Acta Dermatovenerol Croat 2008;16(2):79-82 CASE REPORT

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

Angel Fernandez-Flores, Oliva Orduña, Manuel Aguirrezabal

S. Patología Celular, Clínica Ponferrada, Ponferrada, Spain

Corresponding author:
Angel Fernandez-Flores, MD, PhD
Histopathologist-Cytopathologist
Head, S. Patología Celular
Clínica Ponferrada
Avenida de Galicia 1
24400 Ponferrada
Spain
afernandezflores@clinicaponferrada.com

Received: August 18, 2007
Accepted: March 12, 2008

SUMMARY We report a case of sudden death in a 28-year-old male diagnosed with neurofibromatosis at the age of 6 years. The patient had multiple café-au-lait spots which, although being benign, were an ominous sign in this context. The immediate cause of death was intrathoracic neurofibroma causing compression that led to fracture of the thoracic vertebrae and laceration of the aorta with massive hemothorax.

KEY WORDS: neurofibroma, sudden death, cafe-au-lait spot

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

Acta Dermatovenerol Croat
2008;16(2):79-82

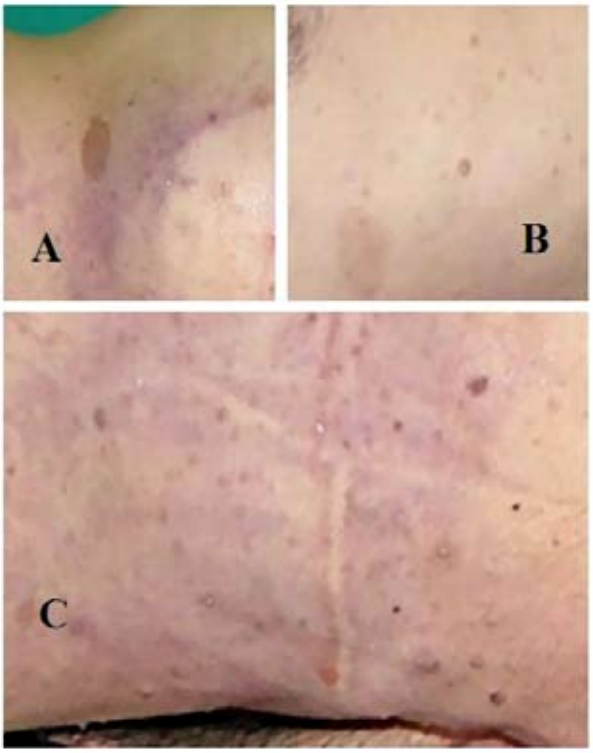

Figure 1. Café-au-lait macules in the patient presented: on the back (A) and front (B) of his trunk. Many neurofibromas are also seen in the front (B) and back (C).

identified it as plexiform neurofibroma (Fig. 3A).

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.

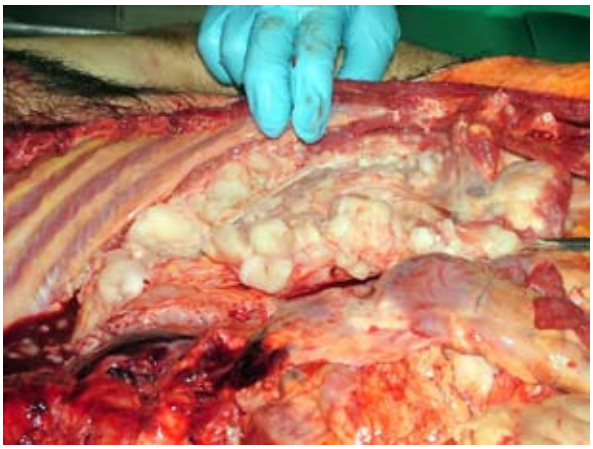

Figure 2. Typical macroscopic aspect of plexiform neurofibroma, with multiple thick tumoral and tortuous cords, running in parallel to each other.

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).

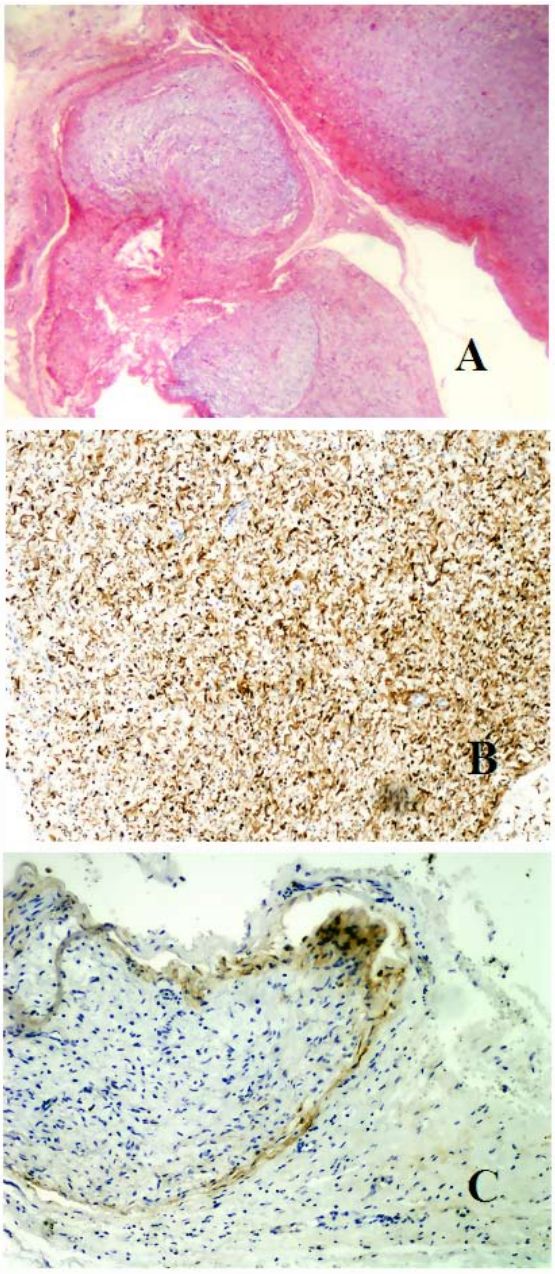

Figure 3. (A) Histopathologic aspect of the tumor, showing several encapsulated individual tumoral cords; (B) tumoral spindle cells immunostained for S-100 protein, while epithelial membrane antigen (EMA) was expressed by the cells of the outer capsule (C), which is typical for the plexiform variant of neurofibroma.

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

1. Karnes PS. Neurofibromatosis: a common neurocutaneous disorder. Mayo Clin Proc 1998;73:1071-6.
2. De Schepper S, Boucneau J, Lambert J, Messiaen L, Naeyaert JM. Pigment cell-related manifestations in neurofibromatosis type 1: an overview. Pigment Cell Res 2005;18:13-24.
3. Tekin M, Bodurtha JN, Riccardi VM. Café au lait spots: the pediatrician's perspective. Pediatr Rev 2001;22:82-90.
4. Unger PD, Taff ML, Song S, Schwartz IS. Sudden death in a patient with von Recklinghausen's neurofibromatosis. Am J Forensic Med Pathol 1984;5:175-9.
5. Koszyca B, Moore L, Byard RW. Lethal manifestations of neurofibromatosis type 1 in childhood. Pediatr Pathol 1993;13:573-81.
6. Hamilton SJ, Allard MF, Friedman JM. Cardiac findings in an individual with neurofibromatosis 1 and sudden death. Am J Med Genet 2001;100:95-9.
7. Kanter RJ, Graham M, Fairbrother D, Smith SV. Sudden cardiac death in young children with neurofibromatosis type 1. J Pediatr 2006;149:718-20.
8. Griffiths AP, White J, Dawson A. Spontaneous haemothorax: a cause of sudden death in von Recklinghausen's disease. Postgrad Med J 1998;74:679-81.
9. Huppman JL, Gahton V, Bowers VD, Mills JL. Neurofibromatosis and arterial aneurysms. Am Surg 1996;62:311-4.
10. Morentin B, Aguilera B, Garamendi PM, Suarez-Mier MP. Sudden unexpected non-violent

Acta Dermatovenerol Croat
2008;16(2):79-82

death between 1 and 19 years in north Spain. Arch Dis Child 2000;82:456-61.

11. North K. Neurofibromatosis type 1: review of the first 200 patients in an Australian clinic. J Child Neurol 1993;8:395-402.
12. Trovo-Marqui AB, Goloni-Bertollo EM, Valerio NI, Pavarino-Bertelli EC, Muniz MP, Teixeira MF, *et al*. High frequencies of plexiform neurofibromas, mental retardation, learning difficulties, and scoliosis in Brazilian patients with neurofibromatosis type 1. Braz J Med Biol Res 2005;38:1441-7.
13. Chow LT, Shum BS, Chow WH. Intrathoracic vagus nerve neurofibroma and sudden death in a patient with neurofibromatosis. Thorax 1993;48:298-9.
14. Jimbow K, Szabo G, Fitzpatrick TB. Ultrastructure of giant pigment granules (macromelanosomes) in the cutaneous pigmented macules of neurofibromatosis. J Invest Dermatol 1973;61:300-9.
15. Jungbauer S, Kemkemer R, Gruler H, Kaufmann D, Spatz JP. Cell shape normalization, dendrite orientation, and melanin production of normal and genetically altered (haploinsufficient-NF1) melanocytes by microstructured substrate interactions. Chemphyschem 2004;5:85-92.

Your children should be on the air; year 1937.
(from the collection of Mr. Zlatko Puntijar)