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GENODERMATOSES (INHERITED DISEASES WITH CUTANEOUS MANIFESTATIONS): MOLECULAR BIOLOGY AND DIAGNOSIS

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SUMMARY – Genodermatoses are a variable group of inherited diseases that initially, or at least very early in life, present with cutaneous findings. They include divergent diseases, which could be divided into, for instance, disorders of pigmentation (example – albinism); disorders of keratinization (example – congenital ichthyosiform erythroderma), etc. The focus of this article is a subset of genodermatoses that are associated with increased risk of various skin neoplasms that develop either very early or later in life. Thus, this subset has often been dubbed as "inherited or heritable cancer syndromes." However, it is important to realize that not all of inherited cancer syndromes have protean skin manifestations, and that indeed, not all of the genodermatoses have neoplastic associations. The particular diseases this article deals with are Muir-Torre syndrome, Cowden's disease, and Carney's complex.

Key words: *neoplastic syndromes, hereditary –neoplasms, sebaceous gland – Cowden's disease – Carney's complex – Muir-Torre syndrome – neurofibromatoses – neurofibromas – sebaceous carcinoma – carcinoma, skin appendage - fibroma, desmoplastic – neurilemmoma – colon neoplasms – stomach neoplasms – neoplasms, breast – schwannoma – neurofibroma, plexiform*

Introduction

As the field of pathology and consequently dermatopathology, steps into a new era of molecular medicine, it becomes increasingly important to not only understand the results of genetic discoveries achieved in the last two decades, but also to incorporate them into the daily work[1]. Genodermatoses, thus, represent an ideal model. Multiple cancers were, in the last 100 years or so, known to have inherited component; however, only recently were we able to understand those at the molecular level[2]. Three examples are chosen here to illustrate this model.

Muir-Torre Syndrome (MTS)

Muir[3] and Torre[4] have had independently reported an inherited syndrome of the skin that is represented by constellation of sebaceous neoplasms (benign and malignant) and / or squamous cell carcinomas of keratoacanthoma type of the skin associated with internal malignancies. While the skin lesions are usually multiple, there are reports of patients with a single sebaceous neoplasm and an internal malignancy, particularly in families with a strong family history of cancer.

Cutaneous lesions encountered most often are sebaceous adenomas, sebaceous carcinomas, sebaceous epitheliomas, keratoacanthoma-type squamous cell carcinomas, or even basal cell carcinomas with sebaceous differentiation [5]. In the spectrum of internal malignancies, one encounters colonic adenocarcinomas most often (slightly over 50% of patients); however, there are numerous reports of neoplasms of the uterus (15% risk of endometrial carcinoma), ovary, kidney, and even ureter [6,7].

Today, we know that the syndrome is inherited in autosomal dominant fashion, but presents with a varied phenotype[7]. Mutations in DNA mismatch repair (MMR) genes MLH1 and MSH2 are implicated most often; and indeed, the syndrome is regarded as a variant of the hereditary non-polyposis colon cancer syndrome (HNPCC). Germline mutations of both genes were described in HNPCC, while in "pure" MTS; germline mutations in MSH2 are encountered more often. Some authors have raised a possibility that MTS might represent the full phenotypic expression of HNPCC. Recently, the immunohistochemical antibodies have been developed, that allow for evaluation of presence of MSH2 and MLH1 gene products in sebaceous neoplasms that arise as a part of MTS. Results show absent staining for MSH2 in most of the sebaceous carcinomas that arise as a part of MTS [8,9]. Some authors have actually shown that loss of at least one MMR gene (not both at the same time) in patients with MTS was detected in 80% of the benign sebaceous lesions associated with internal neoplasia, in contrast to non-MTS patients, where only 23% of sebaceous lesions not associated with internal neoplasia show loss of MMR proteins[10]. Therefore, since the presentation of skin growths neoplasms often precede the internal neoplasias in MTS patients, it would seem prudent to test any sebaceous neoplasm for presence or absence of MMR gene products, in an attempt to identify patients with MTS.

Cowden's Disease

Cowden's disease, or syndrome (CD), is – also known as Cowden's syndrome, as or "multiple hamartoma and neoplasia syndrome" – is another example of an autosomal dominant genodermatosis. The growths traditionally recognized as "hamartomas" include trichilemmomas of the skin, particularly in the facial region (present in 99% of patients with CD), fibroadenomata of the breast (present in ~ 70% of female CD patients), thyroid adenomata and adenomatous hyperplasia of the thyroid (multinodular goiter) in 40-60% of patients, and polyps throughout the gastrointestinal tract (35-40% of patients). Other benign growths include ovarian cysts, subcutaneous lipomas and neuromas, acral keratoses, oral fibromata, and palmar pits. Approximately 50% of CD patients will develop malignant neoplasms, including carcinoma of the breast (25-50%), 3-10% carcinoma of the thyroid gland (3-10%), and there are also reports of non-Hodgkin's lymphomas, and carcinomas of skin, tongue, and uterine cervix in female CD patients [2, 11].

Mutations in tumor-suppressor gene PTEN (phosphate and tensin homologue deleted on chromosome 10) tumor-suppressor gene mutations have been found in many CD patients. This gene has also been known under the name PTEN/MMAC1/TEP1. It is the major 3-phosphatase in the proapoptotic phosphoinositol-3-kinase pathway[12]. Before the discovery of the gene, the incidence of CD was estimated to be ~ 1:1,000,000, but; however some molecular-pathology based studies have revealed this incidence to be closer to 1:200,000[13] suggesting variable penetrance. It is of interest that there is a direct correlation between the size of the gene defect and intensity of skin changes.

Of further interest is the fact that an unusual syndrome, Lhermitte-Duclos disease, has also been recently associated with mutations in the PTEN gene[14,15]. In Lhermitte-Duclos disease, hamartomatous lesion of the cerebellum - (dysplastic gangliocytoma) is coupled with megaloencephaly and epilepsy have also been recently associated with mutations in this gene[14,15]. Another syndrome, Bannayan-Riley-Ruvalcaba Syndrome, which exhibits mutations in the same PTEN gene, is characterized by macrocephaly, lipomatosis, generalized hemangiomatosis and a speckled penis[16,17], as well as Proteus and Proteus like syndromes (the syndrome from which the fabled "elephant man" has suffered) [12].

Carney's Complex (CNC)

In 1985, J. Aidan Carney has described a complex of cardiac myxomas, skin lesions (both myxomas and pigmented lesions), primary pigmented nodular adrenocortical disease (that causes ACTH-independent Cushing's syndrome), myxoid fibroadenomas of the breast, growth hormone-secreting pituitary tumors, and both Sertoli cell and Leydig cell testicular tumors [18]. More recently, a psammomatous melanotic schwannomas were added to the mix[19,20], as well as various types of blue nevi [19,20]. In 1996, Stratakis and colleagues have evaluated 101 patients from 11 families that suffered from CNC. Of these, 96% of patients revealed skin pigmentation (ephelides and lentigines), 63% skin myxomas, 36% cardiac myxomas, 22% breast myxomas, 32% primary pigmented nodular adrenocortical disease, 8% acromegaly 10% thyroid neoplasia, and also 10% Sertoli-cell neoplasms[21].

The other names for CNC are the acronymous NAME syndrome (nevi, adrenal disease, myxomas, and ephelides) and LAMB syndrome (lentigines, adrenal disease, atrial myxomas and blue nevi). The syndrome is inherited in autosomal dominant manner Of interest is the fact that CNC reveals some overlap features with McCune-Albright syndrome (GNAS 1 gene – chromosome 20q), MEN syndrome (mainly MEN I syndrome, involving – MEN1 gene, at chromosome locus 11q13), and Peutz-Jeghers syndrome (involving STK11/LKB1 gene at, 19p13.3)[2].

Recent work in the field via the molecular pathology methods has revealed loss of heterozygosity in a vicinity of PRKAR1A gene (protein kinase A regulatory subunit 1-α (RI α), which is the main mediator of cAMP signaling in mammalian cell; this gene is affected in approximately 50% of CNC kindreds[20]. Other investigators have linked some cases of CNC to the multiple changes at the chromosome 2p16 region, which include loss of heterozygosityand gain of number of gene copies. Although that this locus was the first to be identified in CNC, the genes in that region are yet uncloned[22]. Although CNC is clinically similar with some of the syndromes that present with precocious puberty, the accumulated evidence proves beyond doubt that CNC is a distinct syndrome.

Conclusion

We are witnessing a new era of "molecular based" pathology. Daily, we gain not only understanding of genetic mechanisms behind the diseases that plagued men for centuries, but are able to diagnose them with increasingly greater accuracy As pathologists, we have to understand that sometimes, a carefully worded diagnosis could save a patient's life. Thus, although we might be regarded as "the boy who cried wolf" from Aesop's fables, if one observes a characteristic lesion that could be a first sign of a genodermatosis, clinicians' attention should be drawn to it so that appropriate followup genetic and biochemical evaluations may be performed.

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