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Critical Reviews in Oncology/Hematology 85 (2013) 239–256

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Cancer-associated genodermatoses: Skin neoplasms as clues to hereditary tumor syndromes

Giovanni Ponti [a,*], Giovanni Pellacani [b], Stefania Seidenari [b], Annamaria Pollio [c], Umberto Muscatello [d], Aldo Tomasi [a]

[a] *Department of Clinical and Diagnostic Medicine and Public Health, University Hospital of Modena and Reggio Emilia, Italy*
[b] *Department of Head and Neck Surgery, Division of Dermatology, University Hospital of Modena and Reggio Emilia, Italy*
[c] *Department of Odontostomatological and Maxillofacial Sciences, Oral Medicine Unit, School of Medicine and Surgery, Federico II University of Naples, Italy*
[d] *CNR - Nanoscience Institute, S3 Center, University of Modena and Reggio Emilia, Modena, Italy*

Accepted 3 July 2012

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Abstract

Characteristic skin neoplasms are associated with a large number of hereditary tumor syndromes and their knowledge and early detection may facilitate the diagnosis of the underlying malignancies. We will review the clinical and dermatopathological aspects of cutaneous and visceral lesions and the recent progresses in understanding the etiology, pathogenesis and therapies of selected tumor syndromes. The skin neoplasms we chose to consider are multiple neurofibromas in neurofibromatosis, cylindromas and trichoepitheliomas in Broke–Spiegler syndrome, sebaceous tumors and keratoacanthomas in Muir–Torre syndrome, Gardner fibromas in Gardner syndrome, multiple basal cell carcinomas in nevoid basal cell carcinoma (Gorlin) syndrome, multiple tricholemmomas in Cowden syndrome, multiple fibrofolliculomas in Birt–Hogg–Dubé syndrome and multiple leiomyomas in hereditary leiomyomatosis and renal cell cancer. Hereditary cancers have distinct biological and clinical features as compared to their sporadic counterparts; for this reason, we are now able to experiment new treatment

* Corresponding author at: Department of Clinical Pathology, University of Modena and Reggio Emilia, via del Pozzo 7, 41100 Modena, Italy. Tel.: +39 059 4224748; fax: +39 059 4222647.
E-mail address: giovanni.ponti@unimore.it (G. Ponti).

http://dx.doi.org/10.1016/j.critrevonc.2012.07.001

approaches involving not only tumor detection and prevention, but also tailored therapeutic strategies focusing on the peculiar druggable molecular targets.

Keywords: Hereditary cancer syndrome; Neurofibromatosis; Broke–Spiegler syndrome; Muir–Torre syndrome; Gardner syndrome; Gorlin syndrome; Cowden syndrome; Birt–Hogg–Dubé syndrome

1. Introduction

Several hereditary tumor syndromes are associated with unique cutaneous findings which may facilitate an early diagnosis as a reliable marker for the risk of developing internal malignancies. Hereditary tumor syndromes cover a wide phenotypic spectrum ranging from a benign inherited predisposition to develop cutaneous lentigines connected with a systemic disease, to associations with several syndromes carrying increased risk of developing hamartomas, hyperplasias, and other neoplasms. These syndromes comprise Muir–Torre syndrome associated with sebaceous neoplasms, PTEN hamartoma tumor syndrome (Bannayan–Riley–Ruvalcaba/Cowden/Proteus disease) associated with multiple tricholemmomas, Carney complex associated with multiple superficial angiomyxomas, Birt–Hogg–Dubé syndrome associated with multiple fibrofolliculomas, tuberous sclerosis associated with multiple facial angiofibromas and so-called Koenen tumors, patients with hereditary leiomyomatosis and renal cell cancer syndrome with cutaneous leiomyomas, Gardner syndrome associated with Gardner fibromas, nevoid basal cell carcinoma associated with multiple basal cell carcinomas in young patients and types 1 and 2 neurofibromatosis, associated with multiple neurofibromas. Common features of the syndromes include: an autosomal-dominant pattern of inheritance, development of cancer at an early age, tumor multiplicity, presence of rare histotypes and occurrence of various extra cutaneous manifestations, which characterize each specific phenotype [1].

The clinical aspects of *NF1*, Broke–Spiegler syndrome, Muir–Torre syndrome, Gardner syndrome, nevoid basal cell carcinoma syndrome (Gorlin syndrome), Cowden syndrome, Birt–Hogg–Dubé syndrome and hereditary leiomyomatosis and renal cell cancer are here reviewed in a personal way, basing on our clinical experience. Despite their rarity, the molecular basis of many of these syndromes has been partially clarified with the identification of the responsible gene. These findings contributed (in most syndromes) to support the relevance of the Knudson's two-hit hypothesis in the pathogenesis of inherited tumors and shed further light on the peculiar mechanisms involved in the synchronous and/or metachronous tumorigenesis processes of different organs and districts.

There is no doubt that hereditary tumor syndromes will continue to represent an excellent model for the study of familial cancer. The discovery of the molecular mechanisms associated to hereditary tumors contributed significantly to the understanding of the basic mechanisms of sporadic malignancies and might be the milestone for the development of novel tailored treatment strategies. Further research should elucidate the genotype–phenotype correlations, the specific functioning of the genes and proteins involved in the inherited and sporadic tumorigenesis, as well as the role of possible modifier genes that might be responsible for the great intrafamilial and interfamilial phenotypic variability, which remains an unexplained paradox of several genetic disorders.

Tumors arising in patients with hereditary cancer syndromes may have peculiar drug sensitivity. While the initial practical interest on cancer genetic research was limited to various aspects of cancer detection and prevention, it is now getting increasingly recognized that hereditary tumors have distinct biological and clinical features as compared to their sporadic counterparts and thus require tailored treatment strategies [2].

1.1. Neurofibromatosis type I

NF1 (MIM# 162200), also called "von Recklinghausen disease" or "peripheral neurofibromatosis" is one of the most common autosomal dominant disorders, with virtually 100% penetrance by adulthood [3]. The prevalence of *NF1* is about 1 in 3000–4000 live births [4]. Diagnosis is based on the clinical criteria recommended by a NIH Consensus Conference [5], which include multiple *café-au-lait* spots (CLS), cutaneous or subcutaneous neurofibromas, plexiform neurofibromas, axillary or inguinal freckling, optic gliomas, and iris Lisch nodules (Table 1). Although the three characteristic features (CLS, neurofibromas, and Lisch nodules) occur each in over 90% of all *NF1* patients by puberty, the number of lesions is highly variable (Fig. 1). Approximately 30–40% of *NF1* patients may develop larger and more complex plexiform neurofibromas associated with major nerve trunks [6]. These congenital benign tumors often grow in association with the major nerve tracts, where they may involve multiple fascicles and branches of the nerves (Fig. 7a) [7].

NF1 patients are also predisposed to develop dysplastic skeletal lesions, learning difficulties or mental retardation, myeloid leukemias and other malignancies, and may exhibit vascular abnormalities, thus implicating the *NF1* gene in a wide variety of tissues and disease processes [8].

The *NF1* gene is located at 17q11.2, it contains 60 exons spanning approximately 350 kb of genomic DNA, and encodes a 12-kb transcript [9] (GDB: 120231; Gen-Bank: M82814). The gene product, neurofibromin, has an estimated molecular weight of 327 kDa and is a negative regulator of