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Infantile fibrosarcoma of thigh – a case report –

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ABSTRACT

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Infantile fibrosarcoma is a rare soft tissue malignant tumor, when it occurs, it is usually seen in the first year of life. The clinical course of infantile fibrosarcoma is more favorable and metastasis is rare compared with that in adulthood. While adult fibrosarcoma are common in the thigh, infantile fibrosarcoma affect chiefly the distal portions of the extremities. Standard treatment is primarily wide surgical excision. In this case report, we present our experience of an infantile fibrosarcoma of thigh with good clinical course 36 months after tumor resection and the usefulness of detecting the ETV6-NTRK3 gene fusion in differential diagnosis.

INTRODUCTION

Infantile fibrosarcoma is a fibroblastic tumor occurring specially in newborn and young children, generally in the first year of life [1]. Despite histologic similarities, the infantile type of fibrosarcoma is a clinically distinct entity with better prognosis than the adult type [2, 3]. The incidence of infantile fibrosarcoma is very low, i.e. 5 cases per one million infants which is similar to that of rhabdomyosarcoma [4], and 7% of infants with mesenchymal neoplasm [5]. In infantile fibrosarcoma, the extremities are often involved; 70% of the reported cases occur at this site, followed by head, neck and then the trunk [6,7].

We present a case of infantile fibrosarcoma of thigh in a four months old child. The case is being presented for its rarity and its successful treatment by limb saving surgery and the usefulness of detecting the ETV6-NTRK3 gene fusion in differential diagnosis.

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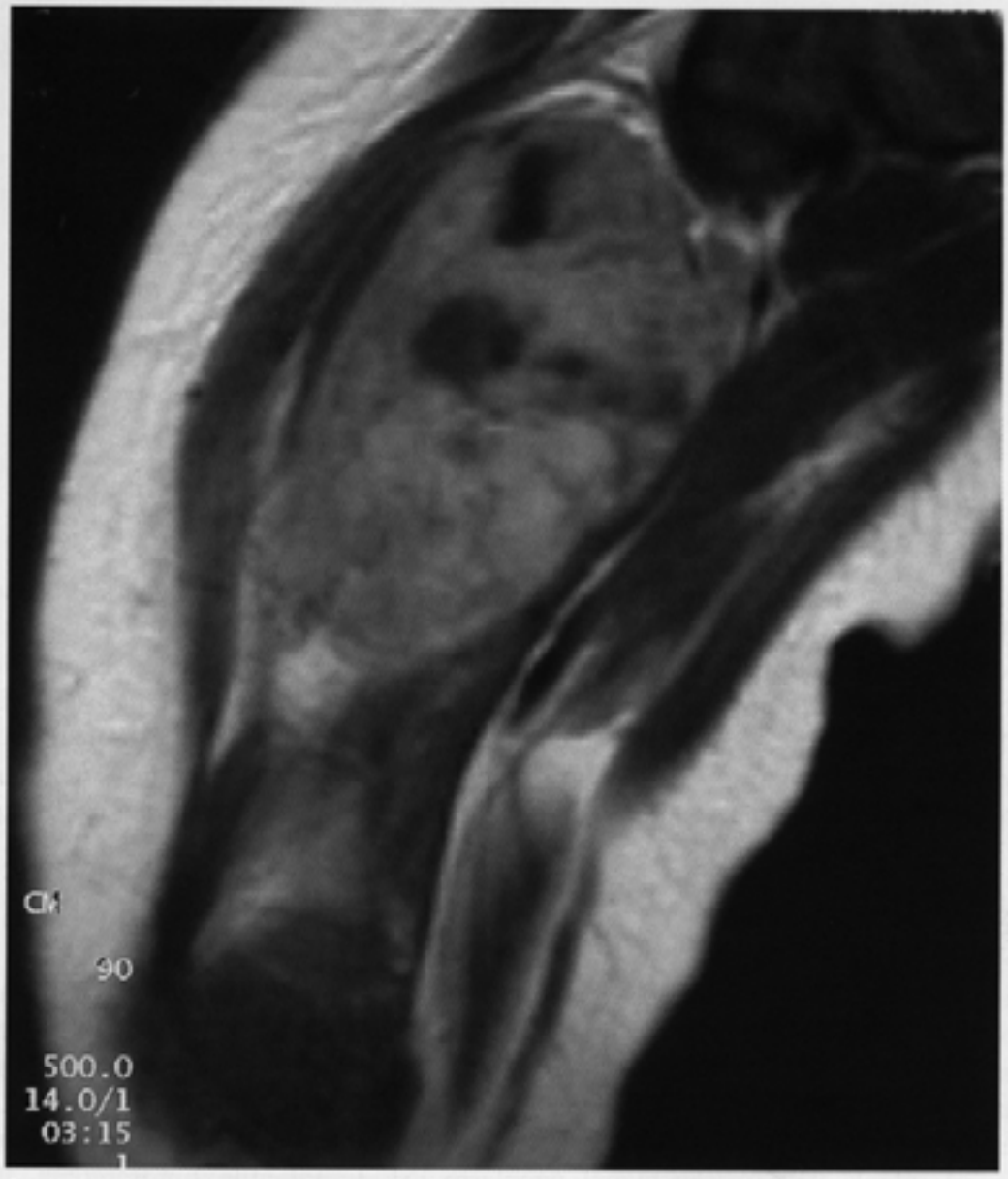

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Fig 1. Magnetic resonance imaging (MRI) showing an 8×5×5 cm heterogeneous mass with central cystic-necrotic areas. a) T1 weighted coronary image after Gd-DTPA enhancement, b) T2 weighted coronary image.

CASE REPORT

A four-months-old male infant visited our outpatient clinic because of swelling of the right thigh, noted by his parents one week before. He was the product of a normal, full-term delivery and weighted 3200 g at birth. Physical examination revealed a firm, unclear marginal mass with smooth surface and restricted mobility to bone and skin without tenderness, local heat and redness, occupying the proximal to mid-

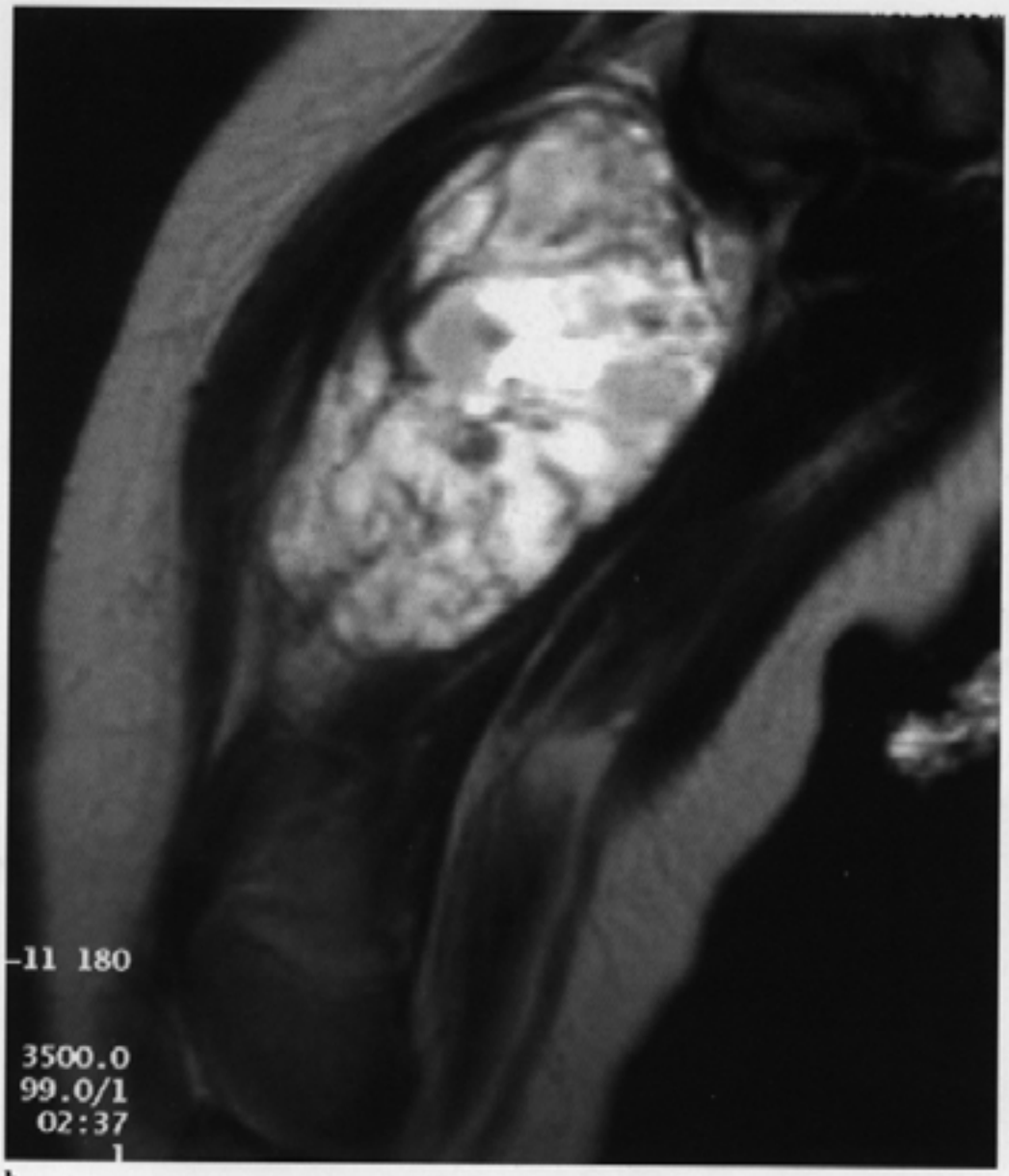

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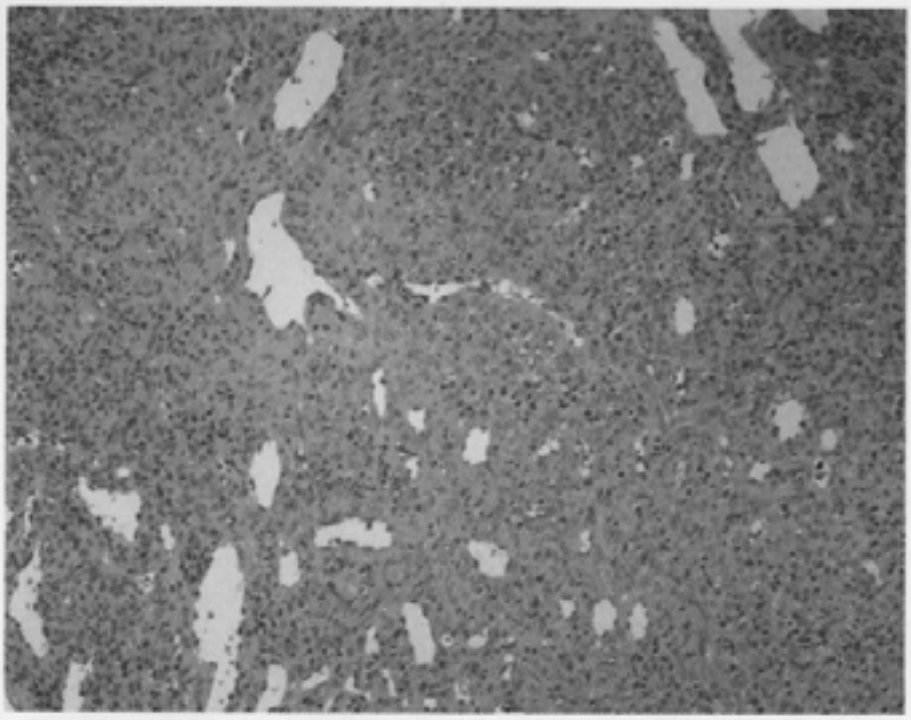
Fig 1. Magnetic resonance imaging (MRI) showing an 8×5×5 cm heterogeneous mass with central cystic-necrotic areas. a) T1 weighted coronary image after Gd-DTPA enhancement, b) T2 weighted coronary image.

dle part of the right thigh. A plain X-ray of the thigh showed a soft tissue swelling but no periosteal reaction of the femoral bone. Routine blood and urine examinations were normal. The chest-abdominal computed tomography and the bone scintigram showed no evidence of metastasis. MRI presented a 8×5×5cm solid inhomogeneous mass in the quadriceps muscle contacting with femoral bone (Fig. 1). Open



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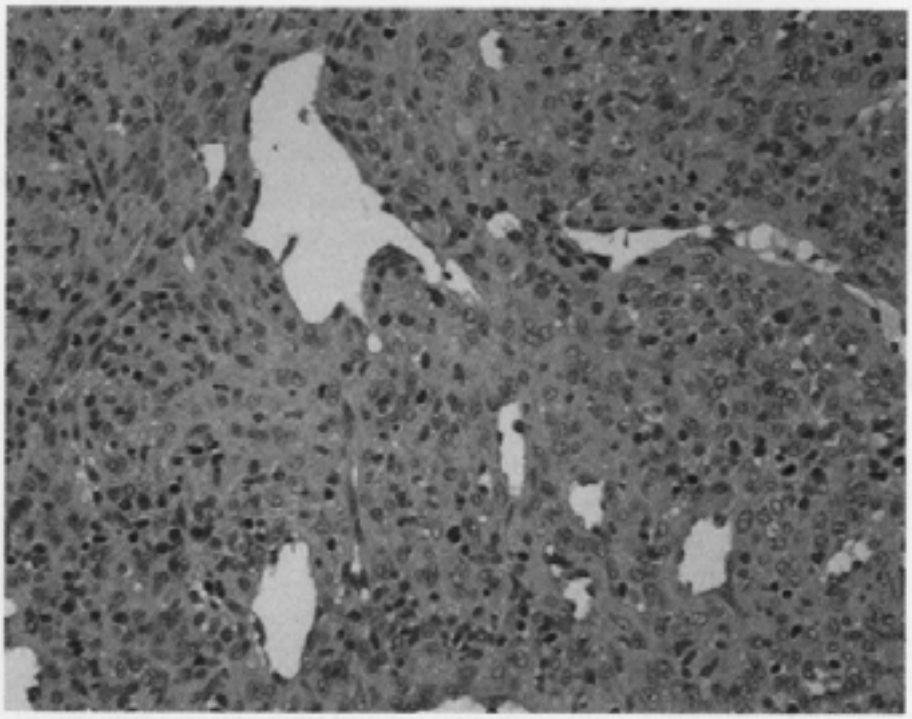

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Fig. 2. Microphotographs of the tumor showing hemangiopericytoma-like appearances composed of atypical oval or short spindle cells with hyperchromatic vesicular nuclei. Mitotic figures are readily encountered. (Hematoxyline-Eosin staining). a) ×4, b) ×20.

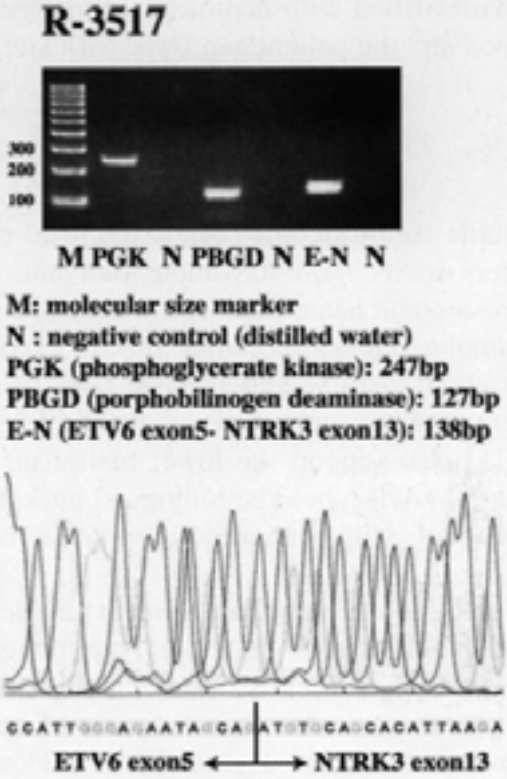

Fig. 3. RT-PCR could identify an ETV6-NTRK3 fusion gene transcript characteristic of infantile fibrosarcoma.

biopsy was performed under general anesthesia for the diagnosis. Microscopically, the intramuscular lesion showed a vague multilobular appearance composed of atypical oval or short spindle cells with hyperchromatic vesicular nuclei. Mitotic figures were readily encountered. They were arranged in a haphazard fashion or in short fascicles around variably gaping or ramifying, thin-walled blood vessels, displaying a hemangiopericytoma-like appearance (Fig 2). Hemorrhage and hemosiderin deposition was occasionally seen with admixture of chronic inflammatory cells.

Immunohistochemically, many tumor cells were positive for muscle specific actin (HHF35), and some of them were also reactive to alpha-smooth muscle actin. Desmin, S-100, CD34, cytokeratins (CAM5.2, AE/AE3) and EMA were negative. RT-PCR could identify an ETV6-NTRK3 fusion gene transcript characteristic of infantile fibrosarcoma (Fig 3).

At the operation, the tumor was resected en bloc with the surrounding muscle and periosteum of the femur. Though a thinning of periosteum of femur with a size of 2×2 mm was observed, intraoperative pathological diagnosis denied tumor perforation into femoral bone. The femoral artery and sciatic nerve were preserved. The excised tumor was poorly circumscribed and there were areas of

necrosis and cystic cavities filled with hemorrhagic material. No recurrence and metastasis had developed and the patient can walk with slight limping 36 months after surgery.

DISCUSSION

Morphologically, infantile fibrosarcoma bears a close resemblance to adult fibrosarcoma, but differs in its more favorable outcome after resection [1,2]. Although infantile fibrosarcoma has a local recurrence rate between 20 and 50% [7–12], it is unique among human sarcomas for its excellent prognosis, with metastatic rate of only about 7–14 % and survival rates of more than 90% [6–8, 11]. Spontaneous regression of untreated or incompletely resected infantile fibrosarcomas [1, 13–15] also support the lower malignant potential of infantile type compared with that of adult type. The biological background may be a lower proliferative index coupled with enhanced apoptosis compared with adult fibrosarcoma [15].

The age is a crucial point in planning the treatment and defining the outcome of the disease. So, the use of the term infantile type rather than adult type of fibrosarcoma should be defined clearly. Some authors consider as infantile fibrosarcomas those forms diagnosed before 4–5years of age [1, 6, 7, 16], while others accept only those cases within 2 years [9, 17]. However, several studies have suggested that patients under 2 years of age have a better outcome than the older ones whereas patients of intermediate age (3–6years) remain a therapeutic challenge [18–20].

There used to be no pathological pictures that allow reliable prediction of the clinical course of the disease [1, 17] other than aforementioned proliferative index [15]. Histologic grading, a predictor of tumor aggressiveness in adults, has not been proved to be an indicative factor in pediatric age [17, 21]. Moreover immunohistochemical and ultrastructural analyses can not identify the two forms.

Recently, Knezevich et al. [22] found a novel gene fusion, ETV6-NTRK3 (EETS variant gene 6; neurotropic tyrosine kinase receptor type 3), in infantile fibrosarcoma resulting from recurrent chromosomal rearrangement of t(12;15) (p13;q25). This gene fusion also has been identified in congenital mesoblastic nephroma, which shares some histologic features with infantile fibrosarcoma and establishes a histogenic link between two lesions [23–25]. The uniqueness of the ETV6-NTRK3 gene fusion is potentially a useful diagnostic tool in differenciating infantile type from adult type, since it has not been detected in adult-type fibosarcoma [22, 26].

Histologic feature of infantile fibrosarocoma has some variants. Some of them demonstrate considerable vascularity, which resembles hemangiopericytomatous pattern like that seen in our case. Sheng reported three cases of infantile fibrosarcoma with this pattern out of ten cases, which is consistent with our case [27]. The infantile fibrosarcomas with considerable vascularity also should be distinguished

from infantile hemangiopericytoma and infantile myofibromatosis [28,29]. Infantile fibrosarcoma and infantile myofibromatosis (infantile hemangiopericytoma) have overlapping morphological features [28,29], the histological diagnosis of fibrosarcoma used to be difficult [6].

Not only in differentiating infantile and adult type, but also differentiating infantile sarcoma from other tumors, the uniqueness of the ETV6-NTRK3 gene fusion is a useful diagnostic tool, since it has not been detected in other soft tissue spindle cell lesions [22, 26, 27].

In infantile fibrosarcoma, magnetic resonance imaging (MRI) demonstrated well-demarcated, low-signal-intensity soft-tissue masses with T1 weighting and inhomogeneous, high-signal-intensity masses with T2-weighting [30], which is consistent with our case. Infantile fibrosarcoma does not have a unique MRI appearance, but it can be distinguished from other soft-tissue tumors such as myofibromatosis, fibromatosis coli, fibrous hamartoma of infancy, and angiofibroma which exhibit a characteristic pattern [31]. MRI was superior to other imaging modalities in the assessment of soft-tissue involvement and proved especially useful for planning of surgery and monitoring chemotherapauetic response [30].

The goal of treatment for infantile fibrosarcoma is primarily surgical, with wide local excision encompassing histologicaly free margins [6, 7, 17, 20, 32], as an initial radical removal is linked to the best prognosis. The combined primary and secondary amputation rate for patients with infantile fibrosarcoma has been reported to be approximately 50%[33]. On the other hand, whenever possible, excision should be performed without sacrificing any significant function of the structure [7]. In this case, the operation, striking balance between them, lead to good outcome with no major dysfunction.

The resection with microscopic residuals does not assure the achievement of cure. In cases with infantile fibrosarcoma, chemotherapy might be recommended if a re-excision is not feasible, while radiation therapy is rarely delivered. Considering the low aggressivity of this form some authors recommend only a strict follow-up.

Chemotherapy has a beneficial role in the management of initial unresectable infantile fibrosarcoma and in reducing the need for extensive surgery or amputation [34–39]. Recently, not only with these cases, initial chemotherapy combined with surgery has been recommended for most cases by some authors because of good results [40].

Unlike adult fibrosarcomas, which are most common in the thigh [41], infantile fibrosarcomas affect chiefly the distal portions of the extremities [6, 7]. Chung et al. and Soule et al. reported the thigh as the primary site in 3/53 and 15/110, respectively [6, 7].

In summary, we have presented our experience of an infantile fibrosarcoma of thigh with good course after tumor resection. Local recurrence of infantile fibrosarcoma has been reported as late as 15 or 31 years following the initial operation [42], long term follow up is mandatory. Detecting the ETV6-NTRK3 gene fusion is useful in differential diagnosis and in predicting the clinical course.

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