ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Aurelian-Udristioiu/152

URF PUBLISHERS
connect with research world

Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 2 & Iss: 4

Literature Review

Atypical Pigment Nevus on the Border with the Melanoma-Case Report and Literature Review

Aurelian Udristioiu[1]*, Liviu Martin[1], Ioan-Ovidiu Gheorghe[2]*, Andreea-Mihaela Banta[3] and Delia Nica-Badea[2]

[1]Titu Maiorescu University of Bucharest, Faculty of Medicine, Medicine Assistance, Targu Jiu, Romania

[2]Constantin Brancusi University, Faculty of Medical Science and Behaviours, Târgu-Jiu, Romania

[3]Municipal Emergency Clinical Hospital Timisoara City, Romania

Citation: Udristioiu A, Martin L, Gheorghe IO, Banta AM, Badea DN. Atypical Pigment Nevus on the Border with the Melanoma-Case Report and Literature Review. *Medi Clin Case Rep J* 2024;2(4):579-583. DOI: doi.org/10.51219/MCCRJ/Aurelian-Udristioiu/152

Received: 22 November, 2024; **Accepted:** 25 November, 2024; **Published:** 27 November, 2024

***Corresponding author:** Aurelian Udristioiu, Aurelian Udristioiu, Titu Maiorescu University of Bucharest, Faculty of Medicine, General Medicine Assistance, BD-ul Ecaterina Teodoroiu Street, no. 100, City Tatgu Jiu Postal Code 210206, County Gorj, Romania, Email: aurelianu2007@yahoo.com

Ioan-Ovidiu Gheorghe, Constantin Brancusi University, Faculty of Medical Science and Behaviours, Tineretului Street, no. 4. City Targu Jiu, Postcode: 210185, County Gorj, Romania, Email: ovis45@yahoo.com

ABSTRACT

Introduction: The work aims to illustrate a differential diagnosis between an atypical melanocytic nevus and melanoma at the dermatological level, thoraco-abdominal. The etiology of blue nevus includes the genetic factor (heredity) but in this case report, the patient diagnosed with the blue nevus don`t had other family members with this condition. Because the diagnosis of atypical nevus is predominantly made by histopathology, was chosen to describe the characteristics of skin lesion from a clinical, macroscopic and microscopic point of view.

Case presentation: An asymptomatic 70-year-old man, presented himself in the dermatology office from the hospital outpatient clinic, for the dermatoscopy examination of multiple benign keratoses, of different dimensions at the level of the dorsal thorax and abdominal-paravertebral.

Results: In the dermatoscopy exam, the appearance of atypical pigment nevus means a change in color, light infiltration or small nodule, with an irregular border, poorly defined. Immunohistochemical, exam, (IHC), confirmation of the diagnosis of blue nevus was made by performing the expression of the Melan-A, (Confirm anti-Mart-1/Mouse Monoclonal Antibodies), which was positive in melanocytic proliferation, (dermal) and the protein, (pKi67), as a prognostic marker in cancer, being positive in very rare tumor nuclei in percentage <1% with P16, (CIN-tec p16 histology).

Conclusions: The Histopathological examination and Immunohistochemical, exam, (IHC), highlight aggregations of atypical melanocytic cells, without monstrosities and multiple mitoses that break the basement membrane, in contrast to the aggressiveness of malignant melanoma.

Keywords: case report, atypical pigment nevus, melanoma, BRAF protein, Ki67 protein

Introduction

Melanocytes originally derived from the neural crest, are situated just above the basal membrane. The known function of melanocytes is the production of melanin pigment. The dendritic structure of melanocytes, creating extensive contacts, especially with keratinocytes, suggests a complex signaling network (the melanocyte-epidermal in situ, (they have intercellular contact structures with the populated tissue and tends to segregate after mitosis, which explains the early dissemination of cells neoplastic. The body responds with a moderate immune response, neoplastic cells being recognized by the immune system[1].

Blue neve, (Jadassohn-Tieche), is the most frequently neve recorded in dermatological practice, the maximum incidence of this tumor benign skin lesion being recorded among those aged between the second and fourth decade of life. The blue nevus is frequently recorded in dermatological practice, predominantly affecting women and in rare cases is present and in old men.

Case Report

An asymptomatic 70-year-old man, without personal pathological antecedents, (APP) and significant hero-collaterals of malignant dermatological tumors in his parents, presented himself in the dermatology office, from the outpatient clinic, for the dermatoscopy examination of multiple benign keratoses from the level of the upper trunk, chest and abdomen.

Diagnostic Assessment

In the clinical exam was palpated a macular lesion, like the eccentric, reddish micronode. This aspect of the lesion is solitary, among the multiple benign keratoses, arranged thoraco-abdominally, **(Figure 1)**.

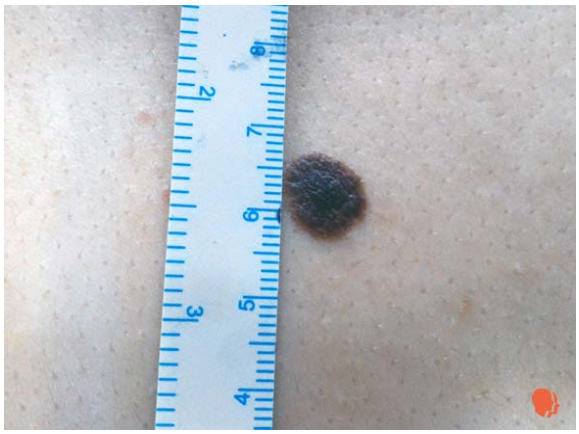

Figure1: Atypical pigment nevus on the surface of the thoracodorsal skin with a diameter of 5 mm and a high risk of metastasis.

Therapeutic intervention

Digital dermatoscopy reveals an atypical dyslasic nevus, with an increased capacity to transform into malignant melanoma.The tumour is described as 5 mm in size, with a bizarre configuration with polycyclic edges, variable colour from pink to dark brown, located dorso-cervical-thoracic. The central lesion is most commonly a compound, junctional or intradermal nevus and the halo usually varies in size from 0.5 to 5 cm **(Figure 2)**.

In the case of this patient, the treatment for dysplastic atypical nevus was surgical and involved the excision of a pigmented skin lesion. After surgical excision, the patient was discharged in good general condition.

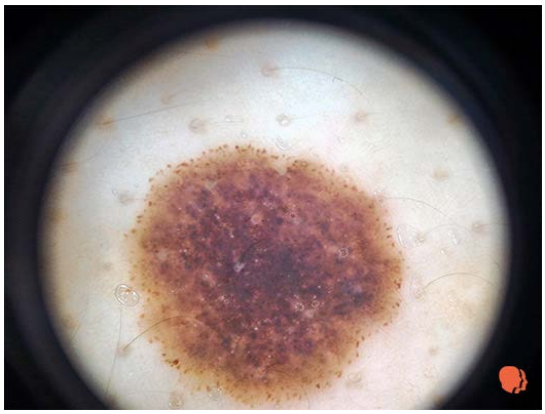

Figure 2: Dysplastic, atypical nevus highlighted by digital dermatoscopy.

Histopathologic exam

In the histopathological examination was described melanocytic proliferation which does not affect the resection margins on the examined sections. The examination in a single block revealed a fragment of the skin showing at the level of the dermo-epidermic junction a melanocytic proliferation arranged in the form of isolated nevi cells or forming very rare isolated nests, without atypia and mitoses on the examined sections. Underlying, frequent melanophages arranged among the collagen fibres and lymphocytic infiltrate arranged peri-axially. The described melanocytic proliferation does not affect the resection margins on the examined sections.

A second opinion of histopathologic exam for the same single block with descriptive pathological report

In the conventional histopathological examination, (standard hematoxylin-eosin staining, H&E), the histological preparation includes a fragment of integument with hypodermis showing a diffusely distributed melanocytic tumor in the upper papillary and reticular dermis. Tumor proliferation is made up of spindle cells, without cyto-nuclear atypia or mitoses, interspersed with frequent melanophages. Associated are small foci of lymphocytic, perivascular inflammatory infiltrate. The epidermis on the surface shows a slight acanthosis and basal epidermal melanic hyperpigmentation. In the examined sections, the lateral or deep edges are not interesting. Conclusion: Junctional melanocytic nevus.

Confirmation of the diagnosis

Confirmation of the diagnosis of blue nevus was made by performing the immunohistochemical examination, [IHC]. The blue nevus shows an intensely positive immunohistochemical reaction for HMB45(anti-Melanosome Mouse Monoclonal Primary Antibody), SOX-10, (Rabbit Monoclonal Primary Antibody) and PRAME, (Ventana anti-PRAME-opti), negative. The expression of the Melan-A, (Confirm anti-Mart-1/ Mouse Monoclonal Antibodies), was positive in melanocytic proliferation, (dermal) and protein, (pKi67), as a prognostic marker in cancer, was positive in very rare tumor nuclei in percentage <1% with P16, (CIN-tec p16 histology), positive in melanocytic proliferation.

Differential Diagnosis

The differential diagnosis can be made with, seborrheic keratoses or actinic keratoses, (solar), pigmentary, benign chronic and malignant melanoma extensive on the surface. Cutaneous melanoma is one of the most aggressive forms of skin cancer and one of the leading causes of cancer-related mortality due to its metastatic power. Melanoma originates in the pigment-forming cells of the skin, melanocytes, which produce melanin. Melanin has a photoprotective function in the skin, guarding against UV-induced DNA damage.

Melanoma is categorized into cutaneous and non-cutaneous. Cutaneous melanoma (CM) comprises neoplasms that arise on most skin surfaces of the body that can be further subcategorized into chronically sun-induced melanomas and non-chronically sun-induced melanomas. The four most common molecular subtypes identified for CM have mutations in BRAF, NRAS or NF1 or a triple wild-type genotype for these genes. Non-cutaneous melanomas are rare and are classified into acral, mucosal and uveal subtypes[2].

Discussion

The dermatologic studies have demonstrated that melanoma spreading is the result of genetic mutations and tumor microenvironmental alterations, characterized by the overexpression of proteins able to favor tumor invasion and surrounding infiltration. In particular, a key role is played by the overexpression of matrix metalloproteinases (MMPs), particularly MMP-9 and MMP-2, that induces the degradation of the components of the extracellular matrix, thus favoring tumor cell infiltration and spreading through the bloodstream.

The overexpression of these proteins and tumor microenvironmental alterations are mediated by genetic alterations and the dysregulation of the nuclear factor, (NF)-κB, pathways. Common acquired melanocytic nevi are neoplasms arising mostly during the first 3 decades of life, whereas congenital nevi are present from birth. Spontaneous immune-mediated regression of nevi is particularly common in childhood and adolescence and could be a reflection of an active immune system that eliminates normal and neoplastic melanocytes and prevents tumour development. Immunodeficiency is associated with a higher incidence of melanocytic nevi during immunosuppression, numerous eruptive nevi may develop, accompanied by an increased lymphocytic infiltration.

Involution of such nevi in transplant patients after suspension of immunosuppressive therapy has been reported. The modest presence of CD8+ cells and markers of cytotoxic activity would explain the absence of histologic regression of the pigmentary lesion. The infiltrating T cells of Meyerson's nevi demonstrate a reduced expression of IL-2 receptors, which is in contrast to the marked IL-2 receptor expression in contact dermatitis **(Figure 3)**.

The most frequent somatic mutations in chronically or intermittent sun-exposed skin melanomas affect genes that control central cellular process, such as proliferation (BRAF, NRAS and NF1), growth and metabolism [phosphatase and tensin homolog (PTEN) and KIT proto-oncogene receptor tyrosine kinase (KIT)], resistance to apoptosis [tumour protein p53 (TP53)], cell cycle control [cyclin-dependent kinase inhibitor 2A (CDKN2A)] and replicative lifespan [telomerase reverse transcriptase (TERT). These genomic alterations typically lead to the aberrant activation of two main signalling pathways in melanoma: The RAS/RAF/MEK/ERK signalling cascade [also known as the mitogen-activated protein kinase (MAPK) pathway] and the phosphoinositol-3-kinase (PI3K)/AKT pathway[3].

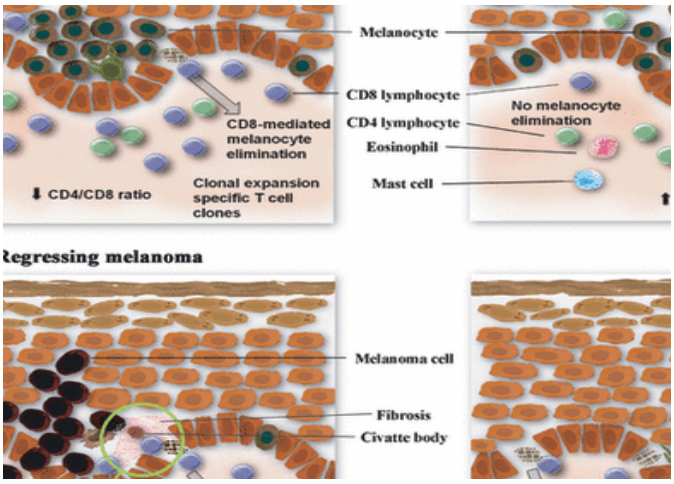

Figure 3: A dense, perivascular infiltrate is present which is mainly composed of activated CD4+ lymphocytes with occasional eosinophils and mast cells.

BRAF protein is a serine/threonine protein kinase of 766 amino acids organized in three domains: Two with regulatory function and one catalytic domain responsible for MEK phosphorylation. The catalytic domain is also responsible for maintaining the protein in its inactive conformation, through a hydrophobic interaction between the 'so-called' glycine-rich loop and the activation segment, making it inaccessible for ATP binding.

In particular, the mechanisms responsible for BRAF (+/−MEK) inhibitor resistance can be divided into genomic (NRAS/KRAS mutation 20%, BRAF splice variants 16%, BRAF amplification 13%, MEK1/2 mutation 7%, bypass track mutations 11%), immunologic (epigenetic and transcriptomic changes of molecules involved in antigen presenting mechanisms) and a combination of both[4].

Tumoral PD-L1 expression has recently been linked to a worse prognosis in melanoma. Loss of MHC-I in melanoma is associated with disease progression. Melanoma cells are also able to express MHC-II, but the co-stimulating molecules CD80 and CD86 are often absent, which induces tolerance. Ectopic expression of HLA-G, a non-classic MHC-I molecule, can protect melanoma cells against natural killer (NK)-cells. Expression and secretion of Fas ligand by melanoma cells leads to apoptosis of immune cells. In more advanced melanoma stages, the absence of P-selectin expression plays a role in inhibiting an efficient antitumoral response[5],

From a histo-pathological point of view, melanomas are grouped according to the level of Clark invasion as follows: Level I, tumor cells located in the epidermis, above the basement membrane, level II, the cells penetrate the basal membrane, in the papillary dermis; level III, cells are visible in the papillary and lenticular derm; level IV, the tumor cell invades up to the papillary and lenticular dermis, level V, the cells invade the subcutaneous tissue[6].

Melanomas with a high risk of metastasis have a thickness of more than 3 mm and present ulcerations and vascular

invasion. As a frequent macroscopic appearance, normal-looking melanocytic nevi can be seen in 70-80% of cases. Nivolumab and pembrolizumab have shown to be effective on BRAF mutant melanoma after BRAF inhibitor resistance has risen, but there are no similar data for ipilimumab or for BRAF-inhibitor therapy in those with primary or secondary resistance to anti-PD-1 therapy. Currently, the combination of two different immune checkpoint inhibitors or the combination anti-PD1/anti-CTLA4 with targeted therapy must be considered an experimental approach in clinical trials. Each strategy has a clear benefit and basic research has demonstrated significant synergistic effects that need to be weighted with the potential increase in toxicity[7].

The expression of the Ki67 protein (pKi67), a prognostic marker in cancer, has been widely studied and was associated with the proliferative activity of intrinsic cell populations in malignant tumors, allowing it to be used as a marker of tumor aggressiveness.

Ki-67 index is a non-histone nuclear protein and correlated with cell growth, cycle progress and the short half-life confers it an effective biomarker for assessing growth fraction of tumor cells. Ki-67 is one of the most widely used immunohistochemistry (IHC) proliferation antigen and has been confirmed as an independent predictive and prognostic factor in cancer tumors[8].

Also, it has been shown that Ki67 expression is significantly higher malignant tissues with poorly differentiated tumor cells, as compared with normal tissue. The Ki67 protein has a half-life of only -1-1.5 h. It is present during all active phases of the cell cycle (G1, S, G2 and M), but is absent in resting cells (G0), **(Figure 1)**.

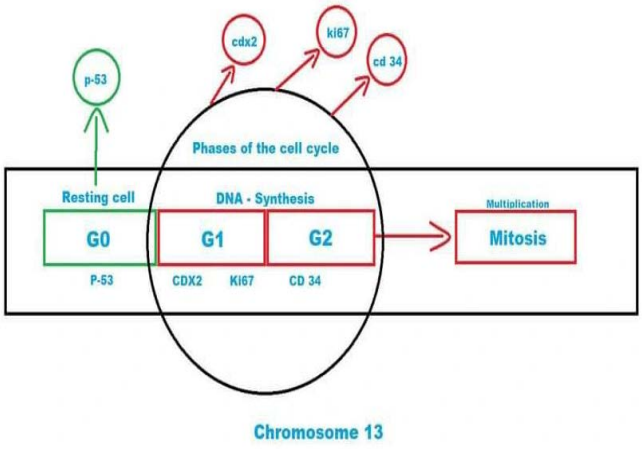

Figure 1: Ki-67 expression varies through cell cycle, with different expression levels in G1, G2/M and S phases but undetectable in G0 phase

In later phases of mitosis (during anaphase and telophase), a sharp decrease in Ki67 levels occur. There was no pathological responder in the cases with a Ki-67 index value <25%. Furthermore, the Ki-67 index values were significantly elevated after recurrence and the cases with a Ki-67 index value of ≥50% significantly increased. Proliferative activity in tumors can be determined by mitotic counting, flow-cytometric determination of synthesis-phase fraction and immunohistochemistry using antibodies reactive against various proliferating cellular antigens. More recent studies on Ki67 have indicated that it undergoes proteasome-mediated degradation during G I phase and upon cell-cycle exit and that depletion of Cdh1, an activator of the Anaphasc Promoting Complex (APC/C), stabilizes Ki67[9].

Patient Perspective

For the identification of genetically predisposed individuals, with BRAF-650 mutations, recently more sensitive molecular diagnostic techniques such, as Next Generation Sequencing, Sigle Nuclear Peptide and Whole-genome sequencing analysis which reveals a high specificity, DNA CRISPR/Cas9 editing. The CRISPR/Cas9 gene editing method has been shown to be promising for cancer treatment. Because gene editing or replacement of defective, mutant genes with new, normally functional genes effectively inhibited the proliferation, invasion and migration of cancer cells, it was observed that the CRISPR/Cas9 system played a key role in editing and controlling genomes related to miRNA. Moreover, due to its precision, efficacy, simplicity and adaptability, CRISPR/Cas9, as an efficient genome engineering tool, has played a vital role in treating various diseases[10].

Conclusion

The Histopathological examination and Immunohistochemical, exam, (IHC), highlight aggregations of atypical melanocytic cells, without monstrosities and multiple mitoses that break the basement membrane, in contrast to the aggressiveness of malignant melanoma.

Informed Consent: The patient gave informed consent by completing the preoperative medical file, agreeing to the surgical intervention and the postoperative treatment to follow, in their declaration of acceptance for the necessary paraclinical investigations, for diagnosis and treatment.

Ethics Statement: The study adhered to the tenets of the Declaration of Helsinki. The retrospective case report described in this manuscript includes no patient-identifying information. Ethical approval was not required.

Authors' contribution: The all authors have contributed to the intellectual content of this paper.

[1]Aurelian Udristioiu: Conceptualization, Methodology,

[1]Liviu Martin: Formal analysis.

[2]Ioan-Ovidiu Gheorghe: Writing review & editing.

[3]Andreea-Mihaela Banta: Supervision, Methodology

[2]Delia Nica-Badea: Investigation, Data curation

Conflicts of Interest: The authors declare no conflicts of interest.

Funding: Not applicable

Acknowledgement: Not applicable

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. 1.Trotter MJ. Melanoma margin assessment. Clin Lab Med 2011;31(2):289-300.
2. Kevinn E, Suzie C, Susan L. Current State of Melanoma Therapy and Next Steps: Battling Therapeutic Resistance. Cancers 2024;16(8):1571.

3. Petitjean A, Achatz MI, Borresen-Dale AL, Hainaut P, Olivier M. TP53 mutations in human cancers: functional selection and impact on cancer prognosis and outcomes. Oncogene 2007;26(15):2157-2165.

4. Leonardi GC, Falzone L, Salemi R, Zanghì A, Spandidos DA, Mccubrey JA, Candido S, Libra M. Cutaneous melanoma: From pathogenesis to therapy (Review). Int J Oncol 2018;52(4):1071-1080.

5. Speeckaert R, van Geel N, Vermaelen, KV Lambert J, Van Gele M, Speeckaert MM. Brochez, L. Immune reactions in benign and malignant melanocytic lesions: lessons for immunotherapy. Pigment Cell Melanoma Res 2011; 24(2): 334-344.

6. Giurcaneanu C, Giurcaneanu D, Nedelcu I. Dermato-Venerelogy, Course notes. Chapter Nevii. Rotech Pro publishing house. Bucharest 2024: 192-197.

7. Guerriere-Kovach PM, Hunt EL, Patterson JW, Glembocki DJ, English JC 3rd, Wick MR. Primary melanoma of the skin and cutaneous melanomatous metastases: comparative histologic features and immunophenotypes. Am J Clin Pathol 2004;122(1):70-77.

8. Tashima R, Nishimura R, Osako T, Nishiyama Y, Okumura Y, Nakano M, et al. Evaluation of an Optimal Cut-Off Point for the Ki-67 Index as a Prognostic Factor in Primary Breast Cancer: A Retrospective Study. PloS one 2015;10(7).

9. Romero Q, Bendahl PO, Fernö M, et al. A novel model for Ki67 assessment in breast cancer. Diagn Pathol 2014;9:118.

10. Cortina C, Turon G, Stork D, et al. A genome editing approach to study cancer stem cells in human tumors. EMBO Mol Med. 2017;9(7):869-879.