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ORIGINAL ARTICLE

Melanoma in children, adolescents and young adults: anatomo-clinical features and prognostic study on 426 cases

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Abstract

Purpose This study was conducted to determine the difference in anatomo-pathological and prognostic features of cutaneous melanoma in children, adolescents and young adults.

Methods This is a retrospective review on 383 young patients ≤ 39 years of age with cutaneous melanoma, in a period from 2006 to 2016 in Area Vasta Nord Ovest, Tuscany, Italy. We subdivided patients in three groups (children ≤ 14 years, adolescents 15–21 years, young adults 22–39 years). We correlated all the anatomo-pathological parameters with age groups.

Results We identified a total of 426 cases of cutaneous melanoma on an overall total of 383 patients. Mean age at diagnosis for all the patients ≤ 39 years of age was 31.2 years: in group A was 11.2 years, in group B 19.2 years and in group C 32.5 years. Incidence, in the subjects between 0 and 14 years, is 14 cases per million inhabitants, between 15 and 21 years of 145, and between 22 and 39 years of 394. Global incidence was 1.6 case per million for group A, 8.9 cases per million for group B, 105 cases per million for group C. No statistically significative correlation could be described for clinical parameters and age groups.

Conclusions Incidence of melanoma in our casuistry results as the highest in the world. These data open new study for this kind of cancer.

Keywords Adolescent · Children · Melanoma · Young adult · Surgery

Introduction

In the last three decades, the incidence of melanoma is rapidly increasing, both in the adults and the pediatric population [1, 2]. The incidence appears to be increasing more rapidly in youngsters (age 21–39 years) and middle-aged adults (age 40–60 years), especially in women [3, 4]. In fact, from 1973 to 2004, the age-adjusted annual incidence of melanoma in men aged 15–39 years increased from a 4.4 to 7.7 cases per 100,000 men, compared to an increase from 5.5 to 13.9 cases per 100,000 in women population [5]. Although melanoma in pediatric and adolescent patients is rare, accounting for only 1–4% of melanomas and for 1–3% of all pediatric malignancies, it is the second most common form of cancer in this age group, after thyroid cancer [6]. The biological behaviour of melanoma in young age appears to be different from the adults' one, even though, in literature, results seem to be contradictory; pediatric melanoma, particularly in pre-pubertal children, adolescents and young adults, is thought to be a biologically unique disease entity that manifests with different anatomo-clinical features. In fact, compared to adults, many youngsters present with higher rates of lymph node metastasis, thicker lesions, and more advanced stage of disease. Even referring to various studies, data regarding survival rates are not in accordance among them [7–12]. Current treatment strategies for pediatric melanoma take their origins from an adaptation of guidelines that mainly refer to adults, which are based on

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trials that only rarely include pediatric patients. At parity of stage with adults, the survival rate for children is better than adults's one [13]. Therefore, the survival rate at 5 years for patients under the age of 20 results in a 100% for melanoma in situ, of 96.1% for localized invasive forms, 77.2% for those with regional involvement, and 57.3 for those with distant metastases, while the overall survival rate was 90.9% [14]. Considering the conflictive nature of data reported in literature for what concerns anatomo-clinical and prognostic features in various age groups, we performed an analysis on 426 cases of melanoma, diagnosed between 2006 and 2016, divided in three age ranges: under 14 years, from 15 to 21 years, and ultimately from 22 to 39 years. The results of our study contribute to improve scientific knowledge for this particular form of skin cancer, the most deadly one among skin cancers in relation to the age of onset, and to speculate about the reasons for such increasing incidence trends.

Materials and methods

We reviewed our database of melanoma patients treated from 2006 to 2016 at: "Melanoma and Skin Cancer Unit at AVNO (Area Vasta Nord Ovest)", Tuscany, Italy. We selected those with an age ≤ 39 years. We divided these patients into three groups: group A (children ≤ 14 years), group B (adolescents 15–21 years of age) and a group C (young adults 22–39 years of age). The eligibility criteria of patients for this study included established primary diagnosis of melanoma and adequate follow-up items of information. Patients with both in situ and invasive melanoma were included. Patients with non-cutaneous primary sites were excluded. Each patient underwent a baseline evaluation, which included medical history assessment, physical examination, and laboratory studies. The stage of the patients' tumor was properly determined at their first presentation for therapy at our unit. We used the melanoma staging system included in the 6th–7th–8th edition of "American Joint Cancer Committee" (AJCC) cancer system manual. The features described were the date of diagnosis, the T stage, anatomical site, lesion diameter, Clark levels, histotype, ulceration, regression, mitosis, intralesional lymphoid infiltrate, perilesional lymphoid infiltrate and vascular invasion. The reports of sentinel lymph node biopsy (SLNB) related to these tumors were also described, recording their responses. Average annual incidence rates by age group, gender, location and invasiveness were calculated using data on the resident population provided by Istituto Nazionale di Statistica (ISTAT), over the period taken into examination. Calculations of incidence rate were made taking into consideration both the single age range and the global population as denominations (rapported to one million inhabitants). After a mean 5 years ± 9 months of follow-up (range 2–11 years), the survival rate data were obtained by reading the medical records of these patients until tracing, if it occurred, the moment of death.

Statistical analysis

Categorical and continuous data were described by frequency (absolute and relative) and median (range), respectively. To compare qualitative variables, chi-square test and Fisher exact test were used, whereas to analyze quantitative variables Kruskal–Wallis test was applied. Differences were considered significant at $p < 0.05$. All analyses, descriptive and inferential, were performed by SPSS v.24 technology.

Results

A summary of demographic, pathologic characteristics of primary tumors for the whole cohort of patients, T stage, diameter of the macroscopic, Clark's levels, histological typization, ulceration, regression areas, mitoses, lymphoid intralesional infiltration, lymphoid perilesional infiltration and vascular invasion are reported in Tables 1 and 2. The total is 383 patients ≤ 39 years of age, from 2006 to 2016. Patients were subdivided into three groups: group A (children ≤ 14 years old), 6 cases (1.6%); group B (adolescents from 15 to 21 years of age), 32 cases (8.3%); group C (young adults, between 22 and 39 years of age), 345 cases (90.1%). 426 newly diagnosed cutaneous melanoma were identified: 224 in situ (52.6%), while 202 (47.4%) invasive forms. Mean age at diagnosis for all the patients ≤ 39 years of age was 31.2 years: in group A was 11.2 years, in group B 19.2 years and in group C 32.5 years. Regarding the sex of the patients, in the whole group of recordings, 242 cases (56.8%) were females, while 184 cases (43.2%) regarded males; in group A, 3 cases (50%) regarded males and 3 (50%) females; in group B, 22 cases (66.7%) females and 11 cases (33.3%) were males; in group C, 217 cases (56.1%) were females while 170 cases (43.9%) were males. In the unique group 0–39, 256 (60.1%) interested the trunk, 111 (26.1%) the inferior limbs, 48 (11.3%) the superior limbs, and 11 cases (2.5%) recognized the head and neck district as the site of origin of the neoplasm. In group A, 3 (50%) cases interested the superior limbs, 2 (33.3%) the inferior limbs, and 1 case (16.7%) the trunk; in group B, 22 (66.7%) regarded the trunk, 4 (12.1%) the superior limbs, 6 (18.2%) the inferior ones, and 1 case (3%) the head and neck district; in group C, 233 (60.2%) interested the trunk, 103 (26.6%) the inferior limbs, 41 (10.6%) the superior limbs, while 10 cases (2.6%) interested the head and neck district. Mean diameter of all the lesions was 0.61 cm, while thickness staging (from which originates T stage) is 0.84 mm. The number of patients submitted to intervention for the asportation of

Table 1 Clinical characteristics of the population of 0–39 years (period analyzed: Jan 2006–Dec 2016)

Characteristics	Statistics
Age (years)	33 (6–39)
Gender	
Male	184 (43.2%)
Female	242 (56.8%)
Diagnostic period	
Jan–Mar	103 (24.2%)
Apr–Jun	127 (29.8%)
Jul–Sep	91 (21.4%)
Oct–Dec	105 (24.6%)
Anatomical site	
Head neck	11 (2.5%)
Trunk	256 (60.1%)
Upper limbs	48 (11.3%)
Lower limbs	111 (26.1%)
Diameter (cm)	
0–0.5	221 (51.9%)
0.51–1	165 (38.7%)
1.01–1.5	33 (7.7%)
1.51–2	5 (1.2%)
2.01–2.5	2 (0.5%)
Stage T	
pTis	225 (52.8%)
pT1	154 (36.2%)
pT2	34 (8%)
pT3	7 (1.6%)
pT4	6 (1.4%)
Sentinel lymph node	
Positive	11 (15.7%)
Negative	59 (84.3%)
5-year survival	
Alive	420 (98.6%)
Dead	6 (1.4%)

426 cases for 383 patients. Statistics: median (range) or frequency

Table 2 Histological features of invasive forms of the population of 0–39 years (period analyzed: Jan 2006–Dec 2016)

Characteristics	Statistics
Histological type	
Superficial spreading	190 (94%)
Nodular	6 (3%)
Acral lentiginous	2 (1%)
Spitzoid	3 (1.5%)
Nevoid	1 (0.5%)
Clark levels	
II	104 (51.5%)
III	63 (31.2%)
IV	33 (16.3%)
V	2 (1%)
Ulceration	
Absent	181 (89.6%)
Present	21 (10.4%)
Regression	
Absent	155 (76.7%)
Present	47 (23.3%)
Mitosis	
<1	102 (50.5%)
≥ 1	100 (49.5%)
Tumor-infiltrating lymphocytes (TIL)	
Absent	136 (67.3%)
Present (non-brisk)	45 (22.3%)
Present (brisk)	21 (10.4%)
Perilesional lymphoid infiltrate	
Absent	54 (26.7%)
Present	148 (73.3%)
Vascular invasion	
Absent	201 (99.5%)
Present	1 (0.5%)

202 invasive cases for 194 patients. Statistics: median (range) or frequency

sentinel lymph node was 70 (16.4%): 11 (15.7%) were positive, while 59 (84.3%) were negative. Moreover, it is important for us to report that all those recorded cases occurred in the coastal area of Northern Tuscany, spacing from Livorno (336 cases, 78.9%) to Massa Carrara (26 cases, 6.1%), and including the area of Lucca and Pisa (34 cases, 8%), while 30 cases (7%) came from zones not reported above. Using ISTAT data on the population residing in the province of Livorno (taking into account the censuary reconstruction), the incidences of melanoma were calculated in the period 2006–2016 in the three age groups covered by our study. The data obtained showed an incidence, in the subjects between 0 and 14 years, of 14 cases per million inhabitants (13 in males and 14 in females), between 15 and 21 years of 145 (102 in males and 191 in females) and between 22 and 39 years of 394 (344 in males and 444 in females). The relationship with the global population is (per million inhabitants) of 1.6 for group A, 8.9 for group B and 105 for group C. The correlation between the month of insurgence during the year when the melanoma was diagnosed, sex, and histological features among the three groups of patients in different year range did not highlight statistically significative variations (Tables 3, 4). Survival rate at 5 years in our study population reaches 98.6%. Of the deceased patients, six (1.4%) were in the first 3 years from diagnosis, due to systemic metastases of melanoma. All the patients belonged to group C (age range between 22 and 39 years); four males (66.7%) and two females (33.3%), with a mean age of 33.8 years (minimum 29, maximum 39); localization of melanoma was in three

Table 3 Association between clinical factors and groups

Factors	Group A	Group B	Group C	*p* value
Age	7.5	20	34	< 0.0001
Gender				0.471
Female	3	11	170	
Male	3	22	217	
Diagnostic period				0.028
Jan–Mar	1	15	87	
Apr–Jun	3	7	117	
Jul–Sep	0	2	89	
Oct–Nov	2	9	94	
Anatomical site				0.074
Head neck	0	1	10	
Trunk	1	22	233	
Upper limbs	3	4	41	
Lower limbs	2	6	103	
Diameter				0.333
0–0.5 cm	4	20	197	
> 0.51 cm	2	12	190	
Stage T				0.512
pTis	2	18	205	
pT1	2	12	140	
pT2 + pT3 + pT4	2	3	42	
Sentinel lymph node				0.856
Positive	(0)	0	11	
Negative	(0)	4	55	
5-year survival				0.737
Alive	6	33	382	
Dead	0	0	6	

Group A: 0–14 years; group B: 15–21 years; group C: 22–39 years. Statistics: median or absolute frequency

cases (50%) in the trunk, while in the other three cases (50%) in the lower limbs, with stage disease: pT2b 4 cases, pT3a 1 case, pT3b 1 case. All the cases were submitted to sentinel lymph node, of which four with a positive result, while two negative.

Discussion

The incidence of melanoma in our cohort study, in patients under 39 years of age, increases dramatically with age, passing from 14 to 145 to 394 cases per one million inhabitants, respectively, in the three groups of age (patients from 6 to ≤ 14 years, from 15 to 21 years and from 22 to 39 years). Compared to the global incidence data regarding melanoma, we can find a rate of 1.6 cases per million in group A, 8.9 per million in group B and 105 cases per million in group C. Incidence data regarding melanoma in our population study result definitely elevated in comparison with other areas of Tuscany and the remaining Italian territory (Italian Association Registers Tumors). In fact, in Tuscany a mean of 140 cases per million inhabitants is reported for females, while 190 cases for males according to ISPO data (Institute for Oncological Prevention). At a national level we record a mean of 13.6 cases yearly in females, and 14.6 cases in males [15]. If we look at the literature [16], we see how these values are clearly higher than European and non-European rates [2, 17]. In children between 0 and 14 years, there is an incidence in Europe that oscillates between 0.6 cases per million inhabitants of Bulgaria to 4.1 cases of Malta. In the US this incidence is 1.9 cases per million, in Brazil 0.8, while in Australia, the nation with highest melanoma incidence rate, 3.2 cases (especially with a peak of 6.6 in Queensland). In adolescents between 15 and 19 years, incidence values oscillate in Europe between 2.8 cases per million inhabitants of Bulgaria to 36.5 cases in Iceland. In extra European countries like the US, the incidence is of 1.41 cases per million, in Brazil of 2.5 and in Australia of 48.5, with a peak of 87 in Queensland. We suspect multifactorial reasons for the increase in melanoma detection in children, adolescents and young adults, even though they are still unlikely. Although congenital melanocytic nevi are considered high-risk lesions for malignant transformation, most young patients with melanoma have no family history of disease and no history of predisposing risk factors including dysplastic nevus, syndrome pigmented xeroderma immunosuppressed and with giant congenital nevi [18–24]. The rapidly increasing incidence is not likely explained by genetic factors alone or increased ultraviolet exposure [14, 25, 26]. Several studies report an association between environmental pollution, and the development of cutaneous melanoma. Jae-Wook Lee et al. [27] in his study highlighted an enhanced melanoma tumor development and growth in mice exposed to di-(2-ethylhexyl)phthalate (DEHP). DEHP in an endocrine disruptor which acts as a xenoestrogen; thus resulting in a toxic effect for both human and animal health, resulting in toxicity for the reproductive and developmental systems and in a carcinogenic effect; it is the most commonly used phthalate in manufacturing of a wide variety of polyvinyl chloride (PVC) are contained in medical and consumer products such as toys, perfumes and skin moisturizers [28, 29]. Due to his activity as an estrogenic stimulating agent, inert paraben esters (*p*-hydrobenzoic acid), contained in body care cosmetics, could encourage the development of melanoma [30]. Besides an increase in incidence and death rate due to melanoma has been reported in petroleum refinery workers [31–34]. Therefore, it is interesting to signal that the geographical area of our study, the coastal area of Northern Tuscany, is the site of siderurgical implant and even oil refineries. Differences in melanoma incidences related to sex are also present and are more pronounced in the 15–21-year-old age range, and tend to be higher in girls than boys; these

Table 4 Association between histological factors of invasive forms and groups

Factors	Group A	Group B	Group C	*p* value
Histological type				0.512
Superficial spreading	4	15	171	
Other	0	0	9	
Clark levels				0.791
II	2	7	95	
III	0	5	58	
IV + V	1	2	32	
Ulceration				0.292
Absent	4	15	162	
Present	0	0	21	
Regression				0.643
Absent	3	10	142	
Present	1	5	41	
Mitosis				0.959
< 1	2	7	93	
≥ 1	2	8	90	
Tumor-infiltrating lymphocytes (TIL)				0.764
Absent	2	11	123	
Present (non-brisk)	1	2	42	
Present (brisk)	1	2	18	
Perilesional lymphoid infiltrate				0.997
Absent	1	4	49	
Present	3	11	134	
Vascular invasion				0.948
Absent	4	15	182	
Present	0	0	1	

Group A: 0–14 years, group B: 15–21 years, group C: 22–39 years. Statistics: median or absolute frequency

differences might be attributed to differing patterns of sun exposure, suggesting a potential sex-based biological difference in the development and behaviour of melanoma related to age at menarche, progesterone levels, testosterone levels and estrogenic status [35–38]. Our study does not highlight any significant difference, between males and females, related to age group. The incidence of melanoma by anatomic localization is not uniform per age and sex. In children, melanoma is equal across all anatomic locations, with the exceptional of truncal melanomas being especially rare in 0–4-year-olds. On the other hand, incidence in patient age 10–19 years is highest in the trunk (one of the most sun exposed in the body), implying that there may be changes in subjective sun exposure; reports for children and adolescents show a major incidence of melanoma in the trunk for males and in lower limbs in females [1, 14, 39]. The statistical analysis in our group study did not report any prevalence of localization. There may be often difficulties in differentiating from anatomo-pathological point-of-view cases of melanoma; the understanding of pediatric melanoma is complicated by challenges such as the similarity, thus difficulty in distinguishing a malignant melanoma from a spitzoid neoplasm [40, 41]. Gill et al. [42] evaluated the genetic behaviour of spitzoid melanoma and found that mutations in B-RAF, N-RAS, and H-RAS, commonly found in melanoma, were not identified in spitzoid melanoma or Spitz nevi. Clinical histopathological features of melanoma include thickness evaluation of the lesion, the presence or absence of histologic ulcerations, dermal mitotic rate, peripheral and deep margin status of the biopsy, and microsatellitosis [7]. In younger age groups, the melanoma with good prognostic indicators has the following features: thin melanoma, no ulceration, no lymph node involvement or no distant metastases. Melanoma with worse prognostic indicators is the one with tumors thicker > 4.01 mm, ulceration, regional lymph node involvement and distant metastases [43]. Stage of disease, thickness and ulceration were found to be highly significant predictors of overall survival among patients with pediatric melanoma similar to adult melanoma [44]. Despite the presence of high-risk features and advanced stage of disease, children aged ≤ 10 years old were not found to have worse survival outcomes compared with their

adolescent counterparts aged > 10 years. Also, the presence of mitotic activity in the primary tumor did not correlate with significant differences in survival [44]. However, Lange et al. [36] reported for patients with lesions thicker than 1.5 mm, that patients aged 1–19 years old had a significantly better overall survival rate than patients aged 20–24 years. However, those studies [45, 46] show worse survival rates for children aged from 1 to 9 years than for people aged from 10 to 24 years; other studies show a more favorable prognosis for younger patients and others demonstrate no difference in survival between age groups. Aldrink et al. [13] found no difference between patients younger than age 12 compared to adolescent patients with regard to primary tumor location, thickness, or Clark level. Other authors [9, 47] have also evaluated the differences between pediatric and adult patients with melanoma, with better stage-specific survival in pediatric patients. A positive lymph node dissection was found to be correlated with poorer overall survival. Patients with negative sentinel lymph node biopsy (SLNB) had survival rates similar to those without undergoing SLNB. Besides, the prognostic impact of lymph node metastases on survival appears to be lower among children aged ≤ 10 years [44], although Howman et al. [48] highlighted that pediatric and adolescent patients have a higher lymph node positivity, and they unexpectedly have a better prognosis than older patients. In our casuistry, we did not notice significative patterns of melanoma-specific characteristics, such as the anatomical side, diameter, stage T, sentinel lymph node positivity, histological type, Clark levels, ulcerations, mitosis, tumor-infiltrating lymphocytes, perilesional lymphoid infiltrate and vascular invasion, in the three age groups taken into examination. Even survival at 5 years did not result statistically significant, even though deceases were reported only in the group of patients aged between 22 and 39 years.

Conclusion

In this study, we tried to identify a possible existence of anatomo-clinical and prognostic differences in the group of children, adolescents and young adults, basing on a high number of cases collected in one center only. All the patients came from the northwestern zone of Tuscany, Italy. We highlighted an elevated incidence rate, higher than other zones of Tuscany and Italy, but dramatically superior even to other European, north-American nations, or to Queensland; the Australian state was considered to be the highest melanoma incidence region in the world. The presence in this geographical area of heavy industries with the likelihood of environmental pollution opens up an important scenario for further studies about the etiopathogenesis of this rare form of cancer. Our data did not show a significant correlation between anatomo-clinical parameters and prognosis in the three examined age groups. The limits of our study are a low number of cases in children and adolescents, and a rapport with a more elevated number of cases in young adults. The low number of patients under 21 years of age limited notably the survival rate analysis; that is because melanoma is a relatively rare disease in teenage population and it is difficult to collect adequate numbers of patients.

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