Journal of Pediatric Surgery xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

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

Original article

Sporadic desmoid tumors in the pediatric population: A single center experience and review of the literature

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ARTICLE INFO

Article history:
Received 2 December 2016
Received in revised form 27 January 2017
Accepted 29 January 2017
Available online xxxx

Key words:
Pediatric population
Sporadic desmoid tumors
CTNNB1 gene mutations

ABSTRACT

Background/Purpose: We present our long experience with desmoid tumors in children.
Methods: Data were retrospectively collected from 17 children/adolescents treated for sporadic desmoid tumors at a tertiary pediatric hospital in 1988–2016. There were 10 girls and 7 boys aged 1–17 years. Tumor sites included head and neck, trunk, extremity, and groin. Eight patients underwent radical resection, with complete remission in 7 and local relapse in one which was treated with chemotherapy. Four patients underwent incomplete surgical resection, three with adjuvant chemotherapy. Five patients underwent biopsy only and chemotherapy. Two of the 9 chemotherapy-treated patients also had intraarterial chemoembolization. Chemotherapy usually consisted of vincristine and actinomycin-D with or without cyclophosphamide or low-dose vinblastine and methotrexate. Two patients also received tamoxifen.
Results: After a median follow-up of 3.3 years, 10 patients were alive in complete remission, 5 had stable disease, and 2 had reduced tumor size. Five-year overall survival was 100%, and event-free survival, 87.5%. Ten were screened for *CTNNB1* mutations. *CTNNB1* gene sequencing yielded mutations in 5/10 samples tested: 3 T41A, 2 S45F. There was no association of *CTNNB1* mutation with clinical outcome or prognosis.
Conclusion: Pediatric desmoid tumors are rare, with variable biologic behavior and morbidity. Treatment requires a multidisciplinary approach.
Level of evidence: LEVEL IV, treatment study.

Desmoid tumor, also known as aggressive fibromatosis, is defined by the World Health Organization as a clonal fibroblastic proliferation that arises in the deep soft tissues and is characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize. It is classified between benign fibrous tissue proliferation and fibrosarcoma [1,2]. Desmoid tumors are extremely rare, accounting for 0.03% of all neoplasms and less than 3% of all soft-tissue tumors. The estimated annual incidence in the general population is 2–4 per million per year [3]. There are two incidence peaks: ages 6 to 15 years and puberty to age 40 years [4]. Most of the tumors occur sporadically, and the rest are associated with hereditary cancer syndromes: autosomal dominant familial adenomatous polyposis (Gardner syndrome), hereditary desmoid disease, and familial infiltrative fibromatosis [4]. The tumors can develop at virtually any body site, although the abdominal wall and soft tissues of the extremities, shoulder, neck, and chest wall predominate [4]. Recurrence rates ranging from 30% to 40% have been reported in major published series [3].

Choosing the optimal therapy for desmoid tumors is difficult because of their variable anatomic presentations and the lack of prospective treatment trials. Watchful waiting is an acceptable strategy for

Abbreviations: CT, computed tomography; EFS, event-free survival; OS, overall survival; MRI, magnetic resonance imaging; MTX, methotrexate; TACE, transcatheter arterial chemoembolization; TNF-α, tumor necrosis factor alpha; VAC, vincristine and actinomycin-D with or without cyclophosphamide; VBL, vinblastine; VCR, vincristine.

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http://dx.doi.org/10.1016/j.jpedsurg.2017.01.068
0022-3468/

stable asymptomatic desmoid tumors. Indications for treatment include symptomatic disease, imminent risk to adjacent structures, and cosmetic concerns [5].

Before 2000, surgery with negative margins was considered the standard of care. Since then, in view of the heterogeneous behavior and benign nature of the disease, physicians have increasingly opted for more conservative resection, with acceptance of marginal and microscopically positive surgical margins, in order to preserve function [5].

Chemotherapy is an appropriate choice for patients who have rapidly growing or unresectable tumors or who are symptomatic. The two most frequently used regimens are so-called "low-dose" regimen of methotrexate and/or vinblastine/vinorelbine and the conventional regimen of doxorubicin with or without dacarbazine [5]. Other drugs used in children include vincristine, actinomycin, etoposide, cyclophosphamide, and/or ifosfamide [6]. Chemotherapy carries a risk of short- and long-term adverse effects, such as second malignancies, fertility problems, cardiotoxicity, and neuropathy, which limit its use.

Other therapies for desmoid tumors have been suggested, including radiotherapy, selective estrogen-receptor modulator, nonsteroidal anti-inflammatory drugs, interferon, tumor necrosis factor alpha (TNF-α), and tyrosine kinase inhibitors [3–8].

β-catenin is a cadherin-binding protein encoded by the *CTNNB1* gene, located on chromosome 3p21. It is involved in cell–cell adhesion and also functions as a transcriptional activator when complexed in the nucleus with members of the T-cell factor/lymphocyte enhancer factor family of proteins. The transcriptional role of β-catenin is important in mesenchymal cells, such as those in desmoid tumor [9]. The phosphorylation of β-catenin is mediated by a portion of the protein encoded by exon 3 of *CTNNB1* [10,11]. Activating *CTNNB1* gene mutations are identified in approximately 85% of cases of sporadic desmoid [12].

In this study, we present our long experience with desmoid tumors in children. The clinical and molecular data of the patients are described.

1. Patients and methods

1.1. Patients and treatment modalities

The study was approved by the local institutional review board. The database of a tertiary pediatric medical center was retrospectively reviewed for all patients diagnosed with sporadic desmoid tumor from January 1988 to May 2016. Patients were excluded if they had hereditary cancer syndromes, such as autosomal dominant familial adenomatous polyposis (Gardner syndrome), hereditary desmoid disease, and familial infiltrative fibromatosis. Clinical and molecular characteristics were derived from the medical files as follows: patient age, sex, and ethnic origin, presenting symptoms and signs, tumor location and initial size, treatment, and follow-up. Tumor characteristics were assessed by ultrasound and/or computed tomography (CT) and/or magnetic resonance imaging (MRI). All pathologic slides were reviewed by our pathologist from Beilinson Medical Center. Surgical procedures were categorized according to the 2005 European Pediatric Soft Tissue Sarcoma Study Group protocol for non-rhabdomyosarcoma soft tissue sarcoma [13] as follows: R0 = radical (microscopically complete) resection; R1 = marginal (microscopically incomplete) resection; R2 = intralesional (macroscopically incomplete) resection; and biopsy only. If radical resection was not possible at diagnosis, various neoadjuvant/adjuvant therapies were used, including systemic chemotherapy (mainly intravenous vincristine and actinomycin-D with or without cyclophosphamide (VAC) or vinblastine and methotrexate (VBL + MTX), and hormonal therapy (anti-estrogens). Transcatheter arterial chemoembolization (TACE) was used for vascular tumors with partial response to chemotherapy and were either at high surgical risk or recurred after surgical resection. TACE was performed by loading doxorubicin onto 100–300 μm inertic spheres (DC Beads®, BTG, London, UK) that were superselectively injected into the feeding vessels of the tumor. This procedure was approved by the local institutional review board.

All patients were followed with either CT or MRI scans on a regular basis.

1.2. Pathological review and mutational analysis

Formalin-fixed, paraffin-embedded desmoid tumor specimens from 10 patients were collected from the pathology archives. The specimens were evaluated by experienced pathologists to confirm the histological diagnosis of desmoid tumor.

DNA was then extracted from the tissue sections using the QIAamp DNA Mini Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's protocol. DNA yield and quality were measured with a NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA, USA). Polymerase chain reaction (PCR) analyses were performed with ReddyMix PCR Master Mix (ABgene, Surrey, UK) according to the manufacturer's protocol, using 100 ng of DNA for each reaction and 10 pmol of each primer [14]. Sequence analyses were run on the ABI 3730 sequencer (Applied Biosystems, Foster City, CA, USA).

1.3. Definitions

Response was defined according to the revised Response Evaluation Criteria in Solid Tumors [15]: complete response - complete radiological and clinical disappearance of all tumor lesions after surgery or medical treatment; partial response - a decrease of more than 25% of tumor diameter on radiological and/or clinical assessment; stable disease - absence of a decrease or an increase of less than 25% of lesion diameter without the appearance of any new lesions; progressive disease - increase of more than 25% in lesion diameter and/or appearance of new lesions. *Relapse* was defined as recurrence of a tumor at least 1 month after the end of treatment in a patient with a previous complete response [15].

1.4. Statistical analysis

Overall survival (OS) was calculated from the start of treatment to the last uneventful follow-up or death. Event-free survival (EFS) was calculated from the start of treatment to disease progression or relapse. OS and EFS were estimated according to the Kaplan–Meier method.

2. Results

The study group comprised 17 children (10 female and 7 male) of median age 3.3 years (range 1–17 years). Their clinical data are presented in Table 1. None had a family history of desmoid tumors, adenomatous polyposis coli, or Gardner syndrome, and none had experienced local surgical trauma prior to the appearance of the desmoid tumor. One patient (no. 10) had psychomotor retardation, blindness, and kyphoscoliosis, without any definitive genetic diagnosis. All other patients were healthy prior to diagnosis of the tumor. Tumor sites were variable: head and neck region, 7 patients; trunk, 7 patients; groin, 2 patients; extremity, 1 patient. Fifteen patients had a solitary lesion, one patient (no. 6) had 2 lesions, and one patient (no. 8) had 3 separate but adjacent lesions. Tumor size ranged from 0.7 to 20.0 cm. The most common presenting sign was a palpable mass/swelling. In one patient (no. 1), the mass, which occupied the oropharyngeal space, hypopharynx, and supraglottic and glottic areas (Fig. 1), caused life-threatening nasopharyngeal stenosis and tracheal deformation warranting tracheostomy tube insertion. He also had eating difficulties because of esophageal stenosis and required insertion of a gastrostomy tube.

The treatment, clinical course, and outcome are summarized in Table 2. Eight patients (nos. 2, 3, 6, 8, 11,12, 14, 17) underwent complete radical resection. Only one of them (no. 8) had a local relapse 1.5 years later which was treated with chemotherapy. The remainder achieved complete remission with no further therapy. Four patients were treated with incomplete surgical resection: 3 (nos. 5, 7, 16) marginal and one (no. 9) intralesional excision. Three out of them (nos. 5, 7, 9) received adjuvant chemotherapy. One patient (no. 5) needed further surgeries,

Please cite this article as: Shkalim Zemer V, et al, Sporadic desmoid tumors in the pediatric population: A single center experience and review of the literature, J Pediatr Surg (2017), http://dx.doi.org/10.1016/j.jpedsurg.2017.01.068