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Case Report

Metronidazole-induced encephalopathy caused by hyperbaric oxygen therapy in a patient with mandibular osteomyelitis☆

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ABSTRACT

Metronidazole (MNZ) is prescribed for the treatment of infection caused by anaerobic bacteria and protozoa. Metronidazole-induced encephalopathy (MIE) has been known to be a side-effect, although its onset ratio is unclear. However, to the best of our knowledge, MIE associated with hyperbaric oxygen therapy (HBO) has not been previously reported.

Here, we present the case of a 68-year-old man with mandibular osteomyelitis who received metronidazole for 49 days and received five times HBO therapy. He visited our hospital for evaluation and treatment of peripheral neuropathy, speech disturbance, nausea, and disturbance of gait after 47 days of initiating metronidazole treatment. Brain magnetic resonance imaging revealed hyperintense lesions in the cerebellar dentate nuclei, which was consistent with MIE. The patient's ataxic symptoms improved in 15 days after the discontinuation of MNZ. This is the first report demonstrating case of MIE could be related with HBO, as far as we had searched.

1. Introduction

Metronidazole (MNZ) has been widely used in the treatment of several protozoal and anaerobic infections worldwide [1,2]. Since antimicrobial resistance, such as carbapenem resistance, is emerging all over the world in recent days, combined therapy with metronidazole offers an effective alternative to carbapenem with low risk of carbapenem resistance [3]. It has also been reported that MNZ could cause serious neurological side-effects, such as peripheral neuropathy, cerebellar dysfunction, gait disturbance, dysarthria, seizures or encephalopathy [1,2]. Among these, metronidazole-induced encephalopathy (MIE) is known to be one of the most serious side effects [4]. On July 2014, injectable MNZ was introduced to Japan and has been used for various infections. While the number of patients with MIE may be increasing with the use of MNZ, the mechanism and etiology of MIE are still unknown. This is the first report of MIE concerning a patient with osteomyelitis which could be related to hyperbaric oxygen therapy (HBO), as far as we had searched.

2. Case presentation and a review of literature

A 64-year old Japanese man visited our institute complaining of intractable tongue pain, which appeared to be caused by an ulcer. He had a history of interstitial pneumonitis and coronary artery bypass graft surgery due to three-vessels myocardial infarction. Tongue biopsy was performed, and squamous cell carcinoma was confirmed. Thus, he was diagnosed as having a tongue cancer (pT2N1M0). He was treated with concurrent chemotherapy (Nedaplatine: 144mg) and radiotherapy (40-Gy). The patient achieved a remission following the initial therapy but experienced a recurrence after 6 months. Tracheostomy, hemiglossectomy, radical neck dissection with pull-through method, and reconstructive surgery were consecutively performed with rectus abdomen free flap. The surgery following this recurrence was successful and the cancer again went into remission.

Radiation-induced mandibular osteomyelitis developed six months after the surgery. A swab test for bacteriologic examination

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was performed on 1 of the fistulae. Bacteriologic examination detected *normal pharyngeal flora*. While a swab smear showed a Gram-positive coccus (4+), the culture was negative. MRSA was detected in a sputum culture. Thus, combination antibiotic therapy of sitafloxacin (STFX), clindamycin (CLDM) and teicoplanin (TEIC) was started empirically. Because oral streptococci, anaerobes and MRSA were considered as causative pathogens. After the treatment for 14 days, his condition improved and he was discharged. Three years after the event, the osteomyelitis recurred which resulted in a mandibular fracture. He was admitted immediately and the treatment was re-started with the combination therapy of 1.5g MNZ iv and 2g pazufloxacin (PZFX) iv daily due to no response to the previous therapy. The symptoms and inflammatory reactions improved and he continued to have the treatment of oral 1.5g MNZ daily (Fig. 1). On the day 47 after starting MNZ and five times HBO therapy (2.0 ATA, 60min), he progressively presented with neurological symptoms such as peripheral neuropathy, speech disturbance, nausea, hearing loss, and disturbance of gait. An audiogram and a nystagmus test were performed with normal results. MRI on T2-weighted fluid-attenuated inversion recovery (FLAIR) revealed signal intensity in the cerebellar dentate nuclei and brain stem symmetrically, which is consistent with MIE (Fig. 2A–C). Then, both MNZ and HBO therapy were discontinued and his neurological symptoms rapidly improved after 5 days. Peripheral neuropathy persisted for a few weeks. Complete resolution of signal changes was noted in the follow-up MRI of the brain performed after 32 days (Fig. 2D–F). The Naranjo adverse drug reaction (ADR) probability scale was "+8, probable" and the case was considered as MIE.

No cancer relapse was confirmed during treatment. He had never been readministered HBO therapy after metronidazole discontinuation.

3. Discussion

MNZ has been widely used worldwide since 1961. Since then, reports on MIE are rare and the incidence rate is unknown. The first case of MIE was reported in 1995 by Ahmed et al., who described the MRI findings of metronidazole-induced cerebellar toxicity [4]. The mechanism of MIE remains unclear and some have reported

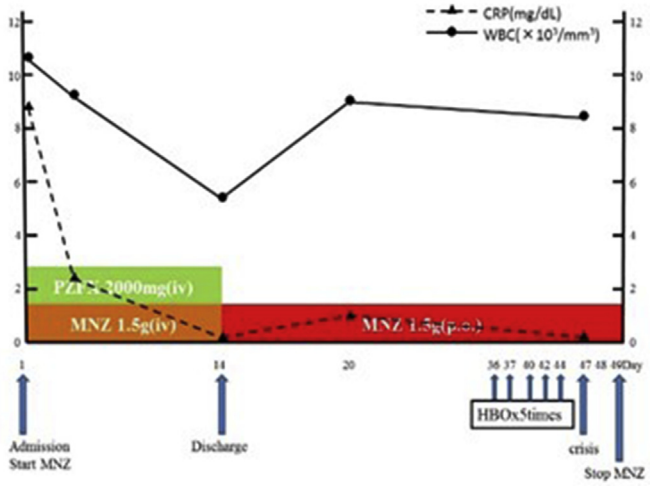

Fig. 1. Shows the clinical course. We continued metronidazole for 49days after the second admission. He was cured by MNZ and STFX for intravenous. He discharged from hospital on 14th days, and we switched MNZ for oral administration. After discharged he received five times HBO because of mandibular osteomyelitis on 36th-44th days. The symptoms developed on 47th days. He had a diagnosis of MIE and stop MNZ on 49th days.

hypotheses as follows. In bacteria and protozoa, metronidazole is changed by nitroso compounds, and the resulting metabolite is believed to interfere with intracellular transcription, translation and cellular division. Furthermore, metronidazole easily crosses the blood brain barrier because its molecular weight is small enough to reach the therapeutic concentration in the cerebrospinal fluid [5]. Some documented that the vasogenic and cytotoxic edema [6], reversible-localized ischemia as observed in cases of diffusion restriction [4], mitochondrial dysfunction [7], protein synthesis inhibition by binding to neural RNA [8], modifying cerebellar and vestibular gamma-aminobutyric acid receptor are the proposed mechanisms [9]. Although the mechanism of MIE remains unclear, these characteristics of MNZ might be related with the occurrence of MIE.

Total doses of MNZ which could induce encephalopathy are highly variable. It was reported that symptoms occur at total cumulative doses of 0.25–1095 g, and the median duration of treatment before the onset of symptoms being 54 days [1]. Another report revealed that the development of MIE required total usage of 21–182 g of MNZ [10]. While occurrence of MIE could be related with total doses and duration of MNZ, some patients had (presented with MIE with less than 0.25g (general dose in the treatment of infections) and shorter duration [11]. Other risk factors for MIE might be existing. Cheong et al. reported that the half-life of MNZ was 3-fold higher in patients with hepatic encephalopathy. In addition, 30%–60% MNZ are metabolized in the liver, leading to increased MNZ concentrations in patients with hepatic dysfunction [12].

Using the Naranjo adverse drug reaction (ADR) probability scale, our patient had a "probable" metronidazole related ADR [13]. This score is suggested by the correlation of clinical symptoms after administration of metronidazole, followed by slow improvement after its discontinuation.

Our case received HBO while using MNZ. HBO is one of the most useful therapeutic options in the treatment of osteomyelitis [14,15]. Its clinical efficacy is explained as follows; modulation of intracellular transduction cascades, leading to synthesis of growth factors and promoting wound healing and ameliorating post-ischemic and post-inflammatory injuries. On the other hand, adverse effects of HBO could generate free radicals, resulting in cell damage. Central nervous system (CNS) oxygen toxicity is one side effect of the HBO therapy. This occurs at an incidence of approximately 1–4 in 10,000 patient treatments [16–18]. Involvement of the reactive oxygen species (ROS) was presumed to be the mechanism of central nervous system dysfunction by HBO therapy [19].

Mechanism of action of MNZ is known to be that it generates free radicals that are toxic to bacteria as well as to cells. Using HBO and MNZ at the same time, synergic overgeneration of free radicals could cause MIE.

Anaerobes could be causative pathogens in head and neck infections [20–22], thus MNZ is one of several good therapeutic options. In our case, "the swab smear showed a Gram-positive coccus (4+) and the culture was negative." Results suggested the possibility of anaerobes as a causative pathogen. In addition, patients with osteomyelitis generally needs an antibiotic treatment for 6 weeks to 3 months longer as our case.

From now on, occurrence of MNZ using HBO would be increased in the treatment of osteomyelitis. Physician should consider MIE when patients receive MNZ with HBO therapy, even when total dose of MNZ is within the normal range.

In conclusion, MIE is not common but could rarely occur. The association between duration or dose of MNZ and toxicity does not seem to exist; small amounts of MNZ can cause MIE. While HBO therapy is useful in the treatment of osteomyelitis, it could be one of the risk factors of MIE.

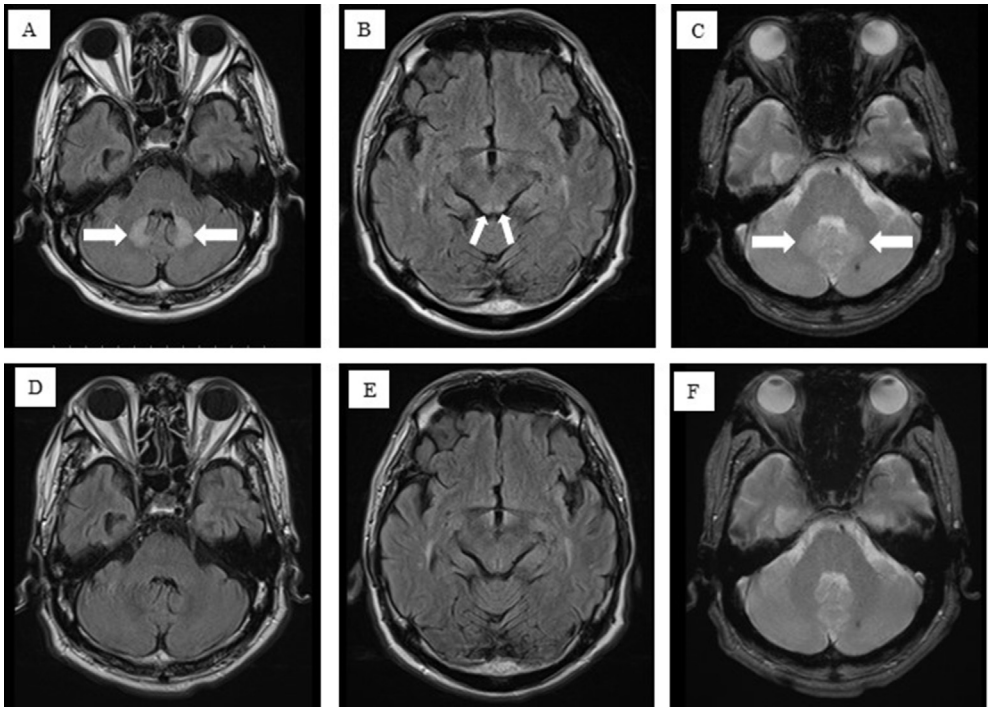

Fig. 2. Shows an axial brain MRI. (A, B, D, E) Fluid-attenuated inversion recovery and (C, F) T2-weighted image. (A, C, D, and F) cerebellar dentate nucleus and (B, E) mid-brain tegmentum.(A–C) MRI showing high-intensity areas (white arrows) at 2 days of hospital visit. (D–F) Complete resolution of high-intensity areas at 32 days of metronidazole discontinuation.

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None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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