Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome presenting as a primary calvarial lesion

Case report and review of the literature

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The acronym SAPHO stands for a recently described and increasingly recognized syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis. This term was coined in 1987 to identify a clinical entity with characteristic features formerly described under a wide variety of names, such as arthritis associated with acne,\(^6,9,26,32\) osteitis associated with pustulosis palmaris and plantaris,\(^15,29,30\) sternocostoclavicular hyperostosis,\(^16,22,28\) and chronic multifocal recurrent osteomyelitis.\(^2,3,8\) The development of sterile osteomyelitic lesions accompanied by dermatological manifestations is regarded as the hallmark of this syndrome,\(^10\) which is most appropriately placed among the seronegative spondyloarthropathies.\(^1,19\) Among the classic triad of the skeletal lesions seen in SAPHO syndrome, osteitis is the most prominent. Pain is the most common symptom,\(^12\) and skin involvement, including palmar and plantar pustulosis, pustular psoriasis, severe acne, and, more rarely, common psoriasis,\(^1,3,5,11,24,27\) is also a prominent feature of this syndrome.\(^12\) Skin involvement can occur synchronously, precede, or follow the bone manifestations.\(^11\)

The origins and pathogenesis of the SAPHO syndrome are poorly understood. Most authors include this syndrome among the seronegative spondyloarthropathies in which results of tests performed in patients with the disorder show a slight increase of human leukocyte antigen B27 typing when compared with a control population.\(^1,5,7\) The treatment is empirical and based mainly on the use of nonsteroidal antiinflammatory agents. The natural history of the disease, however, is self-limited and the long-term prognosis is good.

Since its first description, the SAPHO syndrome has attracted much attention, particularly in Europe and Japan, and, more recently, in North America, as reflected by a growing body of literature. This has led to a better understanding of the syndrome itself, knowledge that is still evolving as new features are identified and characterized. For example, although involvement of flat bones, such as the ilium and the mandible, has been well documented, to our knowledge there are no previous descriptions of SAPHO syndrome involving the cranial vault.

Case Report

History. This 35-year-old Lebanese woman living in Geneva, Switzerland, presented with a history of increasing left frontoparietal tenderness extending to the left jaw and ear which was accompanied by the development of a parietal tumefaction. Approximately 1 year before presentation, the patient had reported the onset of recurrent incapacitating headaches for which she had been admitted to a Swiss hospital. Results of a CT study performed at that time were reported to be within normal limits and a lumbar puncture showed no evidence of meningitis. The patient's hematological workup revealed a slight elevation

Abbreviations used in this paper: CT = computerized tomography; MR = magnetic resonance; SAPHO = synovitis, acne, pustulosis, hyperostosis, and osteitis.
of her leukocyte count (10,430/ml) and C-reactive protein levels (70.8 mg/L). After discharge from the hospital, she continued to report intermittent headaches and was treated with antidepressant and antiinflammatory drugs without complete relief of symptoms. During her hospitalization she also developed sterile pustules on her palms and soles that during the ensuing months evolved into large patches of erythema and coarse scales that were studded with numerous microvesicles.

Examination. At the time of our evaluation, the patient had a palpable, tender lump in the left parietal region. We observed no neurological deficits. Cutaneous findings were consistent with psoriasis or dyshidrotic eczema. Admission CT scans revealed a prominent lytic process within the left superior parietal bone (Fig. 1). Magnetic resonance studies demonstrated on both T₁- and T₂-weighted images a nodular area of increased signal within the diploic space of the left parietal bone that extended both into the epidural space and into the scalp. The intradiploic nodule enhanced after administration of paramagnetic contrast medium and measured approximately 1 × 2 cm. An underlying diffuse enhancement of the meninges on the left side was also seen and was most pronounced under the left parietal nodule (Fig. 2).

Operation. Under sterile conditions and after general anesthesia had been induced, a linear skin incision was made over the left parietal area. Inflammatory tissue within the subcutaneous scalp was noted and resected. The skull appeared to be partially eroded, and therefore, a craniectomy was performed to the extent of the bone lesion by using a high-speed drill. The inner table of the bone also appeared to be involved in the lytic process, and an abnormally thickened dura mater was exposed. Several biopsy samples of the outer layers of the dura were obtained without violating the full extent of the dura. The skull was reconstructed using a titanium plate. Tissue specimens from the scalp, bone, and dura were collected for pathological examination and for fungal, bacterial, and mycobacterial studies.

Pathological Findings. All pathological specimens were negative for neoplastic disease. Histological examination of subcutaneous scalp tissue demonstrated fibrous changes with perivascular lymphoplasmacytic infiltrates. Focal fibrosis with chronic inflammation and extensive reactive changes were found within the abnormal bone (Fig. 3). Tissue removed from the outer layer of the dura also showed signs of perivascular chronic inflammation. All fungal and microbacterial cultures were negative except for a chopped meat–carbohydrate broth plate, which at Day 5 was positive for *Streptococcus viridans* that was thought to be a contaminant.

Postoperative Course. The patient tolerated the surgical procedure well and recovered with gradual improvement of the pain and tenderness. A few weeks later, however, she developed tenderness on the right (opposite) side of the skull. A bone scan showed a focal area of increased radiotracer uptake in the right parietal bone. An MR imaging study was performed, which, in addition to the expected postsurgical changes in the left parietal bone, revealed the presence of a new right parietal intradiploic nodule (Fig. 4), with postcontrast enhancement of the meninges underlying the bone lesion. The meningeal enhancement previously seen on the left side had resolved. The patient was treated conservatively with antiinflammatory drugs with good control of symptoms. The pain in the skull diminished considerably, but she subsequently developed

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**Fig. 1.** Axial bone window CT scan revealing a lytic lesion within the left parietal bone.

**Fig. 2.** A and B: Axial T₁-weighted (A) and T₂-weighted (B) MR images demonstrating a focus of increased signal intensity within the diploic space of the left parietal calvarium. C and D: Contrast-enhanced axial (C) and coronal (D) MR images: the lesion enhanced after paramagnetic contrast medium administration. Images reveal a diffuse enhancement of the meninges on the left side that is most pronounced in the region underlying the bone lesion.

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new discomfort in the chest wall on the left side. A total-body bone scan demonstrated increased radiotracer uptake in the first rib on the left. No increased activity was detected in the skull. A repeated MR image demonstrated resolution of the right-sided parietal lesion (Fig. 5).

**Discussion**

The diagnosis of SAPHO is based on the exclusion of bacterial or fungal infection and the presence of the formal diagnostic criteria.1,10,14 According to Kahn,10 one of the following criteria is sufficient for the diagnosis of SAPHO: 1) multifocal osteitis without skin manifestations; 2) sterile acute or chronic joint inflammation associated with either pustules or psoriasis of palms and soles, or acne, or hidradenitis; or 3) sterile osteitis in the presence of one of the aforementioned skin manifestations. Laboratory findings are of little value given the nonspecific nature of mild elevations of various inflammatory indices such as erythrocyte sedimentation rate and C-reactive protein levels. Differential diagnosis includes tumors, bacterial osteomyelitis, and Paget disease.

The patient in our case showed the clinical features that satisfy the proposed criteria for diagnosis of SAPHO syndrome, including the association of aseptic pustulosis palmaris and plantaris with the osteitis localized in the anterior chest wall. This case, however, is unique in that the early osseous manifestations involved an unusual location, the cranial vault. Moreover, the skull lesion was the presenting sign, with headache as the symptom, followed in later stages by the onset of the typical skin features and archetypal bone lesions. Although the bone lesions in SAPHO syndrome may involve various parts of the skeleton,12-14,20,31,33 the anterior chest wall is the location most frequently involved.12

Reith, et al.,23 described a pattern of histological progression related to the duration of symptoms. Bone lesions progress from an acute phase, indistinguishable from bacterial osteomyelitis, to an intermediate phase, characterized by chronic inflammation, to a late phase with marrow fibrosis and prominent sclerotic bone changes and only mild inflammation. Hyperostosis, another hallmark of this syndrome, may represent a late manifestation.19 Consistent with this spectrum of histological changes, radiographic features are variable19 and include osteolysis, periostitis, sclerosis, and hyperostosis.4,23 Histological examination of the bone specimen obtained in our patient showed chronic inflammation and marked reactive bone changes consistent with the intermediate phase described by Reith, et al. At the time of the onset of symptoms in our patient, a head CT scan demonstrated no abnormal changes. One year later, however, a CT scan revealed the presence of a lytic process involving the left parietal bone.

In patients with SAPHO syndrome, MR imaging demonstrates diffuse or local abnormal bone marrow signal with a broad spectrum of intensities probably reflecting the different stages of disease activity. In our case, MR images revealed involvement of the surrounding soft tissue, namely the overlying scalp and the underlying epidural space and dura mater, which is consistent with observations in other areas of the skeleton.12,20 At the time of our first observation, the bone changes were limited to the left

![Fig. 3. A: Low-power photomicrograph showing fibrous tissue surrounded by reactive bone. H & E, original magnification × 10. B: High-power photomicrograph showing fibrous tissue and a perivascular lymphoid aggregate. H & E, original magnification × 60.](image1)

![Fig. 4. Contrast-enhanced axial (A) and coronal (B) MR images obtained at 1-month follow up demonstrating evidence of prior craniectomy and placement of a titanium mesh over the left parietal region. The left parietal meningeal enhancement is now markedly decreased. However, on the right parietal calvarium an enhancing nodule is located within the diploic space. Enhancement of the meninges underlying the new right-sided parietal lesion is seen, whereas the previously noted contralateral meningeal enhancement appears to be completely resolved.](image2)
parietal bone. Follow-up MR studies demonstrated development of a lesion in the contralateral parietal bone and its subsequent regression.

Bone scintigraphy also plays an important role in the diagnosis of SAPHO syndrome, particularly in detecting lesions when the results of radiographic studies are negative. In our patient, the bone scan readily detected involvement of the first left rib, despite nondiagnostic x-ray films. The demonstration of lesions in sites that are considered typical is crucial for a correct diagnosis.

Interestingly, in our case, the skull involvement was the presenting symptom, accounting for a considerable diagnostic challenge. This observation raises the question of whether the absence of previous reports of skull involvement in the course of SAPHO syndrome is related to the true rarity of calvarial disease or is the result of an underestimation due to misdiagnoses when involvement is localized to the skull. Late histological features reported in some cases of SAPHO syndrome are virtually indistinguishable from those in Paget disease, with trabecular sclerosis, increased osteoclastic and osteoblastic activity, peritrabecular fibrosis, and “cracking artifact.”

A careful review of the literature revealed two cases involving possible SAPHO syndrome within cranial bones. In a report of 12 cases of diffuse sclerosing osteomyelitis of the mandible, one patient presented with multiple osseous lesions, including one in the frontal bone. Unfortunately, in that paper the authors provided no details about the lesion, and there is not yet a consensus about the inclusion of diffuse sclerosing osteomyelitis in the spectrum of manifestations of SAPHO. More recently, Marsot-Dupuch, et al., reported a case of SAPHO syndrome of the temporomandibular joint with extension of the lesion to the temporal bone. In that report, however, the lesion in the temporal bone appeared to be the result of local contiguous extension from the mandible, which is a typical location of SAPHO involvement. This is distinct from our case, in which the bone lesion primarily involved the calvaria.

Conclusions

The SAPHO syndrome is a unifying diagnosis, which encompasses a broad spectrum of manifestations. Diagnosis relies on the association of osteoarticular abnormalities and skin lesions. Since its first description, the growing body of data reported in recent years has broadened the definition of this syndrome. With this report, we now include calvarial location of bone lesions. We suggest that SAPHO syndrome should be considered in the differential diagnosis of any lytic, sclerotic, or hyperostotic lesion of the skull, particularly before considering an invasive procedure to assess the histological nature of the lesion. Patients affected by this entity should be reassured about its benign and self-limiting nature.

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References


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