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Original articles

Desmoid-type fibromatosis-associated Gardner fibromas: prevalence and impact on local recurrence

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ABSTRACT

Although Gardner fibroma is a precursor lesion of desmoid tumor, the prevalence and prognostic importance of Gardner fibroma associated with desmoid tumors has not been systematically studied in adults. From 129 patients with desmoid-type fibromatosis, 170 specimens were re-examined for the presence of an associated Gardner fibroma. Clinicopathologic features of Gardner fibroma-associated desmoid-type fibromatosis were compared to desmoid tumors without associated Gardner fibroma. Recurrence-free survival was compared using multivariate Cox proportional hazard regression to account for known confounding factors. Of 104 evaluable primary desmoid tumor resections, 25 (24%) had an associated Gardner fibroma. When previous incisional biopsies and resection specimens of locally recurrent desmoid tumors were also examined, the overall prevalence of associated Gardner fibroma was 37%. Desmoid tumors arising in high risk anatomic sites (extremities or deep soft tissues of the back and chest wall) were more often associated with Gardner fibroma than tumors at other sites. Median recurrence-free survival for patients with Gardner fibroma-associated desmoid-type fibromatosis was 3.2 years, whereas median survival for patients without associated Gardner fibroma was >25 years (hazard ratio 2.8; $P = 0.001$). Although the presence of Gardner fibroma had no impact on the recurrence rate of desmoid tumors arising at high risk anatomic sites, associated Gardner fibroma increased the risk of recurrence 4-fold for desmoid tumors at low risk anatomic sites. Associated Gardner fibroma is under-recognized in desmoid-type fibromatosis and increases the risk of local recurrence for a subgroup of patients.

Introduction

Although desmoid-type fibromatosis (DTF) has a propensity for locally aggressive behavior, a subset of these tumors does not necessarily follow an aggressive clinical course, as many cases of spontaneous regression or tumor quiescence have been reported [1,2]. Clinical, histopathologic and molecular predictors of DTF outcome remain elusive and the prognostic value of surgical resection margin assessment is controversial [3–7]. Consequently, the optimal management of these tumors remains unstandardized.

Although difficult to estimate accurately, around 5% to 15% of DTF patients have signs of familial adenomatosis polyposis (FAP) or Gardner syndrome at diagnosis or will develop them during their lifetime [8–10]. Preliminary evidence suggests that DTF arising in association with FAP/Gardner syndrome may possess intrinsically greater potential for local recurrence [5]. Some patients with FAP/Gardner syndrome also develop Gardner fibromas (GF), which are benign but infiltrative, densely collagenous masses considered as DTF precursor lesions [11–15]. The prevalence of GF associated with DTF has not been systematically assessed beyond the first two decades of life. In a previous study from our group, GF were found adjacent to DTF in five of eight (63%) patients who were treated with adjuvant radiotherapy, which suggests that the percentage of DTF associated with GF may be far greater than might be expected [16]. Coexistent Gardner fibromas were observed in 20% of children and adolescents with DTF [17]. The odds ratio for local recurrence in patients with GF-associated DTF was 7.5 in this series, further suggesting that DTF associated with GF have an increased propensity for local recurrence.

Surgical outcomes of patients with DTF arising in association with GF have not been previously evaluated or compared to those with sporadic desmoid tumors. We postulated that residual GF left behind during surgical resection of DTF may account for the limited prognostic value of resection margin status and variable disease courses observed in previous studies.

Abbreviations: CTNNB1, β-catenin; DTF, desmoid-type fibromatosis; FAP, familial adenomatosis polyposis; GF, Gardner fibroma; RFS, recurrence-free survival.

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Patients and methods

Clinicopathologic analysis

Surgical pathology files were queried for all primary and recurrent DTF samples accessioned at Vanderbilt University Medical Center between 1983 and 2010. Original slides were reviewed to confirm the diagnosis and record pathologic data, including the presence of an associated GF. DTF and GF (Fig. 1) were diagnosed according to current WHO criteria [12,18]. Cases were considered positive for an associated GF if infiltrative, hypocellular, densely collagenous areas filled at least a 40× field adjacent to areas of DTF. Demographic and clinical data were abstracted from medical records. The study cohort was also cross-referenced with the Vanderbilt Hereditary Colorectal Cancer Registry to identify patients with known FAP/Gardner syndrome. The study protocol was approved by the Institutional Review Board at Vanderbilt University; a waiver of informed consent was obtained.

Statistical analysis

Associations between clinicopathologic parameters and the presence of associated GF were evaluated using standard bivariate statistical methods. Continuous data were compared by Student's t-test assuming unequal variances. Tumor size and volume were log transformed before statistical analysis. Fisher's exact test was used to compare proportions among dichotomous or categorical variables. Kaplan–Meier recurrence-free survival (RFS) curves were plotted and Cox proportional hazard regression was used to assess the associations between covariates and RFS. Clinicopathologic variables marginally statistically significant ($\alpha < 0.1$) in univariate survival analyses or significantly associated with GF in bivariate analyses were included in a multivariate Cox proportional hazards regression model of RFS. To increase statistical power and avoid casewise deletion due to missing variables (for example, missing tumor size from outside primary resection specimens), multiple imputation was employed using chained iterations for anatomic site by multinomial logistic regression (2 imputations) and tumor size by partial means matching (35 imputations). Examination of the Monte Carlo errors of each coefficient and its associated t-statistic suggested that 40 data imputations were adequate. All data manipulations and analyses were performed using the Stata software package (v12.1, StataCorp, College Station, TX).

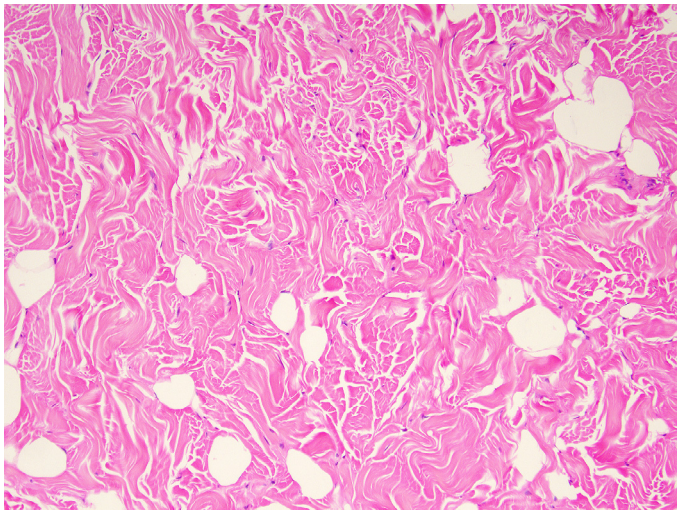

Fig. 1. Gardner fibroma. Gardner fibroma consists of hypocellular, coarsely collagenized tissue with sparse, nondescript fibroblast-like cells (H&E, 400×).

Results

Prevalence of Gardner fibroma associated with desmoid-type fibromatosis

An associated Gardner fibroma was identified in 25 of 104 (24%) primary DTF resection specimens (Fig. 2). When resection specimens of locally recurrent tumor or prior incisional biopsies were also reviewed, the overall prevalence of GF associated with DTF was 37% (45 cases out of 122 patients with evaluable specimens; Fig. 3). Only four patients (3%) had documented FAP/Gardner syndrome (Table 1). Two patients with FAP/Gardner syndrome had GF at another anatomic site but not associated with DTF and one had GF associated with an abdominal wall DTF. GF was not identified in a primary resection specimen of an abdominal wall DTF from the fourth patient.

Of the 45 patients with GF associated with DTF, 7 had prior colonoscopies, and only one had polyposis (14.3%). This proportion was not different from that seen in patients without associated GF (3 polyposis patients among 26 that had prior colonoscopies, 11.5%; Fisher's exact test, $P = 1.000$).

Clinicopathologic characteristics of desmoid-type fibromatosis with and without associated Gardner fibroma

DTF patients with associated GF showed no significant differences in demographics, adequacy of surgical resection, or receipt of adjuvant therapies compared to DTF without associated GF (Table 1). In contrast, DTF with GF were significantly larger than those without GF. The presence of an associated GF was also somewhat dependent on the anatomic site of origin. Whereas tumors of the extremities or deep soft tissues of the back or chest wall often had associated GF, DTF arising at other sites were infrequently associated with a GF (Table 1). In addition, associated GF was more frequently seen in patients who had their desmoid tumors resected at outside institutions (Table 1). Since these patients were referred to the Vanderbilt Sarcoma Center with recurrent disease and DTF associated with GF recur more often (see below), this high prevalence likely represents referral bias.

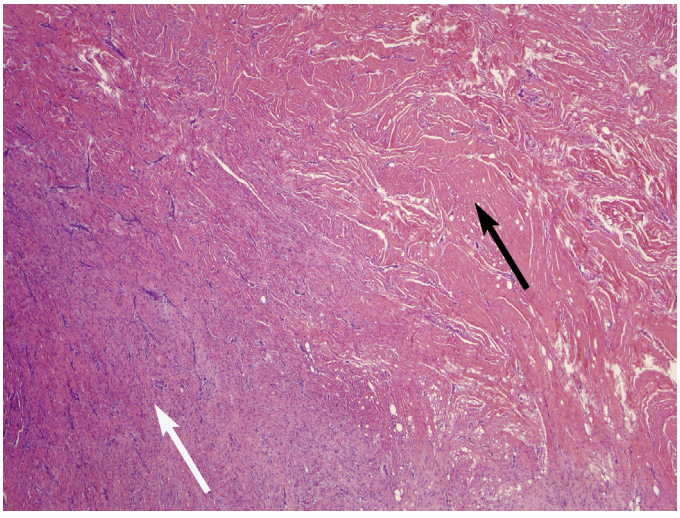

Fig. 2. Desmoid-type fibromatosis with an associated Gardner fibroma. Gardner fibroma (black arrow) adjacent to a desmoid-type fibromatosis (white arrow) composed of moderately cellular, broad sweeping fascicles with variable collagen deposition (H&E, 200×).