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Segmental Lentiginosis and Hypomelanosis of *Ito* with Bilateral *Lisch* Nodules: Is it an Unusual Presentation of Segmental Neurofibromatosis?

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Abstract

Observation: We here report a 16 year-old Turkish girl with an unusual combination of hiperpigmented macules and hypopigmented patch on her right face and neck region with a sharp demarcation to the midline. Her mother defined that they had first appeared when she was two years old. Bilateral lisch nodules in both eyes were determined through the ophthalmologic examination. While histopathology of a brown macule revealed the features of lentigo and hypopigmented patch showed the features of hypomelanosis of Ito the diagnosis of segmental (NF) was made on the basis of these clinical features and the absence of family history and systemic involvement. However bilateral Lisch nodules were found to be a rare accompanying disorder in segmentel NF, we suggest that our patient have a subtype of this entity. Although we could not demonstrate the genetic mutation, the clinical and histopathological findings indicate us the somatic mosaicism.

Introduction

Segmental neurofibromatosis (NF) has been described as pigmentary abnormalities, which include cafe-au-lait macules and/or neurofibromas in a single unilateral segment of the body, with no crossing of midline, no family history of NF and no systemic involvement [1]. Because some patients do not meet the criteria for segmental NF, four different clinical subtypes of segmental NF have been reported including with only pigmentary changes , with only neurofibromas, both with pigmentary changes and neurofibromas, and with only isolated plexiform neurofibromas [2]. In this article, we describe a patient with segmental NF with only pigmentary changes and *Lisch* nodules.

Case Report

16-year-old girl presented to our dermatology outpatient department with multiple brown macules on the right side of the face and a white patch on the right side of the neck. Her mother explained that brown macules had first began to appear when she was 2 years old and they had gradually increased in size over time. The white patch had appeared nearly at the same time. Her medical

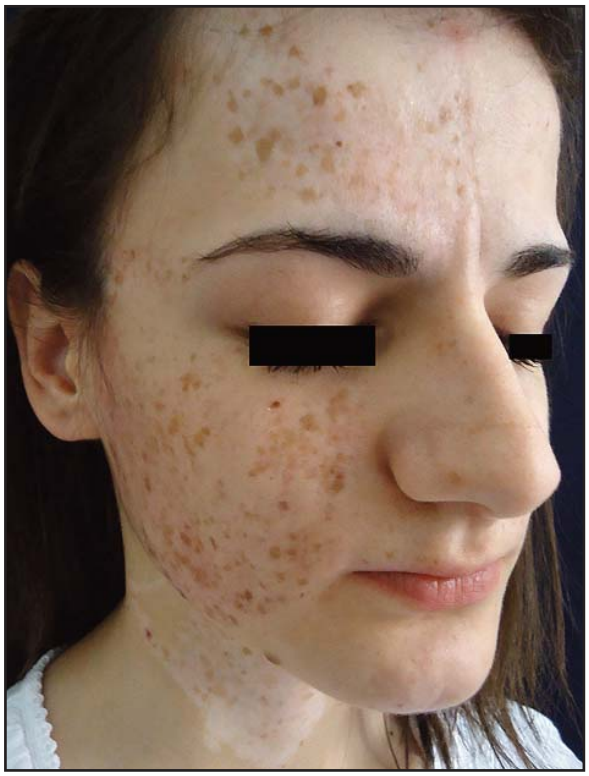

Figure 1 (Left). On the right side of the face there were numerous hyperpigmented macules, ranging in size from 1 to 5 mm in diameter with sharp demarcation in the midline

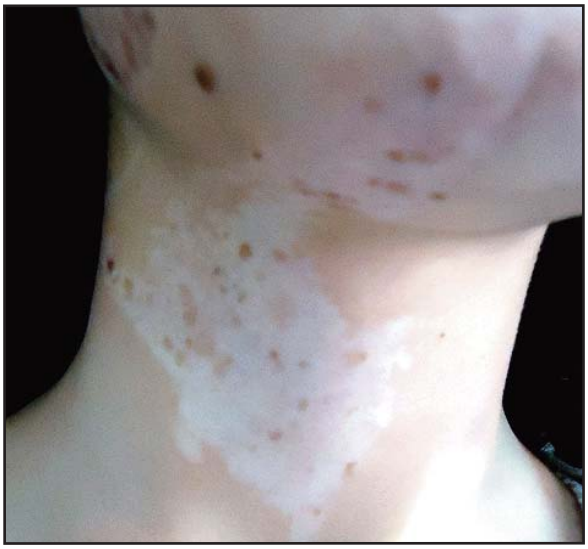

Figure 2 (Upper). There was a hypopigmented patch on the right side of the neck with hyperpigmented macules of 1-3 mm in size

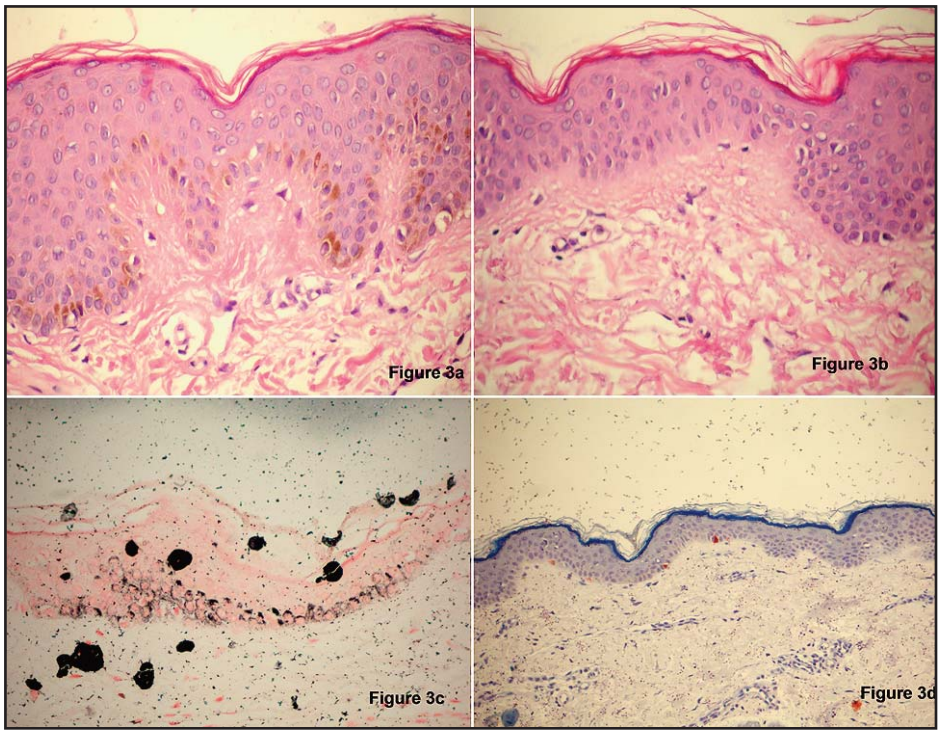

Figure 3. 3a: Hyperpigmented macule revealed increased melanocyte density with elongation of the rete ridges. HEX200. **3b:** There were melanocytes along basal cell layer on the histopathological examination of hypopigmented patch. HE X 200. **3c:** The Fontana Mason staining showed decreased intensity of melanin X 200. **3d:** Melan A and HMB 45 staining showed the decreased number of melanocytes. X 200 Positive nuclear immunostaining with ER (x 400)

history was unremarkable, and family history was negative for NF or other heritable disorders.

On dermatological examination, on the right side of the face there were numerous hyperpigmented macules, ranging in size from 1 to 5mm in diameter with sharp demarcation in the midline (**Figure 1**). There was a hypopigmented patch on the right side of the neck with hyperpigmented macules of 1-3mm in size. The diameter of hypopigmented patch was 10x15 cm beginning from the mid-neck extending to under the chin along the *Blaschko*'s

lines. (**Figure 2**) Under the *Wood* lamp, the patch showed an off-white accentuation. There were no neurofibromas, *café au lait* spots and axillary freckling. Ophtalmologic examination revealed bilateral *Lisch* nodules about 1-2 mm in size on both eyes. Neurologic evaluation was noncontributory.

The results of routine laboratory examinations, including complete blood cell count, hemoglobin electrophoresis, biochemical analysis, and urinalysis and ultrasonography of the abdomen were all normal. There were no bone lesions spesific for NF in the radiograph and computed tomographic scan of the skull, spine, thorax, and limbs. Skin biopsy specimens were taken from hyperpigmented macule and hypopigmented patch lesion. Histolopathologic examination of a hyperpigmented macule revealed increased melanocyte density with elongation of the rete ridges (**Figure 3a**). There were melanocytes along basal cell layer on the histopathological examination of hypopigmented patch (**Figure 3b**). The *Fontana-Mason* staining showed decreased intensity of melanin (**Figure 3c**). Melan A and HMB 45 staining showed the decreased number of melanocytes (**Figure 3d**).

On the basis of these clinical and histopathological findings, we diagnosed the hyperpigmented macules as segmental lentiginosis (SL) and hypopigmented patch as hypomelanosis of Ito. There were no systemic involvement except for *Lisch* nodules and we suggested to perform genetic counsultation for NF 1 gen mutation, but the family disclaimed further investigations.

Discussion

Segmental lentiginosis (SL) is a pigmentary disorder characterized by multiple lentigines that are grouped on a normal appearing skin. Partial unilateral lentiginosis, agminated lentiginous, lentiginous mosaicism and zosteriform lentiginous nevus are other terms used to describe this disorder [**3**]. It can be localized to a body segment at various sites, including the face and neck, trunk, and upper and lower limbs often corresponding to one or more dermatome, and sometimes involving an entire half of the body with a sharp demarcation at the mid-line. In some cases SL have a peculiar arrangement with crowding of dark spots toward the midline of the body or along *Blaschko* lines. The age of onset is usually early childhood [**4, 5, 6**]. Histologically hyperpigmented macules show elongation of rete ridges and an increased number of melanocytes in the basal layer with no nests of melanocytes or cellular inflammation [**7**]. In our patient the hyperpigmented lesions have first appeared in the early childhood, it was localized on the right side of the face and there was a sharp border from the midline of the face.

Segmental lentiginosis should be differentiated from nevus spilus and nevus of *Ota* when it is localized on the face. Nevus spilus is characterized by light brown patch speckled with dark coloured macules or papules. We did not determine hyperpigmentation of the background of the lesion neither with *Wood*'s lamp examination nor on dermatological examination. Nevus of *Ota* is a dermal melanocytic disease presenting as mottled blue-black or slate–gray macules occurring in the skin innervated by the first and second branches of trigeminal nerve. In nevus of *Ota* melanocytes scatter widely in reticular dermis while increased number of melanocytes present in elongated epidermal rete ridges without nests of nevomelonocytes in SL [**7**].

Associated findings with SL have been reported as mental retardation, focal epilepsy due to cerebrovascular abnormalities, pes cavus, neurofibromatosis, cafe au lait macules, lisch nodules [**4**], nevus depigmentosus [**8**], blue nevus [**9**], familial euthyroid goiter and sickle cell anemia [**3**]. Our patient has Lisch nodules and hypomelanosis of Ito.

Hypomelanosis of Ito is a rare, neurocutaneous disease, which is characterized by hypopigmented skin lesions in a whorled, linear or as well as patchy hypopigmented patterns. It has been related to somatic mosaicism. It may be seen along Blaschko's line and is associated with other systemic diseases, including those of central nervous system, and ocular system [**10**]. The hypopigmented lesion in our case was patchy in a V shape localized on right side of the neck along *Blaschko*'s lines. Histopathological findings consisted with the hypomelanosis of *Ito*. Nevus depigmentosus and hypomelanosis of *Ito* are used as synonyms, if systemic abnormalities are present hypomelanosis of *Ito* is preferred [**11**]. We used this term because our patient have bilateral *Lisch* nodules. Coexistence of SL and nevus depigmentosus has been rarely reported. There have been reported only a few

cases of SL within nevoid hypopigmentation [**12**]. There were small lentigines in the hypopigmented patch in our patient similar to those reported cases. Pigmentary mosaicism may be one possible genetic explanation for the presence of segmental hyperpigmentation and hypopigmentation in our patient because when there is mosaicism for a genetic defect involving the skin the lesions follow a pattern as *Blaschko*'s lines. This phenomen may also be explained by twin spotting concept which means that two different, independant recessive mutations occur on the same chromosome, and manifest visibly only in the rare event of somatic recombination occurring at an early developmental stage of embryogenesis [**13**].

Lisch nodules are well-defined, avascular, smooth, regular, dome-shaped elevations of the iris surface, having a yellow to brown color. A recent histological and ultrastructural analysis of a *Lisch* nodules revealed three main cell types; pigmented cells, fibroblast like cells, and mast cells which resembles the neurofibroma cell population. Therefore they are presumed to be neural crest origin embriyonically. They are one of the diagnostic criteria for NF1 [**14**]. Segmental NF with *Lisch* nodules is expected to be unilateral and homolateral to the involved dermatome. If they are bilateral, it would suggest NF-1, which has a high risk of genetic transmission to offspring [**15**]. Genetic consultation is necessary in these cases.

SL and bilateral lisch nodules without any other abnormalities have been reported and proposed a forme fruste of NF [**16**]. We think that SL and hypomelanosis of Ito and bilateral *Lisch* nodules should not be a co-existence in our patient, which are all hypothesized as somatic mosaicism. Our patient can not full fill the criteria for NF-1 diagnosis because she has no cafe au lait spots, neurofibromas, skeletal abnormalities and a consanguiness with NF.

We suggested that our patient clinical findings can be classified as a subtype of segmental NF with only pigmentary changes because there are no involvement of a systemic disorder. However bilateral *Lisch* nodules of the eyes rarely accompany to the segmental NF, this condition may also be defined as undetermined NF variant if the genetic mutation could be shown.

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