

Case Report

Recurrent labial xanthoma infection in a patient with Neurofibromatosis-Noonan syndrome: case report and literature review

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Abstract – Introduction: Noonan Syndrome is a clinically and genetically heterogeneous syndrome, characterized by marked phenotypic variability. All the clinical manifestations of this syndrome are still not fully known. **Observation:** We present the case of a 58-year-old woman with a diagnosis of Neurofibromatosis-Noonan syndrome with SOS2 mutation, observed by her general practitioner for a recurrent left upper lip abscess despite drainage and antibiotic therapy. The anatomo-pathological result of the sample was in favor of an infected xanthoma. **Discussion:** The most common oral manifestation of Noonan syndrome includes malocclusion, dental anomalies and radiologic jaw lesions. Xanthomas of the lip have never been reported in this syndrome. **Conclusion:** Oral xanthomas could be one of the many oral clinical manifestations of Noonan Syndrome. However, more research is needed to understand clinical consequences of mutations in identified genes.

Introduction

Noonan syndrome (NS) is a multisystemic autosomal dominant disorder, clinically and genetically heterogeneous, with an incidence of 1:1000–2500 live births [1]. It is the most common entity among a group of pathologies called “RASopathies”, caused by dysregulation of the RAS-MAPK pathway, an important signaling pathway for cell proliferation, differentiation, survival and apoptosis [2]. This pathway also participates in organogenesis, morphology determination, and growth [3].

Neurofibromatosis-Noonan syndrome describes the association of features of Noonan syndrome and neurofibromatosis type 1, which have a common pathogenic mechanism [4].

Among the clinical manifestations of these pathologies, rare skin anomalies reported in Noonan syndrome include xanthomas of skin and tongue. However, prior to this patient, lip xanthoma and infected xanthoma have not been reported yet in any other cases.

Herein, we describe the case of a patient who was referred to the Oral surgery department by her general practitioner.

Observation

A 58-year-old woman was admitted to the Oral surgery department of Caen University Hospital, for a recurrent upper lip abscess.

The patient had a history of Neurofibromatosis-Noonan Syndrome with SOS2 mutation, including distinctive facial appearance, short stature, chronic lymphedema, combined with thoracic and spinal neurofibromas. She also had periorbital xanthelasma.

The clinical examination revealed swollen lips, due to known chronic lymphedema, with healthy surrounding skin. The upper lip was inflammatory, with an intraoral fistula. Through this fistula, a yellowish lesion was noticeable (Fig. 1).

There were no signs of dental infections, and the patient showed an unremarkable oral condition. The oral mucosa was within normal limits. There was no history of smoking or trauma.

As the blood test showed no sign of coagulation defect, we decided to perform an excision biopsy after draining the abscess (Fig. 2). Several diagnoses were suspected, including diagnoses of mucoïd cyst, lipoma or sebaceous cyst.

The resection specimen was fixed in 10% buffered formalin and then embedded in paraffin, which was then treated with hematoxylin and eosin (H&E) using routine laboratory protocol.

Histological analyses were in favor of a xanthoma.

A blood test was done, including a blood lipid profile, which did not show any abnormalities.

No further treatment was conducted. A control at 3 weeks showed resolution of symptoms.

The patient was then lost to follow-up.

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Fig. 1. Swollen lips with a predominant area in the upper left lip, and intraoral fistula with a yellowish aspect of the lesion.

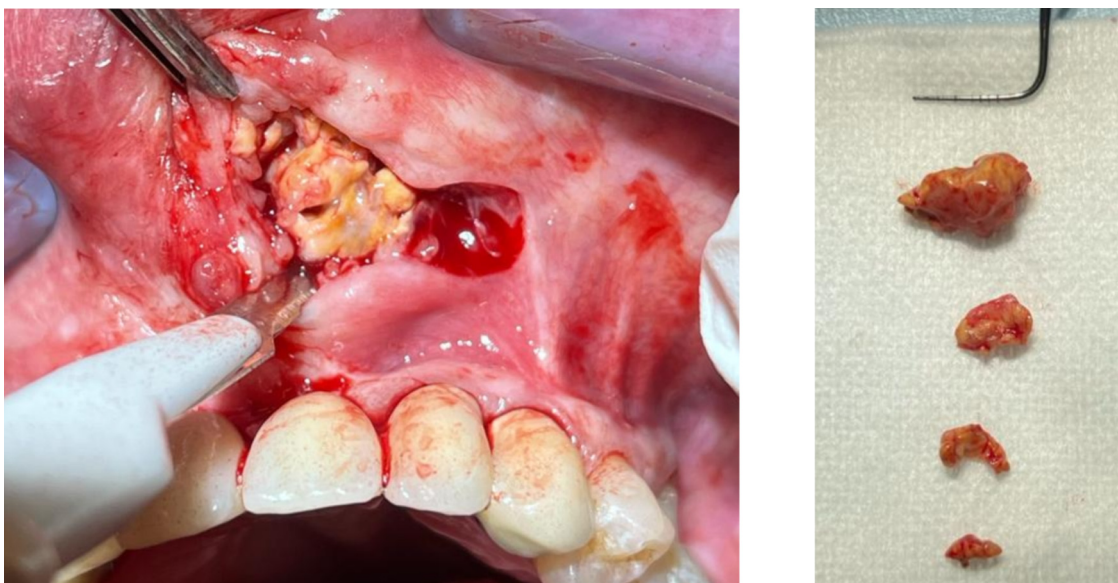


Fig. 2. Excision biopsy showing a rather well defined yellow tissue lesion surrounded by inflammatory tissue, located in the labial mucosa.

The patient came back to the Oral surgery department 2 years later, with a recurrence of the lesion in the exact same area. She had an upper lip abscess, which was drained and treated with antibiotics.

Another excision biopsy was performed with the previous protocol. Immunohistochemistry studies were realized showing a CD68 negative sample. Histological analysis was again in favor of a xanthoma (Fig. 3).

A new blood test was done, and the results were similar to previous ones. Thus, a yearly follow-up was advised to the patient, which is still uneventful to this day (4 years after the first visit).

Discussion

NS was described by pediatric cardiologist Jacqueline Noonan, and is characterized by a phenotypic variability that also changes with time [5]. Thus, it is difficult to diagnose in some cases, especially in adulthood.

Moreover, clinical features of this syndrome can overlap with others from related disorders (such as Neurofibromatosis

as seen in this case, Leopard syndrome, *etc.*) [6]. Among clinical manifestations of this syndrome, short stature, characteristic facial features, congenital cardiac defect, musculoskeletal abnormalities are often found.

The final diagnostic of NS can be done with the help of molecular testing. Nowadays, molecular testing diagnoses up to 75% of the NS. It also potentially provides genotype-phenotype correlations [3].

Early diagnosis of this syndrome is highly recommended, because of cardiac issues and neoplasm predisposition [7].

Therefore, SOS2 was recently described as a causative gene of NS. SOS2 mutations are associated with clinical manifestations resembling those found in SOS1 mutations, with a high rate of ectodermal and lymphatic anomalies and less cases of short stature and cognitive impairment than in the general NS population [8]. There is only few information about genotype-phenotype correlations with SOS2-related NS, as a causal link between a missense mutation in this gene and NS has only just been established. As a result, several clinical expressions, potentially suggestive of NS, are still not fully known.

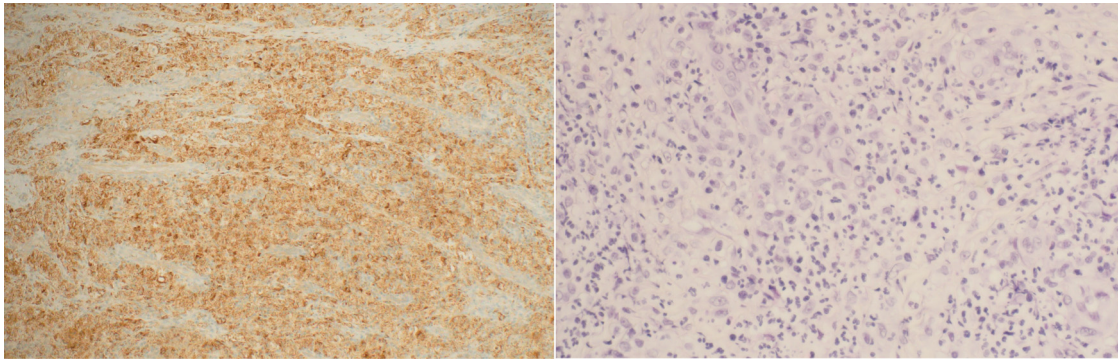


Fig. 3. Views of the lesion with HES and immunohistochemistry with CD68 marking, showing foamy macrophages within a fibrous stroma. Cells are CD68 negative.

Several intraoral manifestations have been reported in NS, such as dental anomalies and malocclusion [9], high arched palate [10], distinctive philtrum, full lips [11], radiologic jaw lesion (such as central giant cell lesions (CGCLs) [7]).

Xanthoma is a xanthogranulomatous reaction, presenting as yellow-brown well circumscribed macules or papules, as a result of yellow pigments accumulation in the skin. It has rarely been described in Noonan Syndrome, occurring in the skin, tongue and in oral mucous membranes [12,13]. This pathology is often related to a disorder in lipid metabolism. Histological analysis shows lipid-rich foamy macrophages in the dermis [14]. It occurs mainly in patients with metabolic or endocrine disorders.

Olson *et al.* recently reported that central xanthoma of the jaw could be a manifestation of NS. It was not associated with hyperlipidemia unlike extragnathic xanthomas, and there was no association with trauma or infection [15].

In our patient, there was no sign of hyperlipidemia, and the blood lipid profile was normal. However, the histological analysis showed CD68 negative cells, unlike Olson's case, which is usually expressed by the monocyte lineage or macrophages.

The link between NS and xanthomas occurring without metabolic disorders or hyperlipidemia remains to be confirmed.

Conclusion

This is the first report to date of a labial xanthoma in NS.

We believe that lip xanthomas, could be related to NS and can be considered as another suggestive oral feature of Noonan syndrome.

Little is known about genotype-phenotype correlations with *SOS2*-related Noonan syndrome, as only a few cases have been published. More research is needed to understand clinical consequences of mutations in identified genes.

Conflicts of interest

The authors declare that they have no conflicts of interest in relation to this article.

Informed consent

Written informed consent was obtained from the patient.

Ethical approval

Ethical approval was not required.

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