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Case report

Oral sialadenoma papilliferum with kras mutation in a patient with linear nevus sebaceous syndrome

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Summary
Linear nevus sebaceous syndrome (LNSS) is a rare neurocutaneous syndrome part of the epidermal nevus syndromes group, characterized by the presence of sebaceous nevi and other extracutaneous lesions genetically related to *RAS* family gene mutations. Sialadenoma papilliferum (SP) is a rare benign intraoral neoplasm which is usually BRAF or HRAS mutated. We report a case of a young female girl diagnosed with a LNSS who developed a SP which had a KRAS mutation. This is the first case of SP with a KRAS mutation in the context of a LNSS.

Key words: linear nevus sebaceous syndrome, Sialadenoma Papilliferum, KRAS mutation

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Introduction

Linear nevus sebaceous syndrome (LNSS) or Schimmelpenning-Feuerstein-Mims-Syndrome is a rare neurocutaneous syndrome characterized by linear sebaceous nevi, in addition to extracutaneous manifestations involving the central nervous system, eyes, skeleton, and other organs [1,2]. Several gene mutations have been identified in the affected skin including HRAS, NRAS, and KRAS [3-6] that are all part of the RAS signaling pathway involved in cell growth regulation.
Several types of oral manifestations have been described in the context of LSSN, but the presence of a sialadenoma papilliferum (SP) has been never identified so far [1]. SP is a rare benign neoplasm of the salivary gland that is typically BRAF (V600E) or seldom HRAS mutated [6].
The aim of the present paper is to describe a previously unreported case of a SP in a LNSS patients with a *KRAS* germline mutation.

Case report

The patient is a 11-year-old girl. At birth, several extracutaneous manifestations were diagnosed (left eye inferonasal limbal opacity, left kidney pelvic bifurcation, frontal cortical malformation in the left temporo-insular region with focal epilepsy, Fig. 1). Moreover, the patient developed a

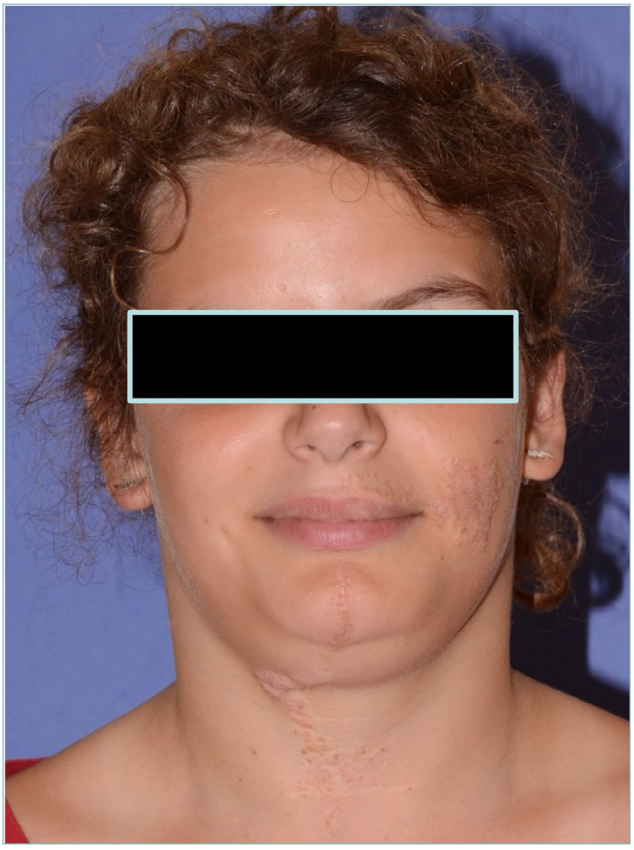

Figure 1. Photo of the patient's face. Scars of the previous ablation are visible on the chin and on the right cheek.

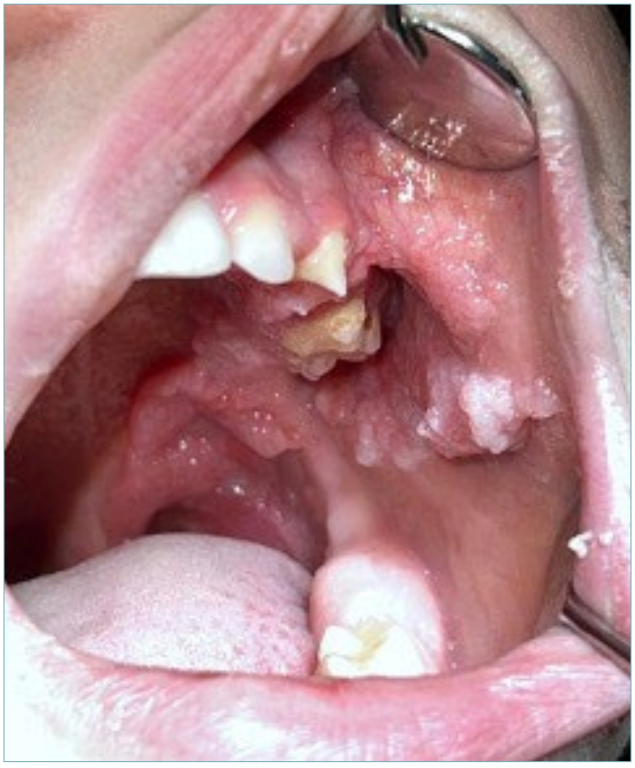

Figure 2. Patient's intraoral lesions located in the left part of the oral cavity.

sebaceous linear nevus on the left side of the face and the neck from the inferior lip to the sternal notch; these cutaneous lesions were treated with three laser ablations (one in 2013 and two in 2014) and two surgical resections afterwards. In 2015 a genetic disease as the cause of these lesions was hypothesized, and a molecular test confirmed a linear nevus sebaceous syndrome with mosaic mutation involving KRAS gene (pGly12Asp); this analysis was performed in another Institute.

Concurrently, the patient developed an intraoral lesion located in the left part of the oral cavity, involving the oral mucosa, the gingiva of the left upper maxilla with associated dental eruption disorder, the left hard palate, the left soft palate and the uvula (Fig. 2).

In 2023 she underwent a surgical resection of the intraoral lesion. Histologically, the intraoral lesion was characterized by biphasic differentiation, consisting of exophytic papillary structures covered by stratified squamous epithelium locally contiguous with a proliferation of papillomatous ductal epithelium located underneath the mucosal surface. The ductal epithelium was double-layered or multilayered structures, lined by luminal cuboidal to columnar cells and cuboidal to flattened basal cells (Fig. 3A). The luminal cells had round to oval, bland nuclei and inconspicuous nucleoli without atypia. Foci of mucinous differentiation were seen in the ductal component. Immunohistochemical studies showed that CK7 (Fig. 3B) was highly expressed in the ductal luminal cells while p63 (Fig. 3C) was strongly expressed in the basal cell layer. Ki67 was less than 10% cells in both components (Fig. 3D). P16 immunostain was negative together with HPV DNA search failed to reveal viral infection. All these histological findings led to the diagnosis of SP. On the other hand, BRAFV600E in both the glandular and squamous tumor components showed negative staining. DNA was extracted from the oral lesion tissue sample and sequenced with a NGS mutigenic panel (NGS custom panel). The same mutation of the *KRAS* gene (p.Gly12Asp) detected as a germline mutation of the patient was detected in the oral lesion (Fig. 4).

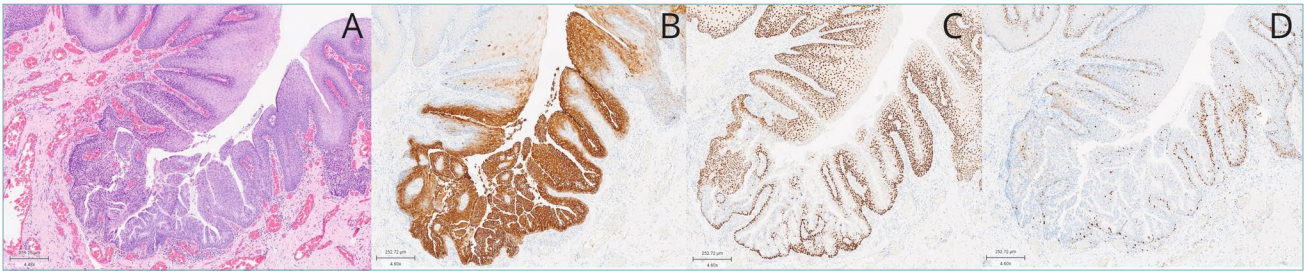

Figure 3. (A) Microscopic view of sialadenoma papilliferum with a double-layered epithelium, stained with hematoxylin & eosin. (B) Ductal luminal cells positive for CK7. (C) Basal cell layer positive for 63. (D) Proliferative index (Ki-67) less than 10% cells in both components.

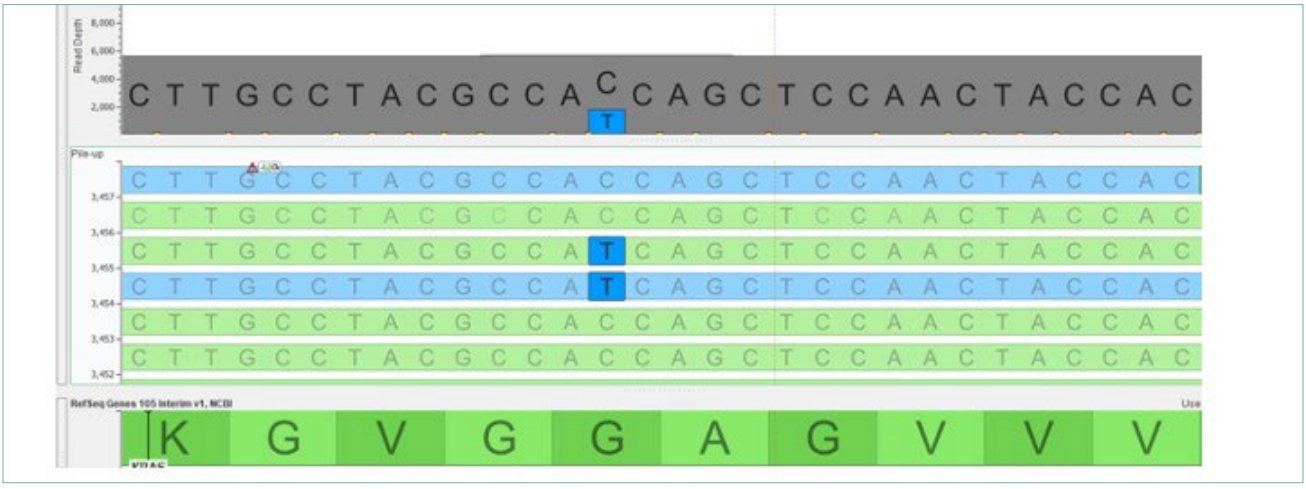

Figure 4. Details of *KRAS* gene (p.Gly12Asp) mutation.

Discussion

Epidermal nevus syndromes (ENS) are rare syndromes characterized by the presence of epidermal nevi and extracutaneous findings [1,2]. LSSN, also called Schimmelpenning-Feuerstein-Mims syndrome, is one of the most frequent ENS. LSSN was originally described as characterized by the presence of the diagnostic triad of nevus sebaceous, cerebral, and ocular findings. More recently ophthalmologic and neurologic findings are not considered mandatory for the LNSS diagnosis [1,2]. Moreover, the wide variation in the phenotype makes the diagnosis of LNSS not always clear. For this reason, molecular confirmation has become mandatory for the diagnosis of ENS (and therefore LNSS), in order to verify the presence of identical mutations in the pathways of cellular growth and proliferation control [3-6]. In details, *RAS* family gene mutations are pathognomonic and should be searched for diagnostic purposes.

Oral findings have been reported in LNSS even though rarely. The most frequently reported oral findings are mucosal hyperpigmentation, papillomatosis; hemihypertrophy and fibrous lesions and enlarged papillae fungiformes of the tongue; uvula bifida; retention of teeth and tooth position anomalies; numerical aberrations and dysmorphia of teeth; bone cyst of jaw; giant cell granuloma of the jaw, odontoma, and further odontogenic neoplasms [1].

SP has been never reported in LNSS. In the present case, the oral lesion had the histological features of SP, but it did not show the typical SP genetic mutation (*BRAF V600 E* or *HRAS q16r*).

On histology the differential diagnosis was considered with squamous HPV-related papilloma, but this diagnosis was excluded due to the absence of HPV DNA and by the presence of a ductal component with mucinous cells.

The present case showed a somatic *KRAS* mutation in the SP tissue, identical to the one detected as germline

in the analysis of the patient's LNSS (pGly12Asp), thus confirming the correlation between SP and LNSS.

Cutaneous findings of ENS are usually diagnosed at birth or in early childhood, while the time of appearance of oral findings can be variable.

Epidermal nevi usually present along the so-called Blaschko lines, which are referred to the skin; nevertheless, given their linear growth patterns, some authors suggested that Blaschko lines can be also referred to the oral mucosa [1]. Consistently, in the present case, oral lesions developed in the patient's late childhood and had a linear unilateral distribution that also involved the midline area, suggesting a Blaschko-line distribution.

In conclusion, the present case of SP arising in a patient with known and genetically characterized LNSS broadens the spectrum of oral lesions affecting patients with LNSS.

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