Multiple adenomatoid odontogenic tumors in a patient with Schimmelpenning syndrome

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Schimmelpenning syndrome (SS) is a congenital neurocutaneous disorder characterized by the presence of linear nevus sebaceous, ophthalmic, neurologic, skeletal, urologic, and cardiovascular alterations. Oral manifestations related to SS mainly include dental defects, papillary lesions in the oral mucosa, giant cell lesions of the jaws, and odontogenic tumors. Here, we report the first case of multiple adenomatoid odontogenic tumor observed in a patient with SS. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:e12–e17)

Schimmelpenning syndrome (SS) (OMIM #163200), or sebaceous nevus syndrome, is a congenital neurocutaneous disorder of uncertain incidence characterized by linear nevus sebaceous as the main feature, along with neurologic, ophthalmic, and skeletal impairments.[1] The sebaceous nevus clinically appears as a smooth and yellowish or verrucous and brownish plaque along the Blaschko lines, mainly in the craniofacial area.[2]

The main extracutaneous manifestations of SS include central nervous system (CNS) abnormalities, such as seizures and delayed intellectual development[3]; ophthalmologic alterations[4]; and skeletal defects, such as kyphoscoliosis, hemihypertrophy of the limbs, and craniofacial exostosis.[5] Although less common, disorders of the genitourinary[6,7] and cardiovascular[1] systems can also occur.[1]

Although rare, SS is also associated with intraoral manifestations, including exophytic papillomatous growth in the mucosa, fibromatous enlargement of the tongue, and bifid uvula.[8–12] In addition, association of SS with benign tumors, such as odontoma,[13] ameloblastic fibro-odontoma,[14] adenomatoid odontogenic tumor (AOT),[15] ameloblastoma,[9,16] and central giant cell lesion of the jaws,[8,15] have been previously reported.

Here, we report the first case of multiple AOTs in a patient with SS.

CASE REPORT

A 6-year-old girl was referred for evaluation of a swelling in the mandible. Physical examination revealed unilateral patches of brownish coloration in the nose, upper lip, left cheek, and neck (Figure 1A) and a brown macule in the left eye conjunctiva. The patient was using medication for the prevention of seizures (valproic acid and carbamazepine) and had no other comorbidities.

Intraoral examination revealed a painless swelling located in the alveolar mucosa of the anterior mandible. The absence of teeth #81, #82, #83, and #63 was also observed. Small papillomatous lesions were observed in the fornix, gingiva, and labial mucosa, contiguous with the cutaneous nevus sebaceous (Figure 1B). Computed tomography revealed multiple unilocular well-defined hypodense areas containing hyperdense foci, associated with nonerupted teeth #81, #82, and #83 (Figure 2) and another mixed image on the left side of maxilla associated with the impacted tooth #63 (Figure 3). Differential diagnoses included odontoma, calcifying odontogenic cyst, and AOT.

The patient was referred to the Dermatology, Neurology, and Genetics services. Biopsy of the brownish patches was performed, and the results showed that the microscopic features were consistent with nevus sebaceous. Magnetic resonance imaging of the brain revealed hippocampal asymmetry. Echocardiography showed discrete bulging at the interventricular septum. Medial deviation of the middle phalanges of the second fingers and scoliosis were observed on radiographic

Statement of Clinical Relevance

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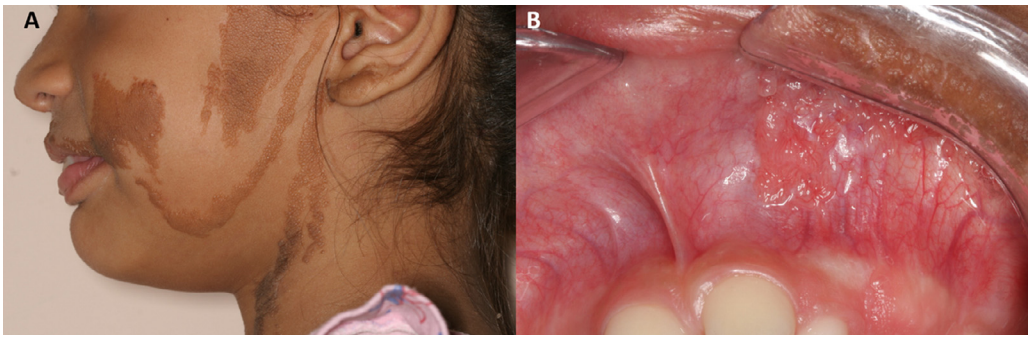

Fig. 1. Extraoral and intraoral clinical images of a patient with Schimmelpenning syndrome. **(A)** Unilateral spots of brownish color on the nose, upper lip, cheek, and neck of left side of the face. **(B)** Papillomatous growth in the gingiva, fornix, and labial mucosa.

images. Left limb hypertrophy was clinically evident. These findings, together with the history of seizures and delayed intellectual development, and the presence of linear sebaceous nevi on the skin of the face and neck with contiguous papillary lesions in the oral mucosa, were consistent with the diagnosis of SS.

Complete excision of the 4 tumors and the impacted primary teeth was performed, with the patient under general anesthesia (Figure 4A). All of the teeth associated with the tumors showed hypoplasia of enamel. Microscopic analysis helped confirm the diagnosis of AOT (Figures 4B to 4D). There was no evidence of recurrence after 60 months of follow-up (Figure 5).

DISCUSSION

SS was first described in 1957 by the German physician Gustav Schimmelpenning.[17] He reported an extensive nevus sebaceous, seizures, CNS disturbances, skull deformities, ophthalmologic impairments, and tumors in a 17-year-old girl. Subsequently, Feuerstein and Mims[18] reported in 1962, for the first time in the English language literature, 2 additional cases of linear nevus sebaceous associated with convulsions and intellectual disability.

SS is a subtype of the epidermal nevus syndrome (ENS). This group of syndromes encompasses different disorders characterized by any type of epidermal nevus associated with other system disturbances.[5,19] Phacomatosis pigmentokeratotica (PPK), nevus comedonicus syndrome, Becker nevus syndrome, Proteus syndrome, and CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome are some of the well-defined phenotypes of ENS conditions.[5] ENS also comprises several less-defined phenotypes, such as nevus trichilemmocysticus syndrome, didymosis aplasticosebacea, scalp syndrome, and Gobello syndrome.[20]

The differential diagnosis of SS includes PPK, nevus comedonicus syndrome, and Proteus syndrome.[5] Proteus syndrome and nevus comedonicus syndrome present similar extracutaneous findings, such as neurologic, ocular, and skeletal abnormalities[21–23]; however, their clinical appearance is significantly different from that of SS.[24–28] Of the syndromes that belong to the ENS group, PPK has the most similarities with SS. The co-occurrence of a speckled lentiginous nevus in a checkboard pattern and nevus sebaceous along the Blaschko lines is a hallmark of PPK,[28–31] whereas craniofacial nevus sebaceous is the main clinical manifestation of SS.[32] In contrast to SS, individuals with PPK may develop basal cell carcinoma and vitamin D−resistant hypophosphatemic rickets.[29,33] In addition, earlier colobomas and epibulbar lipodermoid tumors may be observed in children with SS, but these are usually absent in patients with PPK.[5] These clinical characteristics can help in the differential diagnosis of these 2 syndromes.

SS is characterized by the presence of linear nevus sebaceous, as well as neurologic, ophthalmic, skeletal, urologic, and cardiovascular alterations. The patient in the present report showed unilateral nevus sebaceous, involving the nose, upper lip, cheek, and neck. The lesions respected the midline and showed the classic distribution pattern following the Blaschko lines.[34–36] Although some authors have associated the presence of nevus in the craniofacial area with greater incidence of CNS disturbances,[37–39] there is no consensus about this association.[9,40]

Cognitive deficiency, seizures, hemimegalencephaly, agenesis of the corpus callosum, and brain vessel dysplasia are the main CNS alterations found in SS.[41] In the present case, the patient presented with frequent seizures, intellectual development delay, and hippocampal asymmetry. Ophthalmologic impairments, mainly choristomas[4,42] and colobomas,[43,44] are present in 59% of all SS cases.[2] Our patient had a brown macule in the left eye conjunctiva, but no decrease in visual acuity.

The main skeletal defects noted in SS are bone cysts, incomplete formation or hypoplasia of bone structures, kyphoscoliosis, hypertrophy of limbs, and skull asymmetry.[19,43] The medial deviation of the middle

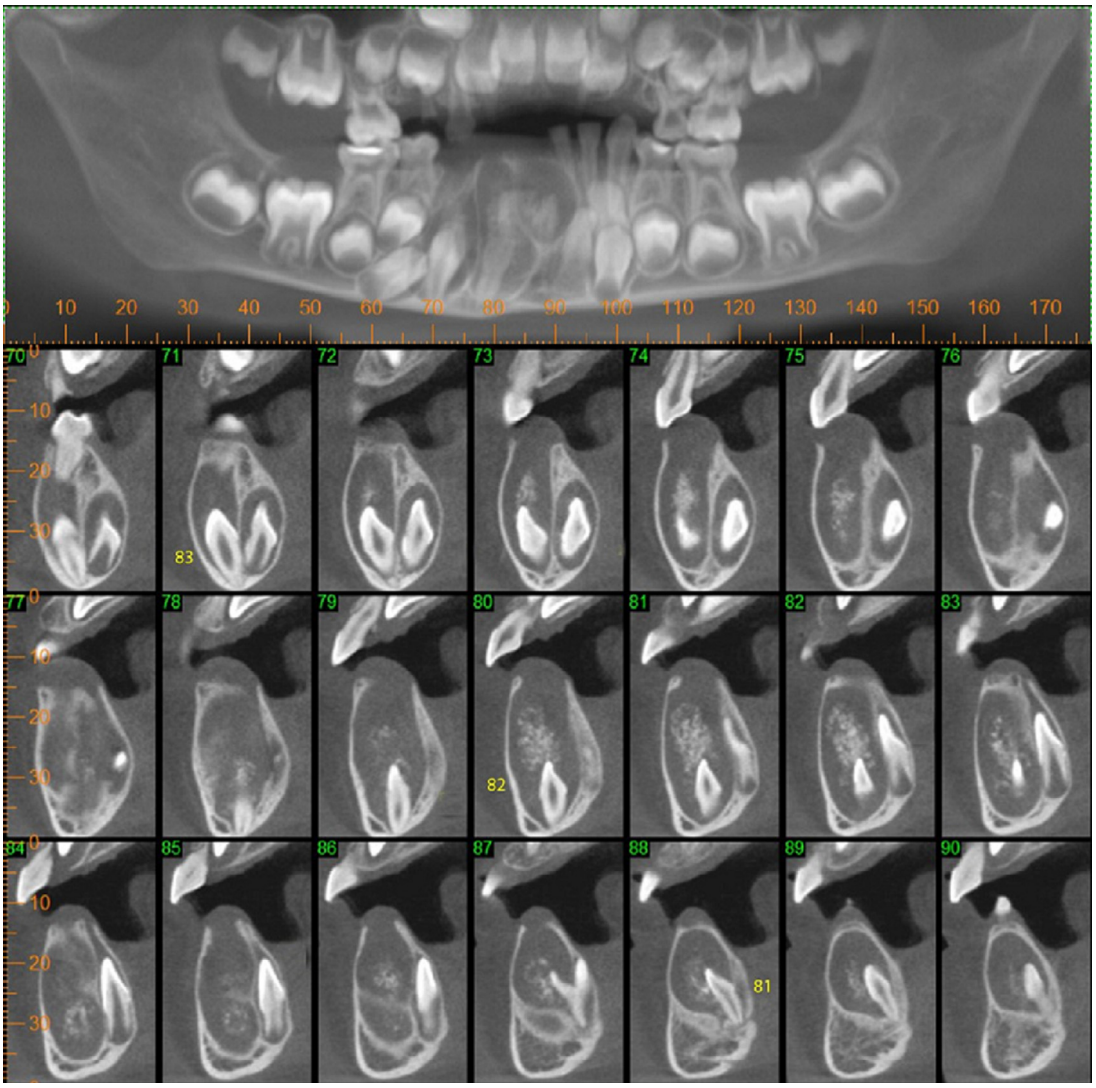

Fig. 2. Computed tomography (CT) scans showing adenomatoid odontogenic tumors in the mandible. Multiple unilocular and well delimited hypodense areas with hyperdense foci associated with nonerupted primary teeth #81, #82, and #83 are observed. Impacted permanent teeth #41, #42, and #43 were located between the tumors and the lingual cortical plate.

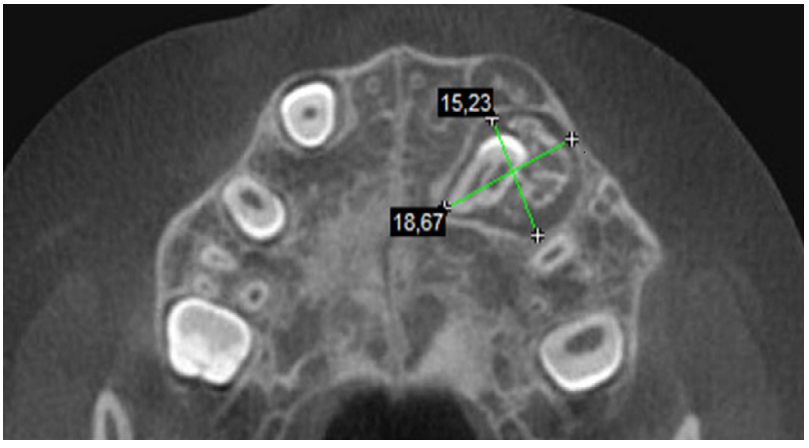

Fig. 3. Axial view computed tomography (CT) scan showing unilocular and well-delimited hypodense area with hyperdense foci associated with nonerupted primary tooth #63.

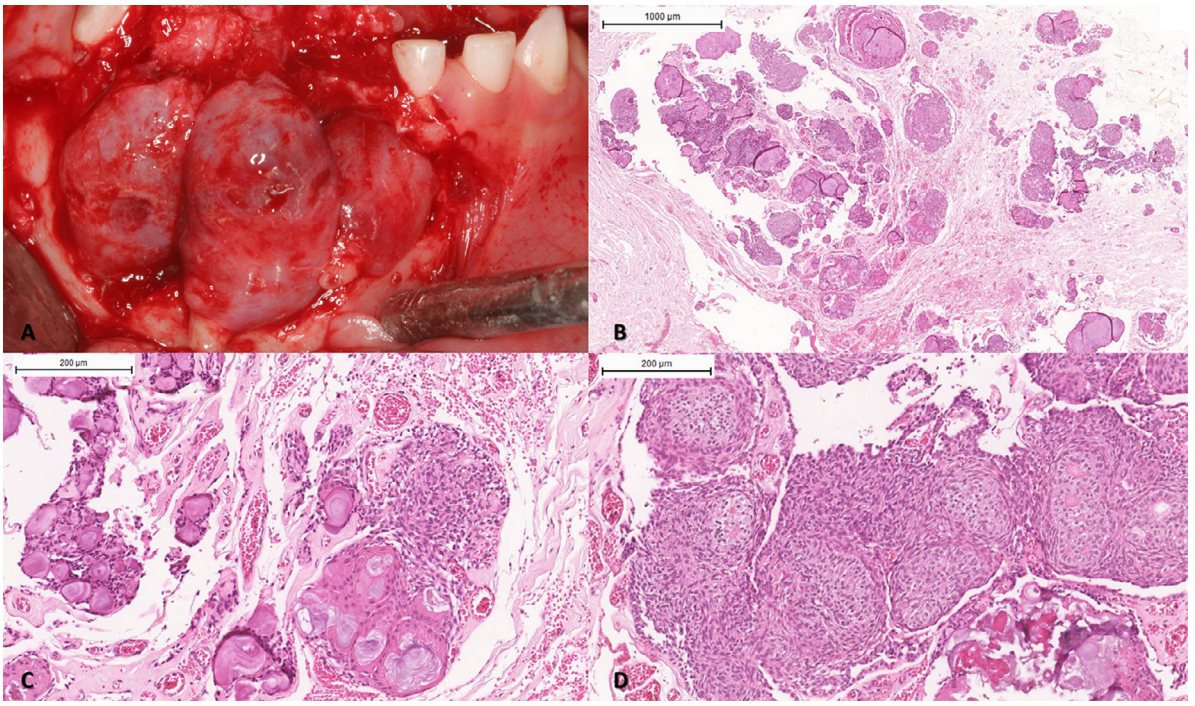

Fig. 4. Clinical and microscopic aspects of the adenomatoid odontogenic tumors. **(A)** Trans-surgical image showing 3 well-defined mandibular tumors associated with primary teeth # 81, #82, and #83. **(B–D)** Histopathologic features of the adenomatoid odontogenic tumors. **(B)** Microscopic features of the tumor showing a well-defined capsule of varying thickness, multinodular proliferation of epithelial cells, and numerous basophilic and eosinophilic mineralized masses. **(C)** Calcifying epithelial odontogenic tumor-like areas and droplets of basophilic mineralized masses. **(D)** Nodules of cuboidal or columnar cells with some scattered duct-like structures and droplets of mineralized tissue. *A high-resolution version of the image is available as eSlide: VM05660.*

phalanges of the second fingers, severe scoliosis, and left limb hypertrophy were the skeletal abnormalities observed in our patient.

Genitourinary and cardiovascular impairments are less frequently observed in patients with SS. Genitourinary alterations include horseshoe kidney, duplication of the excretory system, and arterial duct persistence, whereas ventricular septal defect and coarctation of the aorta are the most important cardiovascular manifestations.[1] In the case presented here, echocardiography showed discrete bulging at the interventricular septum without clinical symptomatology, but no alteration was observed in the genitourinary system.

Papillomatous lesions in the mucosa are the main SS oral findings.[8,9,11,12,19,43] Papillomatous growths are usually observed on the lips, tongue, and hard palate, with a distribution pattern that suggests the extension

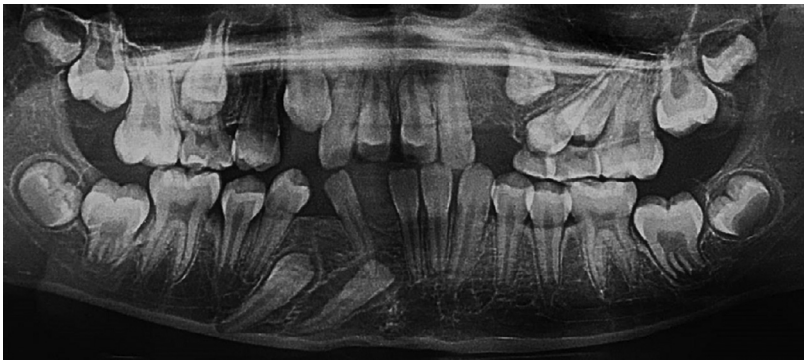

Fig. 5. Panoramic radiograph obtained after 60 months of follow-up showing erupted permanent tooth #42 and impacted permanent teeth #23, #41, and #43.

of the Blaschko lines to the oral mucosa.[45] The papillomatous lesions observed in the present case were contiguous with the epidermal lesions (see Figure 1B).

Central giant cell lesion of the jaws,[8,15] ameloblastoma,[9,16] AOT,[8,15] odontoma,[13] and ameloblastic fibroodontoma,[14] are the main tumors reported in patients with SS. Salivary gland adenocarcinoma is the only oral malignancy reported so far.[46] Fibromatous enlargements of the tongue; bifid uvula; and dental changes, such anodontia and dysodontia, are also observed.[8–11,15,47] There is scarcity of information regarding the prognosis of jaw tumors in SS, but the recurrence of giant cell lesion of the jaws has been previously reported.[15]

HRAS and *KRAS* postzygotic mutations are the main underlying genetic causes of SS. *HRAS* c.37G > C postzygotic mutation leading to *p*.G13R was observed in 91% (59/65) of all cases of nevus sebaceous sequenced, and other *HRAS* mutations at codons 12 and 11 were also detected. In addition, *KRAS* c.35G > A and c.35G > T mutations leading to p.G12D and *p*.G12V were detected in 3% and 2% of the samples, respectively.[48] The patient with SS in the present case was the index patient in a previous study, in which we investigated the presence of oncogenes and tumor suppressor gene mutations in AOT. We detected the presence of *KRAS* *p*.G12V mutation,[49] one of the mutations previously shown to be the underlying genetic event of the syndrome, in the AOT sample of this patient with SS. Subsequently, we detected *KRAS* mutations in sporadic AOT cases, either *p*.G12V or *p*.G12R.[49,50] Interestingly, in the current patient with SS, AOTs developed very early compared with the age of onset of sporadic cases. Of note, ameloblastomas and giant cell lesions of the jaws, which have previously been reported in SS, may also have *KRAS* mutations.[51–53]

There are few reports of multiple AOT in the literature.[54–56] A single case of sporadic AOT associated with SS was previously reported,[15] and this is the first report of a patient with SS presenting with multiple AOTs. Our patient presented with impacted teeth and enamel hypoplasia associated with AOTs. Although AOTs rarely cause impaction of primary teeth, all of the tumors in our case were associated with primary teeth, possibly triggered by the presence of *KRAS* mutations occurring very early in embryogenesis.

CONCLUSIONS

SS should be considered in the differential diagnosis of patients with multiple AOTs.

DISCLOSURES

The authors declare that they have no conflicts of interest with persons, companies or organizations regarding the content of this article. R.S.G. and C.C.G. are research fellows at the National Council for Scientific and Technological Development (CNPq)/Brazil.

PRESENTATION

The abstract was presented at the 44th Brazilian Congress of Oral Pathology and Stomatology, 2018.

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