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Review Article

Genetic profile, risk factors and therapeutic approach of desmoid tumors in familial adenomatous polyposis☆

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ABSTRACT

Introduction: Desmoid tumors are the main extraintestinal manifestation of FAP, presenting high morbidity and mortality. It is a neoplasia without metastasis capacity, but with infiltrative growth and with a high rate of recurrence. In familial forms, these tumors are associated with a germinal mutation in the APC gene, with a genotype–phenotype correlation influenced by other risk factors.
Materials and methods: A review of articles published since the year 2000 in Portuguese, English or Spanish on desmoid tumors in patients with FAP was carried out. A total of 49 publications were included.
Results: The site of the mutation in the APC gene is related to the severity of FAP and to the frequency of desmoid tumor. Mutations located distally to codon 1309 are associated with a more attenuated polyposis, but with higher frequency of desmoid tumors. Clinically, these tumors may or may not be symptomatic, depending on their size and location. In their treatment, priority should be given to medical therapy, especially in intra-abdominal tumors, with surgery being the last option if there are no other complications.
Discussion: These tumors are associated with certain risk factors: genetic (mutation site), hormonal (estrogenic environment) and physical (surgical trauma) ones. In young women, a later prophylactic colectomy is suggested. Moreover, the laparoscopic approach to prophylactic surgery seems to be an option that reduces surgical trauma and consequently the appearance of desmoid tumors.
Conclusion: The step-up medical approach has been shown to be valid in the treatment of intra-abdominal desmoid tumors, and medical treatment should be the first therapeutic option.

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Perfil genético, fatores de risco e abordagem terapêutica dos tumores desmóides na Polipose Adenomatosa Familiar

Palavras-chave:
Doença desmoide hereditária
Fibromatose agressiva
Polipose adenomatosa do cólon
Fatores de risco e terapêuticas

RESUMO

Introdução: Os tumores desmóides são a principal manifestação extraintestinal da PAF, apresentando elevada morbimortalidade. É uma neoplasia sem capacidade de metastização, mas com crescimento infiltrativo e com alta taxa de recorrência. Nas formas familiares associa-se a uma mutação germinativa no gene APC, havendo uma correlação genótipo-fenótipo influenciada por outros fatores de risco.

Materiais e métodos: Foi efetuada uma revisão de artigos publicados desde o ano 2000, em português, inglês ou espanhol, acerca de tumores desmóides em doentes com PAF. Foram incluídas, no total, 49 publicações.

Resultados: O local da mutação no gene APC relaciona-se com a gravidade da PAF e frequência de tumor desmóide. Mutações localizadas distalmente ao codão 1309 associam-se a uma polipose mais atenuada, mas a maior frequência de tumor desmóide. Clinicamente podem ser, ou não, sintomáticos, dependendo do seu tamanho e localização. No seu tratamento deve ser dada prioridade à terapêutica médica, sobretudo nos tumores intra-abdominais, colocando a cirurgia como última opção, caso não hajam outras complicações.

Discussão: Estes tumores associam-se a determinados fatores de risco: genéticos (local da mutação), hormonais (ambiente estrogénico) e físicos (trauma cirúrgico). Nas mulheres jovens sugere-se a realização de colectomia profilática mais tardiamente. Além disso, a abordagem laparoscópica para a cirurgia profilática parece ser uma opção que diminui o trauma cirúrgico e consequentemente o aparecimento de tumores desmóides.

Conclusão: A abordagem médica em step-up mostrou ser válida no tratamento de tumores desmóides intra-abdominais, devendo o tratamento médico ser a primeira opção terapêutica.

Introduction

Familial adenomatous polyposis (FAP) is an inherited pathology that results from the autosomal dominant transmission of a germline mutation in the adenomatous polyposis coli (APC) tumor suppressor gene located on the long arm of chromosome 5.

Phenotypically, FAP is characterized by the development of hundreds to thousands of adenomatous polyps in the colon and rectum, with subsequent risk of developing colorectal carcinoma (CRC) if a prophylactic proctocolectomy is not performed.[1]

However, even after the proctocolectomy, patients with FAP present higher mortality versus the general population, due to the extra-colic manifestations of this disease: desmoid tumors, upper gastrointestinal tract adenomas, osteomas, and epidermoid cysts, as well as thyroid, adrenal gland, and central nervous system neoplasms.[2] Of these, desmoid tumors are the most frequent cause of death in patients with FAP.[3]

Desmoid tumors develop from connective tissue, fasciae, and aponeuroses,[4,5] corresponding to a monoclonal proliferation of well-differentiated fibroblasts.[6,7] From the histological point of view, this is considered a benign neoplasm, since it does not have metastization capacity; but biologically, it is a tumor with great local aggressiveness, given the infiltrative growth and the invasion of adjacent structures,[8] besides the high rate of local recurrence, even after its resection: 25–65%.[2,5]

This neoplasm may occur in the context of FAP or may arise sporadically; in this case, the tumor is a result of somatic mutations in the APC gene or in the beta-catenin gene.[9] Sporadic desmoid tumors are relatively rare, affecting about 2–4 individuals per million in the general population.[10,11]

As for the familial forms, the development of desmoid tumors is related to a germline mutation in the APC gene, and its frequency is much higher. In fact, it is estimated that between 10 and 25% of patients with FAP will develop at least one desmoid tumor throughout their lives,[12,13] with a risk 850 times higher than that for the general population.[5]

Regarding the risk factors for the development of desmoid tumors in a FAP context, studies point to several possibilities, such as family history, previous abdominal surgery, and gender, in addition to the site of mutation in the APC gene,[10,14,15] which is also related to the severity of these tumors.[16]

Thus, since the desmoid tumors are one of the most important manifestations of FAP, with high associated morbidity and mortality, and considering that there is no established therapeutic guideline for these tumors, the aim of this review article is to enumerate the various therapeutic options, as well as to order them in a logical sequence, taking into account the characteristics of these tumors, with the purpose of proposing the best approach.