Case Report

A case of multiple jaw cysts in the Neurofibromatosis-Noonan syndrome

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Abstract

Neurofibromatosis-Noonan syndrome (NFNS) is an uncommon chromosomal disorder showing features of both neurofibromatosis (NF-1) and Noonan syndrome (NS). We encountered a case of NFNS with keratocystic odontogenic tumor and dentigerous cysts. A 19-year-old Japanese girl was referred to our hospital with a chief complaint of swelling in the left side of the mandible. The patient showed symptoms of both NF-1, in the form of café-au-lait spots and neurofibromatosis, and NS, in the form of short stature, intellectual disturbance, webbed neck, and hypertelorism. Panoramic radiography showed three cystic lesions, one on each side of the mandible and one on the left side of the maxilla. All cysts were removed surgically under general anesthesia. Histopathological examination revealed that both mandibular cysts were dentigerous cysts, while the maxillary cyst was a keratocystic odontogenic tumor. No recurrence has been seen as of 5 years postoperatively. Multiple jaw cysts might be added as a potential finding in NFNS.
1. Introduction

Neurofibromatosis-Noonan syndrome (NFNS) is an autosomal-dominant disorder that shows the characteristics of both neurofibromatosis type I (NF-1) and Noonan syndrome (NS) [1]. Seven diagnostic criteria for NF-1 were suggested by the National Institutes of Health in 1988, as follows: 1) six or more café-au-lait spots; 2) two or more lesions representing neurofibromatosis of any type or one plexiform neurofibroma; 3) freckling in the axillary or inguinal regions; 4) optic glioma; 5) two or more Lisch nodules; 6) a distinctive osseous lesion such as sphenoid dysplasia or pseudarthrosis; and 7) a first-degree relative (parent, sibling, or offspring) with NF-1 according to the above criteria. NF-1 is diagnosed with positive findings for two or more of these 7 items [2]. Meanwhile, NS is a syndrome showing short stature, chest deformity, congenital heart disease, webbed neck, short neck, and hypertelorism [3].

Bone cysts are the most common lesion occurring in the jawbones. Jaw cysts are usually solitary, and multiple jaw cysts are rare and generally associated with certain syndromes, particularly nevoid basal cell carcinoma syndrome (NBCCS). Jaw cysts have not been identified as a specific characteristic of NFNS. We encountered a rare case of NFNS presenting with multiple jaw cysts. We present this case and discuss the possibility of an association between multiple jaw cysts and NFNS.

2. Case Report

A 19-year-old Japanese girl was referred to the Department of Oral Surgery at Nagasaki University Hospital with a chief complaint of swelling on the left side of the mandible in November 2008. Nutritional status was good with a height of 151 cm and a weight of 50 kg. She showed hypertelorism, the prominent epicanthal folds, the short and broad nose with a depressed root, the distinctive upper lip with a deeply grooved philtrum, and the short and
wide neck (Fig. 1A). Neurofibromatosis and café-au-lait spots were seen throughout the body (Fig. 1B). Gingival redness and discharge of pus were observed around the crown of a partially impacted mandibular left second molar. Panoramic x-ray showed cyst-like radiolucencies bilaterally in the mandible and in the left maxilla (Fig. 2A). Simple computed tomography (CT) showed cystic lesions from the mandibular second molar to the condylar process involving the crown of the third molar on both sides and a cystic lesion in the posterior region of left maxilla (Fig. 3A, 3B).

In terms of medical history, delayed motor development had been noticed at the 3-month infant examinations. At 4 months old, the patient was referred to the Department of Pediatrics at Nagasaki University Hospital due to high fever, poor suckling, and diarrhea, and NFNS was diagnosed based on clinical findings of café-au-lait spots over the whole body, short stature, webbed neck, low hairline, hypertelorism, and shielded chest, but she did not have congenital heart disease. Since her short stature had not been improved, she took growth hormone with the dose of 0.5 U/kg/week from 5 years old to 11 years old. Then, her stature was improved. Family history was non-contributory.

Swelling of the left cheek was noticed at 10 years old and she visited an oral surgery clinic at another hospital. Although panoramic x-rays and CT revealed a unilocular cyst-like lesion in the left mandible, the decision was made to observe the lesion without treatment. Unfortunately, no information was available on whether any other cystic lesions were present at that time. Although jaw cystectomy was planned in 2008, left ovarian tumor found during the preoperative general examination for cystectomy was surgically removed in the Department of Obstetrics and Gynecology at Nagasaki University Hospital in July 2008, and histopathologically diagnosed as fibroma. Cystectomy was then performed under general anesthesia in April 2009. The mandibular second molars were extracted and the cysts with an impacted third molar on the both side of mandible were removed completely. A cyst with
impacted second molar in the left maxilla was also removed. Cottage cheese-like contents were apparent in the cyst. Since keratocystic odontogenic tumor (KCOT) was suspected clinically, a surface layer of bone surrounding the cyst wall was shaved. Primary sutures were placed at each site. No findings suggestive of recurrence were observed during 5 years of follow-up (Fig. 2B).

The lesion in the left maxilla represented a cyst containing fibrosis connective tissue lined by stratified squamous epithelium of uniform thickness. The epithelium showed parakeratosis, and part had invaginated into the fibrous tissue (Fig. 4A, B). Cyst walls on both sides of the mandible represented fibrous tissue covered by thin, stratified non-keratinized squamous epithelium with epithelial processes. Round inflammatory cells had infiltrated the fibrous connective tissue (Fig. 4C), and odontogenic epithelial islands were also seen in the non-inflamed area (Fig. 4D). The cyst in the left maxilla was diagnosed as KCOT, and cysts on both sides of the mandible were diagnosed as dentigerous cyst.

3. Discussion
Odontogenic cysts are the most common lesion arising in the jawbones. These lesions are usually solitary, and multiple jaw cysts are thought to be rare and generally associated with syndromes and systemic conditions. We encountered a case of multiple odontogenic cysts in a NFNS patient, but no previous reports have described cases showing similar conditions. NBCCS is the most common syndrome presenting with multiple jaw cysts, which histopathologically represent KCOTs [4]. Other than NBCCS, orofacial digital syndrome [5], Ehler-Danlos syndrome [6], Simpson-Golabi-Behmel syndrome [7] and NS [8] can present with multiple KCOTs reportedly in English written literatures, though only a single case report has been reported for each. Odontogenic cysts in the present case were pathologically identified as KCOT and dentigerous cyst. In terms of dentigerous cyst, cases of
mucopolysaccharidosis [9] and cleidocranial dysplasia [10] reportedly show multiple jaw cysts. This is the first report to show both KCOT and dentigerous cysts in a single patient with a certain syndrome.

The present case was diagnosed with NFNS based on clinical findings alone, since she showed many of the characteristic features of NF-1 and NS. The differential diagnosis with NBCCS is important in terms of multiple jaw cysts, but it had been denied with clinical diagnosis since she had only one suspicious major criterion of multiple KCOTs and one minor criterion of ovarian fibroma for NBCCS. The genes responsible for both NF and NS have now been identified. NF-1 is caused by mutations in the $\text{NF-1}$ gene on chromosome 17. $\text{NF-1}$ encodes neurofibromin, a RasGAP, which is a negative regulator of RAS [1]. Meanwhile, seven genes have been shown to be associated with NS to date: $\text{PTPN11}$, $\text{SOS1}$, $\text{RAFI}$, $\text{KRAS}$, $\text{NRAS}$, $\text{SCOHC2}$, and $\text{CBL}$ [3]. The products of all of these genes are associated with the Ras/MAPK pathway. NF-1 and NS are included in a class of developmental disorders termed “RASopathies”, caused by germline mutations in genes encoding components or regulators of the Ras/MAPK pathway [11]. On the other hand, NBCCS, which shows multiple KOCTs, is known to be caused by mutations in the $\text{PTCH}$ gene, which encodes a receptor for Sonic Hedgehog (SHH). $\text{PTCH}$ mutations cause not only syndromic KCOTs, but also sporadic KCOTs [12]. Although crosstalk between the Ras/MAPK pathway and SHH pathway has not been clarified to date, the MAPK cascade has recently been reported to be involved in the positive regulation of SHH signaling in gastric cancer [13], and Ras gain-of-function mutations have also been reported to result in decreased SHH levels in hair follicle development [14]. Hence, mutations in the Ras/MAPK pathway in NFNS patients have also been reported to relate to the development of KCOT through the SHH pathway. Only one of the three cysts in this case was KOCT, but KCOT could be histopathologically diagnosed as dentigerous cyst if the epithelial morphology is changed by inflammation [15]. All cysts in
this case could have represented KCOT. Furthermore, the development of ovarian fibroma could be related to the crosstalk of these signal pathways.

Oral findings in patients with NFNS are likely to include features appearing both in NF-1 and NS. The presence of impacted, displaced or missing teeth, particularly in the mandible, and overgrowth of the alveolar ridge are recognized as oral manifestations of NF-1, and these malformations are strongly associated with plexiform neurofibroma originating from the trigeminal nerve [16]. Disturbance of tooth eruption may cause the development of dentigerous cysts, but neurofibroma was not found in the jaws of the present patient. Oral findings associated with NS include a high arched palate, dental malocclusion, articulation difficulties, and micrognathia [3], none of which were observed in our case. Radiolucent cystic lesions of the jaw are listed among the phenotypic features of NS and NFNS. However, such lesions do not represent dentigerous cyst, but rather multiple giant cell lesions [17]. On the other hand, beside the report by Connor et al. [8] of NS in a 17-year-old male patient who presented with multiple KCOTs, no reports have described multiple jaw cysts associated with NF-1, NS or NFNS. One possibility is that multiple jaw cysts coincidentally developed in the present NFNS patient. According to an analysis of dentigerous cyst in British Columbia by Zhang et al. [18], 51 of 2029 patients (2.5%) showed multiple dentigerous cysts, one of whom had both dentigenous cyst and KCOT.

In conclusion, this is the first report of multiple jaw cysts, including bilateral dentigerous cysts in the mandible and a KCOT in the maxilla. Although multiple jaw cysts might arise by chance in a patient with NFNS, the possibility that the gene mutations in patients with NFNS may indirectly affect the development of multiple jaw cysts cannot be ruled out, given that NFNS features many phenotypes including abnormalities of the jawbones. Multiple jaw cysts might be added as a feature of NFNS.
Figure legends

Fig. 1.
(A) facial photo at the initial visit
(B) neurofibromatosis (back)

Fig. 2.
(A) Pre-surgery (multiple cyst-like radiolucent images in the jaw)
(B) 3rd month after surgery (ossification at the mandibular angle was found)

Fig. 3.
(A) Radiolucent cystic lesion included a third molar clown were found in the area of mandibular molar to condyle on both side
(B) Left maxillary lesion showed bulging posteriorly

Fig. 4.
HE stain (A: x2.5, B: x20, C: x10, D: x40)
Left maxillary lesion (A, B) was a cyst of fibrous connective tissue covered by stratified squamous epithelium showing hyperparakeratinization and a part invaginated into the fibrosis tissue. Cyst wall in the right (C) and left mandible (D) were fibrous tissue covered by thin stratified non-keratized squamous epithelium. The fibrous tissue included round cell infiltration (C) and dontgenic epithelial islands (D).

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Left maxillary lesion (A, B) was a cyst of fibrous connective tissue covered by stratified squamous epithelium and a part was collapsed into the fibrosis tissue. Cysts in the right (C) and left mandible (D) were covered by thin stratified squamous epithelium included dentogenic epithelial masses.
Fig. 1. (A)
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Fig. 2. (B)
Fig. 3. (A)
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Fig. 4. (A)
Fig. 4. (B)