Ann. Ital. Chir., LXXV, 1, 2004

Cutaneous melanoma with neurofibromatosis type 1: rare association? A case report and review of the literature

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Riassunto

MELANOMA CUTANEO ASSOCIATO A NEUROFIBROMATOSI TIPO 1: RARA ASSOCIAZIONE? RESOCONTO DI UN CASO. REVISIONE DELLA LETTERATURA

La Neurofibromatosi (NF) è una patologia relativamente comune caratterizzata da macchie cutanee pigmentate, neurofibromatosi multipla e noduli di Lisch (amartomi pigmentati dell'iride). Si ritiene che questa patologia sia una neurocrestopatia. Anche i melanociti derivano dalla cresta neurale. Sono stati descritti finora in letteratura ventisei pazienti con neurofibromatosi associata a melanoma cutaneo maligno, ma i dati riguardo l'associazione delle due patologie non sono univoci. Riportiamo un ulteriore caso da noi osservato di melanoma cutaneo maligno in un paziente affetto da NF, e viene considerata la possibilità di una maggiore incidenza della associazione delle due patologie, attualmente sottostimata per mancata diagnosi di NF.
Parole chiave: Melanoma maligno, malattia di Von Recklinghausen, neurofibromatosi, cresta neurale.

Abstract

Neurofibromatosis (NF) is a relatively common disorder characterized by cutaneous pigmented maculas, multiple neurofibromas and Lisch nodules (pigmented iris hamartomas). This disorder is retained being a neurocristopathy. Melanocytes are neural crest derivates too. Twenty-six patients with neurofibromatosis associated to cutaneous malignant melanoma have been reported till now, but data on association between these two pathologies are lacking. One more case of malignant cutaneous melanoma in a patient with neurofibromatosis is reported and the hypothesis of a more frequent association than usually believed of these two pathologies is discussed.
Key words: Cutaneous melanoma, Von Recklinghausen's disease, neurofibromatosis, neural crest.

Introduction

Neurofibromatosis (NF) is a relatively common disorder occurring approximately in 1/3000 births (1, 2, 3). Bolande (4), first introduced the term of neurocristopathy to point out the common neural crest origin of all involved tissues in NF. Although the involvement of tissues not derived from neural crest was reported (1, 5), the hypothesis that NF is a disorder of neural crest origin could be well-founded yet because the alterated neural crest derivates could be able to product disorders in not derived from neural crest tissues (1, 3). The melanocytes are derivates of neural crest too. They produce one of the most costant features in NF, the cafè au lait spots. Association between cutaneous melanoma and NF is reported in literature. However, although melanocytes clearly are involved in NF, the association of both the disorders is not demonstrated and the correct incidence of cutaneous melanoma in NF is unknown. We report one case of a patient affected by cutaneous melanoma and NF.

Case Report

On March 3rd, 2001, a 60-year-old man affected by cutaneous malignant melanoma of the right heel was admitted in our institution. He produced the documentation of a biopsy of the heel's lesion and total body CT scan. A diagnosis of ulcerated malignant melanoma was made based on the biopsy. The CT scan showed the enlarg-

Pervenuto in Redazione il 30 Luglio 2003

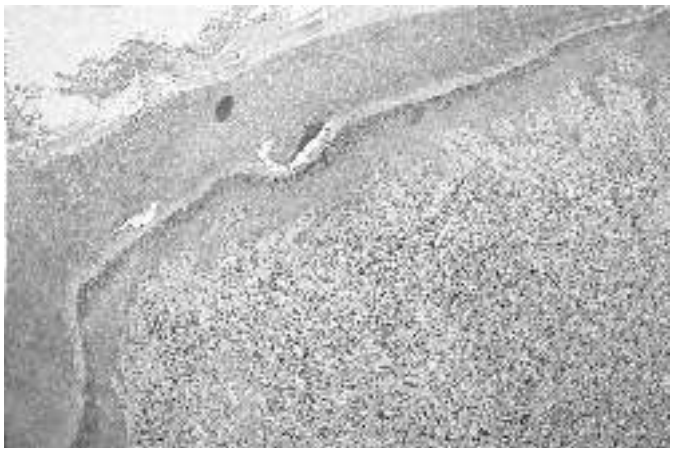

Fig. 1: Dermal and epidermal infiltration by a cutaneos nodular melanoma (EE-4x).

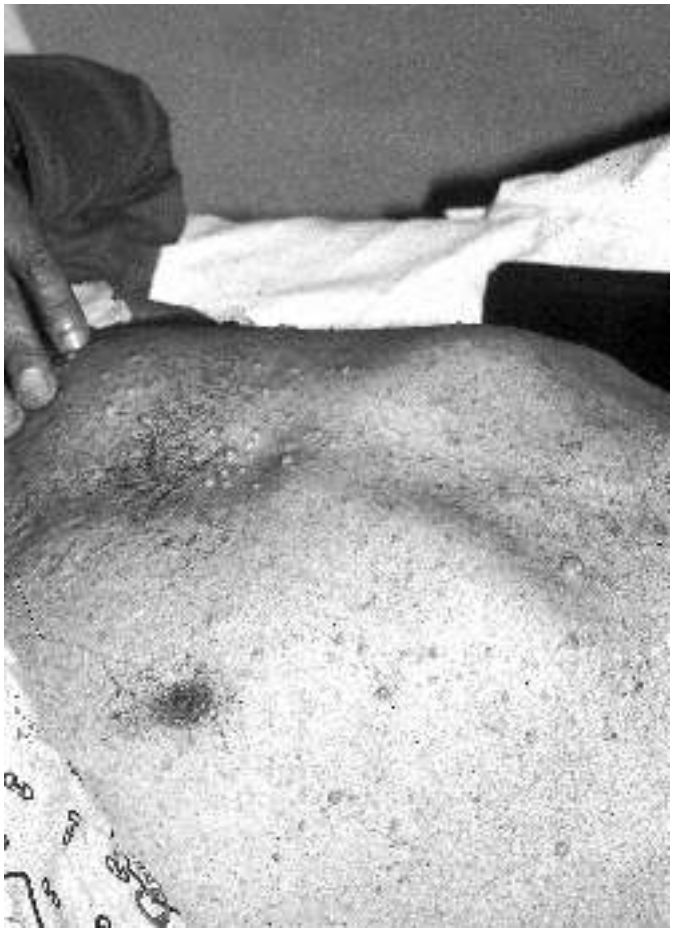

Fig. 2: Trunk and abdomen neurofibromatosis.

ment of two inguinal nodes, 21 and 33 mm respectively, with central colliquative necrosis.
On the general physical examination the patient showed an ulcerated lesion of the right heel of cm 4x4 in dimension, with muddy surface and 0,5 cm elevated edges on surrounding skin. There were multiple cutaneous neurofibromas on the trunk and the extremites and numerous cafè au lait spots especially on the trunk. It was made clinical diagnosis of NF. The patient had not affected relatives and he did not previously know having NF. The examination of the other districts was negative. Tumoral markers (CEA, TPA, aFP and CA 19-9) were normal.
We performed a wide excision of the cutaneous lesion and an inguinal and external iliac lympho nodes toilet. The histopathologic examination of the cutaneous speciments revealed a nodular malignant melanoma vertically growing, with infiltration of subcutaneous tissue and focally of the muscular bundles. The tumor was composed of large cells prevalently epithelioid and less spindle-shaped cells. Mitotic activity was elevated. There was a scanty lymphomonocytic host response. Surgical resected edges were not infiltrated.
Iliac lympho nodes (5 nodes founded) were negative while two on 15 inguinal lympho nodes escissed were metastatic.
The tumor staging was pT4a pN1 pMx, R0, Stage III, (Stage V according to Clark's classification).
On the 14th postoperative day a cutaneous free grafting was performed to fill the tissue loss resolved by previous operation.
On the 23th postoperative day after the first operation the patient was readmitted and referred to the oncologist.
The patient was submitted to an interferon injection once a week and he follows such therapy up till now. He is free from disease at the last CT scan (July 2003).

Discussion

Neurofibromatosis is an autosomal dominant trait with variable expressivity. Riccardi distinguished four different forms of NF at least (3). The most common form (90% of cases) is that so-called classic or peripheral or von Recklinghausen's disease or neurofibromatosis type 1 (NF1) (5, 6). Only one half of all cases are inherited, while the others result of new mutation (2, 7). The most clear and virtually always founded features in NF1 are cafè-au-lait spots, neurofibromas and Lisch nodules.
Cafè-au-lait spots, so-called for their colour, are skin pigmented lesions variable in dimensions (1-2 cm to 15 cm) usually present at birth. They are distributed at random on the whole body increasing in number and size during the first decade and, in women, they become darker in pregnancy (3).
Generally neurofibromas are cutaneous but they can involve the deep nerves too. Most of them appear during or after puberty. They can be nodular and distinct (such as cutaneous ones) or plexiform type (4, 8).
Lisch nodules, or pigmented iris hamartomas, are prominent nodules of the iris surface present in most patients since childhood; at the age of 60 Lisch nodules are present in almost 100% of patients (3, 9).

Another common finding of NF1 is represented by axillary or inguinal freckles (5, 10). However, some lesions clinically appearing as freckles in patients with NF1, can be little cafè-au-lait spots (11). Many other clinical finding can be found in NF1 with variable frequency. Riccardi (3) summarized the following features: macrocephaly, central nervous system tumors, segmental hypertrophy, psudoarthrosis, kyphoscoliosis, short stature, premature or delayed puberty, malignant disease, pheochromocytoma, intellectual handicap, speech impediment, headache, cerebrovascular compromise, hypertension, constipation, visceral neurofibromas, pruritus, seizures, psychosocial burden.

The NF1 clinical diagnosis requires two or more of the following signs (6, 7, 12): six or more cafè-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals; two or more neurofibromas of any type or one plexiform neurofibroma; freckling in the axillary or inguinal regions; optic glioma; two or more Lisch nodules; a distinctive osseus lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis; a first degree relative (parent, sibling or offspring) with neurofibromatosis 1 according to the above criteria.

Association between NF1 and various malignancy is reported (1, 8, 13, 14, 22). A true association between neurofibrosarcomas and brain tumours is demonstrated while the association with medulloblastoma, pheocromocytoma and medullary thyroid carcinoma is not documented. All these tumours derive from neural crest. An association between NF1 and tumors not derived from neural crest has been suggested but not yet demonstred. This does not necessarly contradict the concept that NF1 is a neurocristopathy because the above neoplasms couldn't be really associated with NF1 or, even in case of association, they could be induced by alterated neural crest derivates (1).

Melanocytes are neural crest derivates and in NF1 certainly they are alterated. They produce one of the most costant features in NF1, (the cafè-au-lait spots). The cafè-au-lait spots in NF1 patients seem to show histological differences compared with those of individuals without NF1. The cafè-au-lait spots of patients with NF1 have more melanocytes than the surrounding skin, while in individuals without NF1 cafè-au-lait spot's melanocytes are less than in the normally pigmented skin (in individuals without NF1 the cafè-au-lait spots are really large freckles). Furthermore, patients with NF1 have an increased number of melanocytes also in their normally pigmented skin compared with normal individuals: this seems to suggest that NF1 represents a proliferative process of neuroectoderm (11).

In the patients with NF1 melanocytes contain an increased amounts of large melanosome complexes and higher amounts of melanin than those of health individuals (15). Therefore it is not surprising that some authors have suggested the association between NF1 and melanocytic malignancy such as malignant melanoma of uvea, conjunctiva, choroid and leptomeninges (7, 9, 16, 17, 18).

To our knowledge, in literature 26 cases of cutaneous malignant melanoma associated with NF1 are reported. In addition a case of metastatic melanoma of the small bowel with primary site unknown, is reported (Knight *et al.*, 1973). Baldini (1) (1988) described a case of a 38 years old woman with melanoma arising in a giant nevus of the left buttock. Gallino (6) (2000) reported three cases of cutaneous melanoma; one of these is the same patient described by Baldini in 1988 concerning a 44 years old woman. Guillot (9) (1990) reported the case of 22 years old woman affected by cutaneous melanoma of the left leg and quoted three cases of the japanese literature and one case of Knight (1973). Silverman (20) (1988) described a 64 years old black patient with cutaneous malignant melanoma of right breast. Perkinson (10) (1957) described the cutaneous melanoma of a 44 years old woman arising in a cafè-au-lait spot after sunburn. Duve (5) (1994) reported a case of 37 years old woman with malignant melanoma of the left leg and quoted the case of an anorectal melanoma described by Garcia-Cassola *et al.* (1992) and four cases of melanomas arising in giant congenital nevi described by Rubenstein *et al.* (1985). Mastrangelo (2) (1979) described the case of a 34 years old woman with cutaneous melanoma in the anterior part of chest. Brasfield and Das Gupta (8) (1972) reported 6 cases of cutaneous melanoma occurring in patients with NF1. Hope (1) (1981), in their review, related of 13 cases of cutaneous melanoma in patients affected by NF1; six of these cases are the same previously reported by Brasfield and Das Gupta in 1972 and three cases are those mentioned above of Mastrangelo, Perkinson and Knight. Remaining four cases were previously reported by Strube *et al.* (1975), Lisboa (1961), Neumann *et al.* (1977) and Dalforno *et al.* (1968).

Most of the literature about the association between NF1 and cutaneous melanoma consist of case reports. Data on the association between NF1 and cutaneous melanoma deriving from wide series are not univocal. The review of Hope (1) showed that none of 395 patients with NF1 in Danish and Michigan cohorts had cutaneous melanoma; the same authors quoted a series of cases of Crowe *et al.* in which none of 223 patients with NF1 had melanocytic malignancy. Mastrangelo (2) have founded only one case of NF1 in 900 patients with melanoma. Duve (5) quoted a review of Rubenstein *et al.* in which four of 791 patients with NF1 had cutaneous malignant melanoma. The six cases of cutaneous melanoma reported by Brasfield and Das Gupta (3) come from a work studying 110 patients with NF1. Thus, only Brasfield and Das Gupta series seem to show a significant association between the two diseases and, on the other hand, the single case report are not able to express a well-founded valuation on the association between NF1 and cutaneous melanoma.

It is possible, as some authors emphasized, that so discordant results could be derived by biased samplings. Silverman (20) proposed that the lacked recovery of such association could be due to the death of the patients with NF1 before melanoma occurring: the middle age of other malignancy onset in patients with NF1 is lower than the melanoma onset of the patients with NF1.
It's possible moreover, in case of association between NF1 and cutaneous melanoma, that it could be not emerged for an understimation of the patients with NF1. NF1 in fact presents an extremely variable expressivity and it's possible that scantily simptomatic forms are not recognized. Furthermore, even NF1 types with clear clinical signs, could be not recognized from physicians. Our patient, although he presented evident features of NF1, did not had previous diagnosis of NF1.
Furthermore the stigmate of the disease could be also evident late: five of 110 patients (4,5%) reported by Brasfield and Das Gupta, developed the NF1 manifestations after the age of 36. Moreover the disease can at first be disclosed only through cafè-au-lait spots, or Lisch nodules which are practically pathognomonic of NF1 (21). In the Johnson (11) study concerning the hystological differentiation of cafè-au-lait spots between patients with and without NF1 (8 patients with NF1 and 4 without NF1) one of these patients was recognized to have NF1 only for hystological features of his cafè-au-lait spots; this patient developed the stigmate of NF1 some years after the study. In short, it's possible that patients with NF1 can be dead for melanoma before NF1 becoming evident or can be recognized.

Conclusion

NF1 involves cells of neural crest origin from which peripheral neural cells derive, glial cells, Schwann cells, neuroendocrine cells and melanocytes (6). Although malignant tumours were reported significantly more often in NF1 patients than was expected in the general population (22), association between neurofibromatosis and melanoma, which could be frequent, is rarely reported.
Our further case does not confirm neither denies the existence of the association between NF1 and cutaneous melanoma. We hope that our report can promote new studies about this association supporting the hypothesis that patients affected by cutaneous malignant melanoma or other melanocytic malignancy could have NF1.

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