Melanoma em Idade Pediátrica: Epidemiologia, Patogénese, Diagnóstico e Tratamento

J. M. Neves[1], B. Duarte[1], M. J. Paiva Lopes[1]
[1]Department of Dermatology and Venereology, Hospital de Santo António dos Capuchos, Centro Hospitalar Universitário de Lisboa Central, Lisboa, Portugal

RESUMO – O melanoma é o cancro cutâneo mais comum da idade pediátrica. No entanto, é extremamente raro nesta população, sendo ainda mais raro nas crianças com menos de 11 anos. O diagnóstico é frequentemente difícil, devido à sua raridade e apresentações atípicas.
Existem três subtipos de melanoma em idade pediátrica: melanoma Spitzoide; melanoma que emerge de nevo melanocítico congénito e o melanoma convencional. O melanoma congénito pode ocorrer, embora seja excepcionalmente raro, não constituindo um subtipo distinto de melanoma. O melanoma Spitzoide é o subtipo mais comum que afecta crianças com idade inferior a 11 anos. Embora apresente características locais agressivas, com envolvimento ganglionar frequente, acarreta um prognóstico excelente. A ocorrência de transformação maligna de nevos melanocíticos congénitos apresenta uma grande variabilidade, de acordo com a sua dimensão, número e afeção concomitante do sistema nervoso central. A vigilância e tratamento desta transformação maligna é problemática, sendo associada a pobres resultados. Nos adolescentes, o subtipo de melanoma mais comum é o convencional (tipo adulto). Contrariamente à população adulta, a maioria dos melanomas pediátricos convencionais tem origem em nevos pré-existentes, seguindo a epidemiologia e factores de risco associados ao do adulto. Não existem orientações específicas para a gestão e tratamento do melanoma pediátrico, pelo que esta doença é tratada de forma semelhante ao melanoma do adulto.
PALAVRAS-CHAVE – Criança; Melanoma/diagnóstico; Melanoma/epidemiologia; Melanoma/etiologia; Melanoma/tratamento; Nevo de Células Epitelioides e Fusiformes; Nevo Pigmentado.

Pediatric Melanoma: Epidemiology, Pathogenesis, Diagnosis and Management

ABSTRACT – *Pediatric melanoma is the most common skin cancer in children. However, it is extremely rare this population, being even rarer in younger than 10 years of age. Its diagnosis is often difficult, due to its rarity and atypical presentations.*
There are three main subtypes of pediatric melanoma: Spitzoid melanoma, melanoma arising in a congenital melanocytic nevus and conventional melanoma. Congenital melanomas exist and are exceptionally rare, although they do not constitute a different subtype of melanoma. Spitzoid melanoma is the most common subtype affecting children younger than 11 years. Despite presenting with local aggressive features and frequent nodal involvement, it encompasses an excellent prognosis. The risk of malignant transformation of congenital melanocytic nevi varies widely accordingly to the projected adult size, number, and concomitant abnormalities found in the central nervous system. The surveillance and treatment of melanoma arising in a congenital melanocytic nevus is challenging, enclosing poor outcomes. In adolescents, the most common subtype is the conventional (adult-type). Contrary to the adult population, the majority of conventional pediatric melanoma arises from previous nevi but follows the general adult epidemiology and risk factors. Specific guidelines for management of pediatric melanoma do not exist and it is treated similarly to melanoma in the adult.
KEYWORDS – *Melanoma/diagnosis; Melanoma/epidemiology; Melanoma/etiology; Melanoma/therapy; Nevus, Epithelioid and Spindle Cell; Nevus, Pigmented.*

Correspondência: José Miguel Oliveira das Neves
Hospital de Santo António dos Capuchos
Centro Hospitalar Universitário de Lisboa Central
Alameda de Santo António dos Capuchos
1169-050 Lisboa, Portugal
E-mail: josemoneves@gmail.com
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1-INTRODUCTION

Cutaneous melanoma is a common malignancy in adults,[1] responsible for the majority of the deaths caused by skin cancer. Its overall frequency is increasing worldwide,[2] with an annual incidence rate of 20 per 100 000 people.[1] In spite of being the most common skin cancer in the pediatric population and accounting for 7% of all cancers in 15-19 year old age group,[3] it is extremely uncommon in this population. Less than 1% of all melanomas occur in patients younger than 20 years old,[4] less than 0.4% occur in prepubertal patients[5] and only 0.1% in patients younger than 10 years of age.[6] According to the European Cooperative Study Group for Pediatric Rare Tumors that defines tumors as rare if their incidence is below 1 case/million/year, melanoma is considered rare below 10 years of age (0.7-0.8 cases/million/year) but not between 15-19 years (>10 cases/million/year).[1] The average age of diagnosis is 13.3 years.[6] Though the incidence of melanoma in children younger than 10 years has remained stable, the incidence in adolescents is increasing at a rate of 2.9% per year, in the USA over the past 3 decades.[7]

Several risk factors for pediatric melanomas have been identified. Albeit no considerable sex-based differences are verified in the 0-9 group, an increasing disparity between genders – with higher risk towards white females - is found through adolescence into early adulthood.[8] A similar variance is observed in the relationship between Fitzpatrick phototypes and age, as melanoma incidence between white and non-white ethnicities starts slowly to diverge by 5–9 years of age, ultimately reaching a 40-fold higher risk in the former by the age of 20.[9] Ultraviolet light exposure, mostly due to sunlight, is especially linked with the development of melanomas in white adolescents. A high number of moles (>100 with >2 mm diameter) is regarded as the strongest risk factor in this population.[10] Preexisting conditions known to be associated with melanoma (dysplastic nevus syndrome, congenital melanocytic nevi (CMN), xeroderma pigmentosa, immunodeficiency, prior malignancy and radiation therapy) seem to be more prevalent in children up to 10 years of age[10,11] Familial cases account for 1% of pediatric melanomas.[10]

Pediatric melanoma presents a clinical and histopathological challenge due to its rarity and atypical presentations. Up to 60% of diagnoses in patients younger than 10 years and 40% in patients with 11–19 years do not meet traditional ABCDE criteria (asymmetry, border irregularity, color variation, diameter > 6 mm and evolution).[5] A modified ABCDE criteria was proposed to evaluate suspicious skin lesions in children and adolescents: amelanotic, bleeding or bump, color uniformity, de novo and any diameter, and evolution.[5] Due to the tendency to be amelanotic, pediatric melanoma can be, in a first stage, misdiagnosed with benign skin lesions.[5,10] Pediatric melanoma appears to have a more favorable prognosis than adult melanoma of a similar stage, with a 10 years overall survival of 70% to 80%.[7]

2. PEDIATRIC MELANOMA SUBTYPES

Melanomas affecting the pediatric age can be classified in three subtypes: Spitzoid melanoma, melanoma arising in congenital melanocytic nevi (CMN), and conventional (adult-type) melanoma. In general, melanomas presenting in children younger than 11 years have higher rates of ulceration, thickness, mitotic activity and positive sentinel lymph nodes, albeit this findings do not translate into higher mortality rates.[9] Moreover, they are more often located on the head and neck region and on the extremities and belong to the Spitzoid subtype.[9,12] In adolescents (≥11 years), conventional melanoma is the prevailing subtype,[13] which shares morphologic (superficial spreading and nodular) and molecular features with adult melanoma and is mainly located on the trunk.[4,12] Acral lentiginous melanoma and lentigo maligna types are exceedingly rare.[9] Melanomas can also develop in uterus, although this is extremely rare and does not constitute a different subtype of melanoma.

2.1. Spitzoid melanoma

2.1.1 Epidemiology and pathogenesis

The Spitzoid tumors encompass a biologic spectrum of spindle and epithelioid melanocytic proliferations which include the Spitz tumor without atypia (classic Spitz nevus), the atypical Spitz tumor and the Spitzoid melanoma.[14] Most Spitz nevi do not evolve into melanoma.[15] Although Spitzoid tumors can affect all age groups, they usually arise during childhood or adolescence.

Spitzoid melanomas are the most common subtype of melanoma found in patients younger than 11 years of age.[9,15] As such, environmental exposures and UVR are likely to have a small role in their development; in most cases, chromosomal structural rearrangements are the initiating genomic event. Mutations affecting the most commonly involved genes (*ROS1, NTRK1, NTRK3, ALK, BRAF, MAPK, MET, RET*) have been observed in more than half of Spitzoid neoplasms. The result is the production of aberrant fusion proteins, which constitutively activate and stimulate oncogenic pathways. These genomic fusions are observed across the spectrum of Spitzoid tumors, highlighting that they are not indicative of malignant behavior.[9] By contrast, homozygous deletions in chromosome 9p21 have been linked to Spitzoid melanoma with an increased risk of advanced disease, distant metastases, and death.[16] TERT promoter mutations are usually absent and their presence is highly correlated with the development of metastatic disease.[17] The presence of such mutations worsens the outcome of patients with Spitzoid neoplasms, although they still seem to have a better prognosis than similarly staged conventional melanomas.[18] Typically, BRAF or NRAS mutations do not occur in Spitzoid tumors.[13]

2.1.2 Diagnosis

Clinically, Spitzoid tumors present as a deeply pigmented or amelanotic, pink / reddish, flat- or dome-shaped papule or nodule, located on the head, neck and distal extremities.

Three dermoscopic patterns are suggestive of a Spitz nevus: starburst pattern, regularly distributed dotted vessels and globular pattern with reticular depigmentation.[19] Dermoscopically asymmetric lesions with spitzoid features should be excised, in any age, to rule out melanoma.[9,19] All spitzoid--looking nodules and lesions developing after the age of 12 years should also be considered for excision. On the other hand, a symmetrically looking spitzoid lesion, below the age of 12 years can usually be safely followed up, as the probability of being a melanoma is extremely low.[19] On histology, Spitzoid melanomas present abundant eosinophilic cytoplasm, high degree of nuclear atypia, with ulceration, epidermal consumption, brisk deep atypical mitotic activity, and poor maturation.[9] The distinction between benign Spitzoid tumors and Spitzoid melanomas can be challenging and clinical, morphological and molecular criteria must be employed by an expert dermatopathologist.[9,19,20] Immunohistochemical assays for BRAF and NRAS can be performed, and the presence of these mutations support the diagnosis of a conventional melanoma.[9] A novel technique, using imaging mass spectrometry, discriminated correctly Spitz nevi from Spitzoid melanomas with 97% sensitivity and 90% specificity, although this approach has not yet been clinically validated.[21]

2.1.3 Management

At the time of the excision, Spitzoid melanomas tend to be advanced, usually presenting with a higher Breslow depth and mitotic activity, as well as more frequent nodal disease. Nevertheless, their overall prognosis is excellent (five-year survival higher than 95%).[9] Thus, the decision to perform a sentinel lymph node biopsy (SLNB) should be considered carefully.[9] In a systematic review published in 2014,[22] including 541 patients with atypical Spitz tumours, SLNB performed in more than half of the patients (n= 303; 56%) was positive in 119 (39%). When comparing the group of patients who had positive SLNB and the patients who were treated with wide local excision alone, no significant difference in survival was recorded and 99% of the patients did not show disease progression in a 5-years follow-up.[22] Due to the uncertain prognostic potential of SLNB, limited benefit of lymph node dissections and high morbidity potential, management of an atypical spitzoid tumor should be limited to a wide local excision and long-term follow-up.

2.2. Melanoma arising in CMN

2.2.1 Epidemiology and pathogenesis

CMN affect approximately 1% of neonates.[9] They are classified, according to their projected adult size (PAS), as small (< 1.5 cm), medium (1.5-20 cm) and large or giant (>20 cm).[9,23,24] Giant CMN are present in only 1/20 000 infants and are usually associated with other smaller CMN.[23] CMNs are the result of a somatic mutation in utero, leading into a mosaicism.[23] If the mutation occurs early, it can hit a multipotent cell, leading into multiple cutaneous CMN, with variable sizes and potential involvement of other organ systems.[23] Giant or multiple CMN are often complicated by the presence of neurological abnormalities (e.g. melanosis of the brain parenchyma and leptomeninges), with development of symptomatic neurocutaneous melanocytosis in 6% to 11% of patients with a giant CMN. The association of a giant CMN or two medium-sized nevi, with multiple satellite nevi and neurocongenital melanosis, constitutes the congenital melanocytic nevus syndrome.[23] NRAS mutations are identified in up to 80% of the giant CMN, and are almost universal when the PAS is >60 cm.[25] Moreover, it has been suggested that NRAS mosaicism, in particular postzygotic mutations in codon 61, is associated with the onset of neurocutaneous melanocytosis. Mutations in BRAF occur in approximately 5% –15% of small CMN.[9,26] The presence of MC1R variants has been associated with increased frequency and size of CMN.[9]

The overall risk of malignant transformation of a CMN of any size is estimated to be less than 1%. It varies substantially depending on the nevus size and number of nevi, varying from the almost null risk of a common acquired nevus, in a single small CMN, to a lifetime risk of 10% –15%, in giant CMN with satellite lesions.[9,23] UVR is likely to have no role in the malignant transformation.[9,23] A meta-analysis, including a total of 2578 patients (432 patients with giant CMN), showed that only 2% of the patients developed melanoma and, within this group, 74% had CMN >40 cm (PAS) and 94% had satellite lesions.[3] In a prospective study, which followed 57 patients with giant CMN, the patients that suffered malignant transformation presented with a giant CMN in an axial location, with more than 50 satellite lesions.[24] CMN-melanoma may arise from leptomeningeal or brain parenchymal melanocytic deposits.[27] Primary CNS melanomas account for 33% to 50% of all melanomas occurring in patients with giant CMN.[23,27,28] Kinsler *et al* followed 450 patients with multiple CMN, of whom ten developed melanoma, seven within CNS. The incidence of melanoma (of any location) in children with CMN > 60 cm (PAS) was 8%, and only 1% in the other phenotypic groups.[23] The strongest statistical predictor of melanoma development was an abnormal CNS screening with magnetic resonance imaging (MRI), which was performed in all patients within the first year of life. About 12% of the children with abnormal CNS features developed melanoma, contrasting with only 1% in those with a normal MRI.[23]

2.2.2 Diagnosis

During the long-term follow-up, it is of key importance to distinguish malignant proliferations from benign growths within CMN. Two benign clinical presentations are identified: classic proliferative nodules and neuroid overgrowth.[26] Overall, classic proliferative nodules have a well-defined edge, a round outline and a smooth surface, often lighter than the surrounding CMN. They tend to grow over a period of weeks and then stabilize, normally not exceeding 2 cm. On histology, there is no necrosis, low cytological atypia and no increased proliferative activity. Neuroid overgrowth areas have poorly defined edges, usually ovoid and have a soft consistency. Normally, they are not present at birth, but can

develop at any point in childhood and their expansion may take several years, with the potential to reach over 20 cm. Pathologically, they are characterized by nodules of spindle cells within a myxoid stroma, without significant atypia.[23]

Melanoma arising in giant CMN often presents as a rapidly growing nodule arising in the deep dermis or subcutaneous tissues.[9,13,23] Dermoscopy is not as helpful as in other suspicious lesions.[23] In the presence of clinical suspicion, an urgent biopsy is mandatory to rule out melanoma. On histology, the presence of high-grade nuclear atypia, high mitotic activity, ulceration and necrosis can be interpreted as suggestive of melanoma.[9] Immunohistochemistry of histologically-benign and atypical proliferative nodules in CMN found that Ki67 and phosphohistone H3 staining is useful to identify the malignant lesions.[29] NRAS and BRAF hotspot genotyping is recommended to improve diagnostic accuracy and to guide management, since most CMN-melanomas are NRAS mutated, and BRAF inhibitors are contraindicated in NRAS-mutated melanomas due their paradoxical activation of RAS.[23]

2.2.3 Management

Currently, routine monitoring is not recommended if only a single CMN is present. On the other hand, performing a clinical follow-up of children with multiple CMN or giant CMN is controversial, as the outcomes are apparently not better when comparing to those without follow-up. This is related to the difficulty in the detection of malignant transformations in giant CMN. Moreover, CMN melanomas are considered highly aggressive and its treatment offers less benefit than in other melanoma subtypes.[23,30] However, routine evaluation is often performed, as the patients may benefit from optimized skincare, interdisciplinary follow-up and also for reassurance of the family.[23] Kinsler *et al*, recommends to perform a whole brain and spine MRI with gadolinium contrast, under the age of 1 year (< 6 months ideally) for patients with two CMN at birth, independently of size or site.[23,31] The rationale is to perform this screening exam before the completion of CNS myelination process, which may difficult the visualization of the characteristic signs of melanin. If the scanning is normal, it does not need to be repeated. In the presence of MRI abnormalities, regular clinical and/or radiological monitoring is needed, as there is a higher incidence of melanoma, neurodevelopmental abnormalities and epilepsy in the long-term.[23]

Routine surgical excision of CMN has no evidence of changing melanoma risk.[23] Complete nevus excision, with removal of all deeper tissue layers, would only be beneficial in patients with a PAS > 60 cm or for those with MRI abnormalities. Even for these patients, the nevus excision would only protect a limited proportion of patients, given their high risk of developing CNS melanoma.[28] If a cutaneous melanoma is suspected, wide local excision must be performed and subsequent treatment should be guided by a multidisciplinary tumor board, given its highly aggressive behavior and poor overall prognosis.

2.3 Conventional Melanoma

2.3.1 Epidemiology and pathogenesis

Approximately 40%–60% of pediatric melanomas are considered conventional or adult-type melanoma, since they share a similar natural history and histologic subtypes with melanomas found in adults.[1,2,9,10] Albeit rare among children (<11 years), they're the most common subtype in the adolescent population (11–19 years). The risk factors and baseline characteristics are also distinct between those age groups. Younger patients are more likely to be ethnically diverse, have a personal history of noncutaneous cancer, and develop lesions on the head and neck. For adolescents, risk factors include light skin, UVR exposure and increasing age, following the adult trend, reflecting biological mechanisms and cultural practices (sunburns and indoor tanning habits).[10,13]

Genomic studies have shown a high burden of single-nucleotide mutations, consistent with ultraviolet-induced damage, alongside with the strong prevalence of *BRAF* and *TERT* promoter mutations. Studies on familial melanoma found that germline mutations in *CDKN2A* or *CDK4* are found in up to 40% of familial melanomas.[9,32] The prevalence of these mutations is much lower (<5%) when analyzing all pediatric melanomas.[13] Mutations in both genes are associated with a clinical phenotype characterized by numerous atypical nevi and an increased frequency of multiple primary melanomas.[9] The role of MC1R is also subject of investigation. It has been proposed that MC1R variants could be an inherited susceptibility factor, predisposing to *BRAF*-mutated melanomas, after minimal sun damage in early life.[9,33] An association between MC1R variants and melanomas in patients younger than 40 years old, was established.[9]

2.3.2 Diagnosis

The clinical presentation of melanomas in children can be quite non-specific.[13,12] Compared with adults, children present with thicker primary lesions, often nodular and amelanotic and atypical vascular or crystalline structures can be seen on dermoscopy. As said before, pediatric melanomas do not fulfill the traditional ABCDE criteria.[13] However, for pigmented and macular lesions, a dermoscopy devoid of benign patterns alongside with the presence of melanoma-specific structures increased the likehood of melanoma, just as in adults.[9] The most common histologic subtypes are, by far, the superficial spreading and the nodular. In contrast with the adult melanoma, a substantial proportion of these neoplasms arise from pre-existing nevus (80%).[9]

2.3.3 Management

Globally, the management of conventional pediatric melanoma follows the adult melanoma guidelines. Details on the treatment are included in section "3. Melanoma treatment".

2.4 Congenital melanoma

Melanomas are denominated congenital when diagnosed in utero or at birth.[3,34] There are three different ways in which congenital melanomas can be formed. In the first, melanoma

metastasis migrate through the placentae to the fetus, leading to widespread visceral involvement and usually death of the neonate.[34] In mothers with metastatic melanoma that manage to give birth, the placentae should be sent to histopathological and immunohistochemical evaluation and searched for metastasis. The second way is a form of melanoma de novo or in association with a small congenital nevus that has developed in uterus. There is also a third form of congenital melanoma that is similar to melanoma arising in giant CMN. All of these are exceptional clinical situations which do not constitute different subtypes of melanoma.

3. MELANOMA TREATMENT

At the present day, there is a lack of consensus on the management of pediatric melanoma and therapeutic approaches have been based on the established guidelines for adults.[9,10,13] Local wide excision of primary cutaneous melanoma, with adult-based margins, is the treatment cornerstone.[10] However, due to the anatomical and functional impact, it is not possible to achieve such margins in all situations. When comparing pediatric with adult melanomas with the same thickness, lower risk of local recurrence has been reported in children.[9,10] Following wide excision, SLNB is usually performed in all ulcerated tumors and those thicker than ≥0.8 mm.[10] The prognostic value of SLNB is less clear than in adults. A study reviewing 310 cases of pediatric melanoma who were submitted to SLNB reported that melanoma-specific-survival was not improved in such cases, when matching with a control group.[35] It also compared pediatric and adult patients with microscopic nodal disease, reporting better survival rates in the former.[35] Moreover, the melanoma subtype deeply influences the rates of SLNB positivity, without clear impact on the outcome, as is the case in Spitzoid melanomas.[22] For patients with clinically-evident regional lymph node metastases, complete lymph node dissection (CLND) is indicated.[10] However, when managing a positive SLNB in the absence of clinically or radiologically-evident nodal metastases, an "observation only" approach is recommended in most cases.[36]

Systemic therapy is indicated for patients with regionally advanced or distant metastatic disease.[10] Evidence-based regimens are currently scarce, both due to its rarity and to the exclusion of pediatric patients in most prospective trials. Current treatment strategies are therefore extrapolated from adult data. Adjuvant therapy has been reserved for patients with localized disease at increased risk for dissemination. High-dose interferon is an option for stage IIB and III melanoma, since it has been showed to improve recurrence free survival. The use of adjuvant IFNα-2b in children appears to be safe and it is better tolerated than in adults.[37] In recent years multiple novel agents have been approved for the treatment of metastatic melanoma, with promising results. Ipilimumab is a monoclonal antibody directed against a T-cell receptor antigen (CTLA-4). Its safety in adolescents was demonstrated in a phase I study, and a current phase II study is underway.[10] Pembrolizumab and nivolumab are checkpoint inhibitors of the T-Cell-PD-1 receptors and tumor PDL-1 ligand pathway, and their efficacy and tolerability in children are also being studied. Another pathway that has been a target for novel treatments is the signaling kinase BRAFV6001 activating mutation, (e.g. vemurafenib). Similarly to the previously described treatments, it has been approved for treating adults, while its effects are currently being studied within the pediatric population. MEK1 and MEK2 inhibitors (e.g. trametinib) constitute another agents approved to treat BRAF-mutated melanomas in adults.[10] The use of MEK inhibition has already been employed to control symptoms in NRAS-mutated primary CNS melanomas, with positives outcomes.[38] MEK inhibition has a promising role in the treatment of giant CMNs and to prevent its risk of malignant transformation, although it has not yet moved on to clinical trials.[39,40] KIT mutations occur in 10% of adult melanoma and kinase inhibitors have potential responses in 15% to 50%.[41]

Overall, patients must be selected through molecular profiling in order to evaluate the presence of the previously described mutations, since the effectiveness of these drugs is null in patients without them.[10,41] Data from case series and case reports, in which these agents have been employed, shows similar results between pediatric and adult patients.

4. CONCLUSION

Pediatric melanoma fortunately remains rare. When considering this disease, it is imperative to consider its three main subtypes as they're morphological and biologically different. Spitzoid melanoma is the most common subtype affecting children younger than 11 years and it encompasses the most favorable prognosis. Its pathological diagnosis can be challenging, since it may share overlapping features with atypical Spitzoid tumors. Melanomas arising from congenital nevi are rarer than Spitzoid melanoma, but are likely to be responsible for most melanoma-related deaths in childhood. This is due to the difficult surveillance and treatment, and also to the associated emergence of CNS melanoma. In adolescents, the most common subtype is the conventional (adult-type) melanoma, arising mostly from previous nevi and in relation to sun exposure and lower phototypes. This stresses the paramount importance of the education to the potential hazards of tanning beds and unprotected sun exposure.[13] The management and treatment of pediatric melanoma follows the adult guidelines. Almost all the systemic treatments of advanced/metastatic disease are off-label in pediatrics, although trials are underway. Even though it is a rare disease, there have been continuous efforts and advances in understanding the genetics and molecular processes underlying the emergence of pediatric melanoma, in order to achieve an earlier diagnosis and a more suitable treatment.

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ORCID
José M. Neves
http://orcid.org/0000-0002-9014-2031
Bruno Duarte
http://orcid.org/0000-0003-4757-0679

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Educação Médica Contínua

TEST YOURSELF

1. **Which of the following statements is incorrect about Pediatric Melanoma?**
   a) It is the most common skin cancer in the pediatric population.
   b) Its incidence among children under 11 is lower than among adolescents.
   c) The average age of diagnosis is about 13 years.
   d) Familial cases account for 10% of pediatric melanomas.
   e) There are no considerable sex and ethnic-based differences in the incidence of melanoma in young children.

2. **About Spitzoid melanoma, which of the following statements is correct?**
   a) Although Spitzoid tumors can affect all age groups, they usually arise during adulthood;
   b) The following dermoscopic patterns are suggestive of a Spitz nevus: starburst pattern, regularly distributed dotted vessels and globular pattern with reticular depigmentation;
   c) It encompasses a poor prognosis;
   d) *BRAF* or *NRAS* mutations are typically present in Spitzoid tumors
   e) On the moment of diagnosis, nodal involvement is rare.

3. **Considering the management of melanoma arising in congenital melanocytic nevi, indicate the correct statement.**
   a) Routine monitoring is recommended if a child has a medium-size congenital melanocytic nevus;
   b) There is a tendency towards better outcomes in a patient with multiple congenital melanocytic nevi who is routinely monitored;
   c) A MRI with gadolinium contrast is reccomended, under the age of 1 year, for patients with two CMN at birth, if at least one is a giant melanocytic nevus;
   d) Complete nevus excision, with removal of all deeper tissue layers, in patients with PAS > 60 cm or for those with MRI abnormalities, eliminates the risk of melanoma emergence;
   e) Routine surgical excision of CMN has no evidence of changing melanoma risk.

4. **Conventional (adult-type melanoma) is the most common melanoma in adolescents. About this topic, which of the following affirmations is false?**
   a) Similarly with the adult melanoma, only 25%-33% of these neoplasmas arise from pre-existing nevus;
   b) Young patients are more likely to be ethnically diverse, have a personal history of noncutaneous cancer, and develop lesions on the head and neck;
   c) Genomic studies show a high burden of single--nucleotide mutations consistent with UV-induced damage;
   d) Mutations in *CDKN2A* or *CDK4* are associated with a clinical phenotype characterized by numerous atypical nevi and an increased frequency of multiple primary melanomas;
   e) The most common histologic subtypes are the superficial spreading and the nodular.

5. **About the management and treatment of pediatric melanoma, which of the following statement is incorrect?**
   a) There is a lack of significant evidence in order to establish pediatric specific guidelines;
   b) A lower risk of local recurrence has been reported in the pediatric patients;
   c) The value of sentinel lymph node biopsy is well established in pediatric patients;
   d) The safety and tolerability of adjuvant IFNα-2b in children has been verified;
   e) When managing a positive SLNB in the absence of clinically or radiologically-evident nodal metastases, an "observation only" approach can be recommended.

Key: 1d; 2b; 3e; 4a; 5c.