Hydroxyurea Treatment Can Avoid the Need for Aggressive Surgery in Pediatric Fibromatosis

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Summary: Aggressive fibromatosis (AF), also known as desmoid tumor, is a rare neoplastic proliferation of connective tissue. It occurs in 0.2 to 0.4 per 100,000 population/y and may be associated with Gardner syndrome or familial adenomatous polyposis.1–3 Its pattern of growth is often unpredictable and lesions can go through alternate periods of rapid growth and stabilization, or increase slowly over several years. Spontaneous regressions have also been observed, particularly in pregnancy-associated AF.4 Although it never metastasizes, AF tends to infiltrate nearby organs, interfering with their function. Surgery is considered the mainstay of treatment, but complete resection is often unfeasible and a high local recurrence rate is reported.4 Various systemic treatments have been explored to improve results, mainly involving the administration of chemotherapy or noncytotoxic agents such as hormone therapy or anti-inflammatory agents.5 The response rate varies considerably, making it necessary to investigate other agents potentially active against AF.

We report the case of a 15-year-old boy who developed AF of the left thigh, and who was spared potentially mutilating surgery because the tumor responded to hydroxyurea, an antineoplastic drug generally used for hematological disorders.

CASE REPORT

A 10-year-old boy presented to a local hospital with a days-old history of left thigh swelling. His previous history was unremarkable. Ultrasound revealed a 9 × 5.5 × 4.5 cm mass in the posterior region of the thigh and magnetic resonance imaging (MRI) confirmed the lesion. Total body computed tomography excluded any distant metastases or other lesions. In January 2006, the patient was referred to our Division for further assessment and treatment. Complete conservative tumor resection was judged to be unfeasible because of the extent of the tumor, and the child underwent biopsy.

Histopathologic examination identified an AF, and the child was given chemotherapy according to the guidelines of the EpSSG NRSTS 2005 protocol, that is, methotrexate (30 mg/m²) and vinorelbine (6 mg/m²) delivered weekly by intravenous infusion. After 10 months, MRI showed only minimal tumor shrinkage. The child underwent surgery and the mass was macroscopically resected but histologic examination identified tumor-infiltrated margins. The boy was then given radiation therapy with 50.4 plus a boost of 14.4 Gy. He gradually developed a limp.

On August 2010, 3 years after the end of treatment, a rapidly growing mass became clinically evident and MRI studies confirmed a relapse probably originating from the superior margin of the previous resection. A new biopsy confirmed AF. The lesion infiltrated the obturator internus and adductor muscles, coming into close contact with the femoral neck cortex and the ipsilateral ischium-pubic branch with no bone infiltration. Conservative resection was considered unfeasible, and oral hydroxyurea was administered at a dose of 20 mg/kg/d. The response to therapy was assessed on MRI every 3 months. The treatment was very well tolerated and, over the course of 1 year, we observed a slow but constant volumetric and morphologic tumor response (Fig. 1). The lesion has an irregular infiltrating shape, making it difficult to calculate the real size reduction of the mass. It is even more difficult to quantify the evident change in the signal intensity of the mass due to the presence of areas with different characteristics within the lesion. A free, open-source medical imaging software was used in an attempt to better quantify these changes in the tumor. The 64-bit OsiriX rel. 3.3 was downloaded from: http://www.osirix-viewer.com. A special tool was used to calculate the tumor’s area, which allows for a region of interest to be drawn freehand in a particular slice (Fig. 2). The software returns the area of the region of interest (in cm²) and the mean pixel intensity. An axial slice corresponding to the same portion of the tumor was selected from each 3-monthly MRI and the tumor’s area was calculated and compared (Fig. 3). To quantify tumor vascularity, we calculated the ratio of the mean signal intensity of the tumor to that of healthy muscle remote from macroscopically apparent blood vessels (Fig. 3). Only a minimal reduction in tumor volume was evident, from 29 to 26 cm², but—probably more importantly—its mean signal intensity changed substantially from 1.4 to 1.1. We interpreted the latter as a change in the tumor morphology with a reduction in its vascularity and the fibrotic transformation of a substantial part of the vital tumor. Given the ongoing response at the time of writing this report, hydroxyurea treatment is still underway.

DISCUSSION

AF is a rare mesenchymal tumor classified as an intermediate malignancy because of its strong potential for recurrence and local invasiveness, which can result in significant damage to nearby organs. When complete resection...
is unfeasible, the treatment of AF may be a real challenge because the options are limited and are of uncertain efficacy. Radiotherapy can be used as a complementary treatment but its role is still unclear, especially in children in whom late sequelae are more worrisome. 

Various systemic therapies have been explored in children, based on experience gained with adult AF. Antiestrogens or nonsteroidal anti-inflammatory drugs have shown only limited benefits. On the basis of some AF tumor samples’ expression of platelet-derived growth factor (PDGFRα and PDGFRβ) and cKIT, the multityrosine kinase inhibitor imatinib was recently tested, but only a very limited activity was seen. Chemotherapy is consequently still the most often used systemic treatment. Cycles of multidrug regimens based on doxorubicin, alkylating agents, vincristine, and actinomycin D have recently been replaced by the prolonged administration of methotrexate and vinblastine or vinorelbine. Up to 50% of cases have shown some kind of response to this combination, but this may take time so these drugs should be administered for up to 12 to 18 months.

We initially used the methotrexate-vinorelbine combination in the child described here but only a minimal response was noted. When his disease recurred, we consequently considered a different approach and decided to try hydroxyurea, an antineoplastic drug used in myeloproliferative disorders, and specifically in polycythemia vera and essential thrombocytopenia. It is also used to reduce the rate of painful attacks in sickle-cell disease and has antiretroviral properties. Its mechanism of action is thought to depend on a reduced production of deoxyribonucleotides due to inhibition of the enzyme ribonucleotide reductase by scavenging tyrosyl-free radicals as they are involved in the reduction of ribonucleoside 5’-diphosphates. Whether or not this is the mechanism of action against AF remains to be seen. A possible role of hydroxyurea in children with fibromatosis has recently been published: Balamuth and Wormer reported in abstract

![FIGURE 1](image1.png) T1-fat-suppressed sequence of the thigh with contrast enhancement. Serial follow-up images from August 2010 to June 2011 show a small volumetric and morphologic tumor response.

![FIGURE 2](image2.png) OsiriX interface. The largest region of interest surrounds the tumor, whereas the smallest is used to calculate the average intensity of pixels in healthy muscle.
form on 4 complete responses and 7 tumor stabilizations in a series of 20 patients with fibromatosis. A case reported by Meazza et al. showed an objective response after 3 months of hydroxyurea treatment that persisted until the follow-up assessment 4 months later. Our report confirms the hypothesis that hydroxyurea may be a valuable therapeutic option for children with AF refractory to other treatments.

Stabilizations and, exceptionally, spontaneous regressions of AF lesions have recently been described in adults managed according to a wait-and-see strategy. In a series of 26 patients followed up with no treatment, the tumor growth stabilized at a median 14 months; MRI identified no change in signal intensity in these lesions, however, and this may indicate a still active process posing patients at risk of late progression. There are no factors known to predict tumor stabilization, so it is very difficult to decide whether or not to treat patients with a lesion that is evolving.

In our case, the previously rapid growth of the lesion stopped after starting hydroxyurea treatment, and a continuous response to the treatment was evident on MRI in terms of a reduction in the tumor size and enhancement. This result enabled us to avoid performing demolitive surgery and the patient is now conducting a normal life, despite some sequelae due to the more aggressive treatment adopted after the initial diagnosis. Further studies are needed to establish the role of hydroxyurea in AF therapy, also taking into account its secondary leukemogenic effects.

**REFERENCES**