Clinical Article

Congenital Fibrosarcoma: Report of One Case Treated With Pre-Surgical Chemotherapy

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Abstract

This is a case of Congenital Fibrosarcoma in a 10-day-old baby girl who presented with a mass in the right posterior thigh. Because of involvement of the sciatic nerve, surgery was not indicated. The patient was placed on pre-surgical chemotherapy with Vincristine and Actinomycin-D. No alkylating agents were given. Significant improvement was attained and surgery was successfully performed..
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Introduction

Fibrosarcomas account for approximately 10% of soft tissue sarcomas in children. The clinical behavior of fibrosarcoma occurring in the first 5 years of life (infantile or congenital) differs from that observed in older children and adults. Local recurrence is a common problem in patients with infantile fibrosarcoma, but the development of metastasic spread is rare. Overall survival is greater than 90%.[1]

The treatment of choice is complete excision, with some cases also requiring amputation.[2] It is possible that initial therapy with chemotherapy could convert the surgical approach in selected patients from amputation to less radical surgery.

Case Report

A baby girl was born at term to a 33-year-old woman G4 P2 via c/s due to breech presentation. Birth weight was 7 lb and 8 oz. There were no complications after delivery and the baby was discharged home 72 hours after birth.

At 10-days of life, she presented to the emergency room with two days history of constipation. During physical examination, the patient was found to have a firm, non-mobile mass extending to the right buttock area.

An x-ray of the pelvis and hip was performed with no reported abnormalities. An ultrasound examination was done and revealed a mass in the right posterior thigh, just inferior to the gluteal area. Doppler imaging showed blood flow within the mass.

Subsequently an MRI of the right-lower extremity was obtained and confirmed the presence of a multilobulated enhancing tumor mass in the right posterior thigh measuring 7.4 cm in height, 3.5 cm in AP and 3.1 cm in transverse diameter, extending along the course of the sciatic nerve until the margin of the sciatic notch, but without intrapelvic extension. (Figs 1, 2)

An incisional biopsy was performed and histological studies demonstrated the diagnosis of Congenital Fibrosarcoma.

Histologically the tumor was composed of densely packed sheets of relatively uniform; ovoid to spindle cells (the so called "medullary" type) arranged in short fascicles and imparting a herringbone configuration (Fig 3). There was little by way of nuclear pleomorphism but frequent mitoses were encountered. Small zones of almost palisading necrosis were present (Fig 4). The vascular pattern was vaguely hemangiopericytoma-like. There was a sparsely lymphoplasmacytic inflammatory infiltrate particularly around zones of necrosis.

Immunohistochemical studies were done; the ovoid to spindle cells were characteristically strongly positive for vimentin and factor XIII (Fig 5). There was also focal weak positivity for muscle specific actin. Skeletal muscle stains and myogenin were negative ruling out

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Fig 1 - Coronal T2 weighted images through the region of the buttocks demonstrate a right bilobed well-circumscribed mass displacing the gluteus maximus, semitendinous and adductor magnus muscles. The signal intensity of this tumor is predominantly intermediate signal intensity.

Fig 2 - Axial fat saturation T1 weighted images through the region of the buttocks, to demonstrate lobulated mass that is just deep to the lower aspect of the right gluteus. The signal intensity of this mass is intermediate on T1.

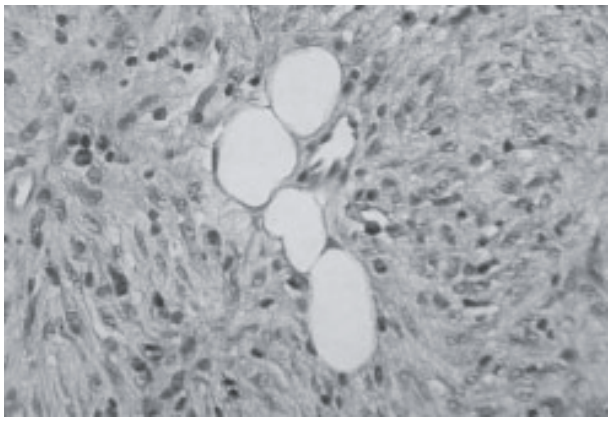

Fig 3 - High power H+E view of Congenital Fibrosarcoma demonstrating short fascicles of fibroblasts with occasional mitoses and scattered inflammatory cells.

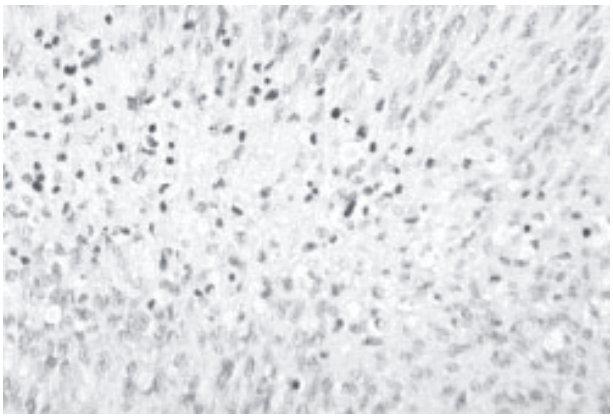

Fig 4 - Palisaded necrosis seen on high power light microscopic examination of Congenital Fibrosarcoma.

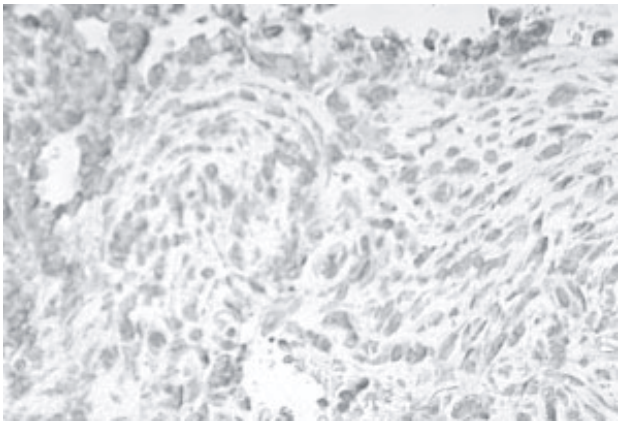

Fig 5 - Diffuse Vimentin positivity in tumor cells.

the more common childhood sarcoma-embryonal rhabdomyosarcoma. The neural markers S-100 were negative as was the epithelial marker keratin, ruling out such entities as neurofibrosarcomas, desmoplastic small round cell tumor and rhabdoid tumors.

Cytogenetic studies were done and attempts were made to isolate the fusion product ETV6:NTRK3. FISH was performed with the 26j23 (specific for the 5' end of ETV6) and 144.23 (specific for the 3' end of ETV6) probes at 12p13 on interphase nuclei extracted from formalin-fixed paraffin embedded tissue. However, the hybridization/detection was unsuccessful technically possibly due to denaturation of DNA strands in the fixation process. The study was attempted courtesy of the Cytogenetics laboratory at Brigham and Women's Hospital.

Complete staging was performed, including CT scan of brain, chest and abdomen; a bone scan and also a bone marrow aspiration, without the evidence of metastasis.

Orthopedic and pediatric surgery services were consulted, but due to the involvement in the sciatic nerve, surgical excision was not recommended. The patient was placed on modified VAC chemotherapy regimen with Vincristine and Actinomycin-D at only 50% of the usual dose, without an alkylating agent. Once the chemotherapy course was finished, a follow-up MRI of the right lower extremity was done. This study showed significant decrease in the mass size, measuring 5 cm in height by 3 cm in AP dimension by 1.2 cm in transverse diameter. All of these findings are compatible with residual tumor. (Fig 6)

Complete excision of the mass was successfully performed and repeat biopsy showed only fibrosis and inflammation without the characteristic tumoral histology seen on the central biopsy. (Fig 7)

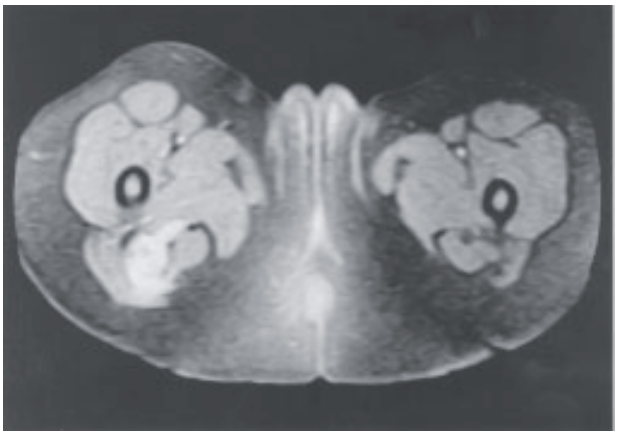

Fig 6 - Axial fat saturation T1 at the right upper thigh demonstrates a focal area of slightly high signal intensity where the previously described mass was; dorsal to the quadratus femoris muscle and ventral to the gluteus maximus muscle.

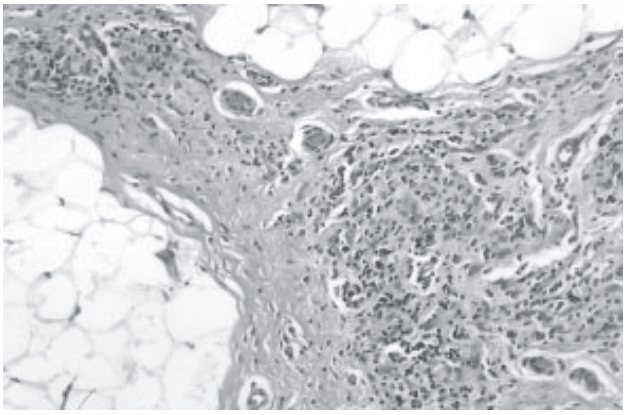

Fig 7 - Inflammatory changes noted on light microscopic examination of post chemotherapy surgical resected specimen.

Discussion

Fibrosarcoma, from birth to early childhood, has a significant morphologic resemblance to its adult counterpart, but it is considered a separate entity because of its very different clinical behavior. It must also be distinguished from infantile fibromatosis, aggressive childhood sarcomas (e.g., embryonal rhabdomyosarcoma) and fibrosarcomas in older children.[2]

Infantile fibrosarcoma is relatively rare. It is called congenital due to the fact that it is present at birth in approximately 37% of the cases.[3] Initially, it usually presents as a nontender, painless swelling or mass that ranges from 1 to 20 cm. Most of the time the mass becomes evident during the first year of life. It is slightly more common in males than in females. The principal site of involvement is the extremity, especially the regions of the foot, ankle, and lower leg and the hand, wrist and forearm. Other areas of involvement include the trunk and the head and neck regions, although these tumors have also been reported in such locations as the retro peritoneum, mesentery and orbit.[1,2]

Radiographic examination may show, in addition to a soft tissue mass, cortical thickening, bending

deformities, and relatively extensive destruction of underlying bone.

Histologically, most of these tumors closely resemble their adult counterparts and are composed of sheets of solidly packed spindle-shaped cells that are relatively uniform in appearance and arranged in bundles or fascicles, imparting a herringbone appearance. The cells show little nuclear pleomorphism and are mitotically active, but their numbers vary from area to area in the same tumor. Tumors with abundant collagen tend to be more fasciculated and often approach the appearance of an adult fibrosarcoma. Tumors with minimal amount of collagen, on the other hand, show a lesser degree of cellular polarity and consist of small, more rounded, immature-appearing cells with only focal evidence of fibroblastic differentiation. Dahl et al distinguished between the "medullary" type, characterized by a compact arrangement of monomorphous ovoid cells with a less conspicuous fascicular arrangement and scant stromal collagen, and the "desmoplastic" type, composed of uniform spindle-shaped cells arranged in a distinct fascicular pattern with more prominent stromal collagen.[4] As in the adult fibrosarcoma, multinucleated giant cells are rare. Scattered chronic inflammatory cells, particularly lymphocytes, are another common, sometimes striking feature that helps distinguish infantile from adult fibrosarcoma. Some tumors are characterized by a prominent hemangiopericytoma-like vascular pattern that may cause confusion with infantile hemangiopericytoma.

Immunohistochemically, the spindle cells of infantile fibrosarcoma stain for vimentin and variably for muscle markers including muscle-specific and smooth muscle actin, and may also stain positive for factor XIII. The more primitive-appearing ovoid cells tend not to express these muscle markers. Stains for desmin, myoglobin and S-100 protein are generally negative.

Ultra structural examination reveals fibroblast-like cells with large irregular nuclei, one or two nucleoli, free ribosomes, a well-developed Golgi apparatus, and a prominent, often dilated rough endoplasmatic reticulum, sometimes containing amorphous material. Bundles of thin filaments characteristic of myofibroblastic differentiation may be present. Some authors have reported cells with histiocyte-like features.[2]

Numerous studies have noted a nonrandom gain of chromosomes 11, 20, 17, and 8 (in descending order of frequency) in infantile fibrosarcoma. Using fluorescence in situ hybridization techniques, Schfield et al found gains of these chromosomes (in various combinations) in 11 of 12 infantile fibrosarcomas in patient less than two years of age. In contrast, alterations of these chromosomes were not found in four fibrosarcomas in patients 6 – 17 yeas of age. Interestingly, one of three cases of "cellular fibromatosis" also showed the above cytogenetic abnormalities, suggesting "these two entities are on spectrum and that their distinction may not be clear-cut".[2]

More recently, it has been found that most infantile fibrosarcomas and cellular mesoblastic nephromas have the same diagnostic chromosomal translocation: t (12, 15) (p13; q25). This translocation results in function of the *ETV6* gene (also known as *TEL*) on chromosome 12 with the neutropin-3 receptor *NTRK3* (also known as *TRKC*) gene on chromosome 15. Although this translocation is difficult to detect by conventional cytogenetic means, it can be readily demonstrated by the reverse transcriptase-polymerase chain reaction or fluorescence in situ hybridization using frozen or paraffin-embedded tissue. Most studies have found infantile fibrosarcoma to be diploid, in keeping with the low-grade behavior. When compared to adult fibrosarcomas, the infantile form has a higher apoptotic index and a lower proliferative index using antibodies to the Ki-67 antigen. In addition, p53 gene mutations are rare in fibrous tumors of infancy and childhood, including infantile fibrosarcoma.[2,5]

The clinical course of infantile fibrosarcoma is more favorable as compared to the adult type. For congenital fibrosarcomas that arise in axial locations, the local recurrence rate is similar to that for extremity tumors (33%); however the metastasic rates are higher (26%) compared with 10% or less for extremity primaries.[2,5,6]

Despite rapid growth and a high degree of cellularity, treatment with wide local excision without additional radiation or chemotherapy is usually successful in most cases. In some cases amputation is necessary if the extent or large size of the tumor precludes surgical therapy. A number of reports have indicated that preoperative chemotherapy is useful for decreasing tumor bulk, enabling a more conservative surgical approach.[1,5,7-9] Chemotherapeutic regimens that have been used included Ifosfamide, Vincristine, and

Dactinomycin; Vincristine, Dactinomycin, and Cyclosphophamide; and Vincristine, Dactinomycin without an alkylating agent. Vincristine and Dactinomycin are preferred initial agents because of their relative lack of long-term side effects and decreased leukemogenesis.[5] There are also reports of success with postoperative chemotherapy and with chemotherapy alone as a mode of treatment for inoperable tumors.[1] There is very little experience with primary radiation therapy for the treatment of infantile Fibrosarcoma. The value of radiotherapy is difficult to assess, as it has been used only in selected cases.[1,2]

As demonstrated in this patient, the use of only two chemotherapeutic drugs at 50% of the regular dose with no alkylating agents was effective, significantly decreasing the tumor size, thus improving the patient's surgical outcome and reducing the risk of permanent damage to the affected limb.

References

1. Grier HE, Perez-Atayde A, Weinstein HJ. Chemotherapy for inoperable Infantile Fibrosarcoma. *Cancer*. 1985;56:1507-1510.
2. Weiss SW, Goldblum JR. Congenital and infantile Fibrosarcoma In: Enzinger and Weiss' *Soft tissue tumors*. St. Louis, MO: Mosby; c2001.
3. Ninane J, Gosseye S, Panteon E, Claus D, Rombouts JJ, Cornu G. Congenital Fibrosarcoma: preoperative chemotherapy and conservative surgery. *Cancer*. 1986;58:1400-1406.
4. Dahl I, Save-Soderberg J, Angervall L. Fibrosarcoma in early infancy. *Pathol Eur*. 1973;8:193-209.
5. Pizzo PA, Poplack DG. Congenital Fibrosarcoma In: *Principles and Practice of Pediatric Oncology*. Philadelphia, PA; c2002.
6. Delepine N, Cornille H. Desbois JC, delepine G, Voisin MC. Complete response of congenital fibrosarcoma to chemotherapy. *Lancet*. 1986;2:1453-1454.
7. Kynaston JA, Malcom AJ, Craft AW. Chemotherapy in the management of infantile Fibrosarcoma. *Med Pediatr Oncol*. 1991;19:378.
8. Desbois JC, Delepine N, Cornille H, Delepine G. Cogenital Fibrosarcoma: a case for neoadjuvant chemotherapy. *Med Pediatr Oncol*. 1991;19:366.
9. Renard M, Brock P, Kruger M, et al. chemotherapy in congenital Fibrosarcoma. *Med Pediatr Oncol*. 1991;19:362.