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Management and follow-up of a patient with Familial Atypical Multiple Mole-Melanoma (FAMMM) Syndrome

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SUMMARY: **Management and follow-up of a patient with Familial Atypical Multiple Mole-Melanoma Syndrome (FAMMM).**

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Introduction. *Familial Atypical Multiple Mole-Melanoma Syndrome (FAMMM) is an autosomal dominant genodermatosis characterized by the presence of a high number of dysplastic nevi and family history of melanoma or pancreatic cancer. Melanomas in FAMMM patients tend to occur at a younger age, although they are clinically similar to sporadic melanomas in terms of overall survival.*

Case report. *A 45 year-old woman with a family history of melanoma, a type II phototype and numerous (>100) nevi was admitted to our Department of Dermatology and Plastic Surgery. Over the past years, the patient underwent several surgical operations to remove pigmented lesions and two are dysplastic nevi. Since 1995, she underwent surgery to remove four melanomas. She is followed for skin examinations including dermoscopy.*

Conclusion. *Identifying high-risk patients for melanoma represents a primary objective for the specialists that are involved in the management of this disease, especially in order to enact all the necessary surveillance and follow-up strategies.*

RIASSUNTO: **Gestione e follow-up di una paziente affetta da sindrome familiare dei nevi atipici multipli e melanoma (FAMMM).**

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Introduzione. *La FAMMM o sindrome familiare dei nevi atipici multipli e melanoma è una genodermatosi autosomica dominante, caratterizzata dalla presenza di un elevato numero di nevi displastici e familiarità per melanoma o tumore del pancreas. L'età di insorgenza del melanoma in pazienti affetti da FAMMM è generalmente più precoce, sebbene il comportamento biologico sia sovrapponibile a quello del melanoma sporadico, soprattutto in termini di sopravvivenza globale.*

Caso clinico. *Una donna di 45 anni con familiarità per melanoma, fototipo II e nevi melanocitari >100, giungeva alla nostra osservazione presso il Dipartimento di Dermatologia e Chirurgia Plastica. Nel corso degli anni, la paziente era stata sottoposta a numerosi interventi di exeresi chirurgica di lesioni pigmentarie, due delle quali mostravano criteri istopatologici di displasia. Dal 1995 alla paziente sono stati asportati quattro melanomi. Attualmente è sottoposta a visite dermatologiche periodiche con l'ausilio della dermoscopia.*

Conclusione. *Riuscire ad evidenziare e selezionare la popolazione di pazienti a rischio per melanoma rappresenta un obiettivo primario per gli specialisti che si occupano della gestione dei soggeetti affetti da tale neoplasia, soprattutto al fine di attuare tutte le necessarie misure di sorveglianza e controllo del paziente.*

KEY WORDS: Management - Melanoma - Familial atypical multiples mole melanoma syndrome.
Gestione - Melanoma - Sindrome familiare dei nevi atipici multipli e melanoma.

Introduction

Melanoma is a fast-growing malignant tumor of melanocytes. Familial Atypical Multiple Mole-Melanoma Syndrome (FAMMM) is an autosomal dominant genodermatosis with incomplete penetrance, characterized by the presence of a high number of dysplastic nevi and family history of melanoma or pancreatic cancer. It is currently estimated that nearly 8-12% of melanoma patients have a first- or second-degree relative with the same disease (1). This fact has been demonstrated for the first time in 1978 by Clark et al. in a study enrolling families whose members presented a higher number of atypical moles than the general population, suggesting a genetical link between the presence of atypical multiple moles and familial melanoma (2,3-5). Germline mutations associated with FAMMM concern regions encoding pro-

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teins involved in cell cycle regulation, particularly CDKN2A, CDK4 and ARF. Nearly 20-40% of families with two or more members with melanoma present CDKN2A positivity, while 5% of these individuals have CDK4 mutations. CDKN2A gene encodes two proteins, according to the transcripted exons, of 156 and 173 amino acids each: p16 (INK4a) and p14 (ARF); both these proteins have a regulatory role in cell cycle G1 progression as they function as stabilizer of the tumor suppressor protein p53, which can initiate apoptosis if DNA damage proves to be irreparable. As such, mutations in these genes increase susceptibility to sun damage, therefore increasing the risk of developing melanoma. Several studies have proved that melanomas in FAMMM patients tend to occur at a younger age (6), although they are clinically similar to sporadic melanomas in terms of overall survival (7). Moreover, because of shared p16 susceptibility mutations, an association between FAMMM syndrome and familial pancreatic cancer has been reported, insomuch as around 10% of pancreatic cancer families may have FAMMM syndrome (8-10).

Case report

A 45 year-old woman was admitted to our Department of Dermatology and Plastic Surgery in March 2008. She reported a family history of melanoma and expressed concern over a change in the appearance of several existing moles. At physical examination the patient presented a type II phototype and numerous nevi (>100) (Fig. 1). Over the past years, the patient underwent several operations to remove pigmented lesions, most of which were benign, although two lesions, one in the sacral region and one in the left paravertebral region, resulted as dysplastic nevi at the histopathological exam. In 1995 the excision of a pigmented lesion in the left gluteal area was performed; histological findings revealed a superficial spreading melanoma, Clark level III and Breslow depth 1mm. In accordance with current guidelines on the management of melanoma patients, the patient underwent a wider margin excision (1 cm margin). Histological examination was negative for neoplastic infiltration. In 2009 a pigmented lesion in the left posterior deltoid area was excised; its histological examination revealed a non ulcerated superficial spreading melanoma, Clark level II and Breslow depth 0,3 mm (Fig. 2). The wider margin excision revealed no neoplastic infiltration. Later, two pigmented lesions in the right scapular area, respectively superior and inferior, were excised; their histological examination revealed that the first lesion was a superficial spreading melanoma, Clark level II, Breslow depth 0,3 mm and the second one was a superficial spreading melanoma, Clark level III, Breslow depth 0,5 mm. Therefore, wider margin excisions were performed; both were negative for neoplastic infiltrations. She is followed for skin examinations including dermoscopy.

Discussion

Melanoma is a high morbility and high mortality neoplasm; its incidence in generally higher in FAMMM patients than in the general population, therefore high-risk

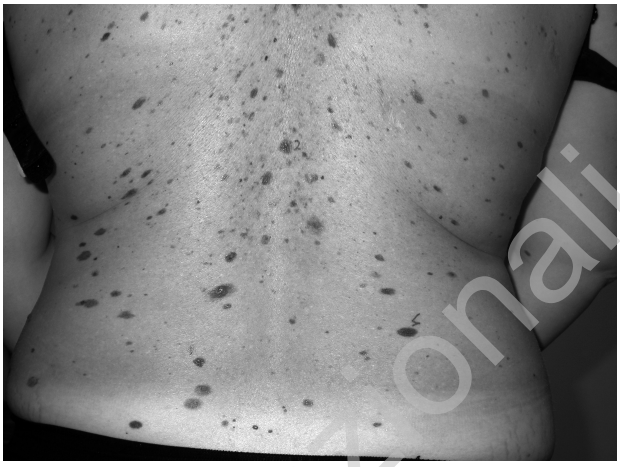

Fig. 1 - The patients presents numerous (>100) nevi, particularly on the back.

members of familial melanoma families should undergo an accurate screening for this disease. However, because of the lack of concordance data on the correlation between CDKN2A gene mutations and oncogenetic risk, genetic screening is not currently recommended to identify high-risk population and for risk stratification. Genetic testing for mutations in CDKN2A is of no value outside the context of clinical research and is not performed to screen FAMMM patients.

The identification of a patient as a member of a high-risk FAMMM family may be suspected by performing a complete cutaneous examination revealing numerous atypical nevi and may be determined by performing a meticulous personal and family history of melanoma and pancreatic cancer in first- and second- degree relatives. The incidence of CDKN2A mutations is indeed higher in individuals with three or more melanomas and/or in families with at least one melanoma and two or more other diagnoses of melanoma and/or pancreatic cancer in first- and second- degree relatives in one side of the family (8). However, in clinical practice it may be difficult to identify, on the sole anamnestic basis, patients from high-risk pedegrees. In fact, family history is often reported in a partial, incomplete or imprecise manner and it is seldom confirmed by pathology reports. Moreover, these patients are not always aware of the added risk to them and may leave out important information. As such, general practitioners play a central role in the follow-up of these individuals and their families and cooperate with the specialists for the management of these patients.

Patients with a suspected FAMMM syndrome must undergo frequent skin examinations, even with the use of dermoscopy, that allows an accurate and non invasive evaluation of pigmented lesion, for the prevention and early detection of melanoma. FAMMM patients, as well

as their first- and second- degree relatives, should undergo complete cutaneous examinations every 6-12 months. Skin examination must be performed on the whole skin surface, including the scalp, the oral mucosa and the genital area. Pigmented lesions are examined according to the "ABCD score" (11,12), that allows a thorough evaluation in terms of morphology and dermoscopic findings: asymmetry, borders, color, different dermoscopic patterns.

The dermoscope is an important diagnostic instrument as it combines the magnification and the elimination of the corneal/air interface, thus allowing a more accurate and objective evaluation of the pigmented lesions and enabling the diagnosis or avoiding useless surgical excisions, that are already very frequent in FAMMM patients (13).

In our case, the pattern asymmetry (Fig. 2) and the starbust aspect (Fig. 3) represent the main dermoscopic criteria for the diagnosis of melanoma.

The specialist has the task to inform the patient and to teach him how to perform skin self-examinations. Monthly self-examinations allow the evaluation of the lesions during the time intervals between check-ups, with the possibility, whenever the patient notices changes, to bring the dermatologic check forward and to proceed for the surgical operation, if it is necessary (14). In patients with personal history of melanoma, follow-up modalities vary according to the histological findings of the neoplasm, anyway they should last no less than 10 years. As regards the management of melanoma patients, periodic check-ups should be scheduled every 3-12 months, according to the initial stage and potential evolution of melanoma. If necessary, hematochemical and instrumental examinations may be repeated over time.

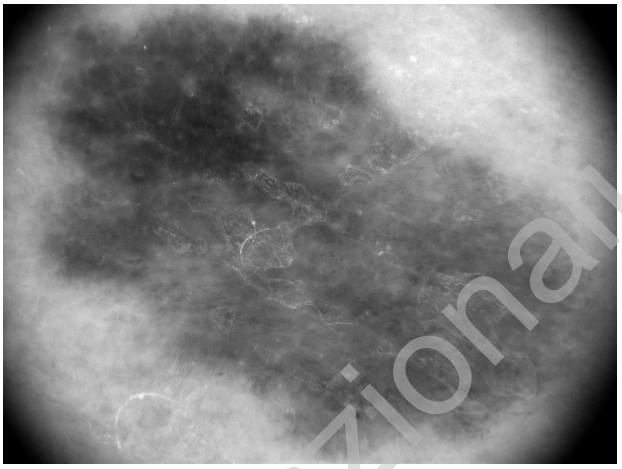

Fig. 2 - The pattern asymmetry represent a main dermoscopic criteria for the diagnosis of melanoma.

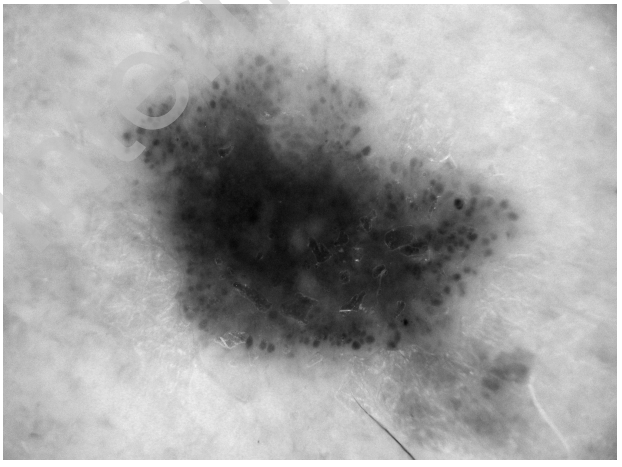

Fig. 3 - The starbust aspect is indicative for the diagnosis of melanoma.

Conclusions

Identifying high-risk patients for melanoma represents a primary objective for the specialists that are involved in the management of this disease, especially in order to enact all the necessary surveillance and follow-up strategies, and, if possible, to detect the disease at the initial stage. The dermoscopy increases diagnostic abilities and proves FAMMM syndrome.

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