Chapter 2

Acral Melanoma — A Distinct Molecular and Clinical Subtype

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Additional information is available at the end of the chapter

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1. Introduction

Skin cancer represents one-third of all cancers that are diagnosed every year worldwide. From all types of skin cancer, cutaneous melanoma is the least frequent among this group of malignant tumors, it is however, the most highly invasive and metastatic tumor. It has also shown an important growth of around 150% in its appearance since 1971, having an estimation of 76,250 new cases diagnosed in the USA in 2012. In 1971 there was only 1 case in 600 white people. In the period of 1992 to 2004, its annual growth was of 3.1%. This led to an estimated incidence of 1 in every 90 white people by 2000. By 2010 it was 1 in every 50, for people above 50 years old in the USA. Its epidemiological importance lies in its high mortality rate, since it is the cause of 90% of deaths for skin cancer and it is potentially the most dangerous form of skin tumor [1]. The outlook for patients with advanced melanoma is often fatal due to a lack of effective treatments.

In Mexico, melanoma incidence is around 1.7 per 100 000 people, and the Histopathologic Record of Malignancies in 2001 reported that it is the second most frequent. Women are the gender most affected by Melanoma (1.6/1). The median age of presentation in this country is 54 years and in 77% of the cases there is no relation to sun exposure. On the other hand, it is important to point out that there is a lack of formal registration of neoplasias in health institutions of our nation [1, 2, 3].

There are four clinicopathological subtypes that Melanoma presents, which usually are correlated to ethnic differences and to exposition to UV radiation: Superficial spreading melanoma (SSM), Lentigo maligna melanoma (LMM), Nodular melanoma (NM) and Acral lentiginous melanoma (ALM) [1, 4]. SSM and LMM, are the most common among Caucasians

and their presence has been directly related to sun exposure. Nodular melanoma is less frequent (10%) than SSM (70%), but both melanomas share pigmentary characteristics in patients. It is probable, however, that these two types of melanoma have a direct relation with sun exposure. However, this risk factor has not been proven in NM, given that this type can be found in any place on the body, not just in skin areas frequently exposed to sun light.

The most frequent subtypes of Melanoma in our population are, NM and ALM [4, 5] (Figure 1). Studies supporting the hypothesis that ALM may be a biological and genetically different subtype, will be mentioned in the following sections. Its distinct development pattern suggests that it may possess molecular and cellular uniqueness.

This may be because of different genetic alterations that control the transformation of melanocytes to acral melanoma, leading to the need for a specific-therapeutic target towards this subtype of melanoma with a high rate among Mexicans and Latin-Americans.

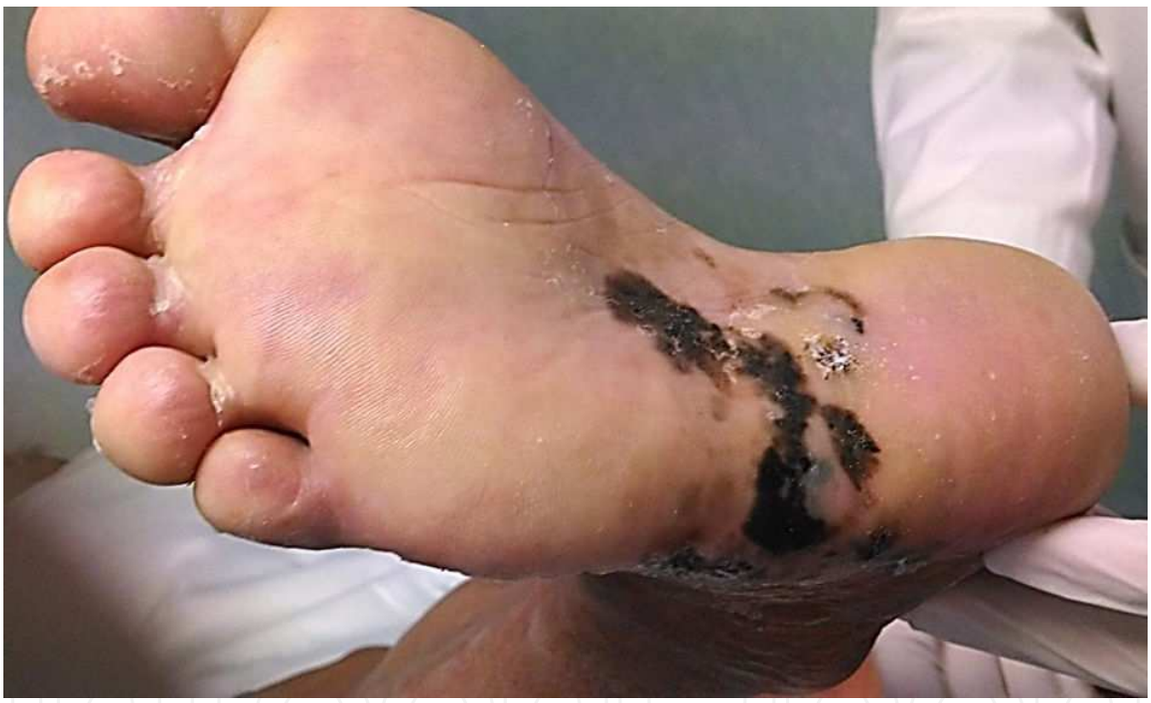

Figure 1. An indolent ALM subtype on the foot of a 58-year-old male patient, with 8 months of evolution. Nodular melanoma (NM) and Acral Lentiginous Melanoma (ALM) are the most frequent subtypes of Melanoma in our population. The lower extremities (mainly on the feet) are the most common anatomic locations reported for ALM.

2. Risk factors

Several studies have identified certain variables associated with an increased risk of developing melanoma: European ancestry, phenotype, UV radiation exposure, personal or family history of malignant melanoma, and molecular alterations are some of the most relevant [6]. Genetic alterations, will receive particularly emphasis later in this review. It is important to

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mention, that the risk factors traditionally associated with melanoma are related principally to Caucasians, where most clinical and basic studies are carried out. However, there are not enough studies supporting the predisposition of such factors for the subtypes of melanoma occuring in Mexican or Latin-American population.

Yamaguchi et al, reported that the risk factors traditionally described such as UV exposure, have a small influence in the pathogenesis of dark skin population. It has been postulated that UV radiation plays a smaller role in the pathogenesis of melanoma in the darker-skinned population. This is due to the fact that with an increase in melanin content, the larger melanosomes (in darker skin), absorb and scatter more energy than the smaller ones in lighter skin [7].

3. Sun exposure

Although various phenotypic characteristics enhance or reduce the risk of developing melanoma, sun exposure has been reported as the main cause of SSM, LMM and NM subtypes. The incidence of this disease is much higher in people who tend to burn rather than tan. (8)

UVA rays constitute 90% of solar radiation. However, UVB rays are greater risks for those who traditionally work or have recreational and daily activities outside. Among those with SSM and LMM, 75% of the affected individuals are sunburned by UVB rays. However, ALM has not been related to this risk factor. In addition, it is known that excessive sun exposure at early ages (childhood and adolescence) has a negative outcome in DNA reparation. The most important exogenous factor for melanoma is UV radiation exposure, particularly intermittent exposition, and it is known as the only etiological agent that can be modified. The increase in sun exposure and the damage to higher levels of the atmosphere because of contamination has resulted in an increase of the amount of radiation [9,10,11].

Sun exposure increases the expression of α-melanocyte stimulating hormone (α-MSH) and of the peptides of pro-opiomelanocortin in the skin. Melanocyte- stimulating hormone belongs to a group called the melanocortins. α-MSH is the most important melanocortin for pigmentation and shows a high affinity for melanocyte stimulating hormone receptor (MSHR). Once α-MSH binds to MSHR, cellular cAMP is activated, as well as other signal transduction pathways. The final result is the production of eumelanin.

Eumelanin, the primary pigment that colors the skin, hair and eyes in humans, also protects the body from UV and other hazardous radiations that can damage skin cells. When eumelanin has been crystalized, it forms both a geometric and a chemical disorder at the same time. It turns out that both kinds of disorders, may play a complementary role in producing eumelanin's broadband absorption. The tiny crystals of eumelanin have a chemically ordered state with intrinsic randomness: the orientations of the stacked molecules are arbitrary and the sizes of the crystals are different. That combination of order and disorder contributes to eumelanin's broadband absorption (12). Recently, it was reported that eumelanin is a naturally existing nanocomposite that has very critical macroscopic properties as a result of its nanostructure

properties. All eumelanin molecules share very similar chemistry, although there are more than 100 variations. It has been proposed that the small variations from one molecule to another may contribute to the disorder that broadens the ability to absorb UV light (13).

Additionally, different alleles for melanocortin 1 receptor (MC1R) gene have been identified. The subtypes related to loss of function reduce the production of cAMP after stimulation of α-MSH, and thus increase the expression of pheomelanin. This is observed in individuals of light skin, increasing the risk of developing melanoma by the formation of free radicals after UV ray exposure.

Recently, a study was performed in 789 patients with diagnosis of melanoma. In order to characterize these patients according to their levels of sun exposure, three groups were established in the study: intermittent, chronic, and absence of exposure [14]. The vast majority of patients were in the first group. These melanomas were present in skin locations exposed to sun radiation in an intermittent manner. SSM and NM belong to this group. Multiple common and atypical nevi may constitute a marker of risk of these melanomas. The second group was formed by patients with melanomas in skin areas with chronic sun exposure, showing all the damage and premise typical of this location. LMM belongs to this group. Finally, the third group corresponds to melanomas present in skin areas with no sun exposure, usually diagnosed in late stages. This group includes ALM and mucosa melanoma, which usually are thicker at diagnosis and have worse prognosis [15, 16, 17]

4. Acral lentiginous melanoma

Acral lentiginous melanoma (ALM) distinguishes itself from the other subtypes for many characteristics, mainly histological and clinical-prognostic. A huge controversy regarding the cause of its worse prognosis, has been going on since its description.

ALM usually occurs on palmoplantar or subungual areas (Fig 2), lacking hair. Similar to NM, it is very aggressive when its proliferative vertical phase develops. It is more commonly found in individuals with dark skin (35-60%), oriental population and Afro-Caribbean. Considering its localization, it is thought to be UV-protected by the thickened stratum corneum and the nail matrix. ALM is rare in Caucasian populations (1-5%), but has a higher incidence among our population and Latin-Americans with dark skin(8, 9, 18). However, for individuals with lighter skin in our population, SSM is the most frequent.

According to the data of The National Cancer Institute Surveillance, Epidemiology and End Results, ALM is the least frequent histological subtype in the USA, with a 2-3% frequency. However, it shows a higher percentage among afroamerican people and Asians.

Reed described for the first time ALM as pigmented lesions of the extremities, mainly of the plantar and palmar regions, that were characterized by a phase of lentiginous (radial) growth, which evolved in months or years to the invasive vertical phase.(19)

Arrington was the first to notice that this type of melanoma was more prevalent among the African American population and that their prognosis was less favorable due to being

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diagnosed at an advanced stage. Yet, it was not documented by the SEER as a different histological subtype until 1986 [20]. Usually, ALM is not associated with nevi, family history or gene susceptibility known to melanoma. In its great majority, ALM are diagnosed as thick melanomas which in most cases are usually presented in their late phase, with a worse prognosis and a lower survival rate than the most common subtypes of melanoma associated with chronic sun exposure [20].

Pereda et al, reported the Clinical presentation of ALM in patients from Spain. In seventeen of them, ALM was found on a foot and in six on a hand. Four ALMs of the hand were subungueal. Most of the foot ALMs were located on the sole (twelve cases) [22].

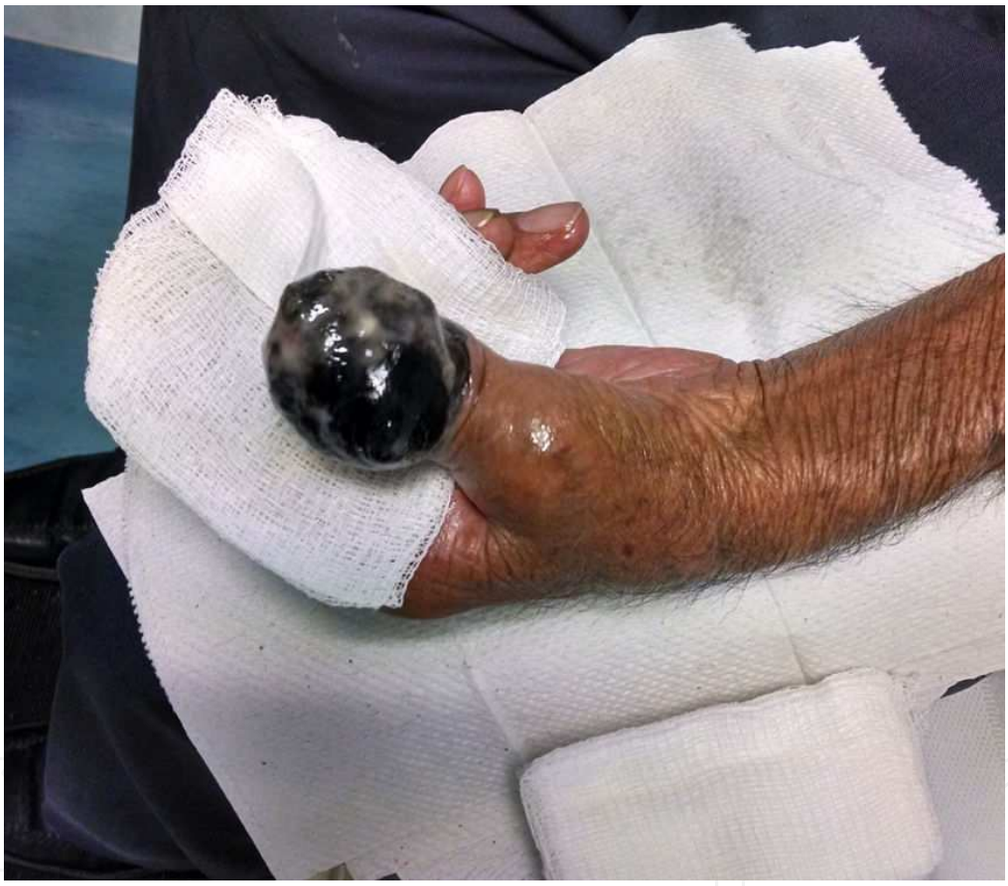

Figure 2. A subungueal tumor of a 71-year-old male patient with an advanced ALM (thick Breslow), on the thumb of the left hand. ALM is the most prevalent subtype in Mexicans and LatinAmericans. It is usually found on hands and feet: palms and soles, wrists and heels, and under the nails. ALM and NM are usually diagnosed in later stages, unlike SSM and LMM. The most affected sites are by far the feet and nails. Initially, they may be misdiagnosed as a mole, an ulcer, an abscess, a wart, a nail bed dystrophy or as the result of a trauma.

The most frequent location of ALM is in the feet (Figure 1), mainly the plantar region and the first finger, as in subungual areas in the majority of non caucasians racial groups. This has led to the conclusion that trauma may be an important factor of ALM, and not sun exposure [22]. Even when the superficial region of the palms and plantar region are similar, in the plantar

region there is a continuous exposure to pressure, friction, maceration and irritation. Nevertheless, there are counterarguments towards this theory, including that the hands are more exposed to UV radiation and acute trauma. In addition, it has not been possible to prove changes in the incidence of plantar melanoma when some African tribes began urbanization and the use of shoes.

Another important factor in the predominance of plantar ALM, is the fact that there is a 50% greater amount of melanocytes there than in the palms [23, 24]. The research of Ghadially proposed that trauma during less than 12 months, did not increase the risk of melanoma in the Xiphophorus fish model [25]. Troyanova [26] described mechanical trauma on previous pigmented skin lesions as a risk factor for the formation of melanoma and remarks that trauma has to be carefully checked. Recently, an amelanotic subungueal melanoma arising after trauma was reported by Rangwala [27]. Melanomas formed on burns scars and tattoos have also been frequently publishedin recent years.Of 687 Chinese melanoma patients, 15.2% showed a strong association between trauma in the extremities and melanoma [28].

Clinical experience coming from medical attention given to patients of melanoma treated in two of the major oncological centers of our nation, shows that AM occurs in no photo exposed areas [5], mainly in lower extremities (more than 80% of the cases) and in subungual regions (Figure 3). This information has been reported by the Mixed Tumor Unit from the Oncologic Service (General Hospital of Mexico) and the Dermatologic Center ”Ladislao de La Pascua”, Mexico City [18]

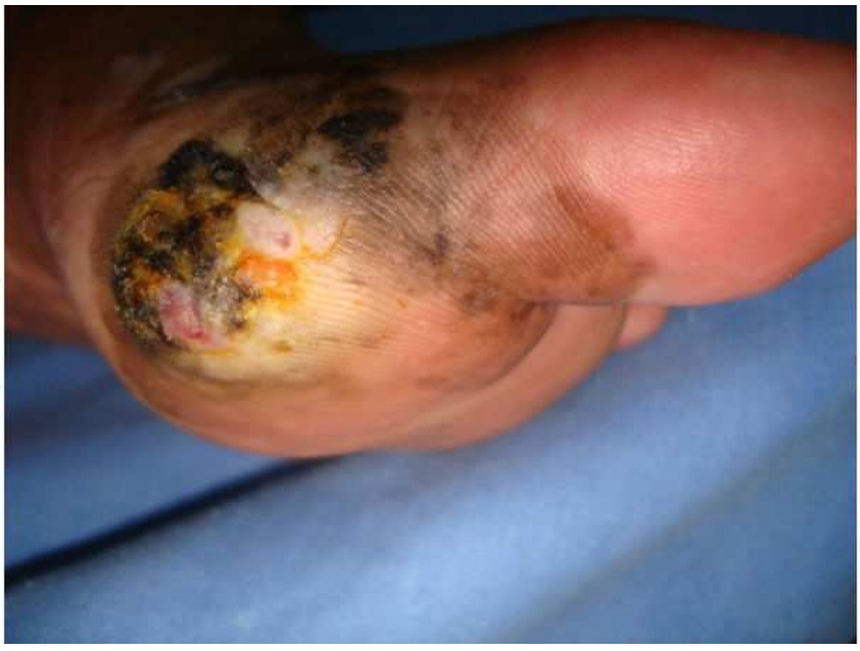

Figure 3. ALM on the foot of a 61-year-old male patient, with indolent growth. The Oncology Unit of the General Hospital of Mexico reports that more than 50% of ALMs are presented on the lower extremities (mainly on the soles and subungueal areas. Being the toe by far, the most affected).

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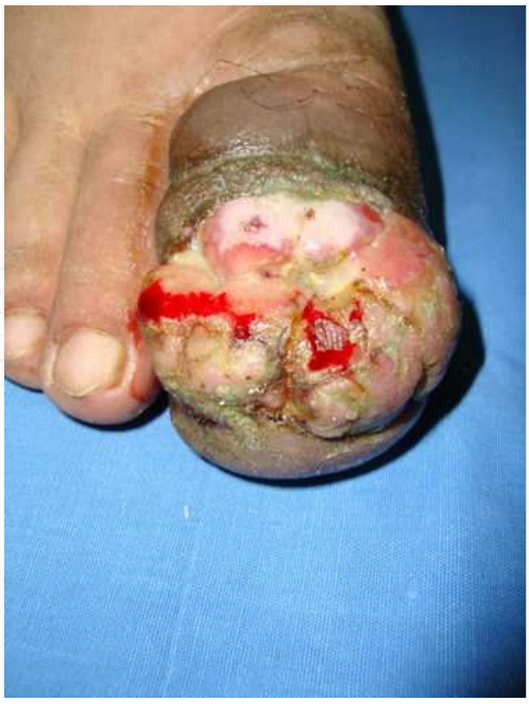

Figure 4. A subungueal tumor of a 54-year-old male patient with an advanced amelanic melanoma. ALMs are usually diagnosed in the later stages unlike SSM and LMM. It was misdiagnosed as a bleeding ulcer of progressive growth.

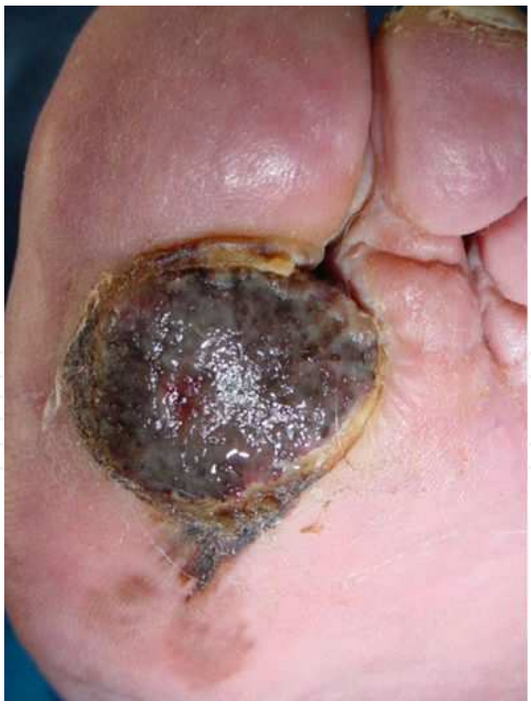

Figure 5. A plantar tumor of a 65-year-old male patient. The lower extremity is the most common anatomic location reported for mexicans. Initially this case was diagnosed as a pigmented lesion of a fast vertical phase progression.

5. Molecular alterations in melanoma

Melanoma arises through a complex process of cellular mutations and a loss of keratinocyte control over growth and differentiation. As malignant melanoma progresses, it develops through interaction between dysfunctional melanocytes and the tumor microenvironment. This in turn, allows the formation of nevocyte nests at the demal-epidermal junction and is accompanied with changes in both, keratinocytes and local adhesion molecules (29). The progression from healthy melanocyte to melanoma occurs through mutations within the tumor and through alterations of the cellular environment.

In the skin, tissue homeostasis is critical in cellular regulation and melanoma breaks this regulation through multiple processes. Defining intercellular molecular dialogues in human skin promises to provide key information about the transformation of melanocyte to melanoma. A great number of genes and proteins have been reported to play an essential role in this transformation. The most important are: B-RAF, c-KIT, PTEN, p16, p53, cyclin1, ARF, K-RAS (30).

6. Familial melanoma

It has been reported by a meta-analysis that the presence of at least one-first degree relative with melanoma increases to double or more, the risk of developing this disease.

Many genetic studies in melanoma-prone families lead to the identification of *CDKN2A* as the main familial melanoma gene. This gene is located at the chromosome 9p21 region. *CDKN2A* encodes two different proteins: INK4A (p16) and ARF (p14). In order to produce these two proteins, the use of alternative promoters and different first exons is necessary. Exon 1α is used for INK4A and 1β for ARF. The second exons of the two transcripts are translated in distinct reading frames, encoding two completely different proteins (with no amino acid homology). Nevertheless, both proteins share potent anticancer activities. *INK4A* inhibits the G1 cyclin-dependent kinases (CDKs) 4/6, which phosphorylate and inactivates the retinoblastoma protein (RB). After that, the S-phase is allowed to occur. Loss of INK4A function promotes RB inactivation resulting in cell cycle progression. *ARF* (Alternative Reading Frame*)* inhibits MDM2 mediated ubiquitination and degradation of p53. Loss of ARF, inactivates p53. Alterations of p16 are associated to familial melanoma in 20% and in 40% to sporadic melanoma [31].

7. Melanomas with intermitent sun exposure

As it was mentioned earlier, more than 90% of melanomas are diagnosed in white and light skinned populations. The majority of the international studies have addressed these populations, since they are at higher risk of developing melanoma. Thus, most reports are drawn from

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data of white and light skinned populations. The main alterations reported in SSM and NM, are B-RAF and N-RAS mutations.

7.1. BRAF

It is a tyrosine and threonine kinase that participates in the signal transduction known as Ras/Raf/MEK/ERK/MAP kinase. *BRAF* functions to regulate the MAPK/ERK pathway, which is conserved in all eukaryotes. This pathway acts as a signal transducer between the extracellular environment and the nucleus, activating downstream transcription factors to induce a range of biochemical processes including growth and differentiation, proliferation and migration associated to the ability of tissue invading [32, 33, 34]. Through direct secuentiation of PCR products, three substitutions of simple bases have been demonstrated. The most prevalent (95% of the cases) is constituted by the transversion of T1799A, occurring on exon 15 of *BRAF*, and causes the substitution of the amino acid valine for glutamic acid in position 599 (V599E). Such position has recently been modified to V600E.

Other *BRAF* mutations that cause carcinogenesis exist, such as K601E or those affecting exon 11, but they rarely occur in melanoma. A fusion of *BRAF* to *AKAP9*, by a paracentromeric inversion of the long arm of chromosome 7 has been observed in cases associated to ionized radiation exposure. This produces an oncogene, *AKAP9-BRAF*, which also results in a constitutive activation of the MAP kinase pathway [35, 36, 37].

Exon 15 BRAF mutations in melanoma were first reported in 2002. The number of reports of BRAF mutations in primary melanoma tissue increases continually. Varying prevalences in primary melanoma tissue have been detected, from 41% to 88% in SSM. These BRAF alterations alone, are not capable of demonstrating neither the immortalization of malignant cells, nor the progression of the disease further more than a nevus [37].

A pilot BRAF mutation study in ALM patients was carried out by collaboration between the Genetic Service of the General Hospital of Mexico and the Molecular Oncology Laboratory of the School of Medicine at the National Polytechnic Institute. DNA sequencing of seven ALM samples of Mexican patients (General Hospital of Mexico) showed no T1799A mutation in any of the studied samples (M. Sc. Thesis, 2012) [38].

7.2. NRAS

RAS are among the most frequently mutated oncogenes in human cancers. They show different mutation patterns and spectrums in all members: *NRAS*, *HRAS* and *KRAS.* The isoforms share a high degree of similarity, although each one displays preferential coupling to particular cancer types.

RAS play a fundamental role in the signaling pathway of MAP kinase. Extracellular signals such as hormones, cytokines, and various growth factors interact with their receptors to activate the small G-proteins of the RAS family. This pathway includes *BRAF* and it contributes to the control of cellular proliferation, particularly malignant cell proliferation. *RAS* also controls apoptosis through the PI3K-PTEN-Akt pathway.

SSM shows mutations almost exclusively in *NRAS*. A prevalence of 5% to 10% *NRAS* mutation has been reported. However for hereditary melanomas, the prevalence increases to 80%. Most cases of *NRAS* mutation are in codon 61. *NRAF* and *BRAF* mutations are mutually exclusive [39].

8. Melanoma with chronic sun exposure

There are similarities between this type of melanoma and those without sun exposure. However, there are differences with ALM since they show much lower mutational characteristics.

KIT (CD117) encodes a tyrosine kinase receptor for stem cells factor and plays a key role in melanocyte development, migration and proliferation. *KIT* is found on chromosome 4 and may be altered in a variety of different types of cancers. It is mutated in 28% of LMM, 36% in ALM, and is absent in melanomas with intermittent sun exposure. KIT over expression during the vertical growth phase of melanoma development supports the hypothesis of its participation in late stages of the disease. It is the target of several small molecules inhibitors such as imatinib, being a therapeutic target for this type of melanoma. Different roles of KIT among different types of melanoma, give additional evidence that each subtype can be considered different biologically and genetically [40].

9. Melanoma without sun exposure

ALM and mucosal melanomas have an inverse correlation among mutations of *BRAF* and *NRAS*. The increase in the copy number of Cyclin D1, CDK4, KIT and ABCB5 has also been reported.

9.1. CYCLIN D1

It is an important regulator of transition of the cell cycle for phases G1/S. It also participates in the phosphorylation of RB protein by binding kinase 4, cyclin dependent. Many studies have revealed a highly organized sequence of events indispensable for promotion of continued proliferation. The decision to continue cell cycle progression occurs when cellular RAS induces the elevation of cyclin D1. These levels are maintained through G1 phase and are necessary for the initiation of S phase, thus resulting in immediately reduced cyclin D1 levels. One requirement for DNA synthesis, is the reduction of cyclin D1 to low levels during the S phase. This forces the cell when it enters G2 phase, to induce high cyclin D1 levels once more. Thus, cyclin D1 is proposed to be a switch activator in the regulation of continued cell cycle progression [41, 42].

Cyclin D1 frequent amplification was reported in 44.4% of ALM by Sauter et al, Cyclin D1 was overexpressed in all cases with amplifications and in 20% of cases without amplification.

Cyclin D1 may be an oncogene in melanoma and that targeting its expression can be therapeutically useful in the future for ALM [42].

9.2. CDK4

It is a union protein of cyclin D1, found in chromosome 12q14. During early stages of phase G1 of the cell cycle, Cyclin D binds to kinase dependent cyclin 4 or 6 (CDK4 or CDK6) and the resulting complex "frees the brake" that limits the progression towards late G1, going into phase S. The cyclin D-CDK4/6 complex releases a potent inhibitor of the cell cycle progression: the one formed by protein pRB and inactive transcription factors. The types of melanoma having an increase in the number of copies of CyclinD1 and CDK4 have less possibilities of responding to the therapeutic target used in BRAF, such as Vemurafenib.

9.3. ABCB5

Human ATP-binding cassette transporter, also known as P-glycoprotein, is related to the subfamily of multidrug resistant genes (MDR). The ABCB subfamily includes eleven members that have different expression patterns. Whereas the functions of several transporters of the ABCB family are not known, there is some information about ABCB5 in relation to its pattern of expression or its associated function [43]. It has been described by Frank et al [44, 45] described it and it was implicated in the regulation of progenitor cell fusion (located in chromosome 7p21-15). Their study used an enriched culture of human epidermal melanocytes isolated from the foreskins of healthy donors and melanoma cell lines. They showed a higher and more intense ABCB5 expression in ALM than in SSM. Herrera-Gonzalez and her team [46], reported a 90% overexpression of ABCB5 in ALM samples of Mexican patients by using RT-PCR. A direct relationship between mRNA expression and the aggressiveness of ALM was also shown.

10. Conclusion

In regard to the progression of human cancer, it is universally thought, that it develops from a single mutated cell, followed by malignant clonal expansion secondary to additional genomic and genetic alterations. As the malignant cells continue to acquire these alterations, tumor subclones with distinct phenotypic advantages (47) for its progression may be produced: for example invasion, proliferation, ability to colonize different organs, etc. In many cancers, regulation of specific signaling molecules also goes awry, affecting a host of other proteins and cellular processes.

In recent years, the histological and phenotypic characteristics of ALM combined with its high proportion among melanomas in Afro-Americans, Asian and Latin Americans, has confirmed the thought that this histological type of melanoma may differ biological and molecularly from its most common counterparts, recognized by its sun exposure and its greater frequency among Caucasians. While ALM is characterized by a high frequency of focal amplifications (mainly involving CCND1, CDK4) and deletions, the most common cutaneous melanomas

exhibit few changes in the number of genetic copies. In a similar way, while *BRAF* and *NRAS* are mutated in 50% and 20% of the cases respectively, mutation in *KIT* (which codifies the tyrosine kinase receptor) seems to be absent in the most common cutaneous melanoma. However, BRAF mutations in ALM constitute approximately 16% of the cases reported by Curtin et al. [40, 41]

A systematic sequencing was used for the human genome sequence. New technologies allow sequencing of randomly generated DNA fragments from cancer genomes and thus detect alterations and copy number variation as well as base substitutions, to identify most somatic mutations in an individual cancer genome. Pleasance et al, sequenced the complete genome of the COLO-829 cell line, an immortal and cancer derived from a metastasis of a melanoma from a 43 year-old-male. In their study they identified 33,345 somatic base substitutions [48, 49]

The study of Turajlic et al. [50] is the first to characterize the mutational spectra in ALM. They used a whole genome sequencing to characterize punctual somatic mutations and structural variation in a primary acral melanoma and its lymph node metastasis. Evidence of transcription-coupled repair was suggested by the lower mutational rate in the transcribed regions and expressed genes. Primary melanoma and metastasis, at the level of global gene copy number alterations, loss of heterozygosity and single expressed genes are very similar[50].

These results may be controversial since their sequenced results were on the genome of only one patient. They cite that despite the perception that acral skin is sun protected, the dominant mutational signature reveals sun damage. We judge that there is no solid data regarding the presence of solar exposure on sites where ALM is developed.

Studies suggest that ungual matrix does not provide a complete protection against UV radiation and it has previously been suggested that UVB can penetrate the human nail [51]. There are substantial variations in the number and pattern of mutations in individual cancers reflecting different exposures, DNA repair defects and cellular origins [52, 53]. It is also possible that characteristics of different mutations are induced by the inefficiency of pyrimidine dimers repaired by excision of nucleotide due to the presence of a mutation in ERCC5 [54, 55].

Several studies support the hypothesis that ALM is a different genetic subtype and its inherent heterogeneity represents a challenge in the era of directed therapy [56].

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References

[1] Alfeirán RA, Escobar AG Epidemiologia del melanoma de piel en México. Rev INCAN | (1999) 44(4): 168-174.

[2] Fernández CSB, León AG, Herrera TMC, Salazar SE, Sánchez DMR, Alcalá ORB et al. Perfil epidemiológico de los tumores malignos en México. Dir. Gral. Epidem. Secretaría de Salud México, D.F. (SINAIS / SINAVE / DGE / SALUD). (2011). p. 46 - 138.

[3] Vásquez MI, Villanueva LCG, Meraz R MA, Magaña M, Herrera GN. Biología molecular del melanoma. Actas Dermatol & Dermatopatol Méx. (2005); 5:5 - 15.

[4] Garbe C., Peris K, Hauschild A, Saiag P. Middleton M, Spatz A. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline Eur J of cancer (2010); 46: 270-283.

[5] Vázquez MI, Meraz RM, Magaña M, Sánchez GD, Herrera-González NE. Quimiorresistencia en el melanoma. Informe preliminar. Act Dermat y Dermapat (2006);6: 8-10

[6] Lascano AR, Kuznitzky R, Cuestas E, Mainard C et al. Factores de riesgo para melanoma cutáneo. Estudio de casos y controles en Córdoba, Argentina. Medicina (Buenos Aires). (2004); 64 (6) : 504-508

[7] Yuji Yamaguchi, Vicent J. Hearing. Melanocytes and their diseases. Cold spring harb perspect med. (2014); 4 : a017046

[8] De la Fuente GA, Ocampo CJ. Melanoma Cutáneo. Gac Méd Méx. (2010); 146: 126 – 135.

[9] Martínez SH, Vega GM, Toussaint CS, Gutiérrez VR, Orozco TR, León E, et al. El primer Consenso Nacional de Expertos en Melanoma. GAMO. (2005); 4: 11 – 13.

[10] Hayat MJ, Howlader N, Reichman ME y Edwards KB. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. The Oncologist (2007);12: 20 – 37.

[11] Geller CA y Swetter S. Screening and early detection of melanoma. CA Cancer J Clin (2011); 61:69-77.

[12] Massachusetts Institute of Technology (2014). Eumelanin's secrets: Discovery of melanin structure may lead to better sun protection. *Sciencedaily.* Retrieved January, 2015 from www.sciencedaily.com/releases/2014/05/140522115754.htm

[13] Chen, C.T., Chuang, J. Cao, V. Ball, D. Ruch, and M. J. Buehler. "Excitonic effecs from geometric order and disorder explain broadband optical absorption in eumelanin" Nature communications 5 (2014): 3859

[14] Nagore E, Botella ER, Requena C, Serra G, Martorell A, Hueso L, et al. Perfil clínico y epidemiológico de los pacientes con melanoma cutáneo según el grado de exposición solar de la localización del melanoma. Act Dermosifil (2009); 100: 205-211

[15] Rouhani P, Hu S, Kirsner RS. Melanoma in Hispanics and Black Americans. Cancer Control (2008); 15: 248-253

[16] Boriani, F O'Learly, Tohill M, Orlando A. EUR REB MED PHARMACOL SCI (2014); 08:1990-1996

[17] Schmerling R, Loria D, Cinat G, Ramos W, Cardona F, Sánchez J, Martínez-Said H, Buzaid A. Cutaneus melanoma in Latin America: the need for more data..Rev Panam Salud Publica. (2011);30(5):431-8

[18] Hernández ZS, Medina BA, López-Tello SA, Alcalá PD. Epidemiología del cáncer de piel en pacientes de la Clínica de Dermato-oncología del Centro Dermatológico Dr. Ladislao de la Pascua. Rev Mex Dermatol. (2012); 56: 30-37.

[19] Reed WB, Becker S, SR., Becker S, JR., Nickel WR. Giant Pigmented Nevi, Melanoma, and Leptomeningeal Melanocytosis: A Clinical and Histopathological Study. Arch Dermatol. (1965); 91(2):100-119.

[20] Arrington JH III, Reed RJ, Ichinose H, Krementz ET. Plantar lentiginous melanoma: a distinctive variant of human cutaneous malignant melanoma. Am J Surg Pathol. (1977); 1:131-143.

[21] Bradford PT, Goldstein AM, McMaster ML, Tucker MA. Acral Lentiginous Melanoma Incidence and Survival Patterns in the United States, 1986-2005. Arch Dermatol. (2009); 145: 427-434.

[22] C. Pereda, V. Traves, C. Requena, C. Serra-Guillén. B. Llombart, O. Sanmartín, C. Guillén, E. Nagore. Clinical presentation of acral lentiginusos melanoma: a descriptive study. Actas dermo-sifiliograficas (2012) 104: 220-226

[23] Feibleman CE, Stoll H, Maize JC. Melanomas of the palm, sole, and nailbed: a clinicopathologic study. Cancer. (1980); 46: 2492-2504.

[24] Phan A, Touzet S, Dalle S, Ronger-Salve S, Balme B, Thomas L. Acral lentiginous melanoma: a clinicoprognostic study of 126 cases. Br J Dermatol. (2006); 155: 561-569.

[25] Ghadially FN, trauma and melanoma production. Nature (1966); 211: 1199

[26] Troyanova P. The role of trauma in the melanoma formation. J Boun (2002); 7: 347-350

[27] Ranwala S, Hunt C, Modi G, Krishnan B, Orengo I. Amelanotic subungual melanoma after trauma: an unusual clinical presentation. Dermatol online j (2011); 17:8

[28] Zanhg N., Wang. L, Zhu.G., Sun. D., He. H., Luang. Q., Liu. L., Hao. F., Lee. C., Gao. P. The associatiom between trauma and melanoma in the Chinese population: a ret-

rospective study. J of the European Academy of Dermatology and Venereology. (2013).

[29] Hsu M, Meier F, Herlyn M. Melanoma development and progression: a conspiracy between tumor and host. Differentiation (2002) 70: 522-536

[30] Herrera-González Norma Estela. "Interaction between the Immune System and Melanoma", Recent Advances in the Biology Therapy and Management of Melanoma" (2013)

[31] Young, R. J., Waldeck, K., Martin, C., Foo, J. H., Cameron, D. P., Kirby, L., Do, H., Mitchell, C., Cullinane, C., Liu, W., Fox, S. B., Dutton-Regester, K., Hayward, N. K., Jene, N., Dobrovic, A., Pearson, R. B., Christensen, J. G., Randolph, S., McArthur, G. A. and Sheppard, K. E. Loss of CDKN2A expression is a frequent event in primary invasive melanoma and correlates with sensitivity to the CDK4/6 inhibitor PD0332991 in melanoma cell lines. Pigment Cell & Melanoma Research, (2014), 27: 590–600.

[32] Sullivan RJ, Flaherty KT. BRAF in Melanoma: Pathogenesis, Diagnosis, Inhibition, and Resistance. J of Skin Cancer 2011; (2011): 1 – 8.

[33] Avruch J. MAP kinase pathways: the first twenty years. Biochim Biophys Acta. (2007); 1773:1150-1160.

[34] Vidwans SJ, Flaherty KT, Fisher DE, Tenenbaum JM, Travers MD, Shrager J. A Melanoma Molecular Disease Model. PLoS One (2011); 6: 1 – 10.

[35] Ciampi R, Nikiforov YE. Alterations of BRAF gene in human tumors. Endocr Pathol. (2005);16: 163-172.

[36] Zafon C y Obiols G. Vía de señalización dependiente de la proteincinasa de activación mitogénica. De las bases moleculares a la práctica clínica. Endocrinol Nutr. (2009); 56(4):176-186

[37] Cantwell-Dorris ER, O'Leary JJ, and Sheils OM. BRAFV600E: Implications for Carcinogenesis and Molecular Therapy. Mol Cancer Ther. (2011); 10: 385 – 394.

[38] Barra-Martínez R. Estudio de la mutación de T-1799A BRAF en melanoma acral lentiginoso y nodular de pacientes del Hospital General de México 2010. Maestría en Ciencias de la Salud. Sección de Posgrado. Escuela Superior de Medicina, IPN.

[39] Jakob, J. A., Bassett, R. L., Ng, C. S., Curry, J. L., Joseph, R. W., Alvarado, G. C., Rohlfs, M. L., Richard, J., Gershenwald, J. E., Kim, K. B., Lazar, A. J., Hwu, P. and Davies, M. A. (2012), *NRAS*mutation status is an independent prognostic factor in metastatic melanoma. Cancer, 118: 4014–4023.

[40] Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol. (2006); 24:4340- 4346.

[41] Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. (2005); 353:2135-2147

[42] Sauter. E., Yeo Un-Cheol., Streem. A., Zhu. W., Litwin. S., Tichansky. E., Pistritto. G., Nesbit. M., Pinkel. D., Herlyn. M., Bastian. B. Cyclin D1 Is a Candidate Oncogene in Cutaneus Melanoma. The American Journal of Cancer. (2002):62;3200-3206.

[43] Ambudkart. S., Dey. S., Ihrycyna. C., Ramachandra. M., Pastan. I., Gottesman. M. Biochemical cellular and pharmacological aspects of the multidrug transported. Pharmacol Toxicol. (1999); 39:361-98.

[44] Frank N, Pendse S, Lapchak P, Margaryan A., Schlain D., Doeing C, et al. Regulation of progenitor cell fusion by ABCB P-glycoprotein, a novel human ATP- binding cassette transporter. J Biol Chem. (2003); 278:47156–47165.

[45] Frank N, Margaryan A, Huang Y, Schatton T, Waaga-Gasser AM, Gasser M et al. ABCB5-mediated doxorubicin transport and chemoresistance in human malignant melanoma. Cancer Res. (2005); 65: 4320–4333.

[46] Vásquez-Moctezuma I, Meraz-Ríos MA, Villanueva-López CG, Magaña M, Martínez-Macias R, Herrera-González NE. ATP-binding cassette transporter ABCB5 gene is expressed with variability in malignant melanoma. IPN. Actas Dermosifil. (2010); 101: 341-348.

[47] Yancovitz Molly, Adam Litterman, Joane Yoo, Elise Ng, Richard L. Shapiro et al. Intra- and Inter-Tumor heterogeneity of *BRAF*^{V600E} mutations in primary and metastic melanoma. PLoS ONE (2012); 07(1); e29336

[48] Pleasance, E.D., Cheetham, R.K., Stephens, P.J., McBride DJ, Humphray SJ, Greenman CD et al. A comprehensive catalogue of somatic mutations from a human cancer genome. Nature. (2010); 463: 191–196.

[49] Lee JT, Li L, Brafford PA,Van Den Eijnden M, Halloran MB. PLX4032, a potent inhibitor of the B-Raf V600E oncogene, selectively inhibits V600E-positive Melanomas. Pigment Cell & Melanoma Res.(2010); 23: 820–827.

[50] Turajlic S, Furney SJ, Lambros MB, Mitsopoulos C, Kozarewa I, Geyer FC, et al. Whole genome sequencing of matched primary and metastatic acral melanomas. Genome Res (2012) 22:196–207.

[51] Parker SG, Diffey BL. The transmission of optical radiation through human nails. Br. J. Dermat (1983); 108:11-16.

[52] Greenman C, Stephens P, Smith R, Dalgliesh GL, Hunter C, Bignell G, et al. Patterns of somatic mutation in human cancer genomes. Nature. (2007); 446: 153–158.

[53] Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. (2009); 458:719–724.

[54] Pfeifer GP, You YH, Besaratinia A. Mutations induced by ultraviolet light. Mutat. Res. (2005); 571:19–31.

[55] Gaddameedhi S, Kemp MG, Reardon JT, Shields JM, Smith-Roe SL, Kaufmann WK et al. Similar Nucleotide Excision Repair Capacity in Melanocytes and Melanoma Cell. Cancer Res. (2010); 70: 4922- 4930

[56] Furney SJ, Turajlic S, Fenwick K, Lambros MB, MacKay A, Ricken G, et al. Genomic characterisation of acral melanoma cell lines. Pigment Cell Melanoma Res. (2012); 25; 488–492.

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