Clinical Case Report

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Hemangiomas of the tongue and the oral cavity in a myotonic dystrophy type 1 patient

A case report

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Abstract

Rationale: Myotonic dystrophy type 1 (DM1) is an autosomal dominant disease caused by a cytosine, guanine, thymine (CTG) trinucleotide repeat expansion in the non-coding region of dystrophia myotonica protein kinase gene, causing a multisystem involvement. To date, few studies have been performed to evaluate skin features in DM1 patients, but none reported on the possible association between the disease and tongue hemangiomas.

Patients concerns: We report a case of a 63-year-old woman affected by DM1 and presenting, at the intraoral examination, several swelling and buish lesions occurring on buccal and palatal mucosa, and in the anterior two-thirds and margins of the tongue.

Diagnosis: Multiple tongue hemangiomas in DM1 patient.

Interventions: Color Doppler ultrasound revealed hypoechoic lesions with intermittent color picking suggestive of vascular lesion. Surgical excision was performed under general anesthesia. Histopathological examination was compatible with the diagnosis of cavernous hemangiomas.

Outcomes: At 6 months follow-up, a part from the cosmetic deformity, patient's hemangiomas did not bleed, but caused functional problems with speaking, mastication, and deglutition, in addition to the same symptoms induced by DM1.

Lessons: This case may add new details to better characterize the DM1 phenotype, suggesting that even tongue hemangiomas may be part of the DM1 multisystem involvement.

Abbreviations: CLCN1 = chloride channels, CUG-BP = CUG binding protein, DM1 = myotonic dystrophy type 1, DMPK = dystrophia myotonica protein kinase gene, MBNL = musclebind-like protein, NMSC = non-melanoma skin cancers.

Keywords: myotonic dystrophy type 1, neuromuscular disorders, tongue hemangiomas

1. Introduction

Myotonic dystrophy type 1 (DM1) is the most common autosomal dominant muscular dystrophy of the adulthood age, affecting the skeletal and smooth muscles, together with a multisystem involvement.[1] The prevalence differs widely between countries, with a mean of 13/100,000 inhabitants.[1] The disease is caused by expansion of a cytosine, guanine, thymine (CTG) trinucleotide repeat in the non-coding region of dystrophia myotonica protein kinase gene, located on chromosome 19.[1] According to the Tsilfidis scale, depending on the CTG expansion size, we can identify 4 DM1 classes: E0 (38–79), E1 (80–499), E2 (500–999), E3 (1000–1499), and E4 (>1500) (3). Indeed, when CTG repeat sequences are between 38 and 49, patients may do not clinically manifest the disease (but their offspring may have a substantial risk to show clinical DM1 symptoms), whereas individuals with >50 repeat sequences would manifest the DM1 phenotype.[1]

These repeatedly amplified sequences are located in the untranslated regions of disease-causing genes and do not change the protein encoding for their location genes.[1] The synergistic effects of various mechanisms, that is, ribonucleic acid (RNA) toxicity associated to a spliceopathy and to the entail regulation of gene expression and translation, are likely to induce the multisystem damage associated with DM1.[1] To date, apart from retrospective analyses concerning the myotonic dystrophies-associated risk of cancer[1–3] there have been shown an association between DM1 and benign cutaneous lesions, that is, dysplastic nevi, alopecia, pilomatricomas, xerosis, and seborrheic dermatitis.[4,5] Among such beningn abnormalities, there are hemangiomas, considered the most common benign tumor of vascular origin, due to the proliferation of endothelial cells,[6] with a typical slow progression. Oral lesions generally appear on the lips, buccal mucosa, and tongue.[7] However, the majority of hemangiomas involve head and neck and they are rare in the oral cavity, possibly occurring even in tongue.[6] They present as a red macula, papule or nodule, depending on the deepness in the tissue and on the congestion degree.[7]

To date, no data are reported on the presence of multiple hemangiomas of the tongue and the oral cavity in DM1. Herein, we report on a 63-year-old woman affected by DM1, presenting

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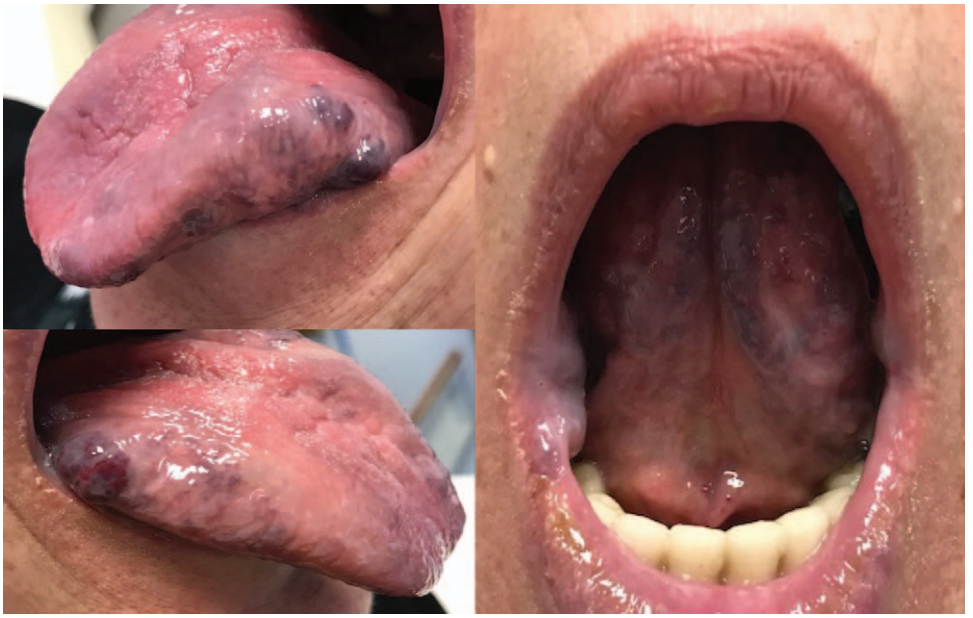

Figure 1. Oral cavity hemangiomas, mainly involving the posterior-lateral edges.

with tongue hemangiomas, with no further benign or malignant associated tumors.

2. Case report

A 63-year-old woman was admitted to our Research Institute because of difficulty to open the fist after a strong muscle contraction, muscle stiffness, and weakness at lower limbs, with walking difficulties, tongue and jaw myotonia, and slurred speech. Family history was positive for early cataracts and baldness. At the age of 30, she underwent a surgery for bilateral cataract. She presented headache on awakening and daytime sleepiness. At neurological examination, she had difficulty to open the fist after a strong muscle contraction (myotonic phenomenon); percussion myotonia was present in the bilateral thenar muscles. She presented a light waddling gait with a bilateral "steppage," and she was not able to walk on heels. She was able to climb the stairs and rise from a chair only with bilateral support. Gowers maneuver was positive. Flexor neck muscles, sternocleidomastoids, digital extensors and flexors, and bilateral foot dorsiflexors muscles were weak. Deep tendon reflexes were absent. She showed a myopathic pattern with myotonic discharges at the neurophysiological study. Intraoral examination revealed several swelling lesions occurring on buccal and palatal mucosa, and in the anterior two-thirds and margins of the tongue (Fig. 1). These lesions showed a bluish discoloration with intact overlying mucosa. They were soft in consistency and non-tender on palpation. Color Doppler ultrasound revealed hypoechoic lesions with intermittent color picking suggestive of vascular lesion. Surgical excision was performed under general anesthesia; histopathological examination confirmed the definite diagnosis of cavernous hemangioma, managed with a conservative approach. Specifically, the lesion was resecated, preserving, and mantaining the tongue function. Blood test, including glucose, liver and renal function, cardiac enzymes, and thyroid function were normal, as well as echocardiography. The electrocardiogram revealed arrhythmias with atrial fibrillation and a right bundle-branch block. Spirometry showed a restrictive respiratory failure. Considering such clinical phenotype, together with the family history of early-onset cataract and baldness (which are some of the DM1 clinical features), a DM1 diagnosis was supposed and confirmed by the molecular genetic analysis, showing a 590 CTG repeats in the untranslated region of the dystrophia myotonica protein kinase gene (DMPK). The patient has provided informed consent for publication of the case.

3. Discussion

In the last years, several studies have been performed to better define a possible cutaneous "phenotype" of DM1, within the well-known multisystem involvement.[5,8–10,11]

As far as we know, the molecular pathogenesis of DM1 is considered to be mediated by toxic RNA with disruption of splicing of pre-mRNA transcripts including CUG binding protein (CUG-BP) and Musclebind-like protein (MBNL).[1,11] Such RNA toxicity mediated process is commonly known as "spliceopathy."[2,12] In DM1, MBNL is sequestered in the nucleus and unable to be utilized by the cell (RNA "loss of function"). CUG-BP, conversely, is elevated in DM1 (RNA "gain of function") via increased activation and phosphorylation through several other protein mediators such as protein kinase C.[1,11] CUG-BP elevation has been noted to inhibit myoblast differentiation, reducing DNA repair, and result in loss of CLCN1 chloride channels through disruption of alternative splicing.[1] Recent studies have suggested that DM1 is associated to an increased risk of benign and malignant tumors. Moreover, some authors have studied the relationship between gene mutation and skin tumors, which are the most frequent cancers in DM1 patients, noting that CTG repeat expansion is higher in tumor than in non-tumor tissues.[9,13] The increased predisposition to cancer in such patients may be related to the increased repeat sequences leading to a DMPK instability,[1,11] thus increasing the predisposition to develop cancers.[8,12] Moreover, Mueller et al[14] have recently shown the possible role of the upregulation of the β-catenin in tumor progression in DM1, via the Wnt signaling pathway, possibly through the actions of CUG-BP or MBNL. Moreover,

CUG-BP has been shown to block calcireticulin-mediated repression of p21 translation,[15] whose expression has been found increased in thymomas, one of the more commonly reported neoplasms in DM1 patients.[16] Furthermore, p21 plays a major role in oncogenesis, and has also been implicated in apoptosis, terminal differentiation, and replicative senescence via interactions with such well-known tumor suppressor genes as p53 and BRCA1, as well genes in the Wnt/β-catenin signaling pathway.[17,18]

Although the functional role of DMPK has not been fully described yet, there is some evidence about its role in Ca^{2+} homeostasis and signal transduction.[15] In fact, in epidermal cells, calcium modulates both cell behavior and differentiation, so that, at lower calcium concentrations (0.02–0.01 mM), there is a higher cell proliferation rate and a lower terminal differentiation and vice versa.[19]

In order to assess this risk, in 2012 Zampetti et al[9] screened 90 DM1 patients for dysplastic nevi, cutaneous melanoma, and other skin neoplasms, demonstrating a higher prevalence of skin tumors than in the control group, and suggesting a striking predisposition for these patients to develop dysplastic nevi, cutaneous melanoma, and pilomatrixoma. These data are in agreement with previous findings on a possible association between DM1 and melanoma/non-melanoma skin cancers (NMSC) and less common cutaneous neoplasm,[11,13,20,21] as also suggested by a large retrospective analysis of 499 patients with DM1 focused on the prevalence of all types of tumors.[1] To overcome the main limitation of the study by Zampetti et al,[9] that is, the lack of a standardized technique for the assessment of prior sun exposure, a more recent study by Bianchi et al[10] specifically assessed for lifestyle factors on a cohort of 255 DM1 patients, demonstrating that there was no association between tumor developments and evaluated personal behaviors. In this paper, the authors concluded that the lack of an association between common cancer risk factors and tumor development in DM1 seemed to support a pathogenic link between tumors and DM1 itself, emphasizing the need for a systematic surveillance.[3] However, recently, Gadalla et al[22] suggested that the risk factors for malignant skin tumors in DM1 strongly resemble the general population, thus recommending that DM1 patients had to adhere to sun exposure protective behavior.

Regarding hemangiomas, these are benign lesions, due to the proliferation of endothelial cells, usually located in the head and neck region is more commonly affected especially the face, oral mucosa, lips, tongue, and trunk.[23] The term cavernous hemangioma has traditionally been applied when lesional vascular channels are considerably enlarged.[24] Cavernous hemangiomas consist of deep, irregular, dermal blood-filled channels, composed of tangles of thin walled cavernous vessels or sinusoids that are separated by a scanty connective tissue stroma.[25]

Clinically hemangiomas are characterized as a soft, smooth or lobulated, sessile or pedunculated and may be seen in any size from a few millimeters to several centimeters. The color of the lesion ranges from pink to red purple and tumor blanches on the application of pressure, and hemorrhage may occur either spontaneously or after minor trauma. They are generally painless.[26] Hemangiomas show a higher prevalence in women.

In our case, the patient presented multiple oral lesions, even though there are reported in literature that since approximately 80% of the patients present a single lesion.[24] We can hypothesize that DM1 may predispose to multiple tongue hemangiomas, compared with the general population.

Moreover, in the present case, we used Color Doppler ultrasound to identify the feeding vessel, and to make easier the differential diagnosis between vascular and non-vascular lesions.

Hemangiomas of the tongue are rare lesions which can cause distressing problem to the patients, producing cosmetic deformity, recurrent hemorrhage, and functional problems with speaking, mastication, and deglutition. The treatment depends on lesion location, size and evolution stage, and the patient's age.

Management of hemangioma depends on a variety of factors, and most true hemangioma requires no intervention and the wait and watch policy, as we did in our case.

However, in cases requiring treatment, intralesional and systemic corticosteroid treatment, embolization, excision, electrolysis and thermocautery, sclerotherapy/laser therapy, immunomodulatory therapy with interferon alfa-2a, and laser photocoagulation are the reported applied techniques.[27] Conservative or aggressive treatment may be tried for the hemangiomas of the tongue. However, both treatment methods have disadvantages. In the conservative treatment, recurrences may be frequent. On the other hand, aggressive treatment could also cause function loss.[28,29] However, the results of cryotherapy have been reported to have high success rates. Kutluhan used plasma knife surgery for excision of hemangioma of tongue.[28]

Considering the frequency of tongue hemangiomas in the general population, it is difficult to establish if the association between DM1 and tongue hemangiomas is casual or part of the multisystem involvement with a complex pathogenic mechanism involving a molecular dysregulation of cell proliferation that DM1 disease implies. Moreover, since hemangiomas may cause functional problems with speaking, mastication, and deglutition, they may apparently worsen the clinical picture of DM1, which cause itself those disturbances. Further studies are needed to deeply investigate and to better evaluate such coexistence in a larger sample of DM1 patients.

Author contributions

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