Marked cutaneous “freckling” and cardiac changes

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A 45-year-old man originally presented in 1995 with a 3-year history of palmar/plantar psoriasis. At that time, examination revealed diffuse lentiginosis of his trunk and limbs associated with larger caf? au lait–like lentigines. He also had a previous myocardial infarction complicated by ventricular tachycardia, which required defibrillation and a permanent pacemaker. His father has a similar “freckling” pattern and also “cardiomyopathy.” His paternal uncles also have multiple freckles. Recent examination disclosed diffuse lentigines associated with large (10 X 50 mm) caf? au lait–type pigmented macules (Figure 1 and 2), with sparing of the axilla, palms, soles, and mucous membranes, including ocular and oral mucosa. In addition, skin tags and lipomata were present. Slight “winging” of the scapula was noted.

For diagnosis and discussion, see the following page.

DIAGNOSIS: Variant of LEOPARD syndrome.

DISCUSSION

Cardiocutaneous lentiginosis syndrome, or the LEOPARD syndrome, has also been referred to as the multiple lentigines syndrome (MLS), generalized lentiginosis, centrofacial lentiginosis, lentiginosis profusa syndrome, lentiginosis-deafness-cardiopathy syndrome, cardiocutaneous syndrome, progressive cardiomyopathic lentiginosis, and Moynahan syndrome (1–10). MLS is an autosomal dominant disorder with variable penetrance and expressivity and a slight preponderance towards men (10). LEOPARD, an acronym first introduced by Gorlin et al in 1969, is used to describe the clinical manifestations of the syndrome (Table 1) (9).
The primary defect is hypothesized to originate from mutations in the neuroectodermal layers, which may explain the association with obstructive hypertrophic cardiomyopathy and other neurocutaneous syndromes such as neurofibromatosis, tuberous sclerosis, and pheochromocytoma (4, 11, 12). Histologically, LEOPARD syndrome is characterized by large membrane-bound accumulations of melanin granules within the Langerhans' cells; giant melanosomes, seen with neurofibromatosis, are generally rare with MLS (13, 14).

The diagnosis of the LEOPARD syndrome is based primarily on a detailed family and genetic history, with clinical findings based on the mnemonic. Voron et al proposed the following “minimum” criteria for a diagnosis: 1) multiple lentigines plus 2 other clinical criteria or 2) if lentigines are not present, then features in at least 3 other categories and an immediate family member with MLS (1).

**Skin manifestations**

The lentigines are dark, brown, irregular-shaped macules from pinpoint to 5 mm in diameter. They vary in size but may be as large as 5 cm. Onset is usually at infancy or childhood with the number of lentigines increasing until puberty. They are present primarily on the face, neck, and upper trunk, with some involvement of the extremities, palms, soles, genitalia, iris, and sclera but sparing the oral mucosa (2, 4, 9, 15, 16). The color and density of the lentigines are not related to the degree of sun exposure, which differentiates them from freckles. Although lentigines are the most frequent finding, other cutaneous anomalies have been reported (Table 2) (15, 17).

<table>
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<tr>
<th>Table 1. Clinical manifestations of LEOPARD syndrome</th>
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<tr>
<td>Lentigines</td>
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<td>Electrocardiographic conduction abnormalities</td>
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<td>Ocular hypertelorism</td>
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<td>Pulmonary valve stenosis</td>
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<td>Abnormalities of genitalia</td>
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<td>Retardation of growth</td>
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<td>Deafness</td>
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<th>Table 2. Cutaneous abnormalities other than lentigines associated with LEOPARD syndrome</th>
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<tr>
<td>- Cafe au lait spots</td>
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<tr>
<td>- Localized hypopigmentation</td>
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<tr>
<td>- Interdigital webs</td>
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<tr>
<td>- Dermatoglyphic abnormalities</td>
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<tr>
<td>- Onychodystrophy</td>
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<tr>
<td>- Multiple granular cell myoblastomas</td>
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<td>- Hyperelastic skin</td>
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Other abnormalities

The most common cardiac anomaly is valvular pulmonary stenosis, occurring in 40% of reported cases (9, 18). Subaortic stenosis, subpulmonary stenosis, and mitral valve involvement also have been described (7, 19, 20). Obstructive hypertrophic cardiomyopathy is frequently a concern in these patients, and therefore, echocardiography is recommended (21). Other structural anomalies that may be assessed with either an echocardiogram or an angiogram include left and right ventricular outflow tract obstruction, atrial septal defect, and atrial myxoma (17). Electrocardiographic abnormalities occur frequently in this syndrome, including left axis deviation and conduction disorders, such as prolonged PR interval, left anterior or left posterior hemiblock, bundle branch block, or complete heart block. These conduction abnormalities may be asymptomatic or result in sudden death (22, 23).

The primary craniofacial feature is ocular hypertelorism, which is observed in 25% of patients with the LEOPARD syndrome (17). Other unusual findings include low-set, posteriorly rotated ears; high palatal arch; epicanthic folds; ptosis; short, webbed neck; and mandibular prognathism (1, 9). Other skeletal abnormalities have been reported, including joint hypermobility, “winging” of the scapula, pectus excavatum and carinatum, rib anomalies, cervical spine fusion, syndactyly, and scoliosis (9, 16, 17). These patients are usually short-statured (<25th percentile) despite normal body weight (9).

Genitourinary abnormalities are found in approximately 25% of patients, with a male predominance (1). Genital hypoplasia, including a small penis and cryptorchid testes (usually bilateral), is most common.

The most common neurological finding is mild mental retardation (1). Deafness, which is of sensorineural origin, is the rarest of the mnemonics and is reported in 25% of affected patients (1, 9). Other reported neurological findings include nystagmus, seizures, abnormal electroencephalograms, hyposmia, and mild atrophy of the brain.

Differential diagnosis

The myxoma syndromes, also referred to as LAMB (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi) and NAME (nevi, atrial myxomas, myxoid neurofibromatomas, and ephelides and endocrine neoplasia), are categorized under cardiocutaneous syndromes and should be considered in the differential diagnosis with the LEOPARD syndrome (24). The lentigines are similar to those in the LEOPARD syndrome, but the mucosal involvement and lack of dysmorphic features are indicative of the myxoma syndromes.

CONCLUSION

The diagnosis of the LEOPARD syndrome is made based on the clinical history and physical findings. There are currently no genetic or biochemical markers. The presence of generalized lentigines should be considered a clinical marker for possible systemic
abnormalities and serve as a clue for cardiac and auditory abnormalities (10). The possibility of an associated cardiomyopathy should be considered in any patient with multiple lentigines and a precordial murmur. The occurrence of multiple lentigines and unexplained systemic arterial obstruction suggests the presence of an atrial myxoma (18). A careful cardiac examination including an electrocardiogram and an echocardiogram is warranted, regardless of whether symptoms or clinical signs are present. If the initial assessment is normal, then follow-up visits are necessary because abnormalities may develop later. Our patient is currently in excellent health and doing well with his pacemaker and daily medications of warfarin sodium, aspirin, vitamin E, bisoprolol (a beta-blocker), and pravastatin.

References


