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Case Report
Head and Neck Oncology

Oral squamous cell carcinoma arising in a patient with Werner syndrome

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N. Kuribayashi, D. Uchida, Y. Hamasaki, H. Kawamata: Oral squamous cell carcinoma arising in a patient with Werner syndrome. Int. J. Oral Maxillofac. Surg. 2019; 48: 1394–1397.

Abstract. Werner syndrome (WS) is an autosomal recessive disorder characterized by physical signs and symptoms, including premature aging and scleroderma-like skin changes. The gene responsible for WS is the *WRN* gene. A significant proportion of WS-related malignant tumours are non-epithelial types, and the incidence of oral squamous cell carcinoma (SCC) is rare. A case of oral SCC of the lower alveolus and gingiva arising in a 63-year-old woman with WS is reported here. Biopsy confirmed moderately differentiated SCC. Surgical resection was performed and there was no recurrence or metastasis at the 3-year follow-up. Mutation analysis using next-generation sequencing, detected no mutations in the genes encoding the molecules strongly involved in the development of oral SCC, such as *TP53* or *PIK3CA*. No obvious mutations were detected. Based on the results of the study, the results of mutation analysis suggest that this case might be genetically different from the common mechanisms of SCC in the oral cavity.

Key words: oral cancer; Werner syndrome; squamous cell carcinoma.

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Werner syndrome (WS) is an autosomal recessive disorder characterized by physical signs and symptoms, including premature aging and scleroderma-like skin changes. Approximately 80% of all cases reported worldwide are Japanese[1]. The gene responsible for WS is the *WRN* gene[2], which encodes the RecQ-type DNA helicase protein, making genetic diagnosis possible[3]. Twenty percent of patients with WS develop malignant tumours; however, unlike malignant tumours in the general population, a significant proportion of WS-related malignant tumours are non-epithelial types, such as malignant melanoma and osteosarcoma, and the incidence of carcinoma is rare[4,5]. A case of oral squamous cell carcinoma (SCC) arising in a patient with WS is reported here.

Case report

The patient was a 63-year-old woman, who visited the Department of Oral and Maxillofacial Surgery at Dokkyo Medical University Hospital for a detailed examination of the buccal gingiva of the right mandibular molar. The patient had been seen in a dental clinic for an erosive and ulcerative lesion of the mandibular molar gingiva. The patient had a history of WS and was diagnosed with a 4/4 mutation, which is a G to C mutation at one base pair upstream of the 5′ end of exon 26 in the *WRN* gene. She was also being treated in

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the Department of Dermatology of Dokkyo Medical University Hospital. There were no other family members with WS and no family history of consanguineous marriage or cancer. The patient had never smoked.

The patient's height was 142 cm and her weight was 36 kg. She exhibited scleroderma-like skin changes, a bird-like facial appearance, and a high-pitched hoarse voice (Fig. 1). In the oral cavity, erythema/ulceration was observed in the mandibular gingiva from the first molar to the second molar on the right side; however, no induration was palpable. She had a dental bridge over the right mandibular first premolar to first molar, which was not loose, and no hypoesthesia was observed in the right lower lip or mental region. No findings of bone resorption were observed on panoramic X-ray corresponding to the right mandibular molar. The gingival lesion was tentatively diagnosed as ulcerative stomatitis and a biopsy was performed to exclude gingival cancer, but only lichenoid reaction was observed and no tumour cells were seen.

The patient was followed up every 1 or 2 months as an outpatient. Upon re-examination at 1 year and 2 months after the first visit, an ulcer was observed on the buccal-side gingiva corresponding to the right mandibular second premolar. This ulceration was surrounded by red, slightly raised granular tumourous tissue (Fig. 2), and the erythematous lesion extended to the lingual side to the first molar. It was suspected that the lesion was a carcinoma of the lower gingiva, and a new biopsy confirmed moderately differentiated SCC (Fig. 3). Panoramic radiographs and computed tomography imaging did not reveal any bone destruction. Fluorodeoxyglucose positron emission tomography (FDG PET) showed uptake at the site of the lesion ($SUV_{max} = 6.5$), but no lymph node or distant metastasis was noted. The tumour was staged T2N0M0 and surgical resection was performed with clear margins. No adjuvant therapy was given. The patient was disease-free at the 3-year follow-up.

As oral cancer associated with WS is very rare, mutations of the driver genes that are commonly associated with oral cancer were analysed[6], using genomic DNA extracted from the patient's tumour. Mutation analysis of the entire exons of *TP53*, *CDKN2A*, *FBXW7*, and *NOTCH1*, exons 10 and 21 of *PIK3CA*, and exons 2 and 3 of *HRAS* was performed using next-generation sequencing (Illumina MiSeq; Illumina Inc., San Diego, CA, USA). Surprisingly, no mutations of these molecules could be detected in this patient (data not shown).

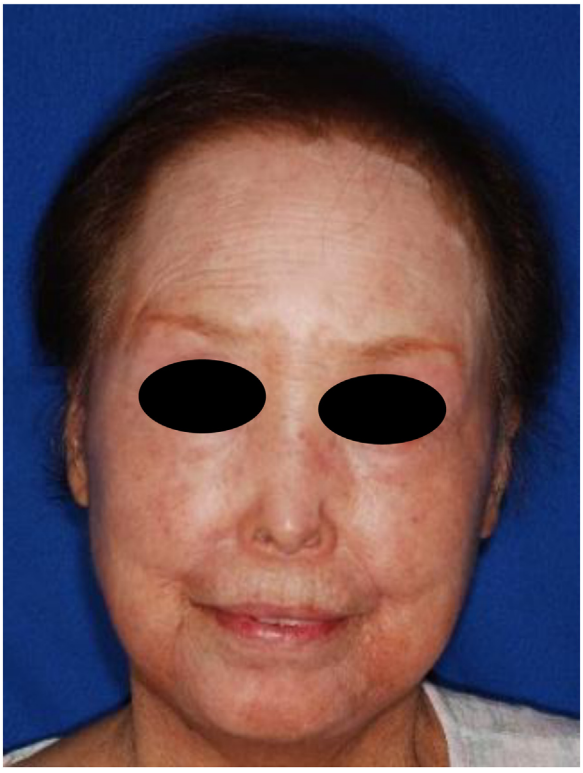

Fig. 1. Facial photograph: characteristic facial abnormalities were observed, including bird-like facial features with a narrow and pointed nose and thin lips.

Discussion

This report describes a case of oral SCC arising in a patient with WS. The *WRN* gene is the gene responsible for WS. This gene is present in a region of the short arm of chromosome 8 (8q11-12) and comprises 35 exons, according to the linkage analysis reported by Goto et al.[3] It was further reported by Yu et al. that the *WRN* gene encodes RecQ-type helicase protein[2]. More recently, it has been reported that the WRN protein likely dissociates telomeric structures during replication of the telomeric loop[7]. In patients with WS, unwinding of the telomere loop during replication is affected, leading to accelerated loss of telomere elongation, causing premature aging[7]. Although three homotypic mutations (1/1, 4/4, and 6/6) are common in Japanese patients with WS[8], the correlation between the type of mutation and the malignant potential of tumours arising in WS is poorly understood. In the case presented here, a 4/4 mutation was detected in the *WRN* gene. In mutation 4/4, a G to C mutation at 1 bp upstream of the 5′ end of exon 26 induces exon 26 skipping (corresponding to codons 1047 to 1048), resulting in the formation of an incomplete WRN protein. In addition, mutation 4/4 is the most commonly observed variant in the Japanese population[8]. Although this case was not associated with a family history of consanguineous marriage, the founder effect, unique to Japanese individuals, was likely involved.

Patients with WS typically exhibit bird-like facial features, grey hair, cataracts, scleroderma-like skin changes, soft tissue calcification, and high-pitched hoarseness, and they often die from cardiovascular diseases or neoplasia in their 50s[4]. This patient exhibited most of the primary clinical signs and symptoms of the diagnostic criteria. Several neoplasms develop in approximately 20% of patients with WS[5]. Moreover, according to a report by Goto et al., while the ratio of epithelial to non-epithelial tumours is 10:1 in the general population, non-epithelial tumours are more common in patients with WS, occurring at a ratio of 1.5:1[9]. Of the epithelial tumours, thyroid cancer is the most common, and it appears that there have been no reports of oral SCC.

Despite the high incidence of malignant tumours, the molecular and genomic characteristics of epithelial tumours arising in patients with WS have not been well studied. Only one study by Tokita et al. could be found, which reported pancreatic cancer arising in patients with WS[10]. They

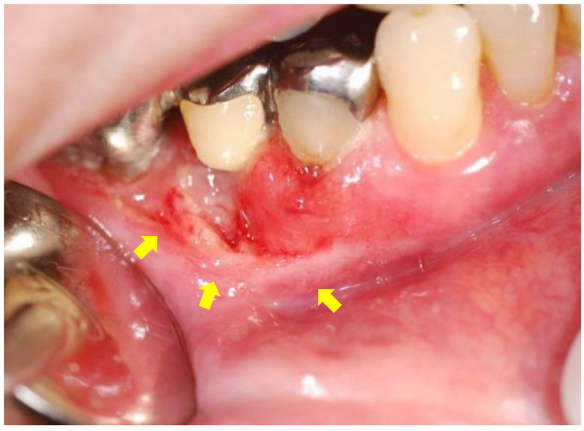

Fig. 2. Carcinoma of the lower alveolus and gingiva: an ulcer was observed on the buccal-side gingiva corresponding to the right mandibular second premolar, and the erythematous lesion extended to the lingual side of the distal portion of the right mandibular first molar.

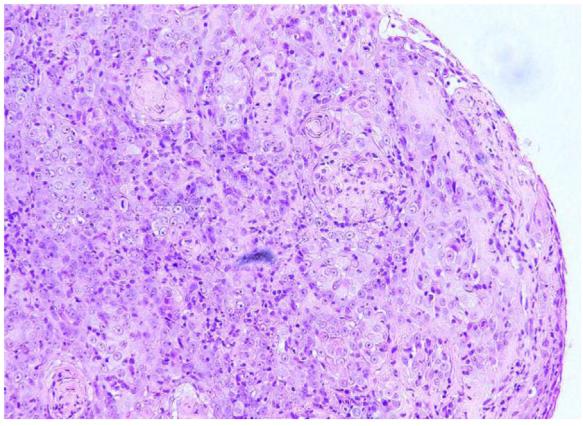

Fig. 3. Histopathology (haematoxylin and eosin staining, ×200): moderately differentiated squamous cell carcinoma was identified in the biopsy sample.

detected mutations in the *KRAS* and *TP53* genes commonly associated with pancreatic cancer progression in the pancreatic cancers that developed in patients with WS, suggesting an association of the gene mutations with WS[10]. A large-scale genomic mutation profile of head and neck SCC was recently revealed, which indicated *TP53* (72% mutation), *CDKN2A* (22% mutation), *PIK3CA* (21% mutation), *NOTCH1* (19% mutation), and *HRAS* (4% mutation) as possible driver mutations in patients with oral SCC[6].

Mutation analysis was therefore performed with these driver molecules for the patient presented here; however, no obvious mutations were detected. The pathogenesis of cancer in WS is considered to be explained by telomeres being shortened due to abnormalities in the DNA helicase, leading to chromosomal instability and increased cell life, resulting in carcinogenesis[10]. Thus, gene(s) that do not mainly function as the driver genes in common oral SCC may lead to or assist in the development of this cancer, because cancer including oral SCC is a genetic disease. Based on the results of the study, the results of mutation analysis suggest that this case might be genetically different from the common mechanisms of SCC in the oral cavity. However, if the developmental mechanism of this tumour is associated with the functional disorder of RecQ-type DNA helicase in WS, abnormality of some helicase target genes might be responsible for the carcinogenesis in the tumour. Although premature aging syndromes, including WS, are rare, future studies on more cases are necessary, as the information obtained could enable the clarification of mechanisms underlying senescence and oncogenesis.

Competing interests

None.

Ethical approval

Not required.

Patient consent

Patient consent was obtained.

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