Chronic Osteomyelitis of the Cranial Vault in an Adolescent Female: A Case Report

Masaki UJIHARA,1 Masahito KOBAYASHI,1 Hiroshi YAMAGUCHI,2 Sachiko HIRATA,1 Kazuhiko TAKABATAKE,1 Kenji WAKIYA,1 Atsushi SASAKI,2 and Takamitsu FUJIMAKI1

1Department of Neurosurgery, Saitama Medical University, Moroyama-machi, Saitama, Japan
2Department of Pathology, Saitama Medical University, Moroyama-machi, Saitama, Japan

Abstract

We report an 18-year-old female patient who developed left temporal headache and fever one month after administration of isotretinoin for acne. Imaging studies demonstrated osteolytic change in the left frontal bone, and the lesion showed gadolinium contrast enhancement. Biopsy confirmed the diagnosis of osteomyelitis, and the symptoms improved after 8 months of medication with antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs). However, the pain recurred when isotretinoin was resumed. Isotretinoin sometimes causes excessive inflammation, which may have been the reason for the osteomyelitis in this case. Although osteomyelitis is usually caused by bacterial infection, a non-bacterial mechanism should also be suspected if the condition is resistant to antibiotics.

Keywords: osteomyelitis, cranial vault, CNO, acne fulminans, isotretinoin

Introduction

Osteomyelitis is a form of osseous inflammation associated with microbial infection, being relatively common in children (approximately 2-13 per 100,000 children). Recently, it has been recognized that a significant proportion of pediatric osteomyelitis cases are due to autoinflammation resulting from dysregulation of the innate immune system. This type of osteomyelitis has been reported under several names, such as chronic non-bacterial osteomyelitis (CNO) or chronic recurrent multifocal osteomyelitis (CRMO). CNO/CRMO occurs most commonly in the lower extremities, but can also arise at other sites. Although skull involvement is rare, a few cases have been reported to date. Herein, we present an adolescent female patient who developed chronic osteomyelitis of the cranial vault, suspected to be caused by isotretinoin-induced autoinflammation.

Case Report

This case report was prepared after informed consent had been obtained from the patient and her family.

An 18-year-old female patient presented at our hospital with a one-week history of left fronto-temporal pain and fever. One month previously, she had started daily medication with isotretinoin 20 mg (0.3 mg/kg), which is not covered by medical insurance in Japan, for acne vulgaris that had persisted for 5 years. On presentation, her temperature was 38.2°C and she complained of severe pain in the left fronto-temporal region. Acne was evident on the face, being especially severe over the outer left eyebrow area (Fig. 1a). There were no skin lesions or pain in the trunk or extremities. Laboratory studies yielded the following abnormal values: white blood cells (WBCs) 13,500 /μL with predominance of neutrophils (82%); platelets 392,000 /μL; serum albumin 3.6 g/dL; C-reactive protein (CRP) 5.3 mg/dL. Blood cultures were negative. Computed tomography (CT) revealed an osteolytic lesion on the left frontal bone (Fig. 1b). Magnetic resonance imaging (MRI) demonstrated a lesion with gadolinium contrast enhancement at the site of the osteolysis (Fig. 1c); signal intensity was intermediate on T1-weighted images, high on T2-weighted images, and slightly high on diffusion-weighted images. The surround-
Fig. 1 Initial findings in the patient. (a) Photograph taken before biopsy surgery shows acne on the face, being especially prominent over the lateral aspect of the left eyebrow. The black dots are the markings for surgery. (b) CT shows the osteolytic lesion on the left frontal bone. (c) T1-weighted gadolinium-enhanced MRI demonstrates marked contrast enhancement at the site of osteolysis. Contrast enhancement is also evident in the surrounding dura, temporalis muscle and subcutaneous tissue. (d) Bone scintigraphy shows increased tracer uptake at a site consistent with the left frontal bone lesion evident on MRI, and mildly increased uptake in the right parietal bone (arrow), but no pathological uptake outside the skull (e).

Isotretinoin was discontinued on admission, and after 4 days of ceftazidime infusion and oral nonsteroidal anti-inflammatory drugs (NSAIDs), the patient’s temperature normalized and her blood test values improved (WBC, 9,700 /μL; CRP 0.56 mg/dL). She continued to take oral antibiotics and NSAIDs for the next two months, but the pain remained, and the lesion showed no change on imaging. Whole-body FDG-PET showed no tracer uptake site other than the left frontal region. At this time, we considered the possibility of bacterial osteomyelitis or a bone tumor such as Langerhans cell histiocytosis. We therefore performed a biopsy of the left frontal bone lesion via a short skin incision along the lateral superior border of the eyebrow. Histopathological examination revealed that most of the lesion was inflammatory granulation tissue, with dense infiltration of neutrophils (Fig. 2a). Bone fragments with osteoblastic rimming, osteoid formation, and fibrosis were also present in some areas (Fig. 2b). There were no obvious tumor cells, and immunohistochemical staining for S-100 protein and CD1a showed no proliferation of positive dendritic cells. These findings were consistent with osteomyelitis. However, tissue culture tests for aerobic and anaerobic bacteria yielded negative results.

Since the possibility of bacterial osteomyelitis could not be ruled out, antibiotics were continued, but the symptoms remained for 5 months after surgery. Because of the combination of osteomyelitis and acne in this patient, we suspected synovitis-acne-pustulosis-hyperosteosis-osteitis...
Chronic Osteomyelitis of the Cranial Vault

Fig. 2  Hematoxylin and eosin staining of the biopsied tissue. (a) Dense infiltration of neutrophils with mixed lymphocytes is evident. Large osteoclasts are also present. (b) In the center of the slide, a bone fragment with osteoblastic rimming and osteoid formation is evident, surrounded by fibrosis.

Fig. 3  Findings at the last outpatient visit. (a) Photograph of the acne taken 4 months after the reintroduction of isotretinoin. The acne has improved with scarring. (b) T1-weighted gadolinium-enhanced MRI shows the osteolytic lesion with slight contrast enhancement. Swelling of the surrounding tissue has improved.

(SAPHO) syndrome and consulted a rheumatologist. However, a diagnosis of SAPHO syndrome could not be made due to the absence of anterior chest-wall lesions and palmoplantar pustulosis. Therefore, we considered that the patient might have CNO and withdrew the antibiotics, maintaining only the NSAIDs. Subsequently, 6 months after the surgery, the pain improved. After another 4 months, as the patient had a strong wish to resume treatment for her acne, she consulted a dermatology clinic elsewhere, and isotretinoin was resumed. Thereafter, however, the left frontal pain flared up. An association between the pain and isotretinoin was suspected, but the pain resolved completely after 2 months of continued administration of isotretinoin with concomitant NSAIDs. The acne also showed improvement in comparison to the initial visit (Fig. 3a). The patient continued to receive isotretinoin for another 6 months and did not experience any pain relapse. MRI at the last follow-up point showed that the enhanced mass remained, but had shrunk (Fig. 3b). The above clinical course is presented in Fig. 4.

Discussion

In the present case, bacterial osteomyelitis was initially suspected, and therefore antibiotics were administered together with NSAIDs for the pain. Although the inflammation improved, the pain remained and imaging showed that the lesion persisted. A biopsy confirmed the diagnosis of osteomyelitis, but the tissue culture was negative. Therefore, it was difficult to determine whether the osteomyelitis was bacterial or non-bacterial, since one-third of cases of bacterial osteomyelitis are culture-negative. However,
the persistence of pain despite long-term antibiotic therapy and the absence of an infection route such as bacteremia, otonasal infection, or head trauma, which is usually the cause of cranial vault bacterial osteomyelitis, led us to speculate that the patient’s osteomyelitis had arisen through a non-bacterial mechanism.

SAPHO syndrome is an aseptic inflammatory osteoarticular disease with skin lesions. The syndrome acronym represents its typical symptoms, i.e. Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis. According to Benhamou’s diagnostic criteria, SAPHO syndrome can be diagnosed when one or more of the following four criteria are met: (1) osteo-articular manifestation of acne, (2) osteo-articular manifestation of palmo-plantar pustulosis, (3) hyperostosis, and (4) chronic recurrent multifocal osteomyelitis. However, septic osteomyelitis, infectious chest-wall arthritis, infectious palmoplantar pustulosis, palmoplantar keratoderma, diffuse idiopathic skeletal hyperostosis and osteoarticular manifestations of retinoid therapy are excluded from the SAPHO syndrome. In the present case, as the acne may have been accompanied by nonbacterial osteomyelitis of the skull, SAPHO syndrome was suspected. However, this possibility was ruled out by the rheumatologist because of absence of any anterior chest-wall involvement, which is the most typical manifestation of SAPHO syndrome, and absence of palmoplantar pustulosis.

CNO and acne fulminans (AF) are conditions considered similar to SAPHO syndrome. CNO is an idiopathic noninfectious inflammatory bone disorder, also called CRMO when it is multifocal and relapses. CNO can be associated with other inflammatory diseases of the skin, intestine, and joints. CNO and SAPHO syndrome are similar, but CNO differs in that it predominantly affects the lower extremities of children, whereas SAPHO syndrome predominantly affects the anterior chest wall and spine of adolescents and adults. CNO can also occur in the skull, albeit rarely. AF is a condition in which mild acne suddenly becomes severe, presenting as ulcerative acne with systemic symptoms such as fever, myalgia, and arthralgia. It is also known to cause osteolytic lesions. It is not clear whether SAPHO syndrome, CNO, and AF are the same disorder or separate conditions, but they are thought to be autoinflammatory osteoarticular and skin diseases.

We considered this case to be one of CNO in the cranial vault and discontinued the antibiotics and continued only NSAIDs, which resulted in improvement of the pain. However, after the patient had resumed isotretinoin for acne at another clinic, the pain flared up again. Furthermore, since she had also taken isotretinoin one month before the initial onset of osteomyelitis, we suspected that this drug might have been partly contributory.

Isotretinoin is an oral medicine administered to patients with severe acne that is resistant to conventional systemic antibiotics and topical therapy. Isotretinoin can induce long-term or permanent remission of acne. Although its mechanism of action is unknown, it is thought to modulate the innate immune response to Propionibacterium acnes via TLR-2. Paradoxically, however, it is well known...
that isotretinoin can cause acne flare (acute significant worsening). In addition, an association of isotretinoin with the development of AF and CNO has also been reported.

In the present patient we hypothesized that isotretinoin had induced an excessive immune response to *P. acnes*, resulting in osteomyelitis. The inflammation was initially improved by antibiotics, suggesting that it had aspects of bacterial infection. However, it took nearly one year for the symptoms to improve, and relapse of the same symptoms after the second course of isotretinoin suggested that a non-bacterial mechanism was involved. Although the patient did not present with obvious symptoms, bone scintigraphy demonstrated accumulation in the right parietal bone in addition to the left frontal bone. Since bacterial osteomyelitis is usually a single lesion, this finding also appeared to suggest a non-bacterial mechanism in this case.

The recommended treatment for bacterial osteomyelitis is short-term intravenous antibiotics until the symptoms, fever, and CRP level improve, followed by conversion to oral antibiotics for at least 3 weeks. Surgery should be considered in cases of abscess formation, adjacent arthritis, or poor general condition due to infection. Currently, there are no guidelines for the treatment of CNO; NSAIDs are the first choice, and steroid, bisphosphonates, and TNFα inhibitors are reportedly effective. Although there are no reports on the treatment strategy for CNO caused by isotretinoin, for cases of isotretinoin-induced AF it is recommended that isotretinoin should be discontinued and steroids administered until the acne improves, followed by resumption of isotretinoin. Paradoxically, continuation of isotretinoin is considered to lead to long-term acne remission, even if isotretinoin itself is the cause. Although antibiotics are not a first-line therapy for AF, some reports have recommended their use before starting isotretinoin. However, concurrent use of tetracycline, steroids and isotretinoin risks inducing pseudotumor cerebri syndrome.

Initially, as we did not suspect an association between isotretinoin and osteomyelitis in this case, antibiotics and NSAIDs were continued for treatment of bacterial osteomyelitis, and isotretinoin was discontinued just to be safe. After the condition was diagnosed as CNO, only NSAIDs were continued. Later, however, we were not informed about the resumption of isotretinoin prescribed at another clinic, and the pain flared up again. Paradoxically, the pain improved after 2 months of administration of isotretinoin and NSAIDs. In retrospect, it appears that this patient may have developed CNO due to administration of isotretinoin one month before onset, and that long-term administration of NSAIDs improved her symptom. Although the inflammation flared up after resumption of isotretinoin, its continued administration together with NSAIDs may have resulted in relatively early remission of CNO. If steroids had been used at the initial onset of osteomyelitis and isotretinoin had been resumed earlier, remission of CNO might have been achieved earlier. In addition, because we were not in direct contact with the dermatologist at the other clinic, we were late to recognize the possibility that isotretinoin may have affected the osteomyelitis.

In summary, non-bacterial inflammatory conditions of the skin and bones may include SAPHO syndrome, CNO, and AF. Although skull involvement in these diseases is rare, we suspect that in the present case CNO may have occurred in the skull in association with isotretinoin administration. Recognition of these diseases is important to avoid unnecessarily prolonged antibiotic therapy, and appropriate collaboration with dermatologists and rheumatologists is vital.

Acknowledgments

The authors would like to thank Dr. David Douglas for the English language review.

Author Contributions

Conception and design of this study: Masaki Ujihara, Masahito Kobayashi, Takamitsu Fujimaki

Analysis and interpretation of data: Masaki Ujihara, Masahito Kobayashi, Hiroshi Yamaguchi, Atsushi Sasaki, Takamitsu Fujimaki

Drafting of the article: Masaki Ujihara, Sachiko Hirata, Kazuhiro Takabatake

Critical revision of the article for important intellectual content: Masaki Ujihara, Masahito Kobayashi, Hiroshi Yamaguchi

Final approval of the article: Masaki Ujihara, Atsushi Sasaki, Takamitsu Fujimaki

Conflicts of Interest Disclosure

The authors have no conflicts of interest to report in relation to the findings described in this paper.

References

1) Gornitzky AL, Kim AE, O’Donnell JM, Swarup I: Diagnosis and management of osteomyelitis in children: A critical analysis review. *JBI Rev* 8: e1900202, 2020
2) Schnabel A, Range U, Hahn G, Siepman T, Berner R, Hedrich CM: Unexpectedly high incidences of chronic non-bacterial as compared to bacterial osteomyelitis in children. *Rheumatol Int* 36: 1737-1745, 2016
3) Wedman J, van Weissenbruch R: Chronic recurrent multifocal osteomyelitis. *Ann Otol Rhinol Laryngol* 114: 65-68, 2005
4) Koizumi H, Utsuki S, Oka H, Shimizu S, Fujii K: Chronic recurrent multifocal osteomyelitis involving the skull. *Internet J Neurosurg* 8: 2012
5) Watanabe T, Ono H, Morimoto Y, et al.: Skull involvement in a
pediatric case of chronic recurrent multifocal osteomyelitis. *Nagoya J Med Sci* 77: 493, 2015
6) Auh JS, Binns HJ, Katz BZ: Retrospective assessment of subacute or chronic osteomyelitis in children and young adults. *Clin Pediatr (Phila)* 43: 549-555, 2004
7) Mortazavi MM, Khan MA, Quadri SA, et al.: Cranial Osteomyelitis: A Comprehensive Review of Modern Therapies. *World Neurosurg* 111: 142-153, 2018
8) Nguyen MT, Borchers A, Selmi C, Naguwa SM, Cheema G, Gershwin ME: The SAPHO syndrome. *Semin Arthritis Rheum* 42: 254-265, 2012
9) Benhamou CL, Chamot AM, Kahn MF: Synovitis-acne-pustulosis hyperostosis-osteomyelitis syndrome (SAPHO), A new syndrome among the spondyloarthopathies? *Clin Exp Rheumatol* 6: 109-112, 1988
10) Jelušić M, Čekada N, Frković M, et al.: Chronic recurrent multifocal osteomyelitis (CRMO) and synovitis-acne-pustulosis hyperostosis-osteitis (SAPHO) syndrome - Two presentations of the same disease? *Acta Dermatovenerol Croat* 26: 212-219, 2018
11) Chua SL, Angus JE, Ravenscroft J, Perkins W: Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome and acne fulminans: Are they part of the same disease spectrum? *Clin Exp Dermatol* 34: 241-243, 2009
12) Meinzer U, See H, Bader-Meunier B, et al.: Clinical characteris-tics of acne fulminans associated with chronic nonbacterial osteomyelitis in pediatric patients. *J Rheumatol* 47: 1793-1799, 2020
13) National Institute for Heath and Care Excellence: Acne vulgaris: management. NICE guideline [NG198], https://www.nice.org.uk/g uidance/ng198 (Accessed May 20 2022)
14) Dispenza MC, Wolpert EB, Gilliland KL, et al.: Systemic isotretinoin therapy normalizes exaggerated TLR-2-mediated innate immune responses in acne patients. *J Invest Dermatol* 132: 2198-2205, 2012
15) Buch K, Thuesen ACB, Brøns C, Schwarz P: Chronic nonbacterial osteomyelitis: A review. *Calcif Tissue Int* 104: 544-553, 2019
16) Greywal T, Zaenglein AL, Baldwin HE, et al.: Evidence-based recommendations for the management of acne fulminans and its variants. *J Am Acad Dermatol* 77: 109-117, 2017

Corresponding author: Masaki Ujihara, MD.
Department of Neurosurgery, Saitama Medical University, 38 Morohonogo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan.
e-mail: ujihara@saitama-med.ac.jp

*Corresponding author: M. Ujihara et al.*