A case of intractable chronic osteomyelitis of the mandible accompanied with pathologic fracture and tardive dyskinesia

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Abstract: A case of severe chronic osteomyelitis of the mandible accompanied with fracture of the mandibular angle and tardive dyskinesia in a 78-year-old male is reported. As treatment with intravenous antibiotics or decortication was not effective, intra-arterial infusion of the antibiotics was performed. This therapy was very effective without complication. In our case, as the patient had had tardive dyskinesia in the past, it was considered that the severe chronic osteomyelitis was closely related to chronic tendoperiostitis caused by muscular overuse.

Key words: chronic osteomyelitis, intra-arterial infusion, tardive dyskinesia

Introduction

Chronic mandibular osteomyelitis subsequently develops after common dental infectious diseases, such as apical periodontitis and periostitis of the wisdom tooth, and it occasionally progresses to an intractable course. Here, we report a patient with tardive dyskinesia in whom a good outcome was obtained upon intra-arterial infusion of antimicrobial agents administered for intractable chronic mandibular osteomyelitis accompanied by pathologic fracture.

Case Report

The patient was a 78-year-old Japanese man who visited the Department of Oral and Maxillofacial Surgery, Mie University Hospital on July 11, 2000 with a chief complaint of swelling of the right submandibular region. The patient had received anti-inflammatory treatment from a physician for gingival swelling of the right mandibular third molar region in May in the same year.

Regarding his past medical history, the patient had experienced depression since his 20's and schizophrenia since the age of 68 years old, and had been diagnosed with tardive dyskinesia due to treatment with an oral antipsychotic agent (haloperidol). In addition, the patient was diagnosed with prostatic hypertrophy, chronic renal failure, and hypertension at the age of 55 years old, and is under treatment with oral hypotensive drugs (ACE inhibitor, Ca antagonist).

Intraorally, it was observed that the right mandibular wisdom tooth is half impacted, and the surrounding gingiva was swelling with tenderness. As panoramic radiography showed the impacted wisdom tooth with radiolucent area in circumference of crown, the diagnosis of periostitis of the wisdom tooth was made (Fig. 1). On July 17, extraction of the right mandibular impacted wisdom tooth was performed. A bone of circumference of tooth was intact and the abnormal findings were not revealed during an operation. Post operatively, the patient was administrated of cefdinir (CFDN) for 3 days (300mg/day) orally. On re-visited our department for the removal of suture, the extraction wound was recognized in healing tendency, and the postoperative course was good. However, after the patient had a fall at the beginning of August,
swelling and pain recurred in the same region, and the patient re-visited our department on August 25 in the same year. Systemic fever higher than 38°C, swelling and pain of the right cheek over the submandibular region, trismus, and, as symptoms of antipsychotic agent-associated tardive dyskinesia, involuntary movement of the mandible accompanied by severe clenching and grinding, were observed, but no difficulty in swallowing or aerophagia was observed. In the oral cavity, failure of excavations to heal after right mandibular impacted wisdom tooth extraction and swelling of the surrounding gingiva were observed. Panoramic radiography showed a fracture line from immediately below the excavations of the extracted tooth to the angle of the mandible, and sclerosis of the surrounding bone was also observed (Fig. 2). CT showed that the masseter and medial pterygoid muscle were thickened, but no abscess was formed (Fig. 3). In clinical blood tests, white blood cell count (9,600/mm³) and CRP (4.0mg/dL) were increased, but no other abnormal values were detected.

Intravenous drip infusion of antimicrobial agents (cefmetazole sodium: CMZ for 2 g/day, amikacin sulfate: AMK for 200mg/day, piperacillin sodium: PIPC for 2 g/day) was initiated, and as dislocation of the fracture bone was little recognized, intermaxillary fixation was performed on the day of admission. Inflammatory symptoms had improved within about a week, however severe clenching and grinding continued, and an X-ray examination performed on day 33 (Fig. 4) showed that the fractured region was opened and that the opening had tended to further dilate, although no marked inflammation was observed. Open reduction and fixation was performed and curettage of the excavations of the extracted tooth was repeated on day 50. Since new bone was observed in the fractured region, and granulation was present in the interstitium
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Fig. 5 Clinical course

of the fractured region, curettage was performed, and the fracture region was fixed with a plate. Intermaxillary fixation was performed after surgery, and the postoperative progress has been good, however swelling and tenderness recurred in the angle of the right mandible on about the 90th hospital day. Antimicrobial agents (cefotiam hydrochloride; CTM for 2 g/day, aspoxillin; ASPC for 2 g/day) were administered, and the symptoms transiently remitted, however swelling and tenderness re-appeared in the same region on about day 110. On day 148, the plate and wire were removed, and curettage of tooth extraction wound was repeated. Intraoperative findings showed that the fractured region had fused, and new bone was added, however the surface was relatively rough, and thus, saucerlization of the lesion was performed. Fibrous tissues were present under the plate, and the screws were loosened. Since the patient transiently became psychologically unstable after surgery, and almost all his teeth became loose due to severe clenching and grinding, intermaxillary fixation with intercalated soft silicon plates was performed. The symptoms tended to improve transiently, however swelling of the angle of the mandible recurred, and a painful abscess was formed in the gingiva of the right premolar region. Hence, intraoral incision and drainage were performed. Since inflammatory symptom has not improved, a catheter was indwelled in the bifurcation point of the right facial artery as inverse insertion from superficial temporal artery under local anesthesia on day 182, and continuance intra-arterial administration of antimicrobial agents was initiated. imipenem/cilastatin sodium (IPM/CS), 0.5g/day, was administered for 9 days, latamoxef sodium (LMOX), 1 g/day, for 10 days, benzylpenicillin potassium (PCG), 600,000 units/day, for 3 days, and arbekacin sulfate (ABK), 100mg/day, for 10 days. Simultaneously, urokinase, 120,000 units/day, was administered intra-arterially for 10 days. Swelling of the angle of the mandible started to remit on the 203rd hospital day, or about 20 days after initiation of intra-arterial infusion, and swelling and tenderness disappeared at the completion of intra-arterial infusion. The patient was discharged on the 242nd hospital day (Fig. 5). Microbial tests detected
no bacteria around the fractured region, but MRSA, α- and γ-Streptococcus, Enterococcus, Pseudomonas aeruginosa, and Candida albicans were identified in the intraoral region that had been repeatedly curetted and incised. The progress after discharge has been good and no exacerbation of the inflammation has been seen on December, 2002.

Discussion

Although there has been progression in the development of antimicrobial agents, chronic mandibular osteomyelitis occasionally progresses to an intractable course, and becomes difficult to treat. Osteomyelitis of the jaw generally occurs more frequently in the mandible than in the maxilla, and is likely to become severe because the mandible contains abundant cancellous bone and a relatively large marrow cavity surrounded by thick and hard cortical bone. Hence, the lesion remains in the bone marrow and readily disseminates and expands. In addition, pharmaceutically, the anaerobic conditions in the mandibular bone marrow decreases antimicrobial activity, and low blood flow reduces tissue transfer of antimicrobial agents. Jacobsson et al have reported that Propionibacterium acnes and Peptostreptococcus intermedia are important as etiological bacteria in diffuse osteosclerotic osteomyelitis. Koorbursh et al also reported the importance of mixed infection with anaerobic bacteria. In our case, because microbial tests were negative at first, antimicrobial agents were selected as assumption of mixed infection with anaerobic bacteria. However, identification of the etiologic bacteria is not possible in many cases, and tolerant strains and biofilm-forming bacteria are considered to be involved. Accordingly, selection of drugs is very difficult, and is made based on an assumption of the etiologic bacteria. The selection of effective drugs and sufficient transfer of drugs to the lesion are the basics of the therapy, however among the cephem antibiotics commonly used for anti-inflammatory treatment, transfer of some drugs to bone tissues is insufficient. To increase drug transfer to the lesion, concurrent use of polymethyl methacrylate beads containing gentamycin with removal of cortical bone, however some problems remain to be solved. These include the potential biological harm caused by residual monomers of the beads, the possibility of hypersensitivity to polymethyl methacrylate, the necessity for multiple surgeries, and the difficulty in selection of antimicrobial agents.

Hyperbaric oxygen may be useful treatment that should be considered as adjunctive treatment for chronic osteomyelitis in expect for the restraint of increase in anaerobic bacteria or progression of restoration system. However, because there was not the facility of hyperbaric oxygen treatment in our hospital and feeling of fear for narrow space, this treatment wasn't done.

Intra-arterial infusion of drugs has often been used as an effective therapy for malignant tumors. Since circulation in the infected lesions is reduced in osteomyelitis of the jaw, and antimicrobial agents do not readily reach the lesions, thereby decreasing the therapeutic effect, intra-arterial infusion of drugs is considered to be effective, since it is able to selectively increase the local concentration of antimicrobial agents in the lesion. In addition, it has been reported that urokinase used concomitantly with such therapy may inhibit biofilm formation and dissolve biofilm, and a combination effect with antimicrobial agents is expected. However, such therapy may cause thrombosis and peripheral ischemic disorder, and thus, application of the therapy requires appropriate caution. However, for patients in whom administration of antimicrobial agents at normal doses is limited, due to underlying diseases such as chronic renal failure, as in our patient, and transfer of antimicrobial agents to the lesion may be insufficient, such therapy is very useful because of its ability to selectively increase the local concentration of antimicrobial agents in the lesion.

Our patient had oral antipsychotic agent-associated tardive dyskinesia. Tardive dyskinesia is characterized by involuntary movement induced by long-term administration of drugs with dopamine-blocker activity, such as antipsychotic agents. Involuntary movement of the region around the mouth and abnormal muscular behavior of the head, extremities, and trunk is generally observed. No effective therapy is currently available, with the basic approach being discontinuation or dose reduction of the causative drug, if this is possible. However, when the causative drug is an an-
tipsychotic agent, the risk of aggravating the primary disease by dose reduction or discontinuation of the causative drug is significant, as has been previously pointed out\textsuperscript{13,14}). In our patient, abnormal movement of the tongue and lip and severe clenching and grinding, causing loosening of teeth, were observed. No discontinuation or dose reduction of the antipsychotic agent was performed because of the possibility of aggravating the primary disease. The patient had these symptoms for 10 years, and excess force may have been continuously loaded on the masseter muscle, jaw bone, and teeth during daily life, and this effect may have been involved in the development of osteomyelitis and the progression of the disease to the chronic stage.

Generally, the involvement of reduced immunity, in addition to bacterial infection, has been pointed out as a cause of chronic osteomyelitis of the jaw, but the details are still unknown. Van Merkersteyn et al\textsuperscript{15}) and Groot et al\textsuperscript{16}) have proposed that diffuse sclerosing osteomyelitis of the jaw can be viewed as reactive osteohyperplasia that results from chronic tendoperiostitis caused by muscular overwork. So it is thought that chronic tendoperiostitis has some influences on the jaw.

It is also possible that our patient may have developed chronic tendoperiostitis due to tardive dyskinesia, and that failure of wound healing after tooth extraction and bacterial infection caused by fracture-promoted chronic osteomyelitis of the jaw contributed to the progression of the disease to an intractable stage. Moreover, sufficient amounts of antimicrobial agents could not be administered because the patient had a previous medical history of chronic renal dysfunction, and age-related reduction of immune function was also observed. Hence, therapy may have been prolonged due to these reasons.

The basic approach to therapy for osteomyelitis is: 1. resting of the local site, 2. administration of effective antimicrobial agents, and 3. surgical treatment at an appropriate time. When improvement is not obtained after surgical anti-inflammatory treatment, such as removal of the sequestrum, and administration of sensitive antimicrobial agents for an appropriate period, or when administration of antimicrobial agents is limited due to underlying disease, the distribution of antimicrobial agents to the infected lesion at a high concentration by intra-arterial infusion may be a promising therapeutic method. In addition, therapy should be performed with consideration of the possibility that tardive dyskinesia-associated chronic tenoperiostitis induces chronic osteomyelitis of the jaw.

\textbf{References}


遲発性ジスキネジア患者の病的骨折を伴った
慢性難治性下顎骨骨髄炎の1例

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遲発性ジスキネジアを有する78歳男性の下顎角部骨折を伴った難治性慢性下顎骨骨髄炎の1例を経験したので報告する。

抗菌剤の投与、皮質骨除去等での治療で効果がみられなかったため、抗菌剤の動脈内投与を試みたところ、副作用もなく、著しい効果を認めた。

自験例では、既往歴に遅発性ジスキネジアがあることから、難治性慢性下顎骨骨髄炎は筋の触発による慢性膿性炎症と密接な関連を有するものと思われた。

キーワード：慢性骨髄炎、動脈内注入療法、遲発性ジスキネジア