MINI-REVIEW

Do Not Let to Be Late: Overview of Reasons for Melanoma Delayed Diagnosis

Maksymilian Gajda[1], Grazyna Kaminska-Winciorek[2]*

Abstract

   Melanoma of the skin is a malignant tumor, which incidence is still increasing. It was estimated that in the United States one person died from this cause every hour. The major risk factor of this disease is exposure to ultraviolet radiation, especially associated with the occurrence of sunburns. Patients diagnosed with distant metastases have median survival of 6-9 months. The aim of this paper was to identify the causes of delayed diagnosis of melanoma as diagnosis at an early stage seems to be the key to improve the survival rates. For this purpose, a search of medical databases such as PubMed, Google Scholar and Cancer Registers was conducted and an analysis of the literature from the years 1979-2013 was conducted.

Keywords: Cutaneous melanoma - delayed diagnosis - melanoma awareness - melanoma prevention

Introduction

   Cutaneous melanoma is a malignant neoplasm developing from melanocytes. The highest incidence of this cancer was reported among Caucasians (The Centers for Disease Control and Prevention, 2010) and the constant increase in the number of new cases is observed. Similarly, the highest risk of death was reported in Caucasians, much lower in other populations (Latino, Afro-American, Asian and Pacific Islanders). In pursuance of the latest Globocan, roughly 230,000 people all over the world were diagnosed with this type of cancer (Ferlay et al., 2013). The highest incidence was recorded in Australia and New Zealand, acting there as the third cause of cancer. High incidence was registered also in the United States of America (USA) and Scandinavia, whereas the lowest concerned the South-Central Asia (Ferlay et al., 2013). An increase in incidence of around 800% among young women and 400% for young men was recorded between the years 1970-2009 in the USA (Reed et al., 2012).

   Covering less than 5% of all skin cancers there, melanoma is a main cause of death (nearly 75%) in this group, killing approximately a single person every hour (American Cancer Society, 2013). In Central and Eastern Europe (CEE) countries melanoma was diagnosed in a more advanced stages. compared to Western Europe. Although, the incompleteness of the data in the countries of CEE was stressed (Forsea et al., 2012). Despite the increased number of new cases in Poland (PL), one of the CEE countries, the age-standardized incidence rate was evaluated to be near two fold lower than an average for European Union countries, in contrast to higher,

by approximately 20%, the age-standardized mortality rate (Ferlay et al., 2013). In 2008, 30% of Poles were diagnosed in stage I) 40% of them in stage II) while 5% in the stage IV) 80% of them were qualified for surgical treatment at the time of diagnosis (Szkultecka-Debek et al., 2012). Whilst in Denmark, locally advanced melanoma accounted for 82% of the cases and only 3.2% patients were diagnosed with distant metastases (Grann et al., 2013). In the region of the melanoma's highest incidence (New Zealand), the early stage detection was even better (Liang et al., 2010).

   Exposure to ultraviolet radiation (UVR) is a major risk factor for developing melanoma, especially when related to the occurrence of sunburns (particularly in childhood). Sunburns relate primarily to individuals with I and II skin phototype (pale skin, red hair, blue eyes). Using tanning beds or outdoor tanning is associated with an increased risk of malignant skin tumors development, including melanoma. Moreover, the risk of melanoma is related to the number of melanocytic nevi and increases with age (Lin et al., 2011; American Cancer Society, 2013; Ferlay et al., 2013).

   The median survival for patients having distant metastases is only from 6 to 9 months and the 5-year overall survival rate is less than 5% (Houghton et al., 2002). In accordance with the AJCC 2009 classification the thickness of the primary lesion, mitotic index and the presence of ulceration are important elements for determining the stage and prognosis (Balch et al., 2009). The relationship between survival and the diagnosis of superficial spreading melanoma (SSM), expression of nm 23 antigen, presence of metastases in regional lymph

[1]*Clinical Oncology Ward, Starkiewicz Specialised Hospital, Dabrowa Gornicza,* [2]*The Center for Diagnostic and Treatment of Skin Diseases, Katowice, Poland *For correspondence: dermatolog.pl@gmail.com*

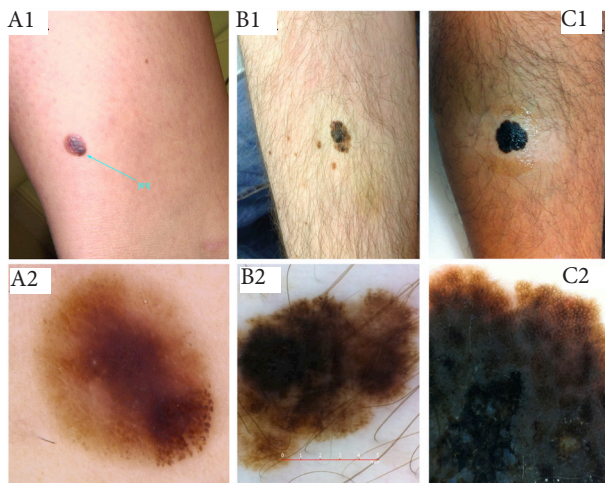*Maksymilian Gajda and Grazyna Kaminska-Winciorek*

Figure 1. Typical Skin Lesions. A1) Skin lesion since adolescence with a slight rapid changing in color within the skin lesion for 6 months. A2) Dermoscopy of suspected lesion revealed the presence of "island sign" characterized by excentric homogenous or spitzoid area located peripherally. Histopathology proved diagnosis of melanoma in situ in preexisting dysplastic nevus. B1) Asymmetrical enlargement of melanocytic lesion for 2 years, surgically excised and the diagnosis of superficial spreading melanoma (Clark II, Breslow 1 mm). B2) Dermoscopy showed asymmetrical arrangement of dermoscopic structures with multiple irregular structures of less brownish and blackish areas, with atypical pigmented network, irregular globules and streaks. C1) Slightly nodular, intense black lesion with rapid growth over 6 months. Subsequently performed histopathological examination was consistent with nodular melanoma (Clark III, Breslow 2 mm). C2) Dermoscopy showed a homogenous structureless blackish-whitish area within the nodular lesion corresponding with regression. Moreover, the abruptly cutted-off atypical melanocytic network was evident

nodes and Ki-67 was also presented (Kycler et al., 2002).

The aim of this paper was to identify the reasons for delayed diagnosis of melanoma and to facilitate the action leading to the detection of this disease at an early stage, crucial for improving survival rates. Search with combinations of keywords: "melanoma, delayed, late, diagnosis" was conducted among the PubMed and Google Scholar. Subsequently an overview of the literature from year 1979 to 2013 was done in correlation with data from Cancer Registries.

Causes of Delayed Diagnosis

As was mentioned previously, the diagnosis of locally advanced melanoma is associated with a much better prognosis. Besides the undeniable impact on prognosis, diagnosis at an early stage significantly reduces the cost of treatment, which was calculated to be 22-fold lower in case of melanoma in situ (Figure 1-A1,-A2) than for the T4b (Alexandrescu et al., 2009).

There are two main groups of causes for melanoma diagnosis and treatment delay. The first, related to the patient, includes the time from the moment of noticing suspicious lesion until seek specialist medical consultation. The second group is related to the diagnosis and therapy having an end point in implementing the appropriate treatment. Some authors distinguish more groups of causes
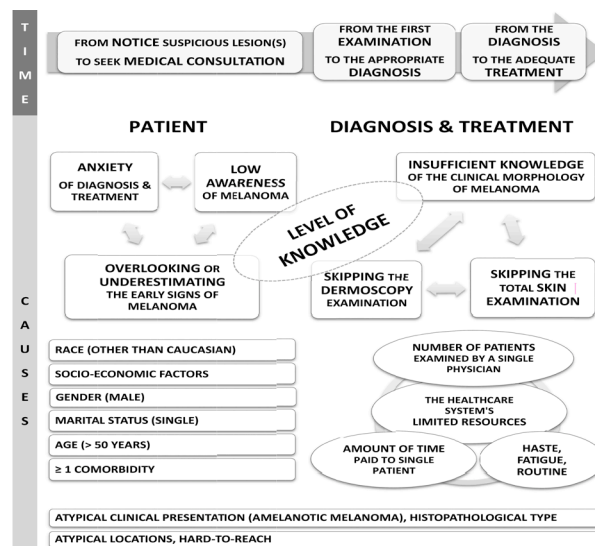

Figure 2. Causes of Delayed Diagnosis and Treatment of Melanoma. Classification in own modification

(Betti et al., 2003). The proposed classification, in our modification, was presented on Figure 2.

Causes for the delay associated with the patient

The laymen's anxiety of the treatment of skin lesions is a major cause of the late diagnosis of melanoma. There is still a belief of no need for surgical excision of congenital melanocytic (Karabeg et al., 2012). Patients do not seek a doctor until the skin lesion significantly raise their concerns (rapid change of shape or color, presence of bleeding or ulceration) (Krige et al., 1991; Kang et al., 2005). The delay associated with the patient (mean 9.8 months) was the major component of the overall delay in the start of treatment (average 11.1 months)-showed a prospective study in a group of 250 patients with stage I melanoma (Krige et al., 1991). As many as 16% of respondents postponed seeing a doctor for over a year. Later detected changes were localized in the head (scalp, face, ears area) with an average delay more than 17 months. The majority of cases was classified as Clark III and IV (34% and 44.8%, respectively). However, no correlation was demonstrated between the infiltration depth and recorded delay. Patients with I and II skin phototype were more likely to have tumors thicker than 1.5 mm than these with III and IV (27% and 14.6 %, respectively) (Schmid-Wendtner et al., 2002). There are some discrepancies in the relationship between delayed diagnosis and thickness of the lesion (Temoshok et al., 1984; Krige et al., 1991; Betti et al., 2003; Baade et al., 2006; Balch et al., 2009) and only few reports acknowledged it in relation to the all histopathological types (Temoshok et al., 1984; Betti et al., 2003). Superficial spreading melanoma (SSM) is the most common pathological variant for Caucasian (Figure 1-B1,-B2), however a correlation between the stage and late diagnosis has been shown only for nodular melanoma (NM) (Krige et al., 1991). It seems that the reason for the divergence may lie in the various early growth pattern forms: horizontal in case of SSM and vertical for NM (Figure 1-C1, -C2).

Rather than the hidden location, overlooking changes

in appearance of existing or omitting new lesions was reported to be the main reasons for the patient-related delay. In 26% of cases the attention was paid only to the late signs of melanoma such as bleeding or ulceration. Compared with the patients' self-reported symptomatic lesions, the incidental diagnosis of melanoma during a routine skin examination was associated with a lower depth. of invasion (0.89 *vs* 1.76mm, respectively) (Krige et al., 1991). Taking into an account that not all melanomas meet the clinical ABCD criteria (e.g., NM), adding the E parameter E ("evolving") was proposed in 2005. It was defined as the change in the thickness, shape or whether each new symptom such as bleeding, itching (Rigel et al., 2005). Other authors suggested more extended version in the form of "EFG" rules, which is an acronym of: suspicious clinical features: Elevated, Firm and progressive Growth (Giacomel et al., 2008).

Number of comorbidities correlated with mortality and the probability of later stage melanoma diagnosis. This relationship was most noticeable during the first year since diagnosis, particularly in patients with metastases (Grann et al., 2013).

Furthermore, unmarried persons were shown to have higher risk of the late stage melanoma diagnosis (McLaughlin et al., 2006).

Role of common superstitions

An incorrect assumption of the melanoma inability to grow in locations not exposed to UVR was noted. Although occurring less frequently, lesions developing in such locations are more likely to be diagnosed in more advanced stages (Matzke et al., 2009). Thus, raising the public awareness on this topic appears to be purposeful.

The common misconception that people of other races than white "cannot get sick from the melanoma" is still present. However, compared to Caucasians, the disease is diagnosed in these patients in more advanced stages (Byrd et al., 2004; Hu et al., 2006). Moreover, there has been an increase in the percentage of an early stage diagnosis for Caucasian population. The analysis of patients from region of northern Poland revealed a tendency for advances in early diagnosis of melanoma (Szczurkowska et al., 2012). However, the latency in diagnosis was noted in significant part of cases. The impact of the delay-related factors including male gender, age (over 50 years) and location (acral, trunk) was highlighted (Szczurkowska et al., 2012). Afro-Americans were more likely to be diagnosed with melanoma at a later stages (stage III or IV) than Caucasians (Byrd et al., 2004, Hu et al., 2006). Melanoma is a rare entity in the Asian population. Retrospective analysis presented the diversity of histopathological types of melanoma for Asian and Caucasian people living in Singapore (Lee et al., 2012). Acral lentiginous melanoma (ALM), the main type of the Asian people (50%) was diagnosed later (27 months of delay) and less frequently with stage I (25%) than the other histopathological types. The total delay in diagnosis and treatment of melanoma was bigger for Asians (22.8 *vs* 7.4 months, respectively) and the disease was diagnosed at an older age (62±18 *vs* 52±11 years) compared with Caucasians. The highest proportion of melanoma in situ (Hu et al., 2006) was noted

in the population of "Non-Hispanic Whites" (NHW), compared with Hispanics (H) and "Non-Hispanic Blacks" (NHB) among patients treated in the center of Miami-Dade County in USA (27%, 22% and 10% respectively). Locally advanced melanoma was mostly diagnosed in the NHW group (57%), less frequently in H (52%) and in NHB patients (38%), Regional or distant metastases were most often reported in group of NHB (52%) than in ethnic minorities (from 16 to 26%). More advanced stages of melanoma in ethnic populations could emphasize differences in secondary prevention in these groups. A skin examination was conducted by 8.9% of NHW and less frequently among NHB and H (6.2% and 3.7%, respectively). Granting to the National Health Interview Survey data, non-white populations are less probable to undergo screening for skin cancer (Saraiya et al., 2004). The diagnostic and therapeutic delays for Hispanic and Afro-Americans may be ascribable to the lower level of knowledge about melanoma and the risk of this disease downplaying. Low awareness was associated with less frequent skin self-examination and overlooking the signs of skin cancer (Pipitone et al., 2002). Therefore, lack of education concerning the risks and prevention methods was also stated to be the reason for late diagnosis of melanoma (Byrd et al., 2004). Educational efforts was conducted mostly among white, especially those of the most sensitive skin phototypes (Hu et al., 2006). Moreover, insufficient knowledge regarding skin cancer prevention (including screening methods) was demonstrated among Malaysian's medical science students (Al-Naggar et al., 2011). Similarly, nurses' knowledge on that field was proved to be insufficient (Andsoy et al., 2013). Training program conducted among the farmers from Turkey is an example of the positive change in attitude to the prevention of skin cancers (Malak et al., 2011).

Another, fairly widespread superstition stating that "lesion must not be touched" was the main reason (58.3% of diagnosed with melanoma) for avoidance of doctor's advice (Schmid-Wendtner et al., 2002). An innate nature of the lesion was indicated by a quarter of patients as the cause of the late notification. Similar percent of respondents did not report sufficiently early due to unnoticing changes. Less common causes were: fear of surgery (10%), recognition of lesions as harmless (4.2%). The inverse relationship between knowledge about melanoma and level of education was also noted. Better education was associated with a smaller thickness (Schmid-Wendtner et al., 2002). Poor education was associated with a greater delay in the diagnosis of melanoma (Richard et al., 2000a).

Delay associated with the diagnostic and therapeutic proccesses

To our knowledge, there are few prospective studies analyzing this type of delay. In the bulk of cases (74.7-87.6%) diagnostic and curative process is not the source of delay (Krige et al., 1991; Schmid-Wendtner et al., 2002). Nonetheless, an improper physicians' approach in the face of melanoma was noted (Richard et al., 2000b). Diagnostic difficulties were related to the type of melanoma, its location, an atypical clinical presentation, primarily

amelanotic melanoma, ALM and melanoma de novo. Lesions developing in hidden locations were diagnosed less often (mostly ALM). Dermatologist's advice was associated with lower response time and thinner tumors compared to the general practitioner's (GP) advice (Richard et al., 2000b). The reason of this situation could be that GPs are more likely to omit medical examination of the entire skin and have less specialist knowledge concerning skin lesions.

General practitioners should be also aware to use dermoscopy for the screening of skin cancer. The main goal of dermoscopy performed by nonexperts is to determine whether the lesion needs more detailed assessment by specialists. (Zalaudek et al., 2006).

Conclusions

Various factors have an influence on delay of melanoma diagnosis and, hence, prognosis, including the geographical and racial diversity of histopathological types. Furthermore, cultural and demographical conditions may lead to the differences in the availability of health care system, education and access to screening. Inability to recognize early changes, when it is usually possible their complete excision, could have serious clinical implications in the form of increased mortality from melanoma. General education program stressing early detection of melanoma can significantly lessen mortality (Smith et al., 1979). Educational campaigns focusing on skin self-examination and recognition of early melanoma's symptoms should lead to reduce of the delay. Recipients of such programs should be, especially, people at high risk of melanoma development (e.g., skin sensitive phototypes), less educated and older. Emphasizing the role of an early diagnosis and appropriate treatment is stressed. Moreover, medical professionals should be subject of constant education, to ensure the on-time and accurate diagnosis. Encouraging careful examination of the entire skin is essential also for the other than dermatology, medical specialties.

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