

Dysplastic nevus syndrome and pancreatic cancer: A case report

LILIANA GABRIELA POPA^{1,2}, CALIN GIURCANEANU^{1,2}, CORNELIA NITIPIR^{3,4},
ANA MARIA POPA³, CRISTIANA STOICA¹, CRISTINA BEIU², TIBERIU TEBEICA⁵,
SILVIUS NEGOITA^{6,7} and MARA MADALINA MIHAI^{1,2}

¹Department of Dermatology, 'Elias' Emergency University Hospital, 011461 Bucharest;

²Department of Oncologic Dermatology, 'Elias' Emergency University Hospital,

'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest; ³Department of Oncology,

'Elias' Emergency University Hospital, 011461 Bucharest; ⁴Department of Oncology,

'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest; ⁵Department of Dermatopathology,

'Dr. Leventer' Centre, 011216 Bucharest; ⁶Department of Anaesthesiology and Intensive Care,

'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest; ⁷Department of Anaesthesiology and
Intensive Care, 'Elias' Emergency University Hospital, 011461 Bucharest, Romania

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Abstract. Multiple primary cancers may occur in the same patient, with a prevalence that follows an ascendant trend. Their development is dictated by a complex interplay between a variety of factors, both patient-dependent and external. The case of a 38-year-old female patient diagnosed and treated for pancreatic cancer (PC) is presented in whom the digital dermoscopic monitoring of melanocytic nevi revealed a marked change of two nevi that acquired rapidly highly atypical features. They were surgically excised and the histopathological examination revealed two completely excised dysplastic compound nevi. Clinicians should be aware of the strong association between dysplastic nevus syndrome and PC, a malignancy associated with an extremely poor prognosis. Familial atypical multiple mole melanoma syndrome (FAMMM) predisposes to the development of melanoma, pancreatic cancer and other neoplasms. The common genetic background of PC and hereditary melanoma is discussed and the importance of regular skin checkup and screening for PC in these patients is underlined.

Introduction

Due to the tremendous efforts of researchers and clinicians during the past few decades, in numerous parts of the world

early diagnosis of cancer is readily achievable. Survival from cancer has considerably increased as a result of systematic screening and the development of novel cancer treatments with improved efficacy. Thus, given the growing number of cancer survivors, the opportunity arose to study the genetic background of these patients, environmental exposure to carcinogens, the long-term side effects of cancer treatments and their risk of developing subsequent primary cancers.

According to the studies carried out, to date, multiple primary cancers occur with a frequency ranging from 2 to 17% (1). As anticipated, their prevalence follows an ascendant trend (2). The development of multiple cancers is dictated by a complicated interplay between a variety of factors, both patient-dependent (genetic predisposition, immune deficiencies, hormonal dysfunctions) and external (infections, exposure to ultraviolet radiation, ionizing radiation, smoking, alcohol consumption, dietary factors). Chemotherapy and/or radiotherapy for previous cancers greatly increase the risk for the development of subsequent neoplasia, either hematologic malignancies or solid tumors (3,4).

Despite the notable progress in oncologic treatment, pancreatic cancer (PC) still portends an extremely poor prognosis, with a five-year survival rate after radical surgery of 10% for node-positive disease, which is the case in approximately two thirds of patients and 30% for node-negative disease (5,6). This is one of the reasons the appearance of a second or multiple cancers in PC patients was long considered highly improbable (7). However, a search of the literature reveals several reports of single or multiple extra-pancreatic cancers, located in the digestive tract, lung, breast, prostate, kidney, and skin arising in patients previously or consequently diagnosed with PC (7).

Although a series of studies (8,9) concluded that the risk of PC is increased in families with atypical multiple mole melanoma syndrome (FAMMM), also named dysplastic nevus syndrome, other studies have not confirmed this hypothesis (7,10). The controversy and puzzle regarding a potential association between PC and melanoma in some patients

Correspondence to: Dr Cristiana Stoica, Department of Dermatology, 'Elias' Emergency University Hospital, 17 Marasti Boulevard, 011461 Bucharest, Romania
E-mail: dobrescucristiana@yahoo.ro

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have been recently untangled owing to in-depth genetic studies (11-15).

The case of a young patient diagnosed and treated for PC is presented, in whom digital dermoscopic follow-up of melanocytic nevi proved to be lifesaving, as it revealed the rapid change of two nevi that acquired highly atypical features. The common genetic background of PC and hereditary melanoma and the optimal approach for these patients is also discussed.

Case report

A 38-year-old female patient was referred to the Department of Dermatology, 'Elias' Emergency University Hospital, in November 2019, for the clinical and dermoscopic assessment of multiple pigmented nevi. The patient had been recently diagnosed with PC with duodenal invasion and had undergone pancreaticoduodenectomy, followed by the initiation of systemic chemotherapy with 5-fluorouracil, irinotecan, oxaliplatin and folinic acid (the FOLFIRINOX regimen). The study was approved by the Ethics Committee of Elias Emergency University Hospital, Bucharest, Romania (approval no. 4902). Written informed consent was provided by the patient.

The patient had a positive family history for oncologic diseases on the paternal side. Three paternal aunts had been diagnosed with solid neoplasms: One had succumbed shortly after being diagnosed with a digestive cancer (the patient was not aware of the exact location of the neoplasm), another had been diagnosed with breast cancer at a young age and the third with thyroid cancer.

The physical examination was within normal limits, except for the presence of numerous atypical melanocytic nevi located on the trunk and limbs.

Close digital dermoscopic monitoring of the atypical nevi, at three-month intervals was initially performed. Contrary to the advice of the dermatologist, the patient missed several scheduled control visits and only appeared a year later, when significant changes in size, shape and structure could be observed on digital dermoscopic examination in two melanocytic nevi, located in the umbilical region and on the inferior abdominal integument, respectively.

The melanocytic lesion located in the periumbilical region was a reticular-homogenous nevus with a diameter of ~7.5 mm. It presented marked asymmetry, irregular borders, atypical pigment network, uneven pigmentation with multiple areas of hyperpigmentation and structureless, hypopigmented areas, irregularly distributed brown and black globules and dots, as well as pseudopods (Fig. 1). Compared with the previous examination, the nevus had increased in size, had changed its shape and exhibited intensification of pigmentation. It had also gained the striking atypical features aforementioned.

The second changing nevus was a compound nevus, approximately 1 cm in diameter, located in the inferior abdominal area. It exhibited asymmetry, was ill-defined, had irregular borders and pigment variegation. The junctional component displayed an atypical pigment network, with focal hyperpigmentation, and irregularly distributed brown and black globules and dots (Fig. 2). Similar to the previously described nevus, it had increased in size and had slightly changed its shape.

The described nevi were surgically excised with a 0.5 cm safety margin.

The histopathologic examination was performed with the following parameters: The nevi were fixed with 10% neutral buffered formalin at 21°C for 24 h on histopathological sections of a 4- μ m thickness. Subsequently, staining was performed with hematoxylin at 21°C for 2 min and eosin at 21°C for 30 sec. A light microscope (Olympus BX43; Olympus Corporation) was used for observation. The histopathological examination revealed two completely excised dysplastic compound nevi (Figs. 3 and 4).

The melanocytic nevi of the patient were carefully monitored thereafter, but no further changes have been noted.

Discussion

According to the numerous studies carried out thus far, an increased risk of melanoma was observed in patients diagnosed with non-melanoma skin cancers, hematologic malignancies, nervous system neoplasms, testicular and breast cancer (11). Common genetic abnormalities, immunological dysfunctions or exposure to environmental risk factors may all play a role.

Conversely, in melanoma patients, a series of second primary cancers appear to develop with a higher frequency than anticipated. Among these are non-melanoma skin cancers, nervous system cancer, chronic lymphocytic leukemia, breast, renal, thyroid, oropharyngeal, testicular, digestive tract, connective tissue, and lung cancers (11).

Additional primary cancers have also been detected in the setting of FAMMM, also known as dysplastic nevus syndrome (8,12,16), an autosomal dominant disease with incomplete penetrance and high phenotypic heterogeneity (17). Kindreds with FAMMM are not only predisposed to develop melanoma, but also certain extracutaneous cancers, particularly pancreatic, breast, lung, and lymphoreticular system cancer (8,16,17).

Genetic susceptibility is decisive for the appearance of hereditary and sporadic melanomas. The most important melanoma susceptibility gene is cyclin-dependent kinase inhibitor 2A (CDKN2A)/p16, harbored on chromosome 9p21. Mutations of this gene have been detected in 20-60% of families predisposed to hereditary melanoma (13-15,18). Mutations in CDKN2A/ARF and other genes, encoding for cyclin-dependent kinase 4 (CDK4; located on chromosome 12q14.1), telomerase reverse transcriptase (TERT; located on chromosome 5p15.33), melanocyte inducing transcription factor (MITF; located on chromosome 3p13), ubiquitin carboxyl-terminal hydrolase (BAP1; located on chromosome 3p21.1), protection of telomeres 1 (POT1; located on chromosome 7q31.33) are less frequently encountered (18).

CDKN2A was also revealed to be implicated in pancreatic tumorigenesis (10,19,20), thus explaining the propensity for PC in FAMMM families.

CDKN2A codes for p16 INK4 and p14 alternative reading frame (ARF). p16 INK4 inhibits the activity of cyclin D1-CDK4 complex, which phosphorylates the retinoblastoma protein in order to allow progression to the G₁ phase of the cell cycle (21). Therefore, CDKN2A/p16 impedes cell growth and acts as a tumor suppressor gene. In Northern Europe, one of the most prevalent mutations of CDKN2A/p16 associated

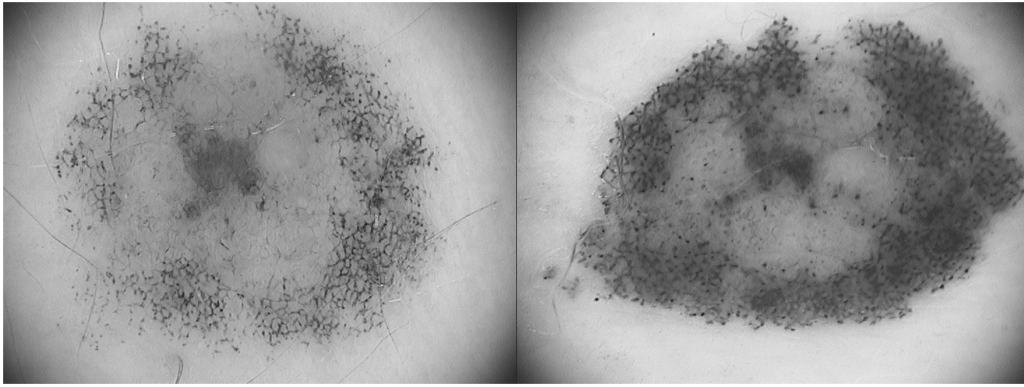


Figure 1. Dermoscopic image of a changing atypical melanocytic nevus, located in the periumbilical region, revealing increase in size, changing shape, intensification of pigmentation and atypical features: marked asymmetry, irregular borders, atypical pigment network, uneven pigmentation, irregularly distributed brown and black globules and dots and pseudopods.

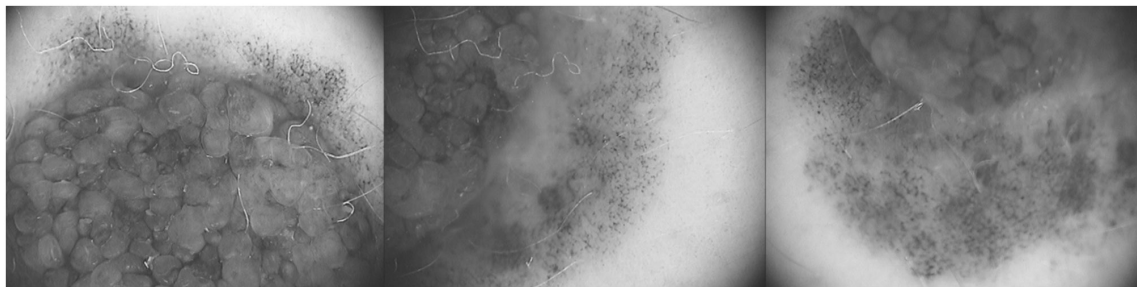


Figure 2. Dermoscopic image of an atypical compound nevus, located in the inferior abdominal area, revealing asymmetry, irregular borders, pigment variegation, atypical pigment network, with focal hyperpigmentation, and irregularly distributed brown and black globules and dots.

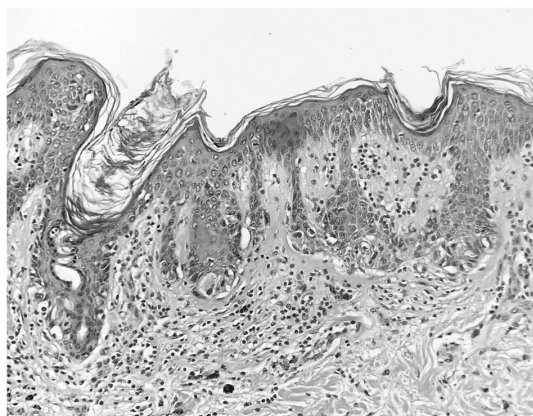


Figure 3. Histopathological examination of the first dysplastic nevus, located in the periumbilical area (magnification, x20; hematoxylin and eosin staining). Melanocytic tumor with a junctional component composed of isolated nests and cells with moderate and focally marked atypia, with rare obvious mitoses and an intradermal component composed of periadnexial nests and focal cells, with maturation towards the deep part of the lesion. The junctional component extends beyond the intradermal one. Moderate melanin pigmentation that involves the whole epidermis thickness, including the stratum corneum is noted. The lesion also displays lamellar fibroplasia in the papillary dermis and a moderate inflammatory lymphocytic infiltrate with melanophages in the perilesional superficial dermis.

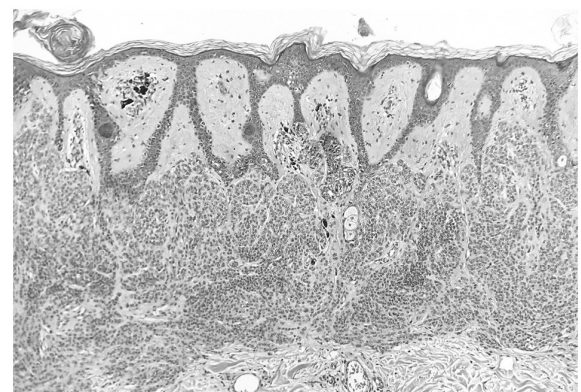


Figure 4. Histopathological examination of the second dysplastic nevus, located in the inferior abdominal area (magnification, x20; hematoxylin and eosin staining). Skin fragment revealing a slightly asymmetric, but well circumscribed, centrally elevated melanocytic proliferation located at the dermo-epidermal junction, consisting of nests with a tendency to merge horizontally and solitary melanocytes arranged in a lentiginous fashion predominantly at the base of the epidermal crests, with a dermal component formed by melanocytic cells in the central portion of the lesion, involving the superior reticular dermis. Although cyto-nuclear atypia scattered at the junctional level can be observed, no mitotic activity is detected. The lesional epidermis is hyperplastic and hyperpigmented. A concentric dermal fibroplasia and a minimal dermal infiltration with melanophages are also present.

with the development of melanoma is the p16-Leiden mutation, represented by the deletion of 19 bp in exon 2 that leads to loss of the tumor-suppressive function of p16 INK4 (22). Approximately 70% of p16-Leiden mutation carriers are

estimated to develop melanoma (23) and 15-20% of them are expected to develop PC (24-26).

The great clinical heterogeneity that characterizes FAMMM syndrome and the variations in associated cancers results not only

from the different types of CDKN2A mutations, but also from the influences of other genetic and environmental factors (27). Given the extremely aggressive behavior and poor prognosis of both melanoma and PC, the identification of individuals at risk for one or both of these cancers and their close surveillance is of utmost importance. Hence, further research has led to the detection of multiple genetic factors that modify the risk of melanoma and PC in p16-Leiden mutation carriers, such as melanocortin 1 receptor gene (MC1R) variants that influence the risk of melanoma (28,29), rs36115365-C, a single-nucleotide polymorphism which controls TERT expression and is associated with increased risk of PC and decreased risk of melanoma (30,31), mutations in glutathione S-transferase genes GSTM1 and GSTT1 (32), as well as in the vitamin D receptor gene that appear to have a slight protective effect against melanoma (33).

The benefits of regular skin checkup of FAMMM kindreds are indisputable. On the other hand, mortality from PC even exceeds mortality attributable to melanoma (34,35). Screening for PC is considerably more complicated. There is no universally accepted screening protocol for PC, but annual laboratory tests, such as the determination of the serum level of alkaline phosphatase, pancreatic enzymes and tumor markers (carcinoembryonic antigen and CA19.9) and imagistic investigations (abdominal ultrasound, computed tomography, or magnetic resonance imaging) are recommended in high-risk individuals (26,36,37).

In conclusion, clinicians should be aware of the strong association between FAMMM and PC. The reported case underlines the importance of regular skin checkups and screening for PC in patients with dysplastic nevus syndrome.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

LGP, CG, CN and MMM conceptualized and designed the study and the methodology. CG and MMM supervised the study. SN, TT and MMM participated in the acquisition, analysis and interpretation of data. CS, AMP, TT and CB researched the literature and drafted the manuscript. LGP, CG, CN, SN and MMM reviewed and edited the final manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Elias Emergency University Hospital, Bucharest, Romania (approval

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Patient consent for publication

The patient provided written informed consent for the publication of the data.

Competing interests

The authors declare that they have no competing interests.

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