Café-au-Lait Macules: Occasional Fatal Sequels of Benign Pigmented Lesions

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INTRODUCTION

In skin pathology, among the worrisome pigmented lesions, melanoma is the most reported one. Nevertheless, some benign pigmented lesions can sometimes have an ominous meaning, due to their clinical implications.

We present a case in which café-au-lait macules (CALM), in the context of neurofibromatosis type-1 (NF-1), anticipated sudden death associated with intrathoracic plexiform neurofibroma.

CASE REPORT

A 28-year-old male was found dead at his home, without any sign of violence or trauma. He had been diagnosed with neurofibromatosis at the age of 6 years, and had developed scoliosis that was thought to be due to the syndrome. The pediatrician had recorded “more than 8” CALM, and noted that the patient’s father and paternal grandmother also had café-au-lait spots. The patient used to occasionally sniff cocaine.

External examination revealed 12 café-au-lait spots located in the lumbar (Fig. 1A), thoracic (Fig. 1B) and abdominal regions as well as at the back of the right thigh. The largest spot measured 1.3 cm. Some cutaneous neurofibromas were also observed on the front (Fig. 1B) and back (Fig. 1C) of the trunk and on the arms, all of which were smaller than 5 mm. Biopsy specimen was obtained from one of them on the right arm when he was 7 years old.

Postmortem examination revealed a soft, yellowish thoracic tumor of 20x10x5.5 cm, closely attached to the internal side of the left thoracic wall and left side of the spine (Fig. 2). Fracture of the anterior pillar of the spine, between the 8th and 10th vertebrae was observed, with preservation of the medulla. This fracture had torn the aorta, and bilateral hemothorax (2 L) was found.

Macroscopic examination showed a tumor of plexiform appearance, while histopathology
Tumor cells expressed S-100 (Fig. 3B), while immunostaining for epithelial membrane antigen (EMA) indicated perineural cells (Fig. 3C). There was no neurospecific enolase or collagen IV expression.

The family received genetic counseling in line with ethical national standards.

DISCUSSION
We present a case of sudden death in a patient who met the criteria for NF-1 as set by the National Institutes of Health in 1987 (1). The patient had a positive family history, as found in 50% to 70% of all patients. Nevertheless, one should also be aware of new mutations of the \( NF1 \) gene (2).
One of the clinical manifestations of NF-1 is the presence of CALM that usually appear in the first year of the person's life and can occur at many sites of the body apart from the palms, scalp and soles (1).

This aim of this report is to emphasize how CALM, although a benign pigmented lesion, can also be dangerously related to death, an ominous “privilege” that is usually attributed to melanoma. It is obvious that such an attribute is due to the relations that CALM have with NF-1, a syndrome that occasionally may cause sudden death. CALM can also appear in healthy people with no increased risk of tumors or symptoms ascribed to any syndrome, in up to 13% of the population, depending on the race considered (3). In the latter context, they are not related to an increase in the risk of sudden death.

Sudden death has been reported as a cause of von Recklinghausen's neurofibromatosis due to many causes, among which the most reported are intracranial tumors (4,5), vasculopathy affecting coronary arteries (6,7) and spontaneous hemothorax (8), the latter being probably associated with sudden rupture of dysplastic arteries that have been described in NF-1 (9,10).

In the case presented, death was related to the thoracic vertebral fracture, with laceration of the aorta and subsequent hemothorax. This fracture was probably due to a combination of factors such as compression by tumoral mass plus scoliosis that the patient presented. Scoliosis is not an uncommon finding in patients with NF-1, and is present in 10% to 20% of these patients (1,2,11,12). Cutaneous as well as diffuse plexiform neurofibromas are the most common tumors seen in NF-1 patients (2).

There is one case in the literature, where sudden death was related to large intrathoracic neurofibroma, as in the case presented (13). In that case, neurofibroma arose from the intrathoracic vagus nerve, although the exact cause of death remained unknown, as admitted by the authors. Several minor neurofibromas were also present in both vagus and recurrent laryngeal nerves.

In spite of its semiologic importance in the diagnosis of NF-1, the pathogenesis of CALM has not yet been fully understood. Several hypotheses based on different observations have been proposed. Among these, some of the most widely accepted are those implying the presence of giant pigment granules (macromelanosomes) in epidermal melanocytes and keratinocytes (14), as well as an increased variation in the number and length of dendrites of the melanocytes (15).

Nevertheless, macromelanosomes can be found in other conditions that do not imply NF-1, which correlates with the fact that CALM are also observed in many conditions other than NF-1. Among these, probably the most commonly reported are McCune-Albright syndrome, tuberous sclerosis, and LEOPARD syndrome (3), together with the evidence of CALM with no known clinical implications in healthy people (2).

In conclusion, our report tries to emphasize the ominous clinical implications that some benign pigmented cutaneous lesions can have and their use in the early diagnosis of some diseases.

References

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