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Solid Tumour Section

Review

Skin Melanoma

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Identity

Other names: Cutaneous melanoma; Melanoma skin cancer

Classification

Note: Skin melanoma is a relatively common human cancer with an increasing incidence trend and originates from skin melanocytes, which are neural crest derived cells. Melanoma arises in more than 95% of cases in the skin, although other sites of primary extracutaneous melanoma include uvea, oral and genital mucosae, gastrointestinal and genitourinary tracts, leptomeninges and lymph nodes.

Clinics and pathology

Embryonic origin

Neural crest cells (this embryonic origin is valid for all forms of melanoma, except for uveal melanoma, which derives from neuroectodermal cells.

Etiology

A wide spectrum of risk factors for skin melanoma has been unravelled in the last decades. They are classically distinguished in 'host' and environmental factors. The strongest 'host' conditions are positive family history for melanoma (especially in first-degree relatives and in a number of 3 or more), multiple benign (often more than 100) or atypical nevi (the so-called 'dysplastic nevus syndrome'), and a previous melanoma. The first two risk factors may coexist in the same pedigree, thus delineating the Familial Atypical Mole - Multiple Melanoma syndrome (or FAMMM syndrome). Among these families, 30-40% of them display mutations in the CDKN2A gene, while a few kindreds are mutated in CDK4. Other 'host' factors that may increase the risk of developing melanoma are previous non-melanoma skin cancer and immunosuppression (such as, transplant recipients or patients with AIDS).
However, solar UVR exposure remains the leading cause for developing skin melanoma. In fact, skin melanoma is strikingly more common in patients with type I skin, freckling, blue eyes and red hair. This evidence demonstrates that 'host' and environmental risk factors cooperate in determining the onset and evolution of skin melanoma (this interaction has been recently demonstrated at the molecular level. In fact, ultraviolet exposure stimulates tanning in part inducing the action of the alpha-melanocyte-stimulating hormone (POMC) on the melanocortin receptor 1 - MC1R. Light-skinned and readheaded people carry specific MC1R polymorphisms that reduce its activity). Accumulated evidences support that intermittent sun exposure is a major determinant for melanoma in contrast with cumulative sun exposure, as well as a history of blistering sunburn, especially in young age (i.e. three or more episodes before 20 years). The risk related to non-solar UVR exposure is still debated.

Epidemiology

Melanoma is the fifth most common cancer in men and the sixth in women (note that this ranking may slightly vary among distinct populations and different epidemiological studies). It accounts for nearly 4% of all dermatologic cancers, but represents the major cause of death for skin cancer. The overall incidence of melanoma ranges from 10 to 42 new cases for 100.000 per year. This apparent wide variability may essentially relay on the ethnic background of the population studied. The incidence of melanoma is rising by 3-8% per year in most people of European origin. Melanoma affects young and middle aged people, with a median

age at diagnosis of 57 years. The cancer incidence increase progressively after the age of 15 years until the age of 50 and then slows, especially in females, who are slightly less affected than men (males are approximately 1.5 times more likely to develop melanoma than females). Nearly half of the patients have an age comprised from 35 and 65 years at diagnosis.

Clinics

Melanoma should be considered for every suspicious pigmented skin lesions. There are specific characteristics to be taken into account for identifying suspicious lesions which request further investigations. The acronym ABCDE summarizes five cardinal features, including:
(i) Asymmetry;
(ii) Border irregularity;
(iii) Color variation;
(iv) Diameter above 6 mm; and
(v) Evolving, which encompasses any significant change in size, shape, surface, shades of color or symptoms (such as, itching).
Clinical suspicion must be supported by assistive optical devices, such as dermatoscopes, epiluminescent microscopes and/or other portable scanning units using visible, infrared and UV sources. However, a firm diagnosis is reached only by excision and histologic examination.

Pathology

Pathologic staging of skin melanoma is crucial for prognosis definition and management planning. The Clark's model identifies 5 steps in the progression from benign nevus and metastatic melanoma:
step 1: benign nevus;
step 2: dysplastic nevus;
step 3: radial-growth phase melanoma;
step 4: vertical-growth phase melanoma;
step 5: metastatic melanoma.
This model also denotes qualitative anatomic levels of invasion:
In level I melanoma, all tumor cells are above the basement membrane (malignant melanoma in situ).
Level II melanoma invades into the papillary dermis.
Level III melanoma fills and expands the papillary dermis.
Level IV melanoma invades the reticular dermis, while level V melanoma reaches the subcutaneous adipose tissue.
Actually, for the T staging of melanoma the primary determinant is the Breslow's technique, that provides a quantitative measurement of the depth of invasion by measuring the tumor thickness with an ocular micrometer (in millimeters).
T1 melanomas are = 1.0 mm in thickness,
T2 between 1.01 and 2.00 mm,
T3 between 2.01 and 4.00 mm, and
T4 above 4.0 mm.
To date, the Clark's level system is the primary prognostic method only for T1 melanomas.
The melanoma clinical staging include four stages.
Stage I melanomas are those with thickness that are 1 mm or less with no evidence of metastases.
Stage II melanoma is diagnosed in patients with thicker cancers without evidence of metastases.
Stage III melanomas are those with regional lymph nodes and/or an in-transit or satellite metastasis.
Stage IV cancer is diagnosed when the melanoma spreads to distant sites.
Specific determinants define the N and M axes for stage III and IV melanomas.
There are unusual variants of melanoma (for which the standard prognostic factors should be taken into account), that must be differentiated form epithelial or mesenchymal neoplasms.
These variants include: desmoplastic melanoma, mucosal melanoma, malignant blue nevus, nevoid melanoma, minimal deviation melanoma, small cell melanoma, spitzoid melanoma, dermal melanoma, amelanotic melanoma, myxoid melanoma, signet ring melanoma, balloon cell melanoma, rhabdoid melanoma, pigment-synthesizing animal melanoma, osteoid melanoma, chondroid and cartilagineous melanoma, and basomelanocytic tumor.

Treatment

After histologic diagnosis of melanoma, the first step is the extent of excision. The radius of this excision depends on the tumor thickness (Breslow's technique).
Sentinel lymph node biopsy is requested in melanomas of Stage I.
In melanomas with thickness above 2 mm, elective lymph node dissection is also recommended. Surgical excision could be considered also for local recurrences, in-transit metastases, regional metastases and in patients with metastatic disease.
In stage III patients, the eradication of clinical undetectable micrometastases at the time of diagnosis may be obtained using adjuvant therapy, including interferon-alpha and ganulocyte-macrophage colony-stimulating factor.
In stage IV cancers the systemic therapy is based on decarbazide, interleukin-2, in isolation or in combination with other chemotherapeutic agents. Novel therapeutic regimens include cancer vaccines, angiogenesis inhibitors and novel cytotoxic agents.

Evolution

Usually, skin melanomas show two distinct phases of local invasion:
(i) the radial-growth phase, during which tumor cells acquire the ability to proliferate intraepidermally;
(ii) the vertical-growth phase, which is characterized by tumor invasion of the dermis in form of an expansile nodule.

Local invasive melanomas may reach distant skin areas and subcutis. The invasion of lymph vessels leads to lymph node metastases.
Finally, metastatic melanomas may metastasize to lungs, liver, central nervous system and other organs.

Prognosis

The prognosis (i.e. % of 10-year survival rate) is directly related to the Pathologic stage. This range from 100% for melanoma in situ to less than 6% for patients with a stage IV melanoma with distant metastases.

Cytogenetics

Cytogenetics morphological

Numerical and structural changes visible by standard cytogenetics are common in sporadic melanoma, which is frequently aneuploid with a modal chromosomal set usually ranging from 24 to more than 100.
The most common abnormality involves chromosome 1 with deletions and translocations usually including the region 1p12-22. A recurrent t(1;19) translocation has been also described in a subset of sporadic melanomas.
Deletions or translocations involving the long arm of one or both chromosome 6, commonly affecting the 6q16-23 region, are observed in nearly 80% of skin melanomas. The 6 chromosome short arm is generally retained in form of an isochromosome (i6p). The gain of the short arm of chromosome 6 may have a role in cancer progression, especially for metastastic evolution (in fact, the NEDD9 gene, whose overexpression in associated to metastatic melanomas, maps in 6p25-p24).
An equally common alteration is the gain of copies of chromosome 7. This finding is usually associated with late stages of skin melanoma.
A second set of chromosome abnormalities includes alterations of chromosome 2, 3, 9, 10 and 11. Among them, a recurrent site of alterations (predominantly deletions) in both premalignant nevi and metastatic melanomas is the short arm of chromosome 9, particularly the region 9q21. Loss of chromosome 10, especially involving the region 10q24-26, seems to be implicated in both the early and late stages of melanocytic neoplasia. In late stage melanomas, chromosome 10 loss often accompanies chromosome 7 gain. At the standard cytogenetic level, the rate of involvement of other chromosomes (i.e. 2, 3 and 11) is less consistent.

Cytogenetics molecular

A large number of studies have searched for loss of heterozygosity (LOH), homozygous deletions (HD) and amplifications in cutaneous melanomas, events that are difficult or impossible to identify at the standard cytogenetic level.
Over the years, the improvement of laboratory techniques has collected a wide range of different approaches, including fluorescent in situ hybridization, standard microsatellite analysis on specific genomic regions and conventional chromosome-based comparative genomic hybridization array. Actually, the most sensitive technique is the high-density whole-genome single nucleotide polymorphism array, which is able to detect variations in number of copies of genomic DNA within an interval of only 9 kb. Therefore, the results of this type of analysis is by far the most sensitive among all available approaches.
Overall, whole chromosome arm LOH is most common on 9p, 9q, 10p and 10q, occurring in 40-50% of the cases. Considering focal (i.e. small portion of chromosome arms) LOH, these chromosome regions are involved in 49-72% of the cases. Over 40% of analyzed melanomas show LOH on 6q, 11q and 17p, while 33% on 5q. A broad spectrum of HD has been also registered and involves regions containing both well known melanoma progression associated genes (such as, CDKN2A and PTEN - for more details, see 'Genes Involved and Proteins' section), and other genes, whose role in cancer evolution awaits further elucidations. In more that one fourth (25%) of melanomas there are chromosome gains involving 7p, 20q and 22q. Amplifications of single genes may be also detected by this technique, but these data will be discussed in the next section. The 8q region, in which maps the C-MYC gene, is amplified in nearly 14% of the cases.

Genes involved and Proteins

Note: Several genes have been discovered as involved in the progression of cutaneous melanoma. Two major groups of genes have been identified: tumor suppressor genes and proto-oncogenes. In order to describe melanoma progression implicated genes, the present section follows this classification. In addition to those here described, other genes, such as NF1, NF2, TTC4, NME2, CDKN1A, and RAB8A, have been sporadically studied in melanomas, but the present data are still very limited and not completely conclusive.

Note: ***Tumor suppressor genes:***

B2M

Location: 15q21.1
Note: Escape by melanoma cells from T cell recognition through a complete lack of HLA class I antigen can be ascribed to beta-2-microglobulin (encoded by the B2M gene) aberrations. The combination of LOH and somatic mutation leading to a biallelic inactivation of B2M is not uncommon in melanoma cells.

CDC2L1

Location: 1p36.1
Note: This genes maps in a chromosome region (i.e. 1q36) frequently deleted in melanoma. However,

mutations in this gene are rare and the role of this gene in tumor progression is probably very limited.

CDKN2A

Location: 9p21
Note: The CDKN2A locus shows LOH in nearly 50% of melanomas, while point mutations of this gene are extremely rare, probably because other mechanisms are involved in its inactivation (such as promoter methylation or homozygous deletion).

CDKN2B

Location: 9q21
Note: CDKN2B maps nearly to CDKN2A and shares with this gene an high sequence homology. Although CDKN2B maps in a commonly deleted region in melanoma, the frequency of point mutations is relatively low and the actual knowledge about the role of this gene in melanoma progression is limited.

MEN1

Location: 11q13
Note: Mutations in menin, the gene responsible for the multiple endocrine neoplasia type I (MEN1), results mutated in nearly 1% of the analyzed melanomas.

PTEN

Location: 10q23.31
Note: The chromosome region in which this gene maps is deleted in about 30-50% of melanomas, while somatic PTEN mutations have been identified in approximately 3% primary melanomas and 8% metastatic melanomas.

RB1

Location: 13q14.1-14.2
Note: Although the implications of CDKN2A and CDK4 (see below) is crucial in melanoma progression, the actual rate of mutations or rearrangement involving this gene, which is implicated in the same pathway, is extremely rare and confined to sporadic cases.

TFAP2A

Location: 6p24
Note: Loss of AP2-alpha (the protein encoded by TFAP2A) expression is a crucial event in the melanoma development. However, the frequency of TFAP2A somatic mutations in melanomas is extremely low, thus suggesting that the AP2-alpha underexpression is very probably caused by the caspasis activity.

TP53

Location: 17p13.1
Note: TP53 mutations in melanomas are rare, occurring in 0-24% (mean 7%) of the analyzed tumors. However, UVR is very likely the cause of these mutations, as well as in other non-melanocytic skin tumors.

Wnt signalling pathway tumor suppressor genes.

Location: Variable (see text).
Note: The involvement of this pathway in melanoma progression is clearly demonstrated by the overexpression of beta-catenin in nearly 30% of the cases. Several genes coding for proteins implicated in the modulation of this pathway has been studied for somatic mutations in relation with melanoma. Among them, the most frequently somatically mutated gene is LKB1 (i.e. the gene responsible of Peutz-Jeghers syndrome ; location: 19p13.3) with an overall mutation frequency in melanoma of 4%. Other related genes, namely PPP2R1A (location: 19q13.4), APC (whose germline mutations are associated with the familial adenomatous polyposis; location: 5q21-q22) and ICAT (location: 1p36.22), are only rarely mutated in melanomas.

Note: ***Proto-oncogenes***

CDK4

Location: 12q14
Note: The primary role of the protein encoded by CDK4 is to inactivate pRB. Mutations that constitutively activate the kinase, in particular those involving the K22 and R24 aminoacid residues, have been identified in a variable proportion, ranging from 1/60 to 5/48, of the cases.

CTNNB1

Location: 3p22-p21.3
Note: This gene encodes for beta-catenin. As this protein is overexpressed in about one third of the cases, several studies investigated the presence of somatic mutations in this gene. The overall frequency of CTNNB1 somatic mutations in melanoma is 2-5%.

MAPK signalling pathway proto-oncogenes.

Location: Variable (see text).
Note: This pathway may be simplified as follows. The growth factor receptor interaction with its ligand induces the activation of RAS. Its activation stimulates phosphorylation of RAF proteins (including BRAF), that in turn activate MEK1 and MEK2. The final step of this cascade is the transcription factors activation by ERK 1 and ERK 2, which are phosphorilated by MEK proteins.
BRAF (location: 7q34) mutations have been identified in more than 60% of melanomas and approximately 80% of these mutations occur at a single site, leading to the substitution of valine at position 600 with glutamic acid (V600E). This change mimics phosphorylation within the activation segment and results in constitutive activation of BRAF. The frequency of BRAF mutations in melanocytic nevi is similar to that in melanomas, suggesting that BRAF function perturbation is an early

event in melanoma development and is not sufficient to determine the neoplastic switch. The rate of BRAF mutation varies among melanoma subtypes and is highest in nodular melanoma and superficial spreading melanoma. BRAF mutations appear to be less common in sun-exposed areas. BRAF mutations are mutually exclusive to those occurring in the NRAS gene (1p13.2). The most common sites of mutation in this gene are codon 12, 13, 18 and 61.

In contrast to BRAF mutations, NRAS alterations are more common in sun-exposed areas. This fact suggests that NRAS mutations may arise as a result of UVR-induced mutagenesis.

HRAS (location: 11p15.5) mutations are less commonly observed and occurs in no more than 1.5-3% of melanomas.

Activating changes in KRAS2 (location: 12p12.1) have been observed in rare cases and often associate with mutations in other RAS genes (i.e. NRAS and HRAS). Therefore, KRAS2 in a not powerful oncogene in melanoma progression.

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