A Case of Multiple Lentigines Syndrome

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The multiple lentigines syndrome or LEOPARD syndrome is an autosomal dominantly inherited disorder with a variety of abnormalities and a familial occurrence. This syndrome is characterized by the presence of numerous dark brown macules on the skin but not the mucous surface, and by a marked increase in the number of lentigines from birth to puberty. The eponym LEOPARD stands for lentigines, EKG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retardation of growth and deafness.

We report a case of multiple lentigines syndrome in 7-year-old boy. He had numerous pinhead to pea sized, dark brownish macules scattered on the entire body and also had pulmonary stenosis, EKG abnormality, ocular hypertelorism and right exotropia. Interestingly, he also had a labial melanotic macule on the lower lip, which is usually spared in the multiple lentigines syndrome.

Histologically, the biopsy specimen taken from the macule revealed an elongation of rete ridges, an increase of melanin pigments in the basal layer and mild inflammatory infiltrates intermingled with the melanophages in the upper dermis.

(Ann Dermatol 9:(3) 219~223, 1997).

Key Words : Multiple lentigines syndrome, LEOPARD syndrome

The multiple lentigines syndrome is a complex dysmorphogenetic disorder transmitted as an autosomal dominant trait with variable penetrance and expressivity. Synonyms for this condition include leopard syndrome[1,2], cardiocutaneous syndrome[3], lentiginosis profusa syndrome[4] and progressive cardiomyopathic lentiginosis[5].

Theories regarding the pathogenesis of the multiple lentigines syndrome are entirely speculative. The major theory suggests that its origin may be a mutation in the stem cell of the neural crest.

This syndrome is extremely catholic in its involvement with many structures. Some changes are clinically striking, such as those of the skin, while others are relatively subtle and would be observed only with careful inspection.

We report herein a case of multiple lentigines syndrome showing numerous lentigines, pulmonary stenosis, electrocardiographic changes, ocular hypertelorism, and right exotropia.

Received January 31, 1997.
Accepted for publication March 20, 1997.
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REPORT OF A CASE

A 7-year-old boy presented with multiple brownish macules and patches on the whole body and a solitary dark brownish macule on the lower lip.

He was delivered after a full-term, uncomplicated pregnancy and had had 1 to 2 mm sized macules and 1 to 8 cm sized brownish patches scattered over the neck, shoulder and trunk since birth. The brownish macules developed on the face at 2 years of age. Since then there has been an increase in their numbers with age. The spots were distributed in profusion on the face, neck and trunk (Fig. 1, 2) and were in less dense in the axillae. No spot was found on the palms and soles. At 5 years of age, the solitary dark brownish macule also developed on the lower lip (Fig. 3). There was no family history of similar lesions. Echocardiography, cardiac catheterization and angiocardiography revealed pulmonary

Annals of Dermatology
Vol. 9, No. 3, July 1997

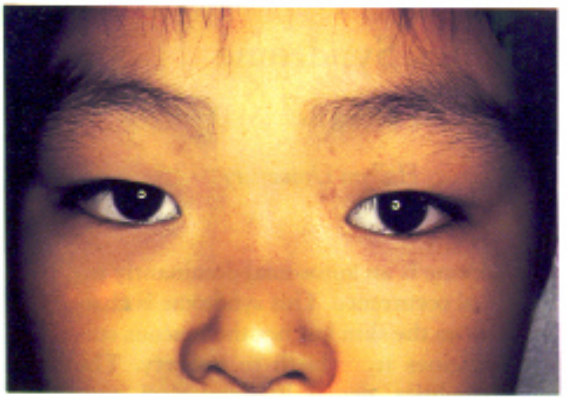

Fig. 1. The face showing numerous lentigines and the wide-set eyes.

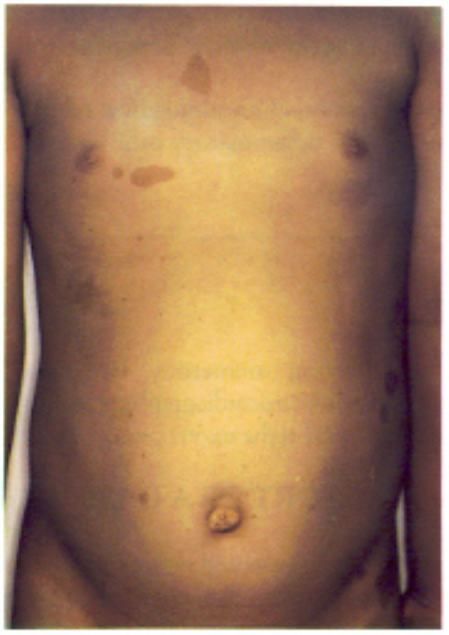

Fig. 2. Numerous lentigines and some caf -au-lait spots on the trunk.

valvular stenosis. So he was treated with ballon valvuloplasty at 2 years of age.

On physical examination, there was no evidence of a hearing disturbance, genital or skeletal abnormalities. His height was 117 cm and his weight was 24 kg. Ophthalmologic examination including the prism and alternative cover test revealed a 20 prism right exotropia, which was treated by resection and recession, but no Lisch nodule was found.

The chest roentgenograms showed a mild car-

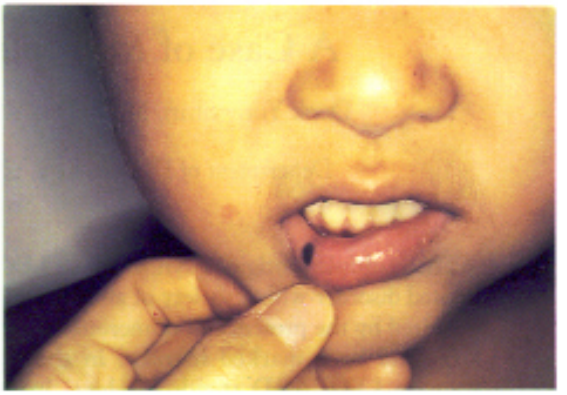

Fig. 3. A solitary dark brownish macule on the lower lip.

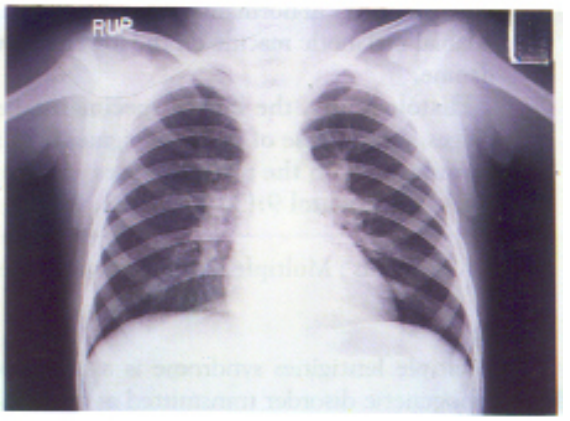

Fig. 4. Chest roentgenograms showing a mild cardiomegaly, a prominent pulmonary artery segment and increased pulmonary vascularities.

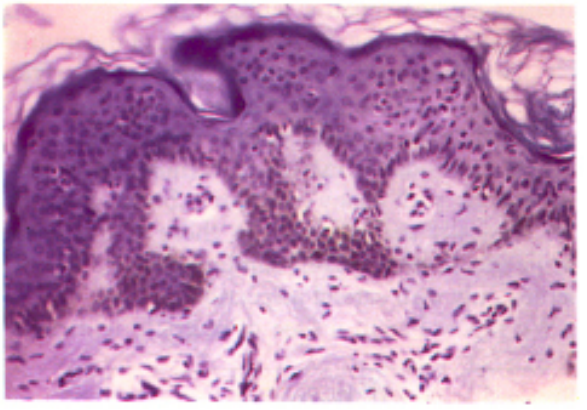

Fig. 5. Histopathological findings of the brown macule of the trunk show elongated rete ridges and an increase in the amount of melanin in the basal layer. Also note the melanophages and mild inflammatory infiltrations in the upper dermis (H&E stain, × 100).

diomegaly, a prominent pulmonary artery segment and increased pulmonary vascularities ; the evidence of pulmonary stenosis (Fig. 4). Other radiological evaluations and brain computerized tomography revealed no abnormal findings. The electrocardiogram revealed a left ventricular hypertrophy in the precordial lead.

Laboratory studies including a complete blood count, urinalysis and routine blood chemistry were either negative or within normal limits.

Histologically, skin biopsy specimens obtained from the macule of the trunk showed elongated epidermal rete ridges, large amounts of epidermal melanin pigments, particularly in the basal layer and mild inflammatory reactions with some melanophages in the upper dermis (Fig. 5).

DISCUSSION

Multiple lentigines syndrome has been reported in association with a variety of abnormalities and a familial occurrence. In 1936, Zeisler and Becker[6] described a woman with multiple lentigines, ocular hypertelorism, pectus carinatum and mandibular prognathism. After that, Rosen[7] reported three siblings (two male and one female) with large numbers of lentigines, but no mention was made of other disorders. In 1950, Pipkin and Pipkin[8] reported a large pedigree in which eight individuals in three generations had lentigines. The pedigrees suggested an autosomal dominant mode of inheritance. In 1969, Gorlin et al[1] and Gorlin and Sedano[2] entitled "Multiple Lentigines Syndrome" tied together a mélange of manifestations that seemed to be incorporated in the syndrome. The findings of more constant importance were included in their mnemonic designation, "leopard syndrome" ; l-lentigines, e-electrocardiographic changes, o-ocular hypertelorism, p-pulmonary stenosis, a-abnormalities of the genitalia, r-retardation of growth and d-deafness. In Korea, Paik and Kook[9] reported a 20-year-old woman who had numerous lentigines without anomalies of other organs in 1978. Since that time, two cases[10,11] have been reported in the literature.

The pathogenesis of multiple lentigines syndrome remains unknown. Several investigators[4,5,12] have suggested the possibility of a mutation in the embryonic neural crest to explain the presence of cutaneous and neurologic defects. Polani and Moynahan[5] also attributed the cardiac abnormalities in these patients to vasoactive substances produced by abnormal neural crest cells in the heart. Nordlund and his coworkers[12] suggested that in the multiple lentigines syndrome, gene products from a mutant neuroectodermal cell population interact with the cells of mesodermal origin to produce the observed abnormalities in mesodermal tissues.

Lentigines are present at birth or appear during childhood, and they become more numerous and darker with age. However several investigators[1,2,6,13] described patients with features of the multiple lentigines syndrome without lentigines. The facial skin and even the scalp can be the site of a few lentigines and the palms, soles, and genitalia as well. According to the literature, the numerous lentigines spare only the mucosal surface. But in our case, the labial melanotic macule developed on his lower lip at 5 years of age and became darker with age. Histological findings of a lentigo reveals an increased number of melanocytes per unit skin area and prominent rete ridges. They should be distinguished from freckles which appear later in life and are induced by exposure to sunlight.

In addition to lentigines, other cutaneous abnormalities including axillary freckling[4,14], café-au-lait spots[3,5,13,14], localized hypopigmentation[3,5,15], dermatoglyphic abnormalities[4,16], etc were also reported

Cardiac abnormalities are a common feature[3,5,17,18], and are represented by both anatomic malformations[3,5] and electrocardiographic disturbances[17,18]. The former usually consists of valvular pulmonic stenosis, but subaortic stenosis and other abnormalities may also occur. Electrocardiographic changes generally reflect the underlying structural abnormalities. The majority of patients are not symptomatic from a cardiac standpoint. However, sudden death may also occur due to severe cardiomyopathy[5].

Primary abnormalities in the neural crest development may cause the neurologic defects found in many patients with multiple lentigines syndrome[3,8,12]. The most common feature is sensorineural deafness[1,4,12,13,19]. Other features are mental retardation, oculomotor defects[3,4,8,19], abnormal electroencephalogram, seizures, etc.

The cephalofacial dysmorphism include ocular hypertelorism[1,4,5], mandibular prognathism, dental abnormalities and so forth.

Growth is retarded, usually below the 25th per-

centile. It is most likely that shortness of stature represents a defect in the skeletal growth center response to physiological levels of various growth factors and is a manifestation of a mesodermal disorder in the syndrome[20].

Since most genitourinary abnormalities involve visible genitalia, male predominance[21] may simply be a reflection of this fact. Cryptorchidism, delayed puberty, hypospadius and other anomalies was reported[20].

Skeletal anomalies are relatively mild. Chest deformity, either pectus carinatum or excavatum[6], is the most frequently observed abnormality. Retarded bone age, kyphoscoliosis, hypermobile joints, etc were reported.

The markedly variable expressivity of this syndrome makes establishment of diagnostic criteria difficult. Nevertheless, based on their analysis of the data they have collected, in 1976, Voron et al[20] proposed the following minimun criteria for the diagnosis ; (1) If the patient has multiple lentigines, features in at least two other categories must be present. (2) If lentigines are absent, a diagnosis of multiple lentigines syndrome may be made if the patient has features in at least three other categories and has an immediate relative with multiple lentigines syndrome as defined in (1)

The multiple lentigines syndrome must be differentiated from Noonan syndrome, neurofibromatosis, Turner syndrome, Moynahan syndrome and so forth[4,22,23].

In our case, the patient had multiple lentigines with other cutaneous involvements, pulmonary stenosis, electrocardiographic change, ocular hypertelorism and right exotropia, which were compatible with Voron's criteria (1).

As previously mentioned, the mucous membranes are invariably spared. But, our case revealed a labial melanotic macule on the lower lip. Although it is not certain whether the labial melanotic macule is a part of multiple lentigines or not, this report will be the first case suggesting a possibility of mucosal involvement in the multiple lentigines syndrome.

Finally, most patients with multiple lentigines syndrome are able to lead normal lives. Cardiac pathology in this syndrome causes the greatest morbidity, and so patients should be re-evaluated at frequent intervals.

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