Abstract:

We report a rare case of a 27-year-old woman with Takayasu arteritis (TAK) complicated by diffuse sclerosing osteomyelitis. She first presented with sclerosing osteomyelitis of the right mandible without evidence of arteritis in the carotid arteries. Eight months later, she complained of left neck pain, and imaging studies revealed the presence of arteritis in the left carotid artery. She was diagnosed with TAK, and immunosuppressive treatment was initiated, which was effective for both the arteritis and the osteomyelitis. Osteomyelitis is an important complication of TAK and bone scintigraphy is useful for its detection.

Key words: Chronic recurrent multifocal osteomyelitis, Osteomyelitis, synovitis-acne-pustulosis-hyperostosis-osteitis syndrome, Takayasu arteritis

Introduction

Takayasu arteritis (TAK) is characterized by inflammation of the systemic large arteries (the aorta and its branches, coronary artery, and pulmonary artery), and results in stenosis, obstruction, and aneurysm formation by the affected arteries (1). Although a correlation with HLA-B52 and B67 has been reported, much of its pathogenesis remains unclear (2). Importantly, TAK is sometimes complicated by other inflammatory conditions, including ulcerative colitis, Crohn’s disease, hypertrophic pachymeningitis, and relapsing polychondritis (3-5). Sterile osteomyelitis is an inflammatory bone disease that presents with bone pain of insidious onset and which is also associated with other inflammatory disorders, such as palmoplantar pustulosis, psoriasis vulgaris, and inflammatory bowel disease. Although both TAK and sterile osteomyelitis have similar comorbidities, the relationship between these two conditions has been poorly investigated. Recently, Vettiyil et al. described an unusual association among chronic recurrent multifocal osteomyelitis (CRMO), pyoderma gangrenosum (PG), and TAK (6). CRMO represents 2-5% of the cases of osteomyelitis and is the term that is often used in pediatrics. Meanwhile, synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome is also known to present with osteomyelitis as a primary clinical feature, and is used more frequently in the adult literature (although the definition of these two terms is uncertain) (7). We herein describe a rare case of TAK complicated by diffuse sclerosing osteomyelitis of the mandible, which developed 8 months before the onset of TAK.

Case Presentation

A 27-year-old woman was referred to our rheumatology department for the evaluation of large vessel vasculitis. Eight months before referral, she had complained of swelling and pain in the right lower jaw. At the time, imaging studies (computed tomography [CT] and contrast-enhanced magnetic resonance imaging [MRI]) revealed an irregular increase in bone density and periosteal reaction in the right mandible (Fig. 1a and b). Tracer accumulation was observed in the right mandible as well as the sternoclavicular joints, the first rib, and shoulder joints, by bone scintigraphy (Fig. 2). The carotid arteries were normal at this point.
(Fig. 1c). The examination of a biopsy specimen from the right lower mandibular lesion revealed infiltration of neutrophils and lymphocytes without malignant cells or microorganisms. A tentative diagnosis of sterile osteomyelitis was made. Five months before referral, C-reactive protein elevation was observed (1.7 mg/dL), and the patient was treated with amoxicillin/clavulanate because infection was suspected. However, antibiotics did not improve her symptoms at all. She was considered to be suffering from diffuse sclerosing osteomyelitis as tracer accumulation was observed from the body to the ramus of the right mandible (Fig. 2). Three months before her referral, she complained of left neck pain, blurred vision, and headache. Because antibiotic treatment was not sufficient to relieve her symptoms, CT was again performed to evaluate the neck lesion. Unexpectedly, CT showed circumferential wall thickening of the left common carotid artery, with intense enhancement. She was then thought to have large vessel vasculitis. Because the patient was negative for antinuclear antibodies (ANA), anti SS-A antibodies were detected. We did not investigate further because she did not complain of sicca symptoms. Tests for other autoantibodies were negative. Neither syphilis nor chlamydia infection were detected. She was serotyped as HLA-B40 and HLA-B44. Carotid ultrasonography revealed irregular wall thickening and stenosis (inner diameter of the stenosis site was 3.4 mm) of the left common carotid artery. A diagnosis of TAK was made as the patient satisfied the diagnostic criteria established by the JCS Joint Working Group (8). Prednisolone (50 mg) treatment was started. Since significant angiostenosis was observed, thromboprophylaxis with acetylsalicylic acid (100 mg/day) was also initiated. At one week after the initiation of corticosteroids, there was improvement in the fever and neck pain, and
the patient’s C-reactive protein levels had normalized. On day 14 of admission, reexamination of the carotid artery by ultrasonography revealed an increase in blood flow from 142 cm/s to 201 cm/s. Repeat MRI showed improvement of the enhancement in the left carotid artery (Fig. 4). She was discharged on the 22nd day after admission. The prednisolone dose had been tapered to 12 mg/day, without relapse. Importantly, the swelling and pain of the right mandible bone had also been alleviated (Fig. 4c).

**Discussion**

To date, the co-existence of TAK and osteomyelitis has been reported in six cases (Table). To retrieve data regarding osteomyelitis and TAK, we performed a search of the PubMed database using the term “Takayasu arteritis AND osteomyelitis OR SAPHO” (9). The references of the retrieved articles were also reviewed for this purpose. Three case reports (6, 10, 11) were found between the years 1995-2017. Among these reports, one case of TAK was complicated by CRMO (6). The other case reports presented in Table (12-14) were found from the reference list of the report by Ferguson et al. (7). In addition to the present case, we identified an additional patient in our institution who initially presented osteomyelitis and who developed TAK 12 years later (Table, case 4). At the time of writing, we are treating 136 patients with TAK (15), and the prevalence of osteomyelitis in adult TAK patients is 1.47%.

Three cases were reported in children and three in adults (Table). CRMO mainly occurs in pediatric patients. CRMO is an idiopathic non-pyrogenic auto-inflammatory bone disorder involving multiple sites, with clinical progression persisting for more than 6 months, which may have episodes of remission and exacerbation over the long term. It is predominantly found in female patients; the average age at the disease onset is 8-11 years (16). CRMO is known to be associated with other inflammatory diseases, such as palmoplantar pustulosis, psoriasis vulgaris, and inflammatory
bone scintigraphy showed lesions in other areas in-
(case 8). Although our patient only showed right mandible
The most commonly affected bones included the mandible,
be recognized that sclerosing osteomyelitis of the mandi-
been observed for eight months. At first, we suspected an in-
fection as the cause of sclerosing osteomyelitis. However,
steroid therapy, the symptoms of our patient showed dra-
found an apparent site of infection and treat-
function as the cause of sclerosing osteomyelitis. However,

bowl disease. Interestingly, two cases were further compi-
cated by PG (Table. cases 1 and 3), suggesting that CRMO,
TAK, and PG are manifestations of one syndrome, espe-
cially in children. There are no reports of adult patients with
TAK complicated by both SAPHO and PG. However, the
combinations of PG and TAK are described in adults. Ujiie
et al. reviewed 35 PG cases of TAK, which revealed that
out of six cases. However, it is very difficult to define the
precise onset of TAK, and there has been no evidence that
TAK was actually absent when patients presented with os-

t patients with Takayasu Arteritis Complicated by Osteom-

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Complications</th>
<th>Order of onset</th>
<th>Interval between osteomyelitis and TAK</th>
<th>Bones involved</th>
<th>Treatment</th>
<th>Response to treatment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 years and 9 months</td>
<td>Male</td>
<td>PG</td>
<td>PG+osteomyelitis→TAK</td>
<td>3 years</td>
<td>Ninth and tenth ribs, Left tibia</td>
<td>High-dose prednisolone for three months</td>
<td>Clinical improvement</td>
<td>[10]</td>
</tr>
<tr>
<td>2</td>
<td>10 years</td>
<td>Female</td>
<td>PG</td>
<td>CRMO→TAK→PG</td>
<td>2 years</td>
<td>Right mandible</td>
<td>Prednisolone (1 mg/kg/day)</td>
<td>Clinical improvement</td>
<td>[6]</td>
</tr>
<tr>
<td>3</td>
<td>15-16 years</td>
<td>Female</td>
<td>CRMO→TAK</td>
<td>6 years</td>
<td>Multifocal</td>
<td>Sulfasalazine Methotrexate Azathioprine</td>
<td>No response</td>
<td>[14]</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20 years</td>
<td>Female</td>
<td>HT, DM</td>
<td>Osteomyelitis→TAK</td>
<td>12 years</td>
<td>Right limb</td>
<td>Tocilizumab Tacrolimus</td>
<td>Clinical improvement</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>21 years</td>
<td>Female</td>
<td>TAK→osteomyelitis</td>
<td>7 years</td>
<td>Clavicles, Left Scapula</td>
<td>Treated conservatively (detail unknown)</td>
<td>Unchanged</td>
<td>[12]</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>27 years</td>
<td>Female</td>
<td>Osteomyelitis→TAK</td>
<td>8 months</td>
<td>Right mandible</td>
<td>Prednisolone (1 mg/kg/day) for two weeks</td>
<td>Clinical improvement</td>
<td>[13]</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>35 years</td>
<td>Female</td>
<td>TAK→osteomyelitis</td>
<td>Uncertain</td>
<td>Left ulna, radius, Right tibia</td>
<td>Prednisolone (0.5 mg/kg/day) for three weeks</td>
<td>Clinical improvement</td>
<td>[11]</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>49 years</td>
<td>Female</td>
<td>AR</td>
<td>TAK→osteomyelitis</td>
<td>Uncertain</td>
<td>Sternum, Clavicles</td>
<td>Methotrexate Azathioprine for two years</td>
<td>Clinical improvement</td>
<td></td>
</tr>
</tbody>
</table>


The bone lesions involved differ among cases (Table). The most commonly affected bones included the mandible, clavicle, rib, and tibia; the sternum was affected in one case (case 8). Although our patient only showed right mandible pain, bone scintigraphy showed lesions in other areas in-
treatment (27). The treatments in other cases included corticosteroids or immunosuppressants such as mycophenolate mofetil, which also resulted in a marked clinical response (Table). Antibiotics, on the other hand, were not effective.

The manifestation of lower jaw pain has been reported in TAK, and ischemia was considered to be one of its causes (28). In a case reported by McConachie et al. (12), bone lesions were located in the clavicles and scapula where the arteritis activity was high. They therefore proposed that ischemic hypoxia due to arterial stenosis was responsible for the skeletal abnormality. However, the locations of the bone lesions in other cases, including our own were not related to the artery lesions, suggesting that osteomyelitis was caused by active inflammation rather than hypoxia. Cell-mediated immunity by T cells is considered to play a key role in the pathophysiology of TAK, which is supported by its relationship with specific HLA. In particular, Terao et al. revealed that the IL12B region was significantly associated with TAK, and indicated that IL12B played a fundamental role in the pathophysiology of TAK in combination with HLA-B*52:01 (29).

Macrophages are one of the major effector cells in TAK (30, 31) and osteoclasts play central roles in sclerosing osteomyelitis (32). Granuloma is one of the characteristics of TAK and these are formed by multinucleated macrophages and giant cells (33). These cells release growth factors and cytokines, which lead to endothelial activation and dysfunction in patients with vasculitis (34). Meanwhile, osteoclast-mediated bone resorption is considered to be a primary disease process that is followed by new bone formation in diffuse sclerosing osteomyelitis (35). The underlying pathomechanisms of TAK and sclerosing osteomyelitis are uncertain, and this rare association suggests that common abnormalities promote the progression of both diseases.

In conclusion, osteomyelitis is an important complication of TAK and bone scintigraphy is useful for its detection. This association suggests a common pathophysiology, and further studies would be helpful in improving the understanding of the mechanisms involved in the onset of TAK.

The authors state that they have no Conflict of Interest (COI).

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Patient Consent

Written informed consent for publication of this case report was obtained from the patient.

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References


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