Agminated lentiginosis or segmental neurofibromatosis: A diagnostic challenge

Sir,
We present two cases with an unusual pattern of segmental spotty pigmentation that posed a diagnostic challenge.

A 16-year-old woman presented to the dermatology department with asymptomatic spotty brownish lesions that were present since early childhood and gradually increased in number over time. No history of excessive sun exposure was evident. Physical examination revealed numerous brown macules, unilaterally distributed on the right side of the neck extending to the right cheek and shoulder [Figure 1].

A 22-year-old woman was referred for evaluation of asymptomatic hyperpigmented spots on her lower abdomen that were present since birth and were progressively increasing in number and size with age. Examination revealed numerous pin-point light brown macules unilaterally distributed on the left groin and buttock extending upward to the lower abdomen and downward to the upper thigh. Four café-au-lait macules ranging in diameter from 1 to 4 cm were seen among brown spots. No neurofibromas could be detected [Figure 2].

In both the cases, physical and mental development was normal. Family history was non-contributory. No other cutaneous, mucosal or systemic findings were evident. Ophthalmic and orthopedic assessment revealed normal findings and routine laboratory investigations were within normal limits. Computed tomography and magnetic resonance imaging of the brain and spine revealed no abnormalities.

Histopathologic examination of skin biopsies from both cases revealed linear (non-nested) melanocytic hyperplasia in the epidermis with a hyperpigmented basal cell layer [Figure 3]. In addition, the second case showed lentiginous elongation and thinning of the rete ridges [Figure 3b and c]. Findings of both the cases were consistent with lentigo simplex. However, the biopsy taken from café-au-lait macules showed only increased melanin content of the basal cell layer.

Based on both clinical and histopathologic criteria, our first case was diagnosed as agminated lentiginosis. However, in the second case, the presence of café-au-lait macules in the same segmental distribution represented a diagnostic problem. The question we faced was whether this was a case of agminated lentiginosis associated with café-au-lait macules as previously reported by some authors, 1 or whether it was segmental neurofibromatosis.

Agminated lentiginosis is a benign condition that is characterized by multiple lentigines that are grouped

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Figure 1: Multiple lentigines localized on the right side of the neck and extending to the right shoulder (note the dermatomal distribution as shown in 1a)

Figure 2: (a) Multiple small, discrete, lightly pigmented macules together with four café-au-lait macules scattered over the left groin extending to the lower abdomen, buttock and upper thigh; (b) frontal view showing the segmental distribution of the pigmented macules with sharp demarcation at the midline
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within an area of normal skin, often in a segmental pattern that can appear anywhere on the body. Differential diagnoses include speckled lentiginous nevus and segmental neurofibromatosis. Speckled lentiginous nevus was excluded in the present cases by the absence of a tan macular background and nevoid melanocytes on histopathology.[1]

Segmental neurofibromatosis is a rare condition characterized by pigmented abnormalities which include café-au-lait macules and/or axillary freckles and/or neurofibromas in a single segment of the body that do not cross the midline. Family history of neurofibromatosis is not seen nor is systemic involvement. It is further subdivided into four subtypes: true segmental, localized with deep involvement, hereditary and bilateral.[2]

The presence of multiple café-au-lait macules in the same distribution as lentigines in cases of agminated lentiginosis has led some authors to suggest that it is a form of neurofibromatosis.[3] Chen et al. reported a case that confirmed that agminated lentiginosis represents a mosaic manifestation of neurofibromatosis 1.[3] Their case was had an unusual combination of multiple lentigines clustered on her left face, café-au-lait macules on her left arm with ipsilateral axillary freckling and Lisch nodules.

There are also reports of agminated lentiginosis in patients with either contralateral or bilateral segmental neurofibromatosis.[2] The diagnosis of segmental neurofibromatosis was based on both neurofibromas and café-au-lait macules in a segmental distribution or combined with Lisch nodules or scoliosis affecting the same side of the body and/or progeny who had classic neurofibromatosis.[4]

In our second patient, the absence of any associated manifestations of neurofibromatosis and the lentiginous hyperplasia revealed by histopathologic examination weighed more towards the diagnosis of agminated lentiginosis. However, in view of the contention that agminated lentiginosis might represent a forme fruste of neurofibromatosis or even be part of the spectrum of segmental neurofibromatosis,[4] the patient has to be followed up for any cutaneous or ocular lesions that may develop later on. The age of presentation of neurofibromas is from puberty to young adulthood but may occur at any age. Also, the presence of Lisch nodules is age-dependent; only 40% of affected children have them by 6 years of age, whereas by late adulthood, more than 95% of people with neurofibromatosis 1 will have Lisch nodules.[5]

In conclusion, the presence of café-au-lait macules does not confirm the diagnosis of segmental neurofibromatosis. Thorough history taking, examination, histopathologic evaluation and follow-up are mandatory to help in careful differentiation and exclusion. Whether they represent the association of two disorders or agminated lentiginosis represents the forme fruste of neurofibromatosis 1 needs to be settled by genetic studies (mutational analysis).

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Figure 3: (a) Case 1 lesion showing linear melanocytic hyperplasia in epidermis with hyperpigmented basal cell layer (H and E, ×200) (b) Case 2 lesion showing lentiginous hyperplasia of epidermal melanocytes with elongation and thinning of rete ridges (H and E, ×100), (c) Higher power view of the same lesion (case 2) with evident basal cell layer pigmentation (H and E, ×400)
Sir,

A 15-year-old girl presented for the evaluation of pigmented lesions which had been progressively appearing for the last 7 years [Figure 1]. Her mother, uncle, grandmother and brothers also had similar multiple pigmented lesions [Figure 2].

Clinical examination revealed multiple lentigines and café au lait macules scattered over her trunk, neck and face. In addition, there was mild facial dysmorphia including hypertelorism, low-set ears and broad nasal bridge. Her mother showed a similar facial appearance and a larger number of lentigines on her trunk and face. An electrocardiogram was performed and no alterations were detected.

The patient also had a history of two subcutaneous nodules on her right foot and left arm which had been excised at the age of 10 and 11 years, respectively. Histologic study of these nodules had demonstrated nests of S100/vimentin positive cells with granular cytoplasm and small hyperchromatic nuclei with a diagnosis of granular cell tumor in both cases [Figure 3].

In view of these clinical signs, there was clinical suspicion of a RASopathy. Genetic testing revealed a p.Gln510Arg PTPN11 mutation in the patient and in her mother. This mutation has been previously described and therefore, a diagnosis of LEOPARD (lentigenes, electrocardiographic conduction anomalies, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness) syndrome was made.

Granular cell tumors are rare, generally benign neoplasms most likely of Schwann cell origin. They usually present as an asymptomatic, solitary, skin-colored nodule or papule in cutaneous and subcutaneous tissue (43%), tongue (23%) or internal organs.[1] These tumors have an excellent prognosis and the treatment of choice is surgical excision with wide margins to prevent recurrence. The characteristic histopathology shows irregularly arranged sheets of polyhedral cells with central hyperchromatic nuclei and coarse granular eosinophilic cytoplasm. These granular cells stain positive for S100 (98–100%), neuron specific enolase (98–100%) and vimentin (100%). Multiple granular cell tumors have been reported in up to 30% of cases but they are infrequent in childhood. In up to 50% of children with multiple granular cell tumors, there are associated systemic abnormalities such as cardiovascular, musculoskeletal and pigmentary disorders.[2]

Several cases of multiple granular cell tumors in association with neuro-cardio-facial-cutaneous syndromes have been described such as Noonan syndrome and neurofibromatosis type 1. We were able to find only two previous reports of multiple granular cell tumors reported in association with LEOPARD syndrome. The first report described a woman with confirmed LEOPARD syndrome with a c. 1403C.