	Type of mandibular sclerosis
1	F	43	3	No	SCO
2	F	41	21	Yes	PCO
3	F	33	21	Yes	Enostosis and PCD of the mandible; PCO of the humerus
4	F	59	6	Yes	PCO
5	F	39	30	Yes	PCO
6	M	14	3	No	PCO (JCO)
7	F	50	7	Yes	PCO
8	M	64	8	Yes	PCO
9	M	69	4	Yes	PCO
10	F	38	24	Yes	PCO
11	M	57	3	No	TP
12	M	63	3	No	SCO





Figs. 7 & 8. Coronal and axial CT-scans of the mandibular molar region showing sclerotic changes (patient 9).

of gentamycin beads. Mild acne was observed during adolescence. Scintigraphy showed increased uptake in the humerus and the sternoclavicular joints. Occlusal splint therapy led to partial relief. Long-term medication with antibiotics did not cure the disease, but provided partial relief of symptoms while on medication. NSAID led to partial relief.

Case 4

A 59-year-old woman had primary chronic sclerosing osteomyelitis of the mandible and SAPHO syndrome. The orofacial complaints of the patient were suspected to be a myofacial pain syndrome caused by insufficient jaw positioning of the edentulous mandible. The history revealed that one year before splinting and myofeedback therapy, the endodontically treated lower canines had been removed. The patient presented with a palmoplantar psoriasis and a unilateral prominent sternoclavicular joint as well as synovitis of the first metacarpophalangeal joint of both hands. The medical history revealed no periods of pustulosis. Scintigraphic enhancement was found in the mandible, sternoclavicular joints and in both wrists. A revision and decortication of the mandibular lesion along with hyperbaric oxygen therapy were applied. Antibiotics were effective while on medication. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 5

A 39-year-old woman was diagnosed with primary chronic sclerosing osteomyelitis of the mandible since childhood and SAPHO syndrome. Decortication, bimaxillary osteotomies (for secondary asymmetry) and hyperbaric oxygen therapy were performed over the 30-year duration of the disease. Acne had been present in adolescence. Clinical examination revealed a palmar pustulosis and synovitis of both elbows. Both sternoclavicular joints were clinically prominent and showed scintigraphic enhancement. Antibiotics were effective. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 6

A 14-year-old boy had juvenile primary mixed sclerosing-lytic osteomyelitis of the mandible. Before referring the patient to the maxillofacial department, the suspected differential diagnosis included juvenile parotitis, fibrous dysplasia and osteosarcoma. Mild acne was observed. Scintigraphically, slight enhancement of both sternoclavicular joints was noted. Microbiologic cultures revealed *Streptococcus sanguis, Veilonellae* and *Actinomyces* species. A transient C4-deficiency was documented after surgical decortication. After long-term antibiotic medication, laboratory testing showed normal C3 and C4 levels. Repeated decortications along with hyperbaric oxygen therapy were performed. Antibiotics were effective while on medication. NSAIDs were ineffective. Since antibiotic medication was aborted, 9 months ago, no more symptoms have been noted. Finally, CT-scans demonstrated complete recovery with restoration of the bony structure.

Case 7

A 50-year-old woman was diagnosed with primary chronic osteomyelitis and SAPHO syndrome. Her orofacial complaints were initially suspected to indicate a myofacial pain syndrome. After 1 year of treatment, pain relief could not be achieved and the third molar was considered as a causative factor. After tooth extraction, her symptoms increased. On physical examination, the patient presented with sternoclavicular hyperostosis, polysynovitis and palmoplantar pustulosis as well as sacroileitis. Decortication along with hyperbaric oxygen therapy was performed. NSAIDs were effective.

Case 8

A 64-year-old man had mandibular primary chronic sclerosing osteomyelitis and SAPHO syndrome. The history revealed plantar pustulosis, especially during summer, and acne lesions in adolescence. Clinical and scintigraphic ex-

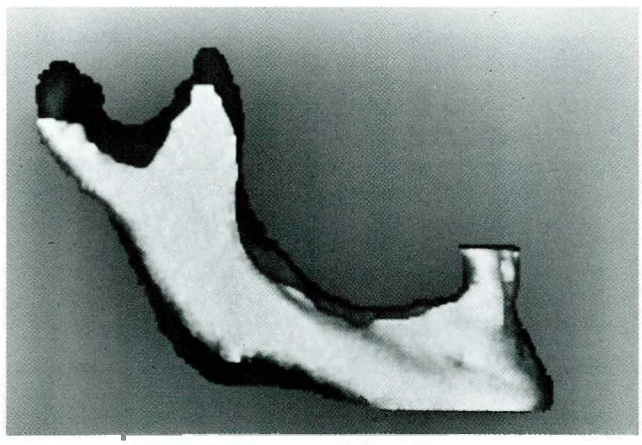


Fig. 9. The lateral aspect of the 3-D (with the software package Gyroview®, ISG Technologies, Toronto, Canada) reconstructed mandible showing deformation of the right mandibular body and condyle (patient 9).



Fig. 10. Coronal CT-scans of the temporomandibular joint revealing osteolytic and cystic destruction of the right condylar head (patient 9).

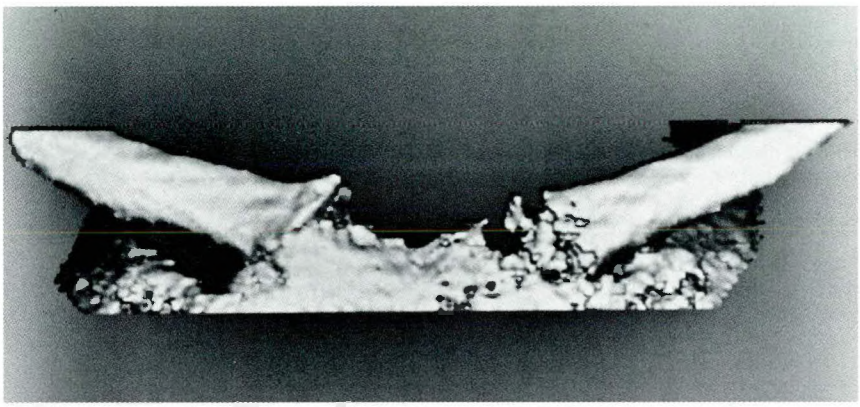


Fig. 11. 3-D CT reconstruction (with the software package Gyroview®, ISG Technologies, Toronto, Canada) of the sternoclavicular joints showing massive destruction of bone on the left and hyperostosis on the right side (patient 9).

amination showed prominent sternoclavicular joints with signs of inflammation. Hyperbaric oxygen therapy was performed. Antibiotics were effective while on medication. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 9

A 69-year-old man with mandibular primary chronic sclerosing osteomyelitis (Figs. 1 & 7–10) of the mandible and SAPHO syndrome was examined. Acne and pustulosis could be observed (Fig. 5). In addition, the patient had hyperostosis on one side and destruction of the sternoclavicular joint (Figs. 11 & 12) on the other side, with impressive scintigraphic enhancement (Fig. 6). Hyperbaric oxygen therapy was performed. Antibiotics were effective while on medication. NSAIDs provided partial relief with reduction of pain and swelling during acute exacerbations.

Case 10

A 38-year-old woman, sister of case 3, was examined with mandibular primary chronic sclerosing osteomyelitis and SAPHO syndrome. After repeated revisions, decortications and hyperbaric oxygen therapy, a resection of the ramus and reconstruction with a costal graft were performed. Unfortunately, the disease process recurred in the transplant. The patient had palmoplantar pustulosis and tender sternoclavicular hyperostosis. Scintigraphy clearly showed enhanced uptake in the mandible and slight elevation in the sternoclavicular joint, as well as in the left sacroiliac joint. Antibiotics were ineffective. In spite of good initial response, NSAIDs became ineffective, while glucocorticoids produced immediate relief.

The following text and Tables 1–4 summarise the results of patients 2 to 10 with PCO.

Eight of nine (88.9 %) patients with primary chronic osteomyelitis demonstrated the SAPHO syndrome. The total of 12 patients also included two patients with secondary chronic osteomyelitis and one patient with tendoperiostitis. The duration (before and after diagnosis) since first onset of mandibular osteomyelitis ranged between 3 and 30 years. The patients' ages at examination were between 33 and 69 years, with the exception of patient number 6. Eight of the nine patients with PCO presented with, or reported a history of, skin lesions. In eight of the nine patients with PCO, extra-mandibular scintigraphic enhancement was detected. Surgical intervention was performed in seven patients with PCO and eight patients underwent hyperbaric oxygen therapy. Six patients responded to antibiotic medication.

Table 4 shows laboratory test results for C-reactive protein, ESR (erythro-

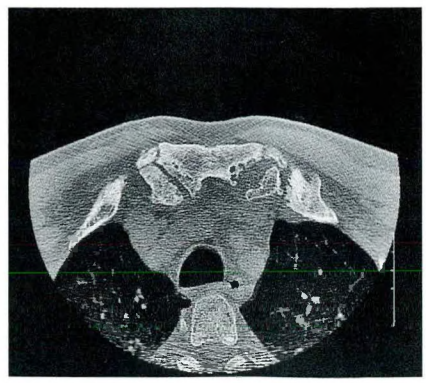


Fig. 12. Axial CT-scan of the chest wall and the sternoclavicular joints are characterised by cystic-osteolytic destructive lesions (patient 9).

Table 2. Diagnostic procedures and results (9 patients with PCO)

Number	SAPHO syndrome	Type of mandibular sclerosis	Skin lesion	CT-scan of the mandible	Scintigraphic enhancement	Biopsy of the mandibular lesion	Microbiology
2	Yes	PCO	Acne (historical)	Yes	Mandible; sternoclavicular	Yes	*Streptococcus; Staphylococcus*
3	Yes	Enostosis and PCD of the mandible; PCO of the humerus	Pustular psoriasis (at examination)	Yes	Mandible; sternoclavicular; humerus	Yes	Coagulase-negative *Staphylococcus*
4	Yes	PCO	No	Yes	Mandible; sternoclavicular	Yes	No
5	Yes	PCO	Pustulosis (at examination); acne (historical)	Yes	Mandible; sternoclavicular; elbows	Yes	Negative
6	No	PCO (JCO)	Acne (at examination)	Yes	Mandible	Yes	*Actinomyces* and *Veilonella* species
7	Yes	PCO	Pustulosis (at examination)	Yes	Mandible; sternoclavicular; sacroiliac	Yes	Negative
8	Yes	PCO	Pustulosis; acne (historical)	Yes	Mandible; sternoclavicular	Yes	*Streptococcus*
9	Yes	PCO	Pustulosis (at examination)	Yes	Mandible; sternoclavicular	No	No
10	Yes	PCO	Pustulosis (at examination)	Yes	Mandible; sternoclavicular; sacroiliac	Yes	*Haemophilus Parainfluenzae; Streptococcus; Actinomyces* and *Veilonella* species

Table 3. Treatment procedures and medications (9 patients with PCO)

Case number	SAPHO syndrome	Type of mandibular sclerosis	Operative treatment	Hyperbaric oxygen therapy (sessions)	Antibiotic effectiveness	NSAIDs effectiveness	Corticoids effectiveness
2	Yes	PCO	Resection (angle, vertical ramus) and reconstruction (costalgraft)	20	Partial: doxicycline clindamycin metronidazole and amoxicillin long-term 6 months	Partial	Not applied
3	Yes	Enostosis and PCD of the mandible PCO of the humerus	Repeated revisions, insertions of gentamycin beads, decortications and biopsies of the humerus	Not applied	Partial: clindamycin rifampicin and ciprofloxacin long-term 27 months	Partial	Not applied
4	Yes	PCO	No	20	Yes: clindamycin	Partial	Not applied
5	Yes	PCO	Decortication; bimaxillary osteotomy	20	Yes: doxicycline clindamycin	Partial	Not applied
6	No	PCO (JCO)	Decortication	60	Yes: metronidazole amoxicillin clarithromycin long-term 24 months	No	Not applied
7	Yes	PCO	Decortication	24	Yes: amoxicillin	Yes	Not applied
8	Yes	PCO	Decortication	60	Yes: doxicycline	Partial	Not applied
9	Yes	PCO	No	30	Yes: clindamycin	Partial	Not applied
10	Yes	PCO	Decortication; resection (angle, vertical ramus) and reconstruction (costalgraft)	124	No: doxicycline metronidazole and amoxicillin long-term 7 months	No	Yes

cyte sedimentation rate) and leucocyte counts as a sensitive indicator of inflammatory processes, such as acute bone inflammation; these were mainly within normal limits. Complement components were decreased in two patients and elevated in one patient. The serum concentrations of IgA, IgM and IgG were elevated in five patients. A dysimmunoglobulinemia was observed in eight patients (including changes in relative distribution of subclasses in seven patients).

Elevated anticardiolipin levels were found in five of nine patients and elevated levels of antinuclear antibodies in eight of nine patients. The frequency of the A2-allele was 78% (7 of 9) in patients with PCO. Serologic testing revealed parvovirus B19 to be the most frequent infectious viral agent (67%, 6 of 9).

Discussion

The term diffuse sclerosing osteomyelitis has been used collectively for different entities and disease stages (1). PCO and SCO, as well as JCO (Garrè), may present as diffuse sclerosing osteo-

Table 4. Laboratory test results (9 patients with PCO)

Patient	2	3	4	5	6	7	8	9	10
ESR	15	36	6	4	6	10	26	13	8
CRP	<3	3	<3	<3	<3	<3	5	18	<3
Leukocytes	3.4	6.2	8.5	10.7	4.8	5.4	7.2	8.9	7.12
Differential white cell count	ly↓	Normal	Normal	Normal	Normal	ly↑	Normal	Normal	Normal
Haemoglobin	11.2	12.8	13.6	13.3	14.6	12.5	12.5	14.4	12.7
Rheumafactors	Negative	Negative	Negative	SP 1:160	Negative	Negative	Negative	Negative	Negative
Dysimmuno-globulinemia	+ IgG↑	+ IgA↑ IgG↑	+	+	Normal	+	+ IgA↑	+ IgA↑ IgE↑	+ IgG↑
IgG-subclasses	SC 1↓ SC 2↑	SC 2↑	SC 1↑ SC 2↓ SC 4↓	SC 1↑ SC 4↑	Normal	SC 4↑	Normal	SC 1↑ SC 2↓	SC 1↓ SC 2↑
Immune complex	Normal	C1q↑ IgG↑	Normal	Normal	Normal	Normal	Normal	C1q↑	Normal
Complement C3	C3↓	Normal	Normal	Normal	C3↓↓	Normal	Normal	Normal	Normal
Complement C4	C4↓	Normal	Normal		Normal	Normal	Normal	Normal	C4↑
Serology	Negative	Parvo B19 IgG	Parvo B19 IgG	Negative	Parvo B19 IgG	Varicella IgG Cytomegalo IgG	Parvo B19 IgG	Parvo B19 IgG	Parvo B19 IgG
Liver enzymes	Normal	Normal	Normal	Normal	Normal	Normal	yGT 84	Normal	Normal
Creatinine	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Glucose	Normal	Normal	Normal	Normal	Normal	7.2	Normal	Normal	Normal
Antinuclear antibodies	Antinuclear 1:80	Antinuclear 1:40	Antinuclear 1:10	Antinuclear 1:80	Normal	Antinuclear 1:40	Antinuclear 1:80	Antinuclear 1:80	Antinuclear 1:160
Anticardiolipin antibodies	Normal	IgG↑	IgG↑	Normal	Normal	Normal	IgG↑ IgA↑	IgG↑	IgM↑
HLA-typing	A24(9), A31(19), B35, B55 (22) DR1 0101–0102/ DRB 0801–0805	A1, A2, B8,B61 (40), DRB1 1601–1601, DRB1 0301	A1, A2, B8, B60 (40) DRB1 1501–1503/DRB 0101–0202 second DRB1 typing failure	A2, Ax, B7, B39 (16) first and second DRB1 typing failure	A2, A68(28), B7, B35, DRB1 0401–04012/ DRB1 0101 DRB1 0701–0702/ DRB1 0101	A26 (10), Ax, B52 (5), B58 (17), DRB1 1501–1503/ DRB5 0101–0202 DRB! 1302/ DRB3 0101–0301	A2, A43, B60 (40), B45 (12), DRB1 0301/ DRB3 0101–0301 DRB1 0901/ DRB3 0101	A2, A26 (10), B44 (12), B58 (17), DRB1 0701–0702/ DRB4 0101, DRB1x	A1, A2, B8,B62 (15), DRB 1301–1306, DRB1 0301

myelitis. Bony sclerosis is a non-specific reaction to any chronic inflammatory process. Clinical course, diagnostic findings and therapeutic response suggest different entities. Moreover, common presentation under the designation DSO complicates evaluation of data.

KAHN *et al.* (12) and SUEI *et al.* (13) offered evidence that suggested DSO to be the mandibular localisation of SAPHO syndrome. In fact, DSO with extramandibular involvement and skin lesions had been described earlier (14). In contradiction to the patient described by FARNAM *et al.* (14), primary chronic osteomyelitis presents a non-putrefactive course. It remains unclear whether SAPHO syndrome might be the predisposing factor for primary chronic osteomyelitis, but the fact that eight of nine patients with primary chronic osteomyelitis of the mandible presented with SAPHO syndrome also supports the hypothesis of an associated disease process. The association of SAPHO syndrome and DSO, and especially with PCO (8 of 9), is noteworthy and appears to support the hypothesis of a common pathologic mechanism.

The great majority of patients with osteomyelitis present abnormal parameters in the immune system (15). The literature expresses contradictory opinions, including a hyperactive, a hypoactive, a cellular exaggerated response or a total impairment of the immune system (15). Complement components were decreased in two of our patients and elevated in one patient. The serum concentrations of IgA, IgM and IgG were elevated in five patients with PCO. A dysimmunoglobulinemia was observed in eight patients with PCO (including changes in relative distribution of subclasses in seven patients). Immunoelectrophoresis failed to reveal increased levels of monoclonal antibodies. MALMSTRÖM *et al.* (15) reported increased concentration levels of IgG, IgA, IgM or IgE in 11 of 15 patients.

The aetiology of SAPHO syndrome and PCO is unknown. One hypothesis advocates an organism of low virulence as a trigger. *Propionibacterium acnes* has been found as the only infectious agent in osteoarticular lesions (12). Beside *Propionibacterium acnes* (16), species of *Actinomyces* and *Eikinella corrodens* have been detected from a large number of biopsy specimens in a prospective study by MARX *et al.* (17). Our series yielded *Actinomyces* species in two of seven cultures. Elevated anticardiolipin levels (5 of 9 tested patients with PCO) support this hypothesis, as they represent immunological stimulation. For example, the antiphospholipid syndrome is associated with vascular thrombosis, skin lesions and persistently elevated levels of antiphospholipid antibodies (18). Anticardiolipin is also suspected to interfere in the arachidonic acid cycle. This might result in decreased prostacyclin production and favour increased platelet adhesiveness and vascular thrombosis (18). PLOTQUIN *et al.* demonstrated elevated PGE (prostaglandin) levels, although PGF (prostacyclin) showed similar quantities in osteomyelitic bone when compared with normal human bone

(19). Medullary vascular thrombosis and vasculopathy (20) have often been mentioned as potential causative factors of mandibular osteomyelitis. BARTKOWSKI *et al.* (21) reported successful treatment of mandibular osteomyelitis with intravenous heparin therapy. However, symptoms only occur in some of the patients with positive anticardiolipin levels; therefore, antibodies may just be markers of the disorder. In contradiction, the offending organism has not been demonstrated in most cases (negative cultures in two of seven specimens). The fact that anticardiolipin antibodies have also been implicated in the development of osteonecrosis, which is often a sclerotic disease in extragnathic bones, and that anticoagulants are able to reduce pain in patients with osteonecrosis, may support the ischemic rather than the infectious character of the disease (22–24). It has to be borne in mind, however, that negative cultures might result from inadequate culturing techniques (17). Genetic factors also have been suspected to play a role in the pathologic scenario (12). In fact, the two sisters (cases 3 and 10), who were evaluated for HLA-typing, revealed common gene loci (A-1, B-8, DR-3; subject of a separate case report). Their haplotype is typically found in autoimmune diseases such as lupus erythematosus and other connective tissue diseases. A higher frequency of the A2 allele [seven of nine patients (78%) with PCO] compared to similar European ethnic groups (21.3% up to 27.8%) was found in our series (25). The fact that antibiotic medication, NSAIDs and corticosteroids can partially alleviate symptoms could be due to the suppression of symptoms but may also support our hypothesis of a microorganism of low virulence. Antibiotic medication may lead to transient partial eradication of the causative microorganism, but cannot prevent recurrence of symptoms. NSAIDs and corticosteroids block the inflammatory cascade on different mediatory levels.

One patient (case 11) of our series, who had a typical myofacial pain syndrome, represents the view that advanced the hypothesis of tendoperiositis (1, 3). Sclerosis in this patient was limited to the mandibular alveolar bone and in addition the patient lacked typical symptoms of acute exacerbations, such as swelling, lymphadenopathy, and typical periodicity. Patients with chronic pain syndromes, such as DSO, often develop secondary myofacial pain. Therefore, treatment with dental splints and myofeedback training may lead to partial relief but can not cure the disease (cases 2, 4 and 7). We agree with MARX (26), who stated that it would seem unlikely to be successful in the face of sclerosis being intramedullary rather than periosteal, and the fact that it occurs in edentulous patients. Also, it would not account for the partial effectiveness of periods of antibiotic medication.

Juvenile chronic osteomyelitis (JCO) may be considered as a rare type of primary chronic osteomyelitis (PCO) and it has also been designated as Garrè's osteomyelitis. Data for case number 6 clearly showed differences in laboratory results, scintigraphic and radiographic findings, while clinical symptoms were almost similar to primary chronic osteomyelitis. We favour the term juvenile chronic osteomyelitis because Garrè did not describe a singular, specific type of osteomyelitis; moreover, he presented 12 different conditions of osteomyelitis in his historical article (27). Hence, we consider JCO as a specific type of PCO, which in later stages may present the typical bony picture of PCO and possibly show development towards SAPHO syndrome.

Open biopsy of the mandibular bone and computed tomography are necessary to establish a precise diagnosis of mandibular osteomyelitis. MARX *et al.* (17) reported consistent microbiologic findings. However, an extraoral approach should be avoided, because possible nerve palsy and scar formation are serious disadvantages, while intraoral biopsies often present contamination. Oral contamination can be excluded when a piece of bone is removed intraorally if an extraoral sterile biopsy (taken by a trepan-bur) is also taken. Only the tip of the cylinder is sent for culturing. Our study incorporated the demands given by MARX (26) for culturing techniques; however, results were inconsistent. Serologic testing revealed parvovirus B19 to be the most frequent infectious viral agent, but positive results may be found in 30–60% of adults (28). Parvovirus B19 infection has been mentioned in association with rheumatic diseases, spherocytosis and bone marrow aplasia (29). MARX (26) also demands PCR-DNA, but preliminary data on four patients in this series still show contradictory results (2 patients with signal overloading, 2 patients with negative results). Tc-scintigraphy is a useful tool for detecting clinically and radiologically silent lesions, especially in extramandibular locations (12).

Because diffuse sclerosing mandibular osteomyelitis responds to treatment inconsistently (30), all treatment options should be applied. Especially in the early stage of the disease, operative procedures such as removal of all necrotic tissue and decortication are usually successful. In addition, hyperbaric oxygen (twice daily sessions at 1.4 atmospheres for 45-min cycles), with at least 20 cycles and long-term antibiotic medication, should always be performed as well. The four patients treated with long-term antibiotic medication showed a decreased frequency of mild symptoms while on medication. Because involvement of reconstructed bone is frequent, resection and second stage reconstruction should be considered carefully in late disease stages. In long-standing refractory chronic osteomyelitis, patients with multiple unsuccessful operative interventions and compromised elderly patients, conservative therapy with NSAIDs or steroids is recommended. Synovitis is most often mild and only rarely destructive. Treatment includes NSAIDs at sufficient dosage levels and, in refractory cases, administration of sulfusalazine. Persistent cases may require administration of methotrexate.

In conclusion, we strongly advocate an association between DSO and SAPHO syndrome. With reference to results from our study and the current literature, we suggest a hypothesis of a microorganism of low virulence functioning as a trigger that causes an exaggerated immune response in genetically predisposed individuals.

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Printed in Denmark by P.J.Schmidt A/S, Vojens