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Case presentation

Generalized lentiginosis in an 11 year old boy

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Abstract

Generalized lentiginosis refers to generalized lentigines without systemic abnormalities, characterized by multiple brown or black macules owing to increased proliferation of melanocytes. There are also lentiginosis syndromes associated with systemic abnormalities such as Peutz-Jeghers syndrome, Leopard syndrome, and Carney complex. Generalized lentiginosis can be diagnosis by patient's history, physical and laboratory examination, and histopathology. We report an 11-year-old boy who presented with multiple dark brown macules, varying in size, but less than 0.5 cm, with no abnormalities of other systemic organs.

Keywords: Generalized lentiginosis, Peutz-Jeghers, Leopard, Carney complex

Introduction

Lentigines are characterized by brown macules owing to increased proliferation of melanocytes at the dermoepidermal junction[1].Peutz-Jeghers syndrome (PJS) is the most well known of the lentiginoses. A number of related disorders are also associated with lentigines and may be confused with PJS, including Leopard syndrome (LS) and Carney Complex (CNC)[2]. PJS is an inherited, autosomal dominant disorder with variable inheritance, characterized by hamartomatous polyps in the gastrointestinal tract, mostly in the small bowel, and pigmented mucocutaneous lesions[3]. LS is a rare multiple congenital syndrome, mainly characterized by skin, facial, and cardiac anomalies. LEOPARD is an acronym for the major features of this disorder, including multiple *L*entigines, *E*lectrocardiographic conduction abnormalities, *O*cular hypertelorism, *P*ulmonic stenosis, *A*bnormal genitalia, *R*etardation of growth, and sensorineural *D*eafness[4]. CNC was described for the first time in 1985 as 'the complex of myxomas, spotty pigmentation and endocrine overactivity'[5].However, numerous lentigines may also appear in the absence of any associated abnormalities[6, 7].We report one case of generalized lentiginosis in an 11-year-old boy.

Case synopsis

An 11-year-old boy presented with a complaint of generalized dark brown macules for eight years with no abnormalities of the skin at birth. At birth he was noted to be full-term and his parents are of a non-consanguineous marriage. Eight years ago, dark brown macules appeared on the patient's face with no obvious causative factors. The skin lesions grew and increased significantly as he got older. It gradually spread to his neck, trunk, and upper limbs but there was no significant lower limb involvement. There were no significant abnormality of growth or intellectual capability.

Physical examination revealed a healthy and well-nourished boy without skull deformities, hearing deficit, ear canal or orbit abnormalities, cardiac murmur, or genitalia abnormalities. The sclera of the right eye showed a 0.2 × 0.5 cm light brown spot. On dermatologic examination, the face, neck, trunk, and upper limbs exhibited scattered dark brown macules, varying in size but less than 0.5 cm(Figure 1).

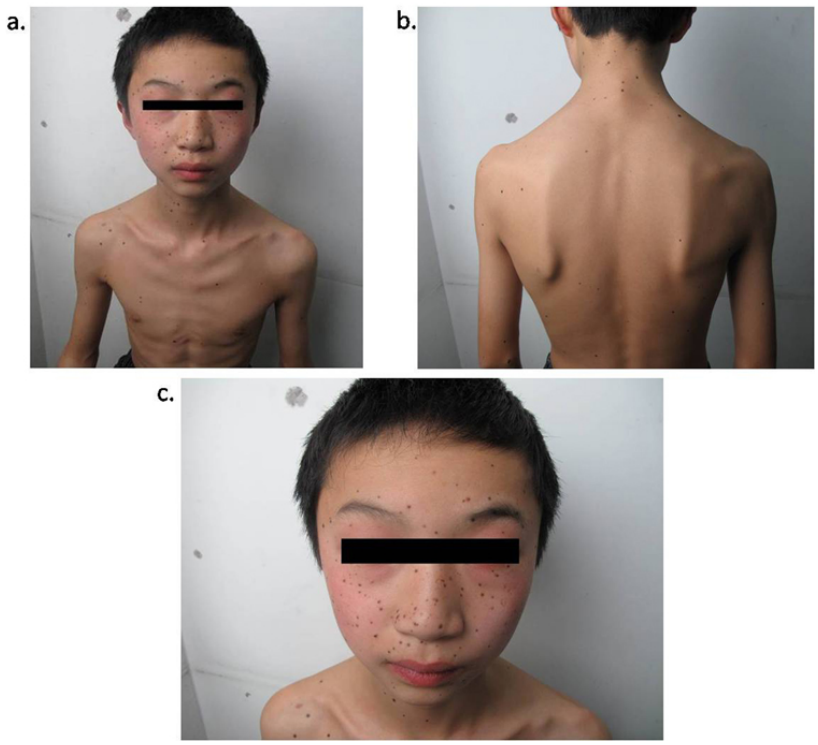

Figure 1. Face (a and c), neck, trunk, and upper limbs (a and b) showed scattered brown macules, varying in size, but less than 0.5 cm.

The patient's blood count, urinalysis, liver function tests, renal function tests, electrocardiogram, and echocardiography were normal.

Histopathological examination (skin lesions from the right flexor side of forearm, 0.1 × 0.2 cm dark macule) shows mild epidermal hyperkeratosis, significant increase of melanin of the basal layer, increased melanocytes in the superficial dermis layer, and no obvious nevus cell nests (Figure 2). A diagnosis of generalized lentiginosis (without associated defined non-cutaneous abnormalities) was made.

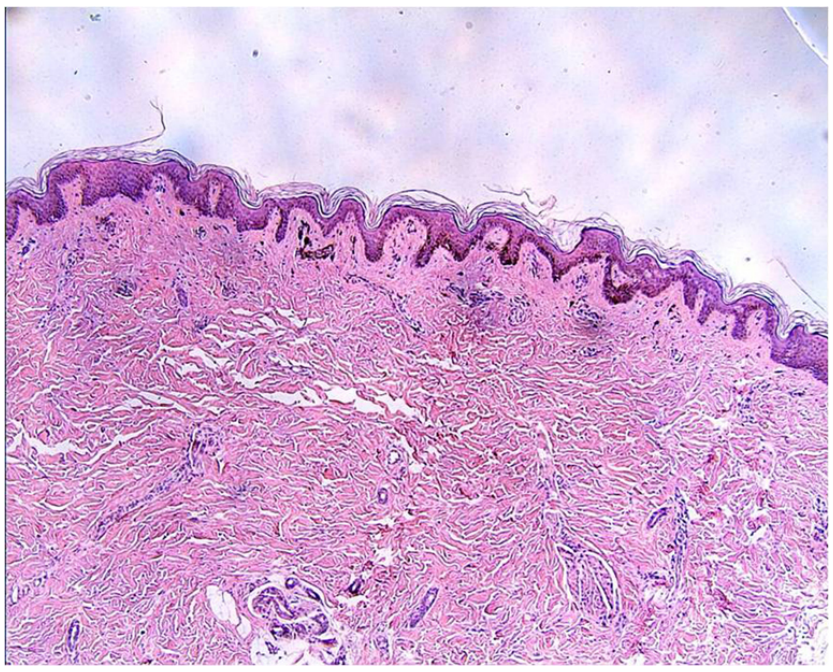

Figure 2. Histopathological examination shows mild epidermal hyperkeratosis, melanin in the basal layer, and increased melanocytes in the superficial dermis layer. There are no obvious nevus cell nests (haematoxylin and eosin staining, magnification ×10).

Discussion

Multiple lentigines in the generalized lentiginosis syndromes usually appear at four to five years of age and the lesions increase in number to thousands until puberty, independent of sun exposure[4, 8, 9]. Generalized lentigines associated with multiple non-cutaneous features, as in the Peutz-Jegherssyndrome, Leopard syndrome, and the Carney complex, have been well reported in the literature. We summarize the lentiginosis syndromes in Table 1[3, 4, 5,10]. Reports of patients with generalized lentigines without systemic abnormalities (termed "generalized lentiginosis") are increasing as well. Despite the lack of systemic features, patients with generalized lentigines should be monitored for further development of other non-cutaneous features, especially cardiac anomalies[6].

Table 1. Summary of lentiginosis syndromes

	PeutzJeghers	Leopard	Carney complex
Diagnostic criteria	2 of 3 criteria: - Characteristic mucocutaneous pigmentation - Histologically confirmed PJS-type polyps - Family history of characteristic polyps or mucocutaneous pigmentation	Presence of multiple lentigines and two cardinal features. In the absence of lentiginosis, three features in the patient and the presence of an affected close relative are diagnostic.	1 criterion from clinical presentation and at least 1 additional criterion from either clinical presentation or tumors
Clinical presentation	- Lentiginosis of lips and buccal mucosa and sparsely on the fingers, soles of the feet, palms, anal area and intestinal mucosa - Gynecomastia and growth acceleration	- Lentiginosis mostly on the face, neck, and upper part of the trunk, but sparing the mucosae - *café-au-lait spots* - short stature - facial dysmorphisms - cardiacanomalies	- Lentiginosis of face, lips, eyelids, conjunctiva, and oral mucosa - Other pigmented lesions such as multiple blue nevi or cafe-au lait spots - Gynecomastia, growth acceleration, acromegaly
Genetics	Autosomal dominant, located on chromosome 19pand 19q loci. Genes: STK11 (LKB1)	Autosomal dominant, located on chromosome 12q24.1. Genes: PTPN1	Autosomal dominant, located on chromosome 2p16 and 17q22e24 loci. Genes: PRKARIA and others
Tumors	- Sertoli cell tumors - Sex cord tumors with annular tubules - Various cancerous and precancerous lesions from: *Breast *Thyroid *Small intestine *Colon *Stomach *Pancreas *Esophagus *Ovary *Lung *Uterus *Uterine cervix	- Myelodysplasia - Acute Myelogenous Leukaemia - Neuroblastoma - Malignant melanoma - Bilateral Choristomas	- Large cell calcifying Sertoli cell tumor - Breast myxomatosis - Breast ductal adenomas - Thyroid carcinoma - Myxomas: cutaneous, mucosal, and cardiac - Growth hormone producing adenoma - Psammomatous melanotic schwannomas - Blue nevus, epithelioid blue nevus - Osteochondromyxoma

Numerous lentigines can be a cutaneous sign of systemic disorders. PJS is among the most important familial hamartomatous polyposis syndromes and is associated with significant morbidity, variable clinical course, and considerable predisposition to malignancy. Diagnosis is defined by the presence of histopathologically confirmed hamartomatous polyps and at least two of the following clinical criteria: family history, hyperpigmentation, and polyps in the small bowel. Screening recommendations for PJS patients includes gastrointestinal screening and polyp removals, but also regular cancer screening[3]. LS is a rare autosomal dominant disease, with high penetrance and marked variable expression, mainly characterized by short stature, facial dysmorphisms, cardiac anomalies, and hyperpigmented skin lesions.Clinical diagnosis of LS may be suspected in the presence of multiple lentigines and two cardinal features[4].Lentigines in LS do not cross the vermilion border of the lips, a characteristic that distinguishes this disorder from CNC and PJS. It is unknown whether pigmented lesions in LS progress to malignancy[2]. Baseline studies at diagnosis should include a complete clinical examination, cardiological, genitourinary and neurological evaluations, and hearing assessment. Laboratory studies should include molecular analysis of the *PTPN11* and *RAF1* genes[4]. Carney complex is a rare, dominantly inherited multiple endocrine neoplasia syndrome, affecting endocrine glands as the adrenal cortex (causing Cushing's syndrome), the pituitary, and the thyroid. Diagnosis is based on the presence of two or more cardinal manifestations confirmed by histology, biochemical testing, or imaging. If the patient has a demonstrated germline *PRKAR1A* gene mutation and/or a first-degree relative affected by CNC, a single manifestation is sufficient for the diagnosis[5]. Nevertheless, numerous lentigines may also appear in the absence of any associated abnormalities[6, 7].

There is little information about the natural course and pathogenesis of this disease[11]. However, considering the fact that lentigines represent the simplest form of melanocytic proliferation[1, 11], and there is some continuity from lentigines to melanocytic nevi, the pathophysiologies of generalized lentiginosis and generalized benign melanocytic nevi might be similar. Diminished immune surveillance in the skin may play a role in the pathogenesis of these lesions. Chemotherapy, medical immunosuppression, or aging may lead to multiple lentigines. Genetic predisposition may play a role in the development of this condition. Moreover, exposure to infectious agents or chemical materials might also contribute[11].

Lentigines are characterized by their small size (< 0.5 cm), irregular borders, and discrete markings of different shades of brown and black[2, 6].They are not limited to sun-exposed areas and are found primarily on the face, neck, and upper trunk, with some involvement of the extremities. Less commonly involved are the palms, soles, and genitalia; the oral mucosa is typically spared[4, 6,12]. Histologically, there is an increase in melanin granules throughout the epidermis with increased numbers of melanocytes[4, 6, 9], elongation of the rete ridges[6, 9], prominent epidermal thickening, and basal cell hyperpigmentation[2]. Most melanosomes are normal.

The main features of the patients were generalized brown macules for 8 years. The number and distribution were increased as he got older, not associated with cardiovascular, nerve, urinary, or reproductive systems abnormalities. Moreover, the histopathology showed significant increase of melanin of the basal layer, more melanocytes in the superficial dermis, and no obvious nevus cell nests. According to the clinical manifestations of the patient, histopathology, laboratory tests, and patient's history generalized lentiginosis without associated abnormalities was diagnosed.

The use of lasers, such as the Q-switched Nd:YAG laser, has been shown to be effective in the treatment of lentigines. Non-invasive agents such as tretinoin cream and hydroquinone cream used in combination have been shown to lighten lentigines after several months of application in some situations [6].

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