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Highly Aggressive Thoracic Desmoid Tumors in Adolescent Siblings with Fatal Outcomes in an FAP Kindred: A Need for Increased Vigilance and Intervention in At-risk AYAs

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Abstract

Desmoid tumors are a manifestation of familial adenomatous polyposis (FAP), associated with mutation of the *APC* gene. Although considered benign tumors, desmoids can be aggressive and cause considerable morbidity. Known risk factors for desmoid tumor growth include location of mutations within the *APC* gene, family history of desmoid tumors, previous surgery, female gender, and pregnancy. Desmoids occur at diverse sites, commonly within the abdomen or at sites of previous surgery; thoracic desmoids are relatively uncommon. Reported here is a highly desmoid tumor-prone FAP family with a truncating mutation in the *APC* gene at codon 1550 (c.4648G>T) in which female siblings developed remarkably similar thoracic desmoids with highly aggressive tumor behavior during the onset of puberty, throughout adolescence, and in one sibling during and following pregnancy. Both siblings had a fatal outcome. This case underscores the potential for aggressive behavior of desmoids during adolescence and the need for close vigilance during the adolescent and young adult (AYA) age range in desmoid-prone FAP kindreds.

Keywords

Desmoid; Familial Adenomatous Polyposis; FAP; Adolescence

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant condition associated with the onset of colorectal polyps in adolescence and without surgical intervention, a nearly universal later development of colorectal cancer (1).

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Desmoid tumors are a manifestation of FAP, affecting 10–15% of patients with FAP and are fibromatosis that can affect abdominal or extra-abdominal structures. Although considered benign because they lack metastatic potential, they may be associated with a significant increased morbidity due to local aggressiveness (2). The management of desmoids is challenging, although multiple approaches have been taken with additional targeted therapies under development (3).

A family history of FAP, especially when noted to have cases of desmoid tumors, should raise the awareness of risk of desmoid tumors (4). However the diagnosis and implications of FAP, particularly in children is often delayed, due to an incomplete family history, lack of physical stigmata, and the rarity the condition leading to a low level of suspicion by providers. Desmoids may also be the first presentation of FAP in a family and may represent *de novo* mutation.

Desmoids often are observed to develop after surgery or local trauma (2,4). In addition, pregnancy and female gender have also been associated with development of desmoid tumors (2, 5). We present here a rare case of female siblings who presented at a young age with desmoids which similarly occurred in the chest and had notably aggressive growth during adolescence and led to fatality.

Case presentation

The family pedigree for the siblings to be described is shown in Figure 1.

Patient 1

A Hispanic female patient presented at the age of 5 at an outside hospital with a 2-year history of painless masses on the back, neck, and skull diagnosed as fibromatosis. Her father had died in his early 20's of an enlarging neck mass, reported to be similar to the patient's tumor. She initially received tamoxifen but due to tumor enlargement, her treatment was changed to weekly vinblastine/methotrexate which she received for 2 years yielding disease stabilization. Two years later a desmoid developed at the site of removal of a port-a-cath. She underwent surgical resection and radiotherapy followed two years later by extensive surgical resection. This was followed by radiotherapy and sorafenib treatment. Germline testing for mutation in *APC* revealed a truncation mutation at codon 1550 (c.4648G>T). At the age of 19 the patient gave birth to a male infant who inherited the mutation as detected by prenatal testing and confirmed by postnatal testing. The patient's chest mass enlarged during the pregnancy and several weeks after delivery she resumed treatment with high-dose tamoxifen, 120 mg daily, combined with celecoxib given for six months during which time tumor progression was slowed. The patient then received liposomal doxorubicin resulting in tumor stabilization. At age 22, she was found to have extensive complex thoracic and extra-thoracic left-sided desmoid tumors completely replacing the left breast and with destruction of left ribs (Figure 2a). She also had a large left-sided mass in the neck, a mass in the left axilla, a right mandibular osteoma and a RLQ abdominal wall desmoid. The patient soon succumbed to her illness at the age of 23. Her surviving son at age 5 has a single osteoma.

Patient 2

The younger sister of Patient 1 presented initially at the age of 13 with a right upper chest wall mass that was surgically resected. The mass recurred at age 15 and was again resected after which the patient was lost to follow-up. At the age of 18, the patient became symptomatic with pain and dyspnea and again sought medical attention. She reported progressive increase in the chest wall mass over 3–4 months. CT imaging showed a large heterogenous soft tissue mass centered in the upper anterior chest wall completely filling the right hemithorax (Figure 2b). Imaging also revealed abdominal and pelvic masses and diffuse osteomas in multiple bones. Consideration was given to retreating with a regimen of tamoxifen and sulindac. However, after a brief attempt at retreatment, the patient opted for palliative supportive care only. The patient succumbed to her disease with respiratory failure at the age of 19.

Discussion

Nearly all FAP cases have an *APC* mutation with over 400 unique identified mutations. The inheritance pattern of *APC* shows a high penetrance with variability in expressing disease manifestations. Mutations towards the 3' region of *APC*, distal to codon 1444, and most commonly in codons 1445 through 1578 have been implicated as an independent risk factors for development of desmoid tumors (6). This region encompasses our family's mutation at codon 1550. Although the *wnt*/β-catenin pathway is implicated *APC*-associated tumors, the precise mechanism by which distal loss-of-function mutations in *APC* contributes specifically to the development of desmoid tumors is still poorly understood.

Desmoid tumors can develop anywhere in the body commonly affecting the extremities and intra-abdominal structures; thoracic tumors are less commonly reported in the literature. Desmoid tumors associated with FAP are thought to be more aggressive than their sporadic counterparts (7) and may develop at any age but with a particular prevalence during early adolescence. The role of age and hormonal change with puberty, menopause, and hormonal therapy in the behavior of desmoid tumors is not fully understood. Estrogen has been hypothesized to increase the risk of developing desmoid tumors with higher incidence in pregnant females and those on combined oral contraceptive pills. Responses with tamoxifen use are observed in approximately fifty percent of patients with desmoid tumors (8). Desmoid tumors have also been noted to show progression during pregnancy, further implicating a stimulatory hormonal effect (5).

The unfortunate family reported here experienced three fatalities from FAP-related extracolonic tumors, all as young adults. Both siblings exhibited growth after surgical procedures, with patient 1 also developed tumor growth at the site of her port-a-cath removal, which ultimately progressed to invasion of her thorax. Although Patient 1 developed her initial desmoid at the prepubertal age of 5, both she as well as her sibling had exacerbations during adolescence, one in association with a pregnancy. Our patients' care was also frequently interrupted due to multiple social determinants, including distance from tertiary care center, financial limitations, and perhaps cultural factors. This family demonstrates the potential for highly aggressive behavior of desmoid tumors, especially in adolescent females. Although a prior family history of desmoid tumors in FAP kindreds is

known to be predictive of increased risk of desmoid tumors in other family members, the remarkable similarities of these two siblings in presentation, the similar anatomic sites, as well as fatal outcome is unusual. Other genetic modifiers could play a role in the development of desmoid tumors, or account for their particular aggressive features, as suggested by the observation of family history as a strong risk factor for development of desmoid tumors (4) and the fatalities noted in three members in this family. However no such genetic modifiers have been definitively identified to date and will await future large-scale genomic studies.

The natural history of desmoid tumors is highly variable and treatment of desmoid tumors is controversial, generally with the main goal of maintaining quality of life and optimal local control of the tumor size. In some asymptomatic patients, the approach may be watchful waiting and follow-up on tumor size and infiltration of surrounding structures. Beside conservative observation, multiple modalities can be utilized in the management of desmoid tumors including surgical resection, pharmaceutical therapy, radiotherapy, conventional chemotherapy (3). Although estrogen blockade, use of the anti-inflammatory agent celecoxib, and the kinase inhibitor sorafenib have all been tried and may be associated with response in some cases, none are effective in all cases and randomized trials are needed to demonstrate efficacy. Clearly additional treatment strategies are needed. Recently the use of oral pazopanib has been studied in comparison to methotrexate-vinblastine and found to have clinical activity and offering additional hope for the future (9).

Screening for lesions associated with Gardner syndrome is recommended according to national and international guidelines to assist with the decision based on the patient's risk, family history, and genetic mutations. Screening guidelines with colonoscopy are commonly accepted and involve an initial screening in early adolescence, then repeat screening in 2–3 years if no polyps found initially, then annually after the detection of adenomas followed by colectomy (10). Screening for desmoid tumors is more controversial. Although most experts agree on annual abdominal physical examination, imaging has not been uniformly recommended until after colectomy in early adulthood. To our knowledge there is no recommendation for increased surveillance in childhood or adolescence or following a pregnancy. However, in families such as described here, intensification of screening could be a future consideration however would best need to be paired with an effective intervention strategy. The vulnerability of the adolescent and young adult in FAP kindreds most at risk of desmoids because of family history and/or specific mutation should at a minimum raise awareness of risk and be a focus of research in the overall strategy of improving prevention, screening, and treatment of desmoid tumors in FAP kindreds.

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* "Neck tumor" was a desmoid by family report,
not pathologically verified

Fig. 1.

Four generation pedigree indicating desmoid tumors age of diagnosis and death. Patient 1's father was presumed to have a desmoid tumor in the neck region based on description and family report. Patient 1's son has a single cranial osteoma.

Fig. 2.

CT chest images of siblings **a.** Patient 1 with infiltrating left chest wall mass extending into the left hemi thorax and obliterating much of the thoracic structure with osseous destruction of the left-sided ribs **b.** Patient 2 with heterogeneous lobular right chest wall mass extending into right hemithorax with shift of mediastinum to left