**MALIGNANT MELANOMA IN YOUNG PATIENTS: HISTOPATHOLOGIC PARTICULARITIES**

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**Abstract**

Malignant melanoma is an aggressive, therapy resistant tumor of the skin with increased incidence. Some studies report a better outcome for young patients, while others failed to demonstrate this feature.

We present a retrospective study including 28 patients with malignant melanoma aged between 15 and 30 years. Some special morphologic features were identified, sustaining the idea that heterogeneity of malignant melanoma in this age group was very high.

In young patients, thin superficial spreading melanomas are more frequent, but there are some patients with very advanced lesions and poor outcome. The high incidence of melanomas developed on preexisting nevi indicates the need for a thorough surveillance of nevi in pediatric patients.

**Keywords:**
- Malignant melanoma
- Young age
- Breslow index
- Mitotic index

**Introduction**

Malignant melanoma (MM) is an aggressive, therapy resistant tumor of the skin with increased incidence, being an important public health problem. Risk factors for the development of MM are: solar UV radiation, personal history of sunburns, fair skin, dysplastic nevi syndrome and family history of melanoma (1, 2). Although it is considered to be a rare disease among very young persons, MM is the third most common cancer diagnosed among adolescents and young adults (aged 15-39 years) (3). Malignant melanoma has been increasing worldwide, but at faster rate than any other malignancies (4). Also, there are studies that show an important increase of MM in young people in the last half-century, especially among women (5). This trend is attributable to an increase of UV exposure (sunlight and tanning beds) in children and adolescents but also to an increased ascertainment of melanoma (6). Some other minor factors can be involved in this rise of incidence such as increased maternal age (7), previous treatments for early age cancers (8), and therapy induced immune suppression (9).

Some studies had identified some minor special features (clinical, histologic and genetic) in mela-
nomas arising at young age. They are frequently amelanotic lesions (almost half of lesions), localized on lower limbs (10), while in adults, amelanotic melanoma is quite rare (less than 5% of cases) (11). Histologically, the most frequent form in both groups is the superficial spreading melanoma. Although in children MM is usually diagnosed in a more advanced stage, overall survival is similar with adult groups (10). Some studies report a better outcome for young patients (12), while others failed to demonstrate this feature (10). From genetic point of view, besides BRAF activation and loss of CDKN2A gene (traits common with adult melanomas) (10), melanomas in children and young adults are frequently exhibiting loss of INK4A and gain of c-KIT (13).

Diagnosis of MM in young patients has some supplementary difficulties, since in this age group there are frequent spitzoid tumors, some of them with atypical features and uncertain malignant potential (14, 15). Sometimes, additional molecular techniques are needed for diagnosis (14, 16).

Although there are a limited number of studies on MM in young patients, current knowledge sustains the fact that outcome predictors are similar in MM regardless of the age of onset. As in adults, the most important prognostic factor of melanoma is the Breslow thickness (18), which represents the maximum depth of invasion, measured from the surface of the skin to the most profound tumor cell (19). Clark level of invasion (the deepest layer of the skin invaded by tumor cells) has a limited value for prognosis in MM, despite the age of the patient (20). Other prognostic factors in MM are: ulceration, mitotic rate, presence of microscopic satellites (dermal or subcutaneous tumor nodules without continuity with the primary tumor), regression (histologically proven complete or partial disappearance of the tumor), vascular invasion, tumor infiltrating lymphocytes (TILs), and status of regional lymph nodes (18, 20).

We are presenting a retrospective morphological study of MM in young patients, including some significant demographic and clinical data.

Methods

We selected all cases of malignant melanoma in patients younger than 31 years, diagnosed between 01.01.2013 and 31.08.2017, from the archive of the Pathology Department of Colentina University Hospital. The youngest patient was 15 years old. Multiple data were identified using clinical and histologic reports, including sex, age, localization, tumor diameter, histologic subtype, Breslow index, Clark level, mitotic rate, ulceration, vascular invasion, microscopic satellite nodules or metastases, and presence of associated nevus.

Sampling of tumors was made according to national and international guidelines for MM (21). All tissue samples were routinely processed using an automatic tissue processor; then, they were embedded in paraffin, and multiple (2-6) 2.5 μm sections were performed from each paraffin block. Hematoxylin-eosin stain was routinely performed using an automatic stainer.

All histologic slides were examined by two independent pathologists with experience in skin tumors. All disagreements were resolved examining the slides with an expert in dermatopathology, using a multi-head microscope.

Statistical interpretation of data was made using the t-test.

This study was approved by Colentina University Hospital Ethic Committee, and all patients included agreed to participate in clinical studies.

Results

The study included 28 patients with histopathological diagnosis of malignant melanoma and age between 15 and 30 years, the median age being 24.25. Age distribution (25% of patients were 15-20 years old, 25% were 21-25 years old and 50% were 26-30 years old) is indicated in Figure 1. Nineteen patients were women and nine men, confirming data from the literature indicating a higher incidence of melanoma among young women (Figure 2). There was no significant difference in median age between women and men.
The majority of lesions (15) were located on the sun-exposed areas (head and neck, anterior thoracic wall, upper limbs, calves). An unusual high number of patients (about 46%) had MM on sun-shielded areas, a higher value than in the general population, in which about 10% of melanomas arise on non-sun-exposed areas (22) (Figure 3). In one case, we identified a special localization: a scrotal MM in a 22-year-old male patient. One patient, a 23-year-old woman, had two synchronous superficial spreading MM, both on non-sun-exposed areas and developed on pre-existing nevus lesions.

From microscopic point of view, we diagnosed 18 superficial spreading melanomas, four nodular and six in situ melanomas (Figure 4).

Breslow index varied between 0.25 mm and 13 mm, with an average of 2.32 mm. In this group, thin melanomas (under 1 mm diameter) were predominant (15 cases). Only seven lesions were thicker than 2 mm (Figure 5). The youngest patient in our group (15-year-old) had the highest Breslow index (13 mm).

Correlation of Breslow index with patients’ age indicated that those who were younger than 21-year-old were more prone to have a high Breslow index than subjects aged between 21 and 30 years (two-tailed t test, p value 0.0070, statistically highly significant) (Figure 6).

Mitotic index varied widely between 0 and 30 mitotic figures on square millimeter (Figure 7). In almost half of patients (13), no mitotic figures were identified in their lesion, three of them having in situ melanoma.

Breslow index also correlates with the mitotic index (measured on square millimeter) (two-tailed t test, p value 0.0100, statistically significant), more advanced tumors having a higher mitotic index (Figure 8).
Interestingly, eight patients had associated nevic lesions: one blue nevus, one Spitz nevus and six usual nevi with or without dysplastic features (Figure 9).

Discussions

Age: In this study, patients with a maximum age of 30 years were included. The youngest patient was a 15-year-old female with an advanced calf melanoma. There are some studies reporting melanomas in children even from birth, observing that the prognosis is better in small children and is worsening with age, particularly after puberty (23). Practically, all our patients were beyond puberty, and therefore, they had a higher risk of metastasis and death due MM. For patients in our group of age, survival had a weaker correlation with age than in older patients (24).

Sex: Although in adult population MM is more frequent in males, in all studies concerning children, adolescents and young adults, the prevalence is higher in females (23, 24). Females also have a better prognosis, partially due to a more precocious diagnosis (14). Our study confirms the predominance of MM in young females, practically all patients under 20-year-old being females. Since our study revealed no statistical relationship between sex and localization on sun-exposed areas, it is probable that some genetic mechanisms underlie the predominance of MM in young women.

Sun-exposure: In young patients, the relationship between MM and sun (or tanning bed) exposure is less important than in adults. Although excessive sun exposure during childhood is considered to be an important risk factor for MM (25), a longer period of exposure is usually needed for the occurrence of MM. Our study indicates an equal distribution of MM on sun-exposed and sun-shielded areas, showing that in young patients there are other than sun-exposure risk factors for MM. Since the incidence of MM among children, adolescents and young patients is increasing (26), these risk factors should be identified in order to tailor more effective prophylaxis and therapeutic strategies for this age group.

Subtype: As in all age groups (27), superficial spreading melanoma was the most frequent microscopic subtype of MM, representing over 64% of the cases in our group. Nodular melanomas represented only 14%, less than the general prevalence of 20% (27). One of the possible explanations is the fact that nodular melanomas are more frequently related to extensive sun-exposure, while superficial-spreading melanomas are more often related to BRAF mutations (27, 28). Low incidence of nodular melanoma is one of the causes of better prognosis of MM in young patients.

Breslow index: In our group, most cases were thin melanomas, with a Breslow index < 1 mm. This is concordant with the general trend, more and more MM being diagnosed in early stages. Explanation stands especially in the increasing awareness about the presence of the disease in young persons. However, it is important to know that some patients with thin MM will not be cured with surgical excision, but will develop fatal metastatic disease (30). These patients have high mitotic index, ulceration and high Clark level (IV or V) (30, 31).

Our study identified a higher risk for young patients to have thicker MM, as also reported by other authors (32). Since Breslow index (thickness of the tumor) is the most important prognosis factor, it is very likely that the youngest patients in our study had the poorest outcome. A special mention should be made about the presence of some patients with very thick melanomas in our group (three subjects had a Breslow index over 10 mm), confirming data from the literature that in young adults and adolescents there is a group of advanced malignant melanomas that are diagnosed when the disease is already metastatic (33).

Mitotic index: From our group, over 46% of patients had no mitogenicity. This confirms the fact that MM in young patients has a better outcome, since many non-mitogenic tumors are incapable of tumorigenesis and metastasis (30).
Clinical study

These patients had thin melanomas, as our study demonstrated a significant correlation between mitotic index and Breslow index, and their prognosis was the best. Thorough identification of mitosis in young patients is very important, since the difference of prognosis between non-mitogenic lesions and mitogenic ones is more significant than in older adults.

Association with nevi: Some studies identified the fact that at least one third of MM in young patients arise from nevi (34). In our study, less than 30% of patients had associated nevic lesions. This data correlated with the fact that, in patients younger than 40 years, the annual cumulative rate of malignant transformation of a nevus was approximately 0.0005% (35); so, it is very important to have an appropriate surveillance and even a “mole mapping” in pediatric patients with high risk of developing melanomas.

Conclusions

Regardless of the age at which it occurs, melanoma is an aggressive cancer. Its incidence is increasing in the young population, women being more prone to have a MM at a young age. Sun-exposure has less importance as a risk factor in young patients, although use of tanning beds may change this feature. MMs in young patients are heterogeneous in terms of outcome: most of the lesions are thin, superficial spreading lesions with low mitotic index and excellent prognosis, while a small group, including especially young females, has advanced tumors with high mitotic count and poor outcome. Development of MM on nevi is frequent among young patients and it has to be a concern even in pediatric facilities.

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Informed consent: obtained.

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