Our Dermatology Online

Case Report

Metastatic brain melanoma in a patient with Noonan syndrome with multiple lentigines

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ABSTRACT

Metastatic melanoma of unknown primary origin often presents a major diagnostic and therapeutic challenge to the clinician. Herein, we present a case of metastatic brain melanoma of unknown primary origin in a patient with generalized lentiginosis and features of Leopard syndrome, which is the first case reported to date as of reviewing the literature. This case presents features suggestive of Leopard syndrome. Clinicians must be aware that a malignancy may occur even in the absence of the complete clinical picture of Leopard syndrome.

Key words: Noonan syndrome with multiple lentigines; Malignant melanoma; Brain metastasis; Cerebral hematoma

INTRODUCTION

LEOPARD syndrome (LS), currently termed *Noonan syndrome with multiple lentigines* (NSML), is a complex, dysmorphogenetic, multisystemic disorder of autosomal dominant heredity and variable penetrance and expressivity [1,2]. Its prevalence remains unknown. Gorlin et al. [3] first introduced the acronym LEOPARD to describe the following manifestations: lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness. The most common gene associated with NSML is PTPN11, identified in 50–85% of patients with NSML [4,1]. Other related mutations include the RAF1 (< 5%), BRAF, and MAP2K1 (< 1%) genes. In 5% of these cases, genes are unknown [5].

Lentigines are seen in more than 90% of cases of NSML and represent the most prominent finding of the syndrome. Other cutaneous manifestations include axillary freckling, café au lait macules, and localized hypopigmentation. Although it is unknown whether the pigmented lesions seen in NSML may progress to a malignancy [6], there are four reports of LS associated with a melanoma [1,7-9].

Herein, we present another case of melanoma in a patient with incomplete signs of NSML.

CASE REPORT

A 63-year-old female was admitted to the neurosurgery unit of our hospital with loss of consciousness. According to her medical history, she had arterial hypertension present for four years, treated with captopril and hydrochlorothiazide.

The patient underwent computed tomography revealing a cerebral hematoma, which was evacuated surgically (Fig. 1a). In the debris of the liquid, a proliferation of HBM45 positive cells was found. The histological picture was compatible with the diagnosis of metastatic brain melanoma of unknown primary origin.

Laboratory investigation and thorough physical examination followed to determine the location of the primary melanoma. Full blood count and liver tests were within the normal ranges. The levels of follicle-stimulating hormone, luteinizing hormone, thyrotropin, 17-hydroxycorticosteroids, and 17-ketosteroids were normal. No abnormality was found on chest

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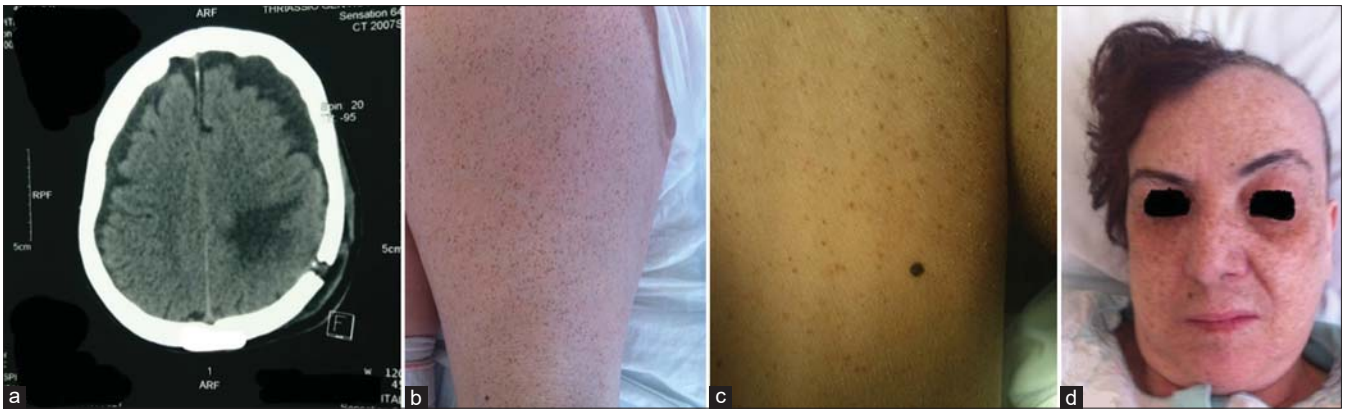

Figure 1: (a) Cerebral hematoma. (b) Lentigines on the left leg. (c) Lentigines and café noir spots. (d) Hypertelorism, triangular face, posteriorly-rotated ears, mandibular prognathism.

radiography, skeletal radiography, electrocardiogram, and echocardiography. Liver and abdominal ultrasonography scans were also normal. Ophthalmological examination revealed ocular hypertelorism. ENT and gynecological examination were normal.

A skin examination revealed multiple lentigines disseminated across the entire body, including the face, trunk, and sun-exposed areas (Figs. 1b and 1c). The lesions were flat, polygonal, irregularly-shaped, brown to dark brown macules (café noir spots), ranging in size from 1 to 3 mm, sparing the oral mucosa (did not cross the vermilion border of the lips), conjunctiva, and genitalia. Several café au lait spots were also on the trunk. The rest of the skin examination was unremarkable. The patient did not report any history of mole removal or shape or color changes in any of her moles. No family history of multiple lentigines syndrome or other inherited condition was mentioned.

According to maxillofacial examination, the patient also had mandibular prognathism, posteriorly-rotated, low-set ears, and a triangular face (Fig. 1d). The height of the patient was 1.72 m. Genetic analysis to detect mutations in the PTPN11 gene was performed yet the patient proved negative. The genetic analysis of the RAF1, BRAF, and MAP2K1 genes was not performed. The clinical findings raised suspicion of an incomplete Leopard syndrome.

The patient died six months later from disseminated metastatic melanoma.

DISCUSSION

NSML belongs to RASopathies, a group of rare genetic conditions with mutations in the genes of the RAS-MAPK pathway, including cardiofaciocutaneous syndrome, neurofibromatosis type 1, Costello syndrome, Legius syndrome, Noonan syndrome (NS), and Noonan-like syndromes (NSML, Noonan syndrome with loose anagen hair).

The diagnosis of NSML is established either clinically or by the identification of a heterozygous pathogenic variant in one of the four genes PTPN11, RAF1, BRAF, and MAP2K1. The clinical diagnosis includes multiple lentigines plus two of the following cardinal features: cardiac abnormalities (hypertrophic cardiomyopathy), a short stature, pectus deformity, and dysmorphic facial features [5]. In the absence of lentigines, three of the cardinal features plus a first-degree relative with NSML are required [10]. Additional features occurring in NSML are a variable degree of cognitive deficits, sensorineural hearing loss, cryptorchidism, skeletal anomalies, and café au lait macules.

It is now well-known that NSML has overlapping clinical features with other syndromes of the RASopathies group, and the genotype–phenotype relationship is commonly complicated [11], creating a dilemma in the final diagnosis.

The clinical findings in our patient included disseminated lentigines sparing the mucous membranes, several café au lait spots on the trunk, and facial dysmorphism (ocular hypertelorism, mandibular prognathism, posteriorly-rotated, low-set ears, a and triangular face), accounting for two cardinal features and one additional. The absence of a mutation in the PTPN11 gene in association with the clinical manifestations was not sufficient to establish the diagnosis of Leopard syndrome in this patient. However, this is not the first reported case of LS with incomplete clinical signs [12].

Four previous cases of NSML associated with melanoma have been described so far. Seishima et al. first reported a 62-year-old Japanese female who presented a somatic BRAF mutation in the melanoma on the left heel and a germline PTPN11 mutation [7]. Cheng et al. reported a 24-year-old female who developed a scalp melanoma and had a germline heterozygous PTPN11 missense mutation [8]. Colmant et al. reported a 62-year-old male with NSML and a mutation in the PTPN11 gene who developed four superficial spreading melanomas (three were achromic or hypochromic) and three atypical lentiginous hyperplasias [1]. García-Gil et al. reported a 44-year-old male with NSML confirmed by the genetic study of a mutation in heterozygosity in the PTPN11 gene who developed a melanoma at the dorsal level of the trunk [9].

Orrego-González et al. [13] described a twelve-year-old female with NSML and a mutation in the PTPN11 gene who presented acute hemorrhage of the right thalamus. CT angiography did not show the source of bleeding (arteriovenous malformations or aneurysms). Recently, Athanasiou et al. [14] have reported a nine-year-old male with Noonan syndrome and a heterozygous missense mutation in the PTPN11 gene who had two intracranial pseudoaneurysms leading to episodes of intracerebral hemorrhage, which were successfully treated with endovascular embolization.

In all cases with NSML and melanoma development, the patients had a heterozygous mutation in the PTPN11 gene. Despite the low number of reported cases, an increased risk of melanoma in NSML patients has been reported [9]. The PTPN11 gene codes SHP-2, a cytoplasmic protein tyrosine phosphatase that participates in the regulation of the activity of the RAS signaling pathway. It has been hypothesized that the suppression of SHP-2 may favor tumorigenesis through the abnormality of the STAT3 pathway, which is involved in the pathogenesis of melanoma [15].

CONCLUSION

Our patient proved negative against the detection of a mutation in the PTPN11 gene, thus the development of her melanoma was, apparently, not associated with the aforementioned hypothesis. It is possible that another pathway may be implicated in the development of melanoma in patients with NSML, yet this remains unclear.

Orrego-González et al. [13] suggested that the phenotype of NSML could be broader, probably including the development of intracerebral hemorrhage. Our patient's cerebral hematoma, although attributed to the metastatic brain melanoma, possibly confirmed that intracerebral hemorrhage has not been correlated with PTPN11 mutations in the literature.

Our case highlights the need for future studies to develop a definite, clinical algorithm for the diagnosis of NSML and to help to distinguish this entity from the other syndromes of the RASopathies group.

Consent

The examination of the patient was conducted according to the principles of the Declaration of Helsinki.

The authors certify that they have obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. The patients understand that their names and initials will not be published and due effort will be made to conceal their identity, but that anonymity cannot be guaranteed.

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