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Cancer Prone Disease Section

Mini Review

Dysplastic nevus syndrome (DNS)

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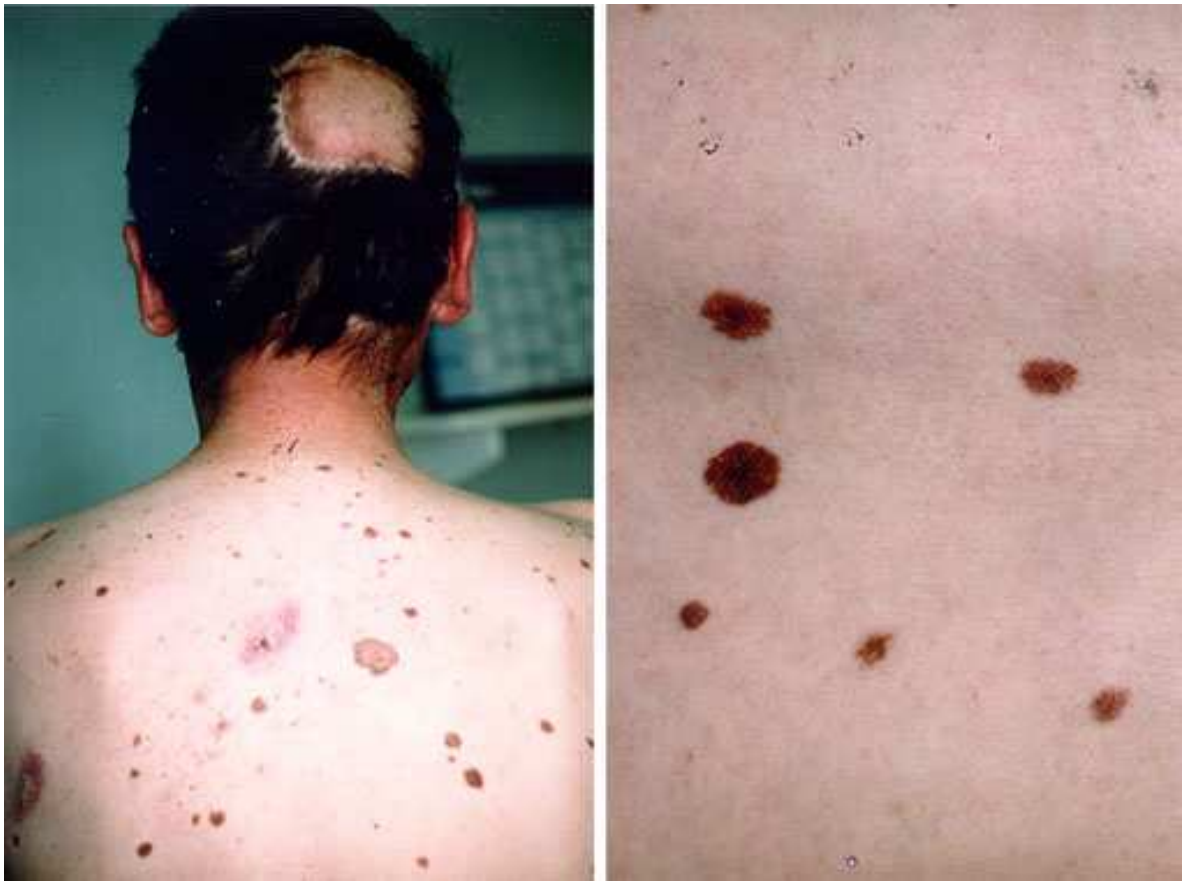
Identity

Alias: Familial atypical mole-malignant melanoma syndrome (FAMMM); B-K mole syndrome

Inheritance: Autosomal dominant with high penetrance and variable expressivity; the frequency of DNS is difficult to evaluate because a number of cases without malignant evolution are not recorded; DNS defines patients with numerous dysplastic nevi. FAMMM defines families where coexist numerous nevi with malignant melanoma (MM).Sporadic forms of dysplastic nevi are not considered as DNS.



Multiple dysplastic naevi on the skin of the back, with (left) a surgically resected malignant melanoma on the scalp - Courtesy Daniel Wallach.

Clinics

Note

The familial dysplastic nevus syndrome is a good example of a genetic disorder which leads to the practice of self prevention and prevention at the family level; the risk is the evolution towards MM.

Phenotype and clinics

Predominant in patients with a clear complexion, blue eyes and/or presence of numerous nevi; the dysplastic nevus or "nevus of Clark" or "atypical melanocytic nevus" is a large mole with a variable size (5 to 15 mm), an irregular border and a color varying from dark brown to depigmentation; lesions are located mainly on the upper trunk, back, limbs, abdomen and arms; the number of moles is variable, from 10 to up to 100.

Histologic studies show the dysplastic nature of these nevi: junctional hyperplasia with isolated or clustered melanocytes, cells with large, irregular, hyperchromatic, and non mitotic nucleus; this aspect is intermediate between benign nevus and MM.

Neoplastic risk

The main risk is to develop a MM but there is also a possible increased incidence of pancreatic cancer, breast cancer, and myeloma; MM usually arises from a dysplastic nevus (DN) but it can also appear de novo or from a benign nevus; it occurs most often in the skin but it may also involve other sites, mainly the eye or the central nervous system; the risk of MM depends on three factors:

1- The number of nevi: MM occurs in 2 to 7% of the population; without DN the risk is multiplied by 2 if the total number of nevi is higher than 25; the risk is multiplied by 4 if they are more than 5 nevi with a diameter higher than 5 cm; the risk is multiplied by 2 with one DN and by 12 with 10 DN; 40% of MM occur on dysplastic nevi, more frequently in superficial than nodular forms.

2- The existence of at least one case of MM in the family (risk x 2); the risk of MM is 100% in case of FAMMM; the patients with DNS who develop MM are notably younger than patients with sporadic forms; the age of onset in FAMMM regresses from generation to generation.

3- The role of UV as a promoting factor is discussed; the number of DN increases with sun exposure.

Treatment

Clinical vigilance and tumour exeresis.

Evolution

The number of DN can increase during life with an increase in MM risk.

Prognosis

According to the tumour expansion at the time of exeresis.

Cytogenetics

Inborn conditions

A chromosome instability disorder was observed in cell cultures from the normal skin and dysplastic nevi over three-generations in DNS families, leading to translocations, duplications and deletions; in another study on MM, translocations involving bands 11q24, 1q25 and Xq13 were observed in patients with DNS, in dysplastic nevi and in the normal skin as well; a loss of chromosome 9 was found in 2 out of 4 DN, suggesting that deletion / inactivation of a gene on 9p may be a primary event in melanocyte transformation; loss of heterozygocity (LOH) for markers flanking the CDKN2A on 9p was described in primary MM and in a metastasis; other putative tumor suppressor genes which could be involved in the process are located in 1p13, 10p, 10q, 11q and 6q15-q23.

DNS is characterized cytogeneticaly by an UV-induced elevated level of sister chromatid exchange (SCE); the post-UV plasmid hypermutability test is a laboratory marker for FAMMM patients, suggesting a defective repair mechanism of UV-induced DNA damage; deficient DNA repair in lymphocyte studies also characterizes some patients with sporadic dysplastic nevi or non familial MM.

Genes involved and proteins

Still unknown

Location

Locus in 1p36 (called CMM1 for cutaneous malignant melanoma): this locus segregates with MM and DNS, but no gene is yet cloned.

CDKN2C/p18 (cyclin-dependent kinase inhibitor 2)

Location

Locus in 1p32; this locus has been found mutated in the germline from patients with MM and other tumors.

CDKN2A/p16/MTS1/CDK4 inhibitor (cyclin-dependent kinase inhibitor 2A)

Location

Locus in 9p21; this locus has been designated as CMM2; germline mutations were found in this locus in 30 to 40% of patients with FAMMM, and in some patients with two cutaneous and/or mucous MM; P16 is a candidate gene for MM susceptibility; there is a p16 mutation in 10 to 14% of patients suffering from sporadic multifocal MM; P16 is also involved in several other types of cancers; other tumor suppressor genes located at 9p are hypothetically involved in MM progression.

CDK4 (cyclin dependent kinase)

Location

Locus in 12q14; 2 germline mutations found in 3 FAMMM families.

Still unknown

Location

Locus in 6q: a 6q allelic loss was identified in 21 of 53 informative loci; the chromosomal region bearing the highest frequency of 6q allelic loss was defined by the markers MYB and ESR located at 6q22-q23 and 6q24-q27, respectively; this may indicate genetic heterogeneity.

MC1R (melanocortin receptor)

Location

Locus in 16q24.3; defined as possible susceptibility gene.

P53

Location

17p13; P53 mutations were found in benign and dysplastic nevi from patients with previous personal or familial history of MM; however, these mutations are considered to be late events and cannot be used as a marker to identify patients at high risk of MM.

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