THE IMPORTANCE OF EARLY DIAGNOSIS IN MALIGNANT MELANOMA. DIAGNOSTIC METHODS

Bonta Marinela*, Daina Cristian, Daina Lucia, Bud Corina, Venter Alina

*University of Oradea, Faculty of Medicine and Pharmacy, P-ta 1 Decembrie nr. 10, Oradea, Romania, e-mail: bontamarinela@yahoo.com

Abstract

The malignant melanoma is a malignant affection of the pigmentary system of the skin and is developed from melanocytes. It can appear anywhere the melanocytes are, on the skin and mucous. The melanoma represents 7% of the cutaneous cancers, being most frequently met in elder persons with the age between 20 and 60. The etiopathogenic factors involved in the appearance of the melanoma are the genetic factor, the excessive exposure to the sun, the type of pigmentation of the skin, the chronic trauma and irritations. The tumor can appear on the healthy skin or on the pre-existent pigmentary lesions. The dermoscopical clinical examination, the biopsy and the histopathology examination allow the diagnostic and staging of the melanoma. According to the TNM classification, the computer tomography, the nuclear magnetic resonance and the tomography with emission of positrons are the radio-imagistic method that allows the early discovery and diagnostic of the metastasis. The prognosis of the melanoma is made depending on the histopathology criteria. The unfavorable prognosis is given by the large dimension, by the bleeding and ulceration of the tumor and by the metastasis.

In conclusion the early discovery and staging of the tumor according to the TNM classification allows the fast beginning of the treatment depending on the evolution stage. Thus, in the early stages the healing can be obtained and in the advanced stages, with metastasis, the rate of surviving increases.

Key words: malign melanoma, dermoscopy, metastasis, melanocyte, pigmentation

INTRODUCTION

The malignant melanoma, one of the most serious and aggressive cutaneous cancers, was known even before Hypocrates, but the one that gives it the name of “melanoma” is Carwell in 1838. It is a malignant tumor of the pigmentary system, the melanocyte representing the origin cell of the melanoma, this being formed by the malignant transformation of the melanocytes.

It is located on the teguments and mucous where these melanocytes are, first of all on the skin, but also on the oral, nasal, esophagus, genital mucous. The eyes, the meninx and the nervous system represent anatomic regions where the melanoma can be developed.

The malignant melanoma represents approximately 2% of the cancers and approximately 7% of the cutaneous cancers. The statistical data show an increase of the frequency of the melanoma on the entire globe, their incidence being double in the last decades. To these is added also the

decrease of the age of its appearance, being most often met also in younger persons.

Rarely in the childhood and puberty, the persons with the age between 20 and 60 are the most often affected, being more frequent in women.

In the present the melanoma represents 5% of the cutaneous cancers without diagnostic in men and 6% in women.

The localizations most often met are:

- lower limbs, 27%, especially on the calves, most frequently in women
- torso approximately 24%, especially in men and especially on the posterior thorax upper region
- head and neck in a percentage of 22%
- upper limbs approximately 10%
- under the nails region 2,9%
- and the rest in other regions.

The present statistical data show that the deaths caused by the melanoma are registered at younger ages compared to the deaths caused by the other types of cancer.

ETIOPATHOGENETIC FACTORS

The early discovery and diagnostic of the melanoma in stages as early as possible is the most important thing, considering its aggression and fast dissemination. The diagnostic and beginning as quick as possible of the treatment prevents the appearance of the metastases. The numerous studies accomplished along the time show that the etiology and pathogenesis of the cutaneous melanoma remain unknown.

There are mentioned more etiopathogenetic factors that can favor the appearance of the melanoma.

An important role is that of the genetic predisposition and the studies accomplished demonstrate that the genes involved in the appearance of the melanoma are situated on the chromosome 9p21. For approximately 66% of the melanoma there were identified mutations of the BRA gene, there were identified mutations of the MC_1R gene and mutations of the gene for kinasa 4 dependent on cyclins, $CDKN_2a$.

Also to the genetic factor is owed the existence of the family malignant melanoma.

The exposure to the sun represents another factor of risk in developing the cutaneous melanoma. The exaggerate exposure to the solar radiations followed by sun burns, the decreasing of the ozone layer of the terrestrial atmosphere favoring the increased penetration of the ultraviolet radiations with role in carcinogenesis.

The persons with white skin, light color with photo type 1 and 2, present a higher risk to develop a melanoma.

The family antecedents of melanoma and of the dysplastic nerves is also a risk in the appearance of the melanoma.

This can be developed in approximately 30% of the cases on preexistent melanocytic lesion, being considered precursors of the melanoma. They are benign lesion what have malignant potential and which in certain conditions can be transformed in melanoma.

The following types of pigmented lesions are considered precursors of the cutaneous melanoma:

- melanocytic nerves that are met in all the ages and that have an increased risk of malignity depending on their histologic structure. Here are included two different groups and namely the congenital nerves that appear at birth and the nerves achieved that appear beginning with the first childhood. The congenital nerves have a higher risk of malignant transformation especially those that have larger dimensions or the giant ones. The risk of the appearance of the melanoma on a congenital nerve is of 6,3% and the melanoma has a reserved prognosis.

The possibility to develop a melanoma is doubles in the case of the dysplastic melanocytic nerves.

The malign setting met in elder persons is considered a melanoma in evolution.

The hormonal factors underline the rarity of the cancerous lesion before the puberty and in women the faster evolution of a melanoma is during the pregnancy.

The chronic irritations and trauma represent by far one of the factors that set off the malignant transformation of the melanocytic nerves.

The melanoma can appear also on the apparently healthy skin and is called d'emblée melanoma.

Xeroderma pigmentosum, the blue nerve, the Spitz juvenile nerve or any pigmented lesion can be the basis of the development of a melanoma.

THE CLINICAL FORMS OF THE MELANOMA

The most frequent clinical forms of the melanoma are:

1. The melanoma extensive in the surface is the clinical form most frequently met of the malignant melanoma and of d'emblée: it represents 70% of the total melanoma.

2. The melanoma developed at lentigo maligna is the most frequent in the ages over 65.

3. The desmoplastic melanoma is a form of melanoma associated most often with the lentigo maligna melanoma, but it can be formed also on

a solar lentigo, on an acral lentiginous melanoma, on an melanoma extensive in the surface.

4. The nodular melanoma, the second type of cutaneous melanoma as frequency can be developed either on the healthy skin or on the nerves.

5. The acral lentiginous melanoma, situated on the palms, plants, nails and nail bed, met more often in men.

Other clinical forms less frequent are the achromic melanoma, melanoma of the mucous and metastatic melanoma.

MATERIAL AND METHOD

Because 70% of the cutaneous melanomas are developed either on a healthy skin, and 30% of them are formed on a pre-existent melanocitary lesion, it is very important that any pigmented lesion that appeared on the normal skin or the modification of a pre-existent pigmented lesion to be examined as quick as possible by a specialist for the correct diagnostic, evaluation and indication of the most efficient method of treatment depending on the stage of the tumor.

In the present there are numerous possibilities of diagnostic of the melanoma that allow not only the early diagnostic but also the presence of the metastasis in the advanced stages of the disease.

The dermatological clinical examination of the entire tegument, inclusively the mucous and skin appendages represent the first step of diagnostic. In order to distinguish a benign pigmented lesion from a malignant one it is applied the ABCDE rule. The recognition of the melanoma is made based on the clinical criteria established by the ABCDE rule. The six signs of the melanoma are: A- asymmetry, namely the two halves are not the same; B- the border or the edge, in the melanoma the edges are irregular; C- the color is uniform, there can be shades of brown, black, grey, red, white; D- the diameter, in the melanoma the diameter is larger than 6 mm; E- evolution, the transformation or the over-subsidence underlines the wide black aspect of the melanoma.

One of the most important signs of the malignant melanoma is represented by the history of its diameter growth.

The dermatoscopy is a method of diagnosis that is made with the help of the dermatoscope. The dermatoscopy comes to confirm the clinical examination, visually it represents a complementary method of diagnosis.

The dermatoscopy is a noninvasive method that allows the visualization with great precision of the pigmented and structural characteristics of the epidermis, of the dermo-epidermal junction and of the dermal papillas, allows the consideration of the margins and of the surface of the lesion. There were established three dermatoscopic criteria that allow

the differentiation of the melanoma from the other benign pigmented lesions. These criteria are: A- pigmented and structural asymmetry of the lesions characterized by the presence of a pigmentation and non-uniform structures on one or two perpendicular axes. B- is the atypical reticulation that consists of the presence of a pigmented network and irregular areola or of brown globules but also of a more accentuated drawing. C- is referring to the color and consists of the presence of some ciano-leuco-pigmented structures, namely structures of blue or white color and other colors.

The presence of two of the three criteria of dermatoscopic diagnosis – ABC criteria, of the dermatoscopic diagnosis suggest a lesion with high risk of malignity and the presence of all three criteria recommends the surgical excision.

The modern dermatography uses the crossed polarized light, by contact. There were introduced or are in process of introduction sophisticated imagistic methods and techniques as the diagnosis of image analysis assisted by the computer that use sophisticated programs.

Another method is the confocal microscopy that uses a laser of low power with visible light or infrared with digital microscope with scanners and computer that allows the strengthening of the image and the examination of the epidermis and of the papillary derma ”in vivo”.

The multispectral imagistic and the automatic diagnostic uses two systems. The system of intracutaneous spectrophotometric analysis.

SIAscope TH, uses a SIAscope Th devices that uses the visible and infrared light and examines the cutaneous components up to 2 mm under the skin delivering data about the pathological modifications.

The second system is Mela Find ^{R} which is a non-invasive system, on the computer, that allows the early detection of the melanoma and the posting of the multispectral digital images from blue to infrared helping to the confirmation and denying of the melanoma.

Biopsy

Represents the basis of the diagnosis in the melanoma and allows the histopathology examination of the tissue with biopsy. The histopathology examination allows the differentiation between the melanoma and the benign lesion.

In the melanoma the histopathology examination underlines the cellular and nuclear pleo-conformism, cellular monstruosities and frequent mitosis, a peritumoral inflammatory infiltrate, the increasing of the number of capillaries. The histopathology examination allows the staging of the melanoma.

Other methods of paraclinical diagnosis are cytodiagnosis, immunohistochemistry, lymphography, thermography, scintigraphy. In case it is suspected the presence of the metastasis, they can be observed

with the help of the computerized thermography. The computed tomography scanner allows the scanning of the head, thorax, abdomen and pelvis. Other radio-imagistic methods used are the nuclear magnetic resonance, RMN and tomography with emission of positrons or PET, an imagistic technique of great precision that underlines the presence of cancerous cells in the any region of the body. To the patient is administered intravenous radioactive glucose that is captured fast by the cells of the melanoma being able thus to identify the metastasis.

Immunohistochemistry uses the immunologic tests that allow the prognostic diagnosis of the malignant melanoma, offers data about immune globulins from the 4^{th} Ig G subclass, specific antibodies as S103 antiprotein, HMB 45antibodies.

In order to establish the definitive diagnosis there are used ”microrray” techniques that analyze the genes and DNA detecting the mutations on the level of the genes.

Staging of the melanoma

It is very important because, depending on the evolution stage is beginning the treatment of the melanoma.

The evolution stage of the melanoma is established depending on certain criteria.

In the classification of Anderson there were four evolution stages recognized: - stage I – non invasive local lesion without adenopathy; stage II – invasive local lesion in the surface and depth; stage III – local invasive lesion with regional adenopathy; stage IV – metastasis at a distance cutaneous, ganglionic visceral.

For the consideration of the prognosis are used the histopathological criteria, depending on the level of invasion. Up recently it was used the level of invasion of Clarch that indicates the number of cutaneous layers invaded by tumor. But in 2010 AJCC introduces a new system of staging that allows a great precision of the diagnosis and prognosis of the melanoma, the new system is called Breslow. In this system are included three criteria and namely: thickness or depth of the tumor, the presence of the microscopic ulceration, the mitotic rate or the speed of cellular division. The thickness of Breslow measures in millimeters the distance between the upper layer of the epidermis and the deepest point of the tumoral penetration.

CLASSIFICATION OF THE TNM OF THE MELANOMA

T-tumor; N-ganglion; M-metastasis.

Depending on the tumor there are the following stages: - Stage Tis – noninvasive tumor in situ, remains in the epidermis: Stage Tra – noninvasive tumor smaller or equal with 1 mm in Breslow depth, without

ulceration, the mitotic rate smaller than 1 mm^2; - Stage Tib – tumor smaller or equal with 1 mm, with ulceration, mitosis greater or equal with 1 mm^2 ; - Stage T2a – the tumor has the thickness between 1,01 – 2,0 mm without ulceration; - Stage 2b presents ulceration; - Stage T3a – has the thickness of 2,01 – 4,0 mm, without ulceration and - Stage T3b – presents ulceration; - Stage T4a – has the thickness of over 4 mm without ulceration; - Stage T4b – presents ulceration.

Classification N includes the presence of the lymphatic ganglions

No – without touchable ganglions; N1a – non invasive unilateral ganglions; N1b - invasive unilateral ganglions; N2 – bilateral or contralateral ganglions; N3 – fixed ganglions (4 or more ganglions or adenopathic block).

Classification M – includes the presence of the metastases.

Mo – without metastases; M1a – tegument at a distance subcutaneous or ganglionic metastases; M1b – pulmonary metastases; M3 – visceral metastases or any metastases at a distance.

Stages I and II are incipient stages and stages III and IV are advanced stages. In stage IV were metastasized the lymphatic ganglions at a distance, the internal organs, especially the lungs then the brain, the gastro-intestinal tube. Another element is the increased serum level of the dehydrogenase lactate.

The factors of risk for the development of the malignant melanoma

These factors can favor the appearance of a melanoma, thus they have to be known, the persons that present these factors have to be observed and examined periodically in order to find as early as possible the appearance of the tumor. These factors of risk are: genetic markers - CDKNa2, BRAF, MC1R.

- cutaneous phenotype 1 and 2
- family antecedents of dysplastic nerves or melanoma
- personal antecedents of melanoma
- excessive exposure to solar radiation
- the number greater than 50 and the dimensions greater than 5 mm of the melanocitary nerves
- congenital nerves
- the number of dysplastic nerves greater than 5
- Syndrome of dysplastic melanocitary nerves.

Evolution and prognostic of the malignant melanoma

Being an aggressive tumor with possibility of pretty fast dissemination on the lymphatic and blood path, the prognosis of the melanoma is reserved and almost 100% of them lead to death. In the

literature are mentioned rare cases of healing by the spontaneous regression of the tumor.

The following are considered factors of non-favorable prognosis: the large dimensions, the bleeding and ulceration of the tumor, the localizations from the level of the cephalic extremity and from the median line of the torso and the metastases. It is important to be known the hystopathological criteria in the consideration of the prognosis – the level of invasion, the thickness of the tumor and the mitotic activity.

In its evolution, the melanoma presents a fast growth, intra-epidermal, preinvasive or minimally invasive and a vertical growth that indicates the penetration in the dermis and have a role in the appearance of the metastases.

RESULT AND DISCUSSION

In the last years, according to the statistical data, the number of the persons diagnosticated with malignant melanoma is in continuous increase, the same as the number of deaths caused by it.

The number of deaths caused by the melanoma is greater among the young persons compared to the number of deaths caused by the other types of cancer.

It was found also the decrease of age of appearance of the melanoma, being frequently met in young persons, aspect confirmed by numerous studies.

Also there are necessary a series of measures of prevention of the tumor appearance especially for persons that present factors of risk for the development of melanoma and the most important measure is that of early finding of the tumor, the most important measure being represented by the dermatologic clinical examination, performed periodically, because 30% of the melanoma appear on the preexistent pigmentary lesion, precursors of melanoma and 70% of the melanoma appear on the normal, healthy tegument.

The visual clinical examination of the entire tegument and the applying of the ABCDE rule allows the recognition of the melanoma, being differentiated from the other benign pigmented lesions. According to the ABCDE rule the lesion is analyzed depending on the asymmetry of the lesion, its margins, color, diameter and ST elevation of the lesion and depending of these characteristics it is made the differentiation of the melanoma from a benign lesion.

The dermatoscopic examination supplements the visual examination, identifying a series of details, thus facilitating the detection and diagnostic of the melanoma in the beginning phase. The early

discovery of the melanoma leads to the prevention of the appearance of the metastases and of the death, especially because the mortality by this affection was up to the last years of almost 100%.

But the possibility of the complete healing has a direct and very tight relation with the dimension and deepness of the tumoral invasion because the melanoma presents initially a phase of radial growth, followed by the phase of vertical growth and in the phase of radial growth the metastases appear extremely rare, aspect confirmed by numerous authors.

For this reason the discovery of the tumor in the phase of radial growth is essential, because the identification of the ”thin” melanoma, in the beginning stage by clinical and dermatoscopic examination represents the most important method of fighting it and is supported entirely by specialists.

The vertical growth of the cutaneous melanoma indicates the invasion of the tumor in depth, in the dermis, favoring the appearance of metastases. The histologic examination offers data about the level of invasion, the thickness of the tumor by the Breslow index, the mitotic activity, but also about cellular pleomorphism and the modifications of the capillaries. The presence of the metastases indicate an advanced stage of the disease.

The detection and localization of the metastases is performed with radio-imagistic methods of diagnosis, computed tomography, nuclear magnetic resonance and especially with the tomography of emission of positrons.

Depending on the evolution stage of the melanoma which is established according to the criteria of the TNM classification, is started as fast as possible the treatment of the tumor, first of all the surgical excision with safety margins.

The early discovery of the melanoma increases the rate of surviving and ameliorates the prognosis of the disease.

CONCLUSIONS

1. The malignant melanoma is the most aggressive and severe form of cancer due to the fast dissemination on the lymphatic and blood path.
2. The melanoma can appear for any person and at any age.
3. The possibility to develop a melanoma is greater for the persons that present factors of risk.
4. The decrease of the age of the appearance of the melanoma and the increase of its frequency for young persons.
5. The increase of mortality by the melanoma in young persons, compared to the mortality by other types of cancer.

6. The clinical and dermatoscopical examination allow the detection and diagnostic of the melanoma in the beginning phase.
7. Methods of radio-imagistic diagnostic allow the early detection and localization of the metastases.
8. Staging of the cutaneous melanoma is made depending on the criteria of the TNM classification.
9. The early discovery, in beginning phases increases the rate of surviving of the patients and decreases the mortality by melanoma.
10. The possibility of healing the melanoma due to the early discovery and its diagnostic in the beginning stage.
11. The early discover and diagnostic gives the disease a favorable prognosis.

REFERENCES

1. Argenziana G., Soyer HP., Chementi S., Ruocco V., 2002, Impact of Dermatoscopy an the Clinical Management of Pigmented Skin Lesions. Clin. Dermatology
2. Colțoiu A., Mateescu D., Popescu S., 1983, Dermato-Venerologie – Ed. Didactică și Pedagogică, București
3. Dumitrescu A., 1997, Dermatologie Ed. Național, București
4. Dumitru J., Diaconu C., Coman O. A., Benea V., 2002, Tratat de Terapeutică Dermato-Venerologică. Editura Viața Medicală Românească, București
5. Gheorghe Bucur, Dana Angela Opriș. Boli Dermatovenerice – Enciclopedie. Ed. Medicală Națională, București, 2002.
6. Johr R., Peter Soyer H., Argenziano G., Hofmann-Wellenhof R., Scalvenzi M., 2009, Deramtoscopia. Aspecte Esențiale. Editura Medicală Callisto
7. Kitter H., Binder M., 2002, Fallow up of Melanocytic Skin Lesions with Digital Dermatoscopy: Risks and Benefits. Arch. Dermatol
8. Kittler H., Pehamberger H., Wolff K., Binder M., 2002, Diagnostic Acuracy of Dermatoscopy. Lancet Oncol
9. Maier N., 1999, Patologie Cutanată. Editura Casa Cărții de Știință, Cluj, 1
10. Perry Robins, Maritza Perez, 2011., Să Înțelegem Melanomul. Editura Techno Media Sibiu,
11. Stolz W., Braun Falco O., Bilek P., et al., 2002, Color Atlas of Dermatology. 2nd ed. OxfordEngland: Blackwell Scientific Publications
12. Wolff K., Johnson R. A,, Saavedra A. P., 2017, FITZPATRICK – Atlas color și compendiu de Dermatologie Clinică. Ediția a Șaptea. Editura Medicală CALLISTO, București