Seminars in Diagnostic Pathology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Review article

Uncovering Hereditary Tumor Syndromes: Emerging Role of Surgical Pathology

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ARTICLE INFO

Keywords:
Hereditary tumor syndromes
Mendelian inheritance
multifocal
HLRCC
SDH-deficient
Neurofibromatosis
cancer predisposition

ABSTRACT

With the increased use of modern next generation sequencing technologies in routine molecular pathology practice, the proportion of cancer cases with a definite or probable hereditary background seems to be steadily increasing. Currently, it is assumed that ≥10% of all malignancies develop in the setting of germline predisposition. Diagnosis and recognition of cancer predisposition syndromes relies not rarely on distinctive histopathological features that proved to be highly valuable and reproducible in uncovering those diseases that would otherwise have gone undetected by clinicians as being hereditary in nature. This is especially true in case of new mutations without suspicious family history. Example of such entities are fumarate hydratase-deficient renal cell carcinoma (RCC), succinate dehydrogenase-deficient RCC, hereditary gastrointestinal stromal tumor syndromes and many other diseases. It is remarkable that many of these inherited cancer syndromes do present as unifocal disease with highly variable age of onset so that many of them are misinterpreted as sporadic on clinical grounds. Availability of specialized cancer screening programs and disease-specific follow-up schemes for several hereditary cancer syndromes encourages the recognition of such disorders, so that "at risk patients" can be enrolled in such programs for early detection and timely intervention/ treatment of these malignancies which are in the majority of cases aggressive. In several conditions, as in familial adenomatous polyposis coli (FAP), well established prophylactic surgical interventions may be adopted to prevent the disease manifestations, highlighting the importance of the timely recognition of these potentially life-limiting neoplasms. In this review, the clinicopathological, demographic and histological features that are considered highly suggestive of a hereditary basis of "a neoplasm under consideration" are highlighted and discussed briefly. The details of some of these entities are in addition dealt with in reviews devoted to them in this special issue

Introduction

With the increasing application of modern genetic methods such as whole-genome and whole-exome-sequencing using next generation sequencing (NGS) technologies, the proportion of cancers related to a germline predisposition seems to be steadily increasing. According to current knowledge, no less than 10% of all malignant neoplastic diseases are related to a well-defined hereditary predisposition.[1] However, a comparable, if not higher, number of cases are shown to be associated with specific germline variants suggestive of a hereditary etiology, albeit yet of undefined phenotype and significance.[2,3] The figure is even much higher in the pediatric and adolescent population approaching up to 35% of patients for specific cancer types.[4,5] The majority of these diseases are inherited in an autosomal dominant Mendelian fashion. This mode of inheritance highlights a significant predisposition risk of those inheriting the mutation with often high penetrance of the disease approaching 100% (as in NF1 and others), albeit with highly variable disease expression. On the other hand, there is increasing tendency to adopt carefully designed screening and/or detection methods as well as establishing prophylactic therapy concepts to safe lives of "at risk individuals" given the availability of several highly sensitive imaging and endoscopic diagnostic tools.[5,6] This underscores the significance of recognizing and identifying potential hereditary diseases during routine medical practice. In recent years, it has been illustrated that a significant proportion of hereditary neoplasia displays distinctive or unusual histopathological and/or immunophenotypic features that make pathologists the first medical specialists to suspect and/or recognize their inherited nature.[7] Furthermore a combination of specific tumors suggesting a hereditary cancer syndrome is not infrequently detected by the pathologist. However, recognizing or suspecting these diseases is only feasible if one is familiar with their clinicopathological, demographic and specific phenotypic characteristics that permit their distinction from their sporadic counterparts. Due to the complex medical, ethical, social and psychological aspects of these diseases, it is the

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https://doi.org/10.1053/j.semdp.2018.01.001

role of the medical geneticists in an interdisciplinary team to clarify these issues with the index patients before initiating any genetic testing, as the patients are in need of genetic counseling before initiation of genetic testing and after having the results of genetic testing.[8,9] Accordingly, the role of the pathologist resides only in recognizing or suspecting these disorders and alerting clinicians, e.g. in the interdisciplinary tumor board, to the possibility of inherited predisposition so that additional clinical and genetic examinations for clarification be performed or recommended.

The list of hereditary cancer syndromes and cancer-predisposing genes is steadily expanding

Recent developments and the introduction of comprehensive genetic tests such as NGS and whole genome sequencing have increased our understanding of the deep molecular biological aspects of familial cancer syndromes. Several new genes have been identified as etiological for cancer predisposition and several new syndromes are now identified or redefined.[5] Moreover, several new cancer-predisposing gene candidates are being identified in tumors not otherwise expected to be related to these deleterious genes.[2–4,10] In addition, odd-looking neoplasms that would otherwise have been unexpected in the setting of a defined genetic syndrome are increasingly being explained by the concurrence of more than one single pathogenic germline mutation in a sense of mixed phacomatosis or concurrent two distinct syndromes.[11,12] Among the well characterized inherited neoplastic syndromes are familial adenomatous polyposis (FAP) syndrome, hereditary non-polyposis colorectal cancer syndrome (HNPCC; Lynch syndrome), hereditary breast and ovarian cancer syndromes (BRCA1/2), multiple endocrine neoplasia syndromes (MEN1 & MEN2 syndromes), retinoblastoma syndrome (RB1 syndrome), Li-Fraumeni (and Li-Fraumeni-like) syndrome and others. While some of these monogenic syndromes are the consequence of a mutation in a single gene, mainly a tumor suppressor (such as *RB1*) and rarely a proto-oncogene (such as familial GIST syndromes caused by activating *KIT* mutations), others may be caused by a mutation in one of several functionally homologous or related genes such as the mismatch repair gene complex in HNPCC *(MLH1, MSH2, MSH2, PMS2*), the SDH-related diseases (*SDHA, SDHB, SDHC, SDHD*) and the SWI/SNF deficiency syndromes (*SMARCB1, SMARCA4, SMARCE1, ARID2*, etc.). Diseases related to these above-mentioned gene complexes highlighted the value of a wide thinking approach in terms of whole functional gene complex rather than the classical single-gene-approach. For example, it has been well illustrated in recent studies that families with the rhabdoid tumor predisposition syndromes but having intact *SMARCB1* (*INI1*) gene harbor instead mutations in a closely related member of the SWI/SNF gene complex, namely *SMARCA4* as an alternate etiology of their disease.[13,14]

Why Pathologists?

Although the age of onset, the family history and several other clinical aspects are routinely addressed as sentinel for hereditary cancer syndromes in medical practice, these features have proven of limited sensitivity in recognizing hereditary cancer predisposition, particularly in the adult and elderly population. The fact that pathologists are frequently the first *uncoverer* of hereditary neoplastic diseases is still not generally appreciated by clinicians, which is reflected at least in part in the occasional ignorance of pathologists' suggestions and comments regarding a possible hereditary basis of a neoplasm. On the other hand, some studies have shown that awareness of the benefit of risk reduction strategies is still relatively low among some clinicians in the clinical sarcoma community.[15] Several factors however make pathology the central medical discipline in suspecting or recognizing hereditary cancer predisposition syndromes in routine practice: (Table 1)

1) Several hereditary cancer syndromes have highly variable penetrance and disease expression resulting in limited or subtle manifestations of the disease at a highly variable age range, thus masking its hereditary nature by a *unifocal disease manifesting at an advanced age*, etc. In such scenario, the genetic nature of the disorder might be only histologically recognizable on the basis of observing multifocal precursor proliferative lesions or via recognizing distinctive pathological features of that entity. In the same sense, recognizing additional neoplasms as distinctive or independent primary neoplasms and distinguishing them from recurrence or metastases of a previously resected tumor can only be verified by histology.
2) The pathologist reviews tumor specimens from different medical specialties and hence has the best opportunity to recognize syndromic setting via specific combinations of certain tumor entities in the same patient, e.g. observing a colorectal cancer specimen coming from the surgeon of one hospital and a specimen of endometrioid adenocarcinoma coming years later from the gynecologist from another hospital.
3) Several newly defined cancer syndromes are characterized by identification of a specific key tumor entity that is defined by pathological and immunophenotypic characteristics as heritable entity irrespective of the actual clinical hereditary background including in particular the hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated uterine smooth muscle tumors and RCC[16,17] and succinate dehydrogenase (SDH)-deficient neoplasms.[18–20]
4) It is well known that several hereditary cancer syndromes are associated with a plethora of benign and hamartoma-like lesions of both epithelial and mesenchymal origin. These harmless lesions serve as sentinel of the disease and are easily recognizable by pathologists while they usually are ignored by clinicians due to their benign nature and this frequently results in forgetting them when recording the clinical history of the patient.

General features of hereditary tumor syndromes: clues to their recognition (Table 1)

Early-onset of disease

Being generally considered an important feature of hereditary cancer syndromes, the age of first manifestation proved to be very insensitive for suspecting inherited cancers as the index patient might be as old as > 70 years.[19,21] Nevertheless, the early onset is still one of the most important and relatively specific features of most of hereditary cancer syndromes.

Multifocal primary disease versus metastases?

Multifocal involvement is a characteristic but insensitive clinicopathological feature of hereditary cancer syndromes. The value of this feature has been reflected in the set of criteria proposed to clinically diagnose some hereditary diseases such as NF1.[22] However, while recognizing multiple benign lesions such as cutaneous and/or visceral neurofibromas in NF1 is straight forward, it is on occasion confusing and rather difficult if not impossible to distinguish multiple distinctive neoplasms from metastatic disease. This distinction has dramatic clinical impacts: 1) Mistaking multiple independent primaries for metastatic disease would ultimately result in over-staging and hence disastrous overtreatment for individual patients. 2) On the other hand, the same error would prevent recognizing a hereditary neoplastic disease as such. It is to be underlined that in the appropriate clinical context distinguishing *primary versus metastatic neoplasm* is mainly possible on histopathological grounds. The histopathological features that would permit recognizing a neoplasm as primary is largely dependent on the site and histogenetic type of that lesion. For example, detecting a focus of in-situ carcinoma or intraepithelial neoplasia is considered a defining feature of primary carcinomas in organs such as the GI tract, the genitourinary system as well as others. However, for most of mesenchymal