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AGGRESSIVE FIBROMATOSIS – CASE REPORT

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Aggressive fibromatosis or desmoid tumors are slowly growing fibroblastic neoplasms of intermediate malignancy. They are very rare in children. The optimal treatment modality has not been established. We report a case of a 6-year-old girl with a desmoid tumor of the nasal region. After surgical excision and re-excision, she had an evident local progression and received systemic chemotherapy. The complexity of recognition and multidisciplinary management with an individualized approach is highlighted.

Key words: Aggressive fibromatosis ▪ Desmoid tumor ▪ Child

Introduction

Aggressive fibromatosis (AF), also known as desmoid tumor, is very rare pediatric neoplasm arising from musculoaponeurotic connective tissue. AF is characterized by local invasive growth, a high tendency to local recurrence, and the absence of metastatic potential. The pathogenesis is most likely multifactorial, and includes genetic predisposition, endocrine factors and trauma. The typical clinical presentation is a painless, slowly growing deep-seated mass. Due to the localization, AF is usually divided into abdominal and extra-abdominal (1,2). Extra-abdominal AF of nasal structures is extremely rare (3). This paper presents a girl with the nasal AF who was referred to the pediatric oncologist after two surgical resections and progressive local growth.

Case report

A six-year-old girl was transferred to the Division of Hematology and Oncology, Department of Pediatrics, Clinical

Hospital Center Rijeka, after reoperation of the tumor in the nasal area at the Department of Head and Neck Surgery. Two months before the first hospitalization in another institution, the mother noticed a painless mass on the ridge of her nose, increasing in size during the following weeks. The medical history was unremarkable. The first complete macroscopic resection was done. Subsequent examination of medical records revealed that surgical margins were microscopically positive. The histopathologic findings described distinct cellularity and high proliferative activity. The definitive diagnosis was not established, considering well-differentiated fibrosarcoma and myofibroblast-fibrohystiocytic tumor. Three weeks after the first surgery, re-growth of the mass was observed. The surgeon decided to re-operate, and complete resection was performed with a plastic reconstruction of the skin defect using a flap from nasolabial area. The patient was referred to our Clinic for further evaluation and treatment.

At admission the girl was in good general condition, with weight and height below the 10th percentile for age. The local finding included visible and palpable soft tissue edema in the nasal ridge and right nostril, with the longest diameter of 3 cm. Other clinical findings were unremarkable. Laboratory findings were within normal limits. X-ray of nasal bones showed no bone destruction. Ultrasound demonstrated soft tissue edema without residual tumor. Given the inconclusive pathohistological findings, additional review of two independent pathologists was requested. Definitive diagnosis of aggressive fibromatosis was established. Histologically, the tumor was characterized by numerous mitosis and positive surgical margins.

Two weeks after the second operation local tumor re-growth on the flap edges was observed, verified by magnetic resonance imaging (MRI). Further treatment was done with adjuvant systemic chemotherapy. The girl received vinblastine (5 mg/m2 per dose) and methotrexate (30 mg/m2 per dose) intravenously, once weekly for the first 26 weeks, and once every other week for the next 26 weeks. Two weeks after the start of the treatment, there was an evident regression of the tumor, confirmed by ultrasound. Control MRI after 3 months of chemotherapy was normal. During the treatment, mild hematological (grade 1) and hepatic (grade 2) toxicity was observed, which did not require discontinuation of therapy. Hospitalizations were often prolonged due to the poor compliance of parents and geographical isolation. In the seventh week of the treatment the girl was admitted due to the paralytic ileus, which resolved with conservative measures. On several occasions she had suppurative sinusitis and was treated with antibiotics. After one year of chemotherapy, MRI was performed which confirmed the remission. Three months after the end of the treatment, the patient is well without signs of disease.

Discussion

AF or desmoid tumor is a rare mesenchymal neoplasm arising from the muscle connective tissue, fasciae and aponeuroses. The annual incidence is 6 to 8 persons per million, with relative peaks in incidence between 6 and 15 years of age and between puberty and age 40 in women (4). AF is more frequent in women than in men with odds ratio from 2:1 to 5:1 (2). The incidence of pediatric AF is estimated at 2 to 4 children per million per year. The most frequent is at around 8 years of age with a slight prevalence in boys (1).

The pathogenesis of AF is not well defined. Prior trauma, radiation, endocrine factors and genetic predisposition may be causative factors (2, 4). Besides sporadic cases, AF may also occur as a part of familial adenomatous polyposis (FAP) and Gardner's syndrome. The incidence of AF in FAP is 10

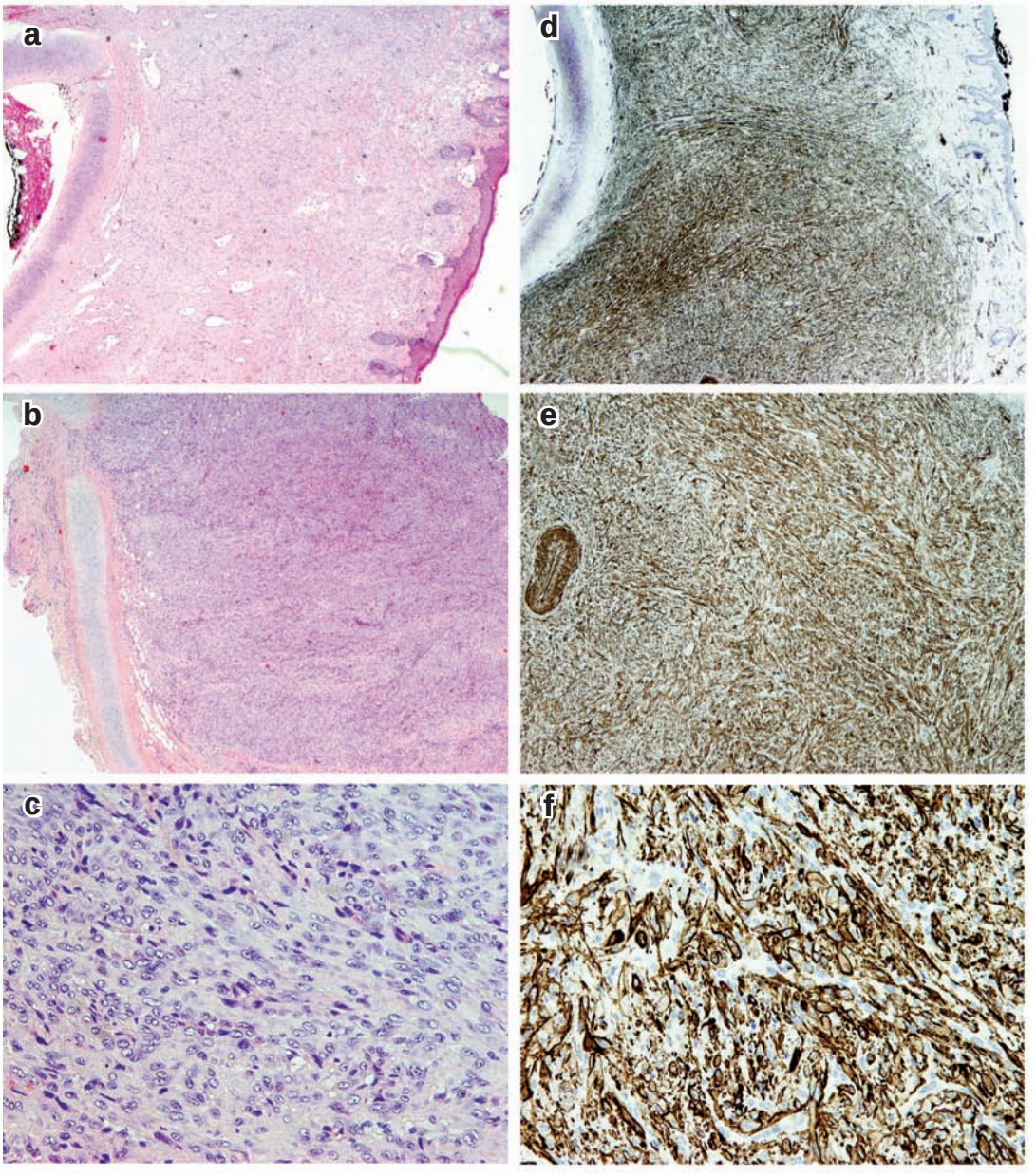

Figure *Aggressive fibromatosis – hemalaun eosin (HE) stain section (a, b, c) and immunohistochemical staining for smooth muscle actin (SMA) (d, e, f). Low-power view of the lesion involving the dermis (a, d, e) and hyaline cartilage of the ala of nose (b). High-power view shows cellular proliferation of ovoid cells without atypia (c) and positive for SMA (f)*

to 15%, and the risk of developing desmoid tumors is 1000 times greater in patients with FAP as compared to the healthy population. AF occurs in 30% of patients with Gardner's syndrome, characterized by by the presence of multiple polyps in the colon, soft tissue tumors and multiple osteomas (2).

Histologically, AF is characterized by monoclonal proliferation of well differentiated fibroblasts and myofibroblasts, surrounded or separated by abundant collagenous stroma (1). Cellularity and mitotic activity are extremely variable. Tumor cells do not show any hyperchromasia or atypia. Immunohistochemically they are positive for actin and vimentin, and the extent of staining correlates positively with cellularity. They are rarely positive for desmin and S-100 protein (1, 2).

Most sporadic desmoid tumors contain a somatic mutation in either beta-catenin or APC genes, resulting in beta-catenin protein stabilization. This protein plays an important role in cell-to-cell adhesion, signal transduction, regulation of gene expression, and interaction with other proteins. The degradation of beta-catenin is responsibility of the APC protein. Beta-catenin acquires oncogenic activity when it is mutated or when it is up-regulated as a result of inactivation of APC (2, 5).

AF is usually classified according to localization into abdominal and extra-abdominal. This classification has a clinical significance. Abdominal AF involves either the abdominal wall, particularly the lower part of the flat abdominal muscles, or the abdominal cavity where it arises from the mesentery or any muscle structure. It is primarily characterized by hereditary nature, diffuse infiltrative growth and surgical inoperability. Therefore systemic therapy is considered as a first-line treatment. In 70 to 90% of cases it occurs in women of child-bearing age. Extra-abdominal AF can occur anywhere in the body but most commonly it involves the shoulder girdle and upper arm, the thigh, the buttock, and the trunk (2). In 10% of cases it occurs in the head and neck area. Almost always it infiltrates skeletal muscles, and is rarely multicentric (5). Extra-abdominal form is predominantly sporadic. In general, surgical resection is the first-line treatment and systemic therapy is reserved for refractory tumors. The majority of patients are between 15 and 45 years of age, and sometimes it occurs in children. The most common presentation is a slowly growing painless formation. Due to the pressure or infiltration of surrounding structures, there might occur pain, deformity and organ dysfunction. AF has a high tendency to local relapse, even after surgical resection (6). It has no ability to metastasize. Magnetic resonance imaging is the modality of choice, for the best demonstration of the lesion extension or recurrence.

Given the heterogeneity of the disease in terms both of localization and biological behavior, the optimal therapeutic approach has not been established (7). There are several treatment options: surgical resection, radiotherapy, chemotherapy and non-cytotoxic therapy. The standard treatment for sporadic localized AF is wide surgical resection (8, 9). The rate of recurrence after surgical excision varies from 10% to 80%, depending on whether the surgical margins were negative or positive (4). Local control of disease is achieved by radiotherapy at doses of 50 to 60 Gy in 75 to 85% of adults (10, 11), either as a single therapeutic option or combined with surgery. The use of radiation in children is very limited because of the potential long-term cosmetic effects, functional deformities and risk of developing secondary neoplasms. Pharmacotherapy is not clearly defined due to the small number of treated patients and different combinations of drugs (12, 13). Drugs that are used are cytostatics (vinblastine, vincristine, vinorelbine, methotrexate, dactynomicin, doxorubicin, dacarbazine, cyclophosphamide, carboplatin) alone or

more frequently in combinations (12, 14, 15, 16), hormonal agents (mostly estrogen antagonist tamoxifen, toremifen, progesterone, medroxyprogesterone acetate, aromatase inhibitor testolactone, gonadotropyn releasing hormone agonist goserelin), nonsteroidal anti-inflammatory drugs (indomethacin, sulindac) and biological agents (interferon-α and-γ, imatinib mesylate) (13, 17).

This paper presents pediatric extra-abdominal AF of extremely rare localization. Our case points to several important observations. Although rare, desmoid tumors should be considered in children. Infiltrative nature of the tumor makes it difficult for the surgeon to assess the true microscopic extent. According to the literature, the percentage of positive surgical margins varies from 44% to 61%. (5). Given the great variability of tumors, it is to be bear in mind that negative surgical margins do not mean absolute control of the disease, neither positive margins necessarily predict local recurrence. Histopathological diagnosis is of crucial importance. The differential diagnosis includes fibrosarcoma, nodular fasciitis and reactive fibroblastic proliferation. Cellularity and high mitotic activity in this patient confirm the extreme histological variability of AF. Our observation about more aggressive tumor growth after surgery is also described in the literature (2). In the case of relapsed or refractory tumors, it is necessary to apply systemic therapy instead of mutilating surgery procedures. With low-dosage combined chemotherapy (viblastine/methotrexate), remission was achieved, and the girl tolerated therapy well.

Conclusion

AF is a benign tumor but not benign disease; it has variable localization, histological and biological behavior. The paper emphasizes the complexity of recognizing and treating these tumors. Multidisciplinary individualized approach leads to the optimal treatment (8). Due to the high rate of local relapses it is necessary to perform long-term follow-up.

Conflict of Interest: The authors declare that they have no conflict of interest. This study was not sponsored by any external organisation.

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