Introduction

History
Dysplastic nevus (DN) is an acquired, melanocytic, skin lesion with a potential to alter into a malignant melanoma (MM). The association between dysplastic nevus and melanoma was described by Norris in 1820; whereas Clark et al defined dysplastic nevus as a new clinical and histological entity at Pennsylvania University in USA in 1978 [1]. At first, it was named B-K mole, after the first letters of two family names in whose members it was identified. However, several suggestions for new names were given afterwards. To day, there are a few synonyms: dysplastic nevus (lat.), atypical nevus (and atypical nevus syndrome), Clarks’ nevus (and syndrome) as well as FAMM syndrome (familial atypical multiple mole syndrome). Modern terminology differentiates atypical nevus as a clinical entity from dysplastic nevus as a pathohistological entity.

The association between dysplastic nevi and familial melanoma susceptibility was recognised by Munro in 1974. Further investigations showed a 10 times higher risk of developing melanoma in persons with dysplastic nevi and those with history of familial melanoma [2].

The National Institute for Health (NIH) in the USA held a consensus conference on controversies concerning DN in 1992 [1] and the conclusion was that the DN is an acquired skin lesion, whose histological and clinical characteristics differentiate it from an ordinary mole. One of the suggestions was to use the term atypical nevus instead of the widely spread name dysplastic nevus, and to diagnose dysplastic nevus as an architectural disorder as well as to use the term FAMM syndrome in families prone to developing skin melanoma [3]. The criteria for FAMM syndrome are:

- Appearance of skin melanoma in one or more first or second degree relatives
- Appearance of multiple melanocytic nevi (often more than 50), where some of them are atypical nevi
- Multiple moles with certain histological characteristics

However, suggestions concerning terminology given by NIH have never been accepted by clinical doctors, and, therefore, the names “dysplastic nevus” and “dysplastic nevus syndrome” are used today.

Epidemiology
The incidence of DN in general population is high, ranging between 2% and 50%. This incidence is 17% in the Caucasian population in the USA. Dysplastic nevi can be hereditary or can appear sporadically. Familial dysplastic nevi have autosomal dominant inheritance. Sporadic lesions are those appearing in patients without any familial atypical nevi.

The risk of developing MM from DN depends on the number of DN in individuals as well as on other parameters such as having a family history of melanoma. Data found in literature point to a 2-12 times higher risk of developing MM in persons with DN.

Only a few retrospective studies analyzed the incidence of skin melanoma in patients with DNS [4]. In a 10-year retrospective study, Marghoob et al. calculated that the risk of developing skin melanoma was 10.7% in patients with DNS compared to the controls, whose risk was 0.62%.
Pathogenesis

The strongest evidence of the existence of dysplastic nevus as a clinical and pathohistological entity is its association with familial melanoma. Persons with family history of skin melanoma have not only a higher risk of developing melanoma but multiple dysplastic nevi on the body as well [5]. According to the gene mapping of these families it is most likely an autosomal dominant inheritance. A few genes have been isolated: 1p36, 9p21, p16, but none of these, as isolated, is responsible for alteration of DNA into skin melanoma. This alteration is most probably a consequence of polygenetic inheritance and environmental factors.

Some cytogenetic abnormalities of fibroblasts and lymphocytes were found in patients with DNS, and, hence, a hypothesis has been postulated that DNS is a consequence of chromosomal abnormalities [1,6]. Taking this into account, the question can be asked why these persons are at a higher risk of developing skin melanoma but not another malignant tumour.

The most important risk factor of developing DN and its alteration into skin melanoma is the exposure to ultraviolet (UV) radiation [7]. The exposure of patients with similar genetic characteristics to solar radiation makes the risk of developing DNS three times higher. UV light leads to chromosomal instability, which results in the development of apoptosis in keratinocytes and melanocytes. Since melanocytes are more resistant to chromosomal instability and sequential apoptosis, mutations accumulate until the appearance of skin melanoma.

Clinical features

Dysplastic nevus is acquired, melanocytic nevus which has a lot of clinical characteristics common with skin melanoma if the ABCDE (A - Asymmetry, B – Border is irregular, C – Colour is uneven, D – Depigmentation, E – Elevation above skin surface) rule is applied for making a clinical diagnosis of skin melanoma [5,7-9]. The diagnosis of DN is made if nevus has a diameter greater than 6mm, has uneven colour or irregular borders. Sometimes it is really hard to distinguish MM from DN clinically.

The most common areas for the appearance of DN are the back, thorax and abdominal wall, including the extremities and head.

The diagnosis of DNS is made if there is an evidence of family melanoma and one or more DN. In 2000, British researchers, Bishop et al suggested a scoring system for diagnosing DNS:

- 100 or more moles larger than 2mm (or 50 or more moles if the patient is younger than 20 or older than 50 years);
- Two or more dysplastic nevi (defined as a nevus larger than 5mm in diameter, with irregular borders and uneven pigmentation);
- One or more nevi on thighs or one or more nevi on dorsal side of feet.

Patients with two or more criteria are considered to have DNS.

The study was aimed at analyzing patients with melanoma and dysplastic nevi and at determining the incidence, origin, localization and histological type of melanoma as well as the development of metastasis and mortality rate in patients with both skin melanoma and dysplastic nevi.

Material and methods

A retrospective study was conducted covering a 10-year period (1999-2009) at the Department for Plastic and Reconstructive Surgery, Clinical Centre of Vojvodina. Data were provided from the medical files of patients with both dysplastic nevus and skin melanoma.

Results

During a 10-year period (1999-2009), 482 patients with skin melanoma were treated at the Department for Plastic and Reconstructive Surgery, Clinical Centre of Vojvodina. Dysplastic nevus was diagnosed in 165 (34.2%) patients with skin melanoma. In the whole group of patients with melanoma (N=482), 263 (54.6%) were male; whereas in the group with both MM and DN (n=165) the male to female ratio was almost equal (83 male patients – 50.3%).

The highest incidence of MM (53 patients – 32.1%) was in the patients with both DN and MM aged between 51 and 60 years, followed by incidences of 26.7% (44 patients) and 17.6% (29 patients) in the age groups 41-50 and 31-40, respectively (Graph 1).

The evolution of melanoma ranged from three months to two years.

Melanoma was most frequently localized on the thoracic wall (159 patients – 96.4%).

Graph 1. Distribution of patients with dysplastic nevi according to their age when melanoma was diagnosed

**Abbreviations**

DN – dysplastic nevus
MM – skin melanoma
DNS – dysplastic nevus syndrome
FAMM syndrome – familial atypical multiple mole syndrome
NIH – National Institute for Health in United States of America
UV radiation – ultraviolet radiation
In the group of patients with both DN and MM (n=165), melanoma developed de novo in 112 patients (67.9%), while in 53 patients (32.1%) melanoma developed as a malignant alteration of dysplastic nevus. In all patients with melanoma (N=482), malignant alteration of dysplastic nevi developed in 11% (Table 1).

Table 1. The origin of melanoma

<table>
<thead>
<tr>
<th>Patients with DN and MM/Pacienti sa DN i MM (n=165)</th>
<th>All patients with MM/Svi pacienti sa MM (N=482)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant alteration of DN/Maligna alternacija DN</td>
<td>53 (32.1%)</td>
</tr>
<tr>
<td>De novo development of MM/Razvoj MM de novo</td>
<td>482 (23.2%)</td>
</tr>
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</table>

Regarding the histological picture of melanoma, the nodular type was most frequent (116 patients – 70.3%), followed by the superficial type (49 patients – 29.7%). Other histological types were not found in the study sample. More than one third of the patients with melanoma (63 – 38%) had skin invasion of Clark IV: 54 patients (32.7%) were diagnosed with Clark III and 48 patients (29.1%) with Clark V. None of the diagnosed melanomas was the one in situ. Breslow’s depth of invasion of 3.1-4 mm was found in 67 patients (40.6%), while 51 patients (30.9%) had melanoma invasion exceeding 4 mm. Forty patients (24.8%) had invasion of 1.1-2 mm according to Breslow.

Dysplastic nevus syndrome was diagnosed in 53 patients (32.1%) in the group with both DN and MM (n=165) (or 10.9% in the whole group of patients with MM). Five patients (3%) claimed to have family history of melanoma.

Primary melanoma with regional metastasis was diagnosed in 7 patients (4.2%). Regional metastases were twice as frequent in the second year compared to the first year after the surgical removal of primary lesion. In three patients (1.8%), satellite metastases were diagnosed two years postoperatively (Table 2).

Table 2. The incidence of melanoma metastases

<table>
<thead>
<tr>
<th>Patients with regional metastasis/Pacienti sa regionalnim metastazama</th>
<th>Patients with satellitosis/Pacienti sa satellitosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>First check-up/Prvi pregled</td>
<td>4.2%</td>
</tr>
<tr>
<td>One year after the operation</td>
<td>x</td>
</tr>
<tr>
<td>Godina dana nakon operacije</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Two years after the operation</td>
<td>x</td>
</tr>
<tr>
<td>Dve godine nakon operacije</td>
<td>12 (7.30%)</td>
</tr>
<tr>
<td>Dve godine nakon operacije</td>
<td>3 (1.80%)</td>
</tr>
</tbody>
</table>

According to this research, the 5-year survival rate in patients with both DN and MM (n=165) was 72.7%, while the ten-year survival rate was 50.3%. The 5-year and 10-year survival rate was 90.7% and 83%, respectively in all examined patients with melanoma (N=482) (Graph 2).

Discussion

It is considered that the risk of malignant alteration of atypical nevus is 1/200,000 [10]. Superficial spreading melanoma is usually developed from atypical nevus. However, nodular melanoma develops when vertical growth pattern becomes dominant. According to this research, over 70% of melanomas were of nodular type, that probably being the consequence of its late detection. The data on microstaging obtained by both Clark and Breslow methods corresponded to the previously mentioned result. When 5 and 10 year survival rates are considered in this research, one can make a conclusion that prognosis is better in patients with MM but without DN compared to the group of patients with both MM and DN. This statement can also be explained by the fact that most of melanomas were of nodular type with undoubtedly worst prognosis possible.

Batallie et al. showed a difference in melanoma incidence in populations with close genetic characteristics when exposed to UV light for different periods of time [11]. They demonstrated that the prevalence of dysplastic nevus syndrome was 6% in the population chronically exposed to UV light compared to the control group where the prevalence was 4%. Therefore, it is interesting to estimate the incidence of DN in a specific geographical region, and calculate a relative risk of developing melanoma consequently. Due to insufficient medical data in this research and uncertain anamnesis in examined population, it cannot be said with certainty to which extent these patients were exposed to the sunlight.

The most important single risk factor in developing melanoma is the presence of dysplastic nevi [1-5,9]. Dysplastic nevi should not be considered as obligatory precursors of skin melanoma, but more as differences in the phenotype identifying persons at greater risk of developing melanoma. Literature data show that the risk of developing MM is 2-12 times higher in persons with dysplastic nevi. In this research, we found that the risk of developing MM was 3 times higher in persons with DN.

Conclusion

Even nowadays, dysplastic nevus, as an acquired melanocytic lesion, is a topic of interest not only for
scientists but for clinicians as well. The reason for this is the fact that dysplastic nevus is a single, most important risk factor for developing one of the most malignant skin tumours – melanoma. Our ten-year study data are in accordance with those found in literature because the patients with dysplastic nevi accounted for 34% of all the study sample. The clinical importance lies in the fact that two thirds of all patients had the worst histological type – nodular melanoma, and it was reflected in the 5 and 10-year survival rate.

References