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Case Report

Dental treatment for patients with Nakajo-Nishimura syndrome: Report of three cases

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ABSTRACT

Nakajo-Nishimura syndrome, which is a specific autoimmune disorder characterized by chronic inflammation, emaciation, and exhaustion, is inherited in an autosomal recessive fashion and is representative of proteasome dysfunction. Its main clinical features include pernio-like red-to-purple skin plaques on the hands and feet, periodic fever, progressive localized atrophy of fat and muscle, emaciation, elongated and thickened fingers and toes, joint contractures, enlarged liver, basal ganglia calcification, and a heliotrope rash. The dental treatment for three patients with Nakajo-Nishimura syndrome is described. Dental extractions and procedures were successfully performed without causing any obvious intraoperative or postoperative complications, although all three patients showed progressive trismus. When performing a dental procedure in patients with proteasome dysfunction, preoperative antibiotic therapy should be given because they are susceptible to infection due to the long-term use of high-dose steroids. Drug-related osteonecrosis of the jaw should also be considered. Proteasome dysfunction is characterized by joint contractures and progressive fat and muscle atrophy; thus, the patients are also likely to have reduced mouth opening, and it is a challenge for them to clean their teeth by brushing, which may lead to the occurrence of dental caries in molars. Therefore, scheduling regular interventions by dentists needs to be considered for patients with proteasome dysfunction.

1. Introduction

Nakajo-Nishimura syndrome, which is a specific autoimmune disorder characterized by chronic inflammation, emaciation, and exhaustion, is inherited in an autosomal recessive fashion. This disease was first reported by Nakajo et al. in 1939 as secondary hypertrophic periostitis with pernio [1]. In 1950, Nishimura reported three cases in which hypertrophic periostitis occurred in two families of blood relatives, suggesting the possibility that the condition may be a primary genetic disorder [2]. Since then, roughly 30 cases with Nakajo-Nishimura syndrome have been reported in Japan [3]. Although this disease was initially considered Japanese-specific, two clinically very similar conditions were reported in 2010, one by Torrelo et al. in Spain as CANDLE syndrome (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome) and the other by Garg et al. in America as JMP syndrome (joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome) [4,5]. Later, PSMB8 gene mutations were found to be the cause of the three diseases, including Nakajo-Nishimura syndrome, revealing the global distribution of proteasome dysfunction [6].

These three syndromes are known to be due to proteasome dysfunction resulting from different mutations within the same gene, and there are at least 60 known cases worldwide. Its main clinical features include pernio-like red-to-purple skin plaques on the hands and feet, periodic fever, progressive localized atrophy of fat and muscle, emaciation, elongated and thickened fingers and toes, joint contractures, enlarged liver, basal ganglia calcification, and a heliotrope rash. These three syndromes were diagnosed based on these features and the presence of PSMB8 gene mutations.

To date, there have been no reports of the oral features or dental care in patients with proteasome dysfunction. In 2015, Roberts et al. described a patient with CANDLE syndrome, focusing on the dental aspects, though they were able to elucidate dental diseases and characteristics associated with the disorder for only one case [7]. The dental treatment of three patients with Nakajo-Nishimura syndrome is described.

2. Case reports

2.1. Case 1

In March 2018, a 46-year-old man with Nakajo-Nishimura

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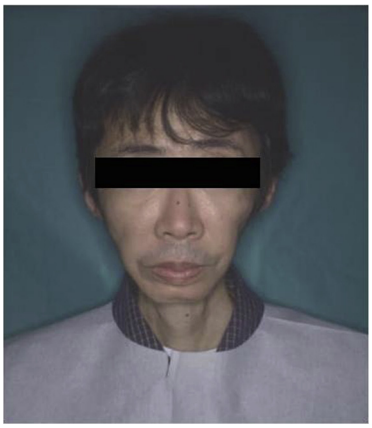

Fig. 1. Case 1: The patient has an emaciated, bony face.

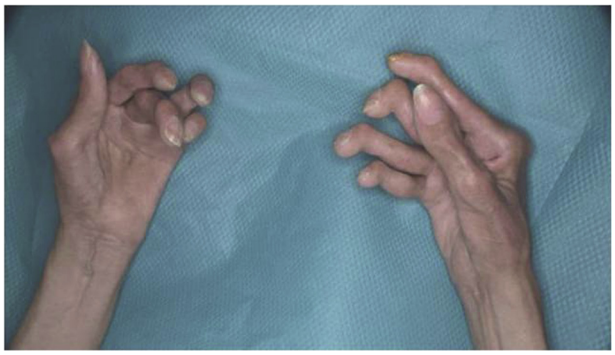

Fig. 2. Case 1: Contractures of elongated and thickened fingers.

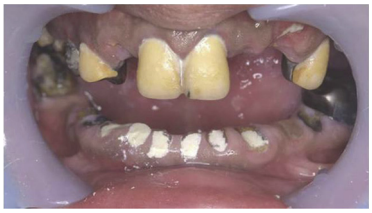

Fig. 3. Case 1. Maximum opening position.

syndrome presented to our hospital with a chief complaint of difficulty opening his mouth that had progressed gradually since 2012. The patient had been under outpatient follow-up for Nakajo-Nishimura syndrome by the dermatologist of our hospital who had made the diagnosis [8]. The patient had a prior history of hypothyroidism and was taking haloperidol, neostigmine methylsulfate, and magnesium oxide. He had no other family member affected by this disease. On general examination, the patient was emaciated and had a bony face, contractures of elongated and thickened fingers, and a pernio-like rash along the lateral side of the foot (Figs. 1 and 2). Oral examination showed many dental caries, and mouth opening was 10 mm, showing severe trismus (Fig. 3). Oral hygiene was somewhat poor.

A panoramic X-ray showed no jaw abnormalities or lesions in the mandible (Fig. 4).

In April 2018, a routine root canal procedure was performed to treat apical periodontitis in the mandibular anterior teeth.

No intraoperative or postoperative complications were noted. There were no marked changes in his general condition, and wound healing was uneventful. The patient has since been followed-up with oral cleaning.

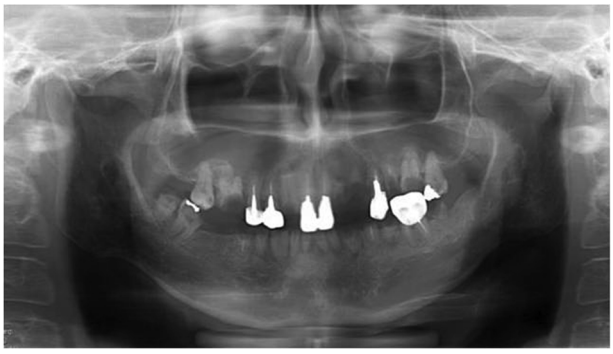

Fig. 4. Panoramic X-ray of case 1.

2.2. Case 2

In December 2014, a 39-year-old man with Nakajo-Nishimura syndrome noticed a dental caries in the left maxillary third molar and mild pain around the left mandibular third molar. The patient has been under outpatient follow-up for Nakajo-Nishimura syndrome by the dermatologist of our hospital who had made the diagnosis. He was referred to our department for extractions of the left maxillary and mandibular teeth. He had a prior history of pneumonia and was taking prednisolone 10 mg/day, methotrexate, omeprazole, eldecalcitol, ritonavir, alprazolam, and metoclopramide. He had no other family members affected by this disorder.

On general examination, the patient was emaciated and had an angular face, with a heliotrope rash, elongated and thickened fingers, and a pernio-like rash along the lateral side of the foot. Oral examination showed dental caries in the left maxillary third and fourth molars and mild redness and swelling around the left mandibular third molar. Oral hygiene was good, and no malocclusion was noted. Forced mouth opening was 30 mm, showing mild trismus.

A panoramic X-ray showed no jaw abnormalities or lesions in the mandible (Fig. 5).

In April 2015, we diagnosed dental caries in the left maxillary third and fourth molars and periodontitis at the left mandibular third molar as hopeless tooth. The left maxillary third and fourth molars were extracted one hour after the administration of levofloxacin 500 mg. In July 2015, the left mandibular third molar was also extracted one hour after the administration of levofloxacin 500 mg. No intraoperative or postoperative complications were noted at the time of tooth extraction, and wound healing was uneventful, without marked changes in his general condition.

2.3. Case 3

In May 2016, a 47-year-old man with Nakajo-Nishimura syndrome presented to our hospital with a chief complaint of difficulty opening his mouth. The patient has been under outpatient follow-up for Nakajo-Nishimura syndrome by the dermatologist of our hospital who had made the diagnosis [8]. The patient had a prior history of pneumonia and was taking prednisolone 10 mg/day. He had no other family members affected by this disease.

On general examination, the patient had a characteristic angular

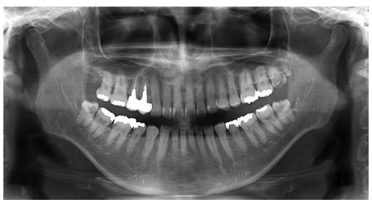

Fig. 5. Panoramic X-ray of case 2.

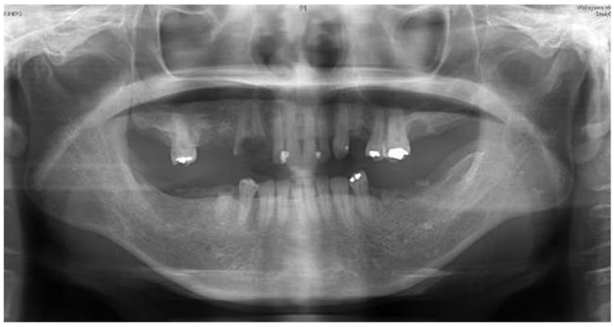

Fig. 6. Panoramic X-ray of case 3.

face with marked fat and muscle atrophy in both upper extremities. Oral examination showed many dental caries. Mouth opening was 14 mm, showing severe trismus. Oral hygiene was somewhat poor.

A panoramic X-ray showed no jaw abnormalities or lesions in the mandible (Fig. 6). Since May 2016, the patient has been receiving oral cleaning to reduce inflammation. There was uneventful without any complications or marked changes in his general condition. The patient has since been followed-up with oral cleaning.

3. Discussion

Dental extractions and procedures were successfully performed in three patients with Nakajo-Nishimura syndrome without causing any obvious intraoperative or postoperative complications, although all of them showed gradually progressive trismus, with no trigger. In these cases, the temporomandibular joint (TMJ) itself was normal, and the limitation occurred due to contraction of peri-articular soft tissues or masticatory muscular atrophy. It seems that the cause of trismus was the same as that of the finger contractures. In three cases, the finger joints progressed earlier than the TMJ. Activities of daily living were markedly deteriorated due to progressive localized atrophy of fat and muscle in all cases.

Nakajo-Nishimura syndrome is known to be due to proteasome dysfunction. The present patients had onset in infancy. The proteasome is an intracellular protease complex specializing in degrading poly-ubiquitinated proteins [9]. It is involved in not just degradation and quality control of waste proteins, but also various cellular functions such as cell cycles, DNA repair, and signal transduction represented by NF-kB activation.

The physical characteristics of proteasome dysfunction are a pernio-like rash, nodular erythematous rash, and panniculitis in early childhood and gradual progression of elongated and thickened fingers, joint contractures, and partial fat and muscle atrophy affecting mostly the face and upper extremities. These characteristics have not yet been clearly elucidated, although they may reflect some of the proteasome inhibition effect.

Although there are reports of joint contractures of the hands and feet resulting from proteasome dysfunction, the disorder also affects the TMJ; three patients with the same disorder, as presented in the current paper, came to our department for routine check-ups but were unable to receive dental treatment readily due to excessively reduced mouth opening.

Although this disease was initially considered specific to Japanese people, cases that have similar clinical features were reported in 2010 from Western and Middle Eastern countries as JMP and CANDLE syndromes. All three syndromes have been reported to be associated with mutations in the PSMB 8 gene, which encodes an inducible subunit of proteasome complex [8,9]. Proteasome dysfunction is an extremely rare disorder, and there are at least some 60 patients affected worldwide, of which around 10 are from Japan. The treatment of Nakajo-Nishimura syndrome has not been established. Gina suggested that JAK1/2 inhibition with baricitinib was effective in the treatment of CANDLE syndrome, and lipodystrophy was improved [10].

The present three patients and another patient receiving dental treatment for CANDLE syndrome have been described to date. As for the dental characteristics, the patient with CANDLE syndrome had diastemas in the anterior maxilla, a hypoplastic air sinus, and osteopenia of the jaw. However, these were not obvious in the present three patients. In addition, there were no abnormalities in the bone of the TMJ on panoramic X-rays. Further studies are necessary to examine the dental characteristics of patients with proteasome dysfunction. When performing a dental procedure in patients with proteasome dysfunction, preoperative antibiotic therapy should be given because they are susceptible to infection due to the long-term use of high-dose steroids. In Case 2, the patient was prescribed levofloxacin for recrudescent pneumonia. However, there is room to reconsider the choice of levofloxacin with respect to antibiotic stewardship for preoperative antibiotic therapy.

Drug-related osteonecrosis of the jaw should also be considered. Proteasome dysfunction is characterized by joint contractures and progressive fat and muscle atrophy [11]. The patients had early finger contractures and reduced mouth opening. It is a challenge for them to clean their teeth by brushing, which may lead to serious dental caries and periodontitis in the oral cavity. Therefore, scheduling regular interventions by dentists needs to be considered for patients with proteasome dysfunction.

Ethical approval

The authors have obtained the informed consent of patients for taking and publishing photographs.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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