Childhood soft-tissue sarcoma associated with Sotos syndrome

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We report a case of a four-year-old female with Sotos syndrome (cerebral gigantism) whose initial clinical, pathologic, and imaging presentation was considered suspicious for a vascular malformation of her left thigh. Following 17 months of attempted treatment, excision of the supposed vascular malformation was performed. Pathology tests revealed high-grade sarcoma. The delay of diagnosis resulted in an above-the-knee amputation for definitive treatment. If this etiology had been considered earlier in this patient's clinical course, her treatment could have commenced sooner, and amputation of her leg may have been avoided. While soft-tissue sarcoma arising in childhood is rare, malignancy should be given consideration when evaluating a mass in a young child with characteristic physical examination findings of Sotos syndrome, since these children have an elevated risk of malignancy over the general population.

Introduction

Sotos syndrome (cerebral gigantism) was first described by Sotos et al in 1964. Patients tend to be large at birth and continue to grow rapidly during early childhood (1-3). Affected children are typically greater than the 97th percentile, or greater than 2 standard deviations above normal, for height and head circumference. This syndrome is also associated with typical physical findings (Fig. 1) including macrodolichocephaly, high forehead, frontal bossing, hypertelorism, downward-slanting palpebral fissures, flushed cheeks, prominent jaw, large low-set ears, pointed chin, high arched palate, large hands and feet, variable mental retardation, and poor coordination (3). The incidence of Sotos syndrome is estimated to be 1 in 14,000 births, although it is thought to be more common than reported. More than 300

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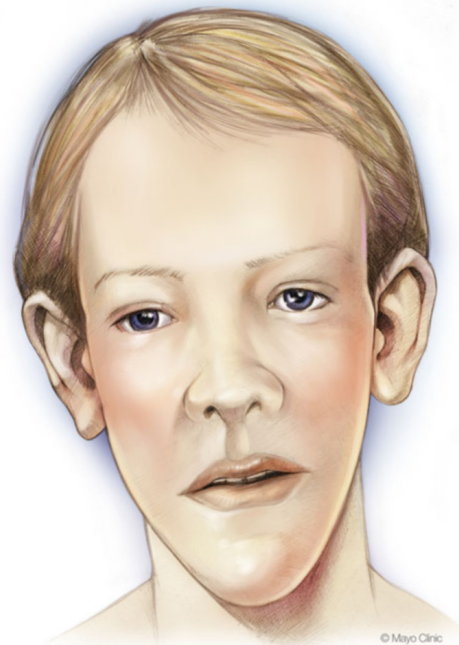
Figure 1. Artist's rendering of the typical facies of a patient with Sotos syndrome. Used with permission from the Mayo Foundation for Education and Research.
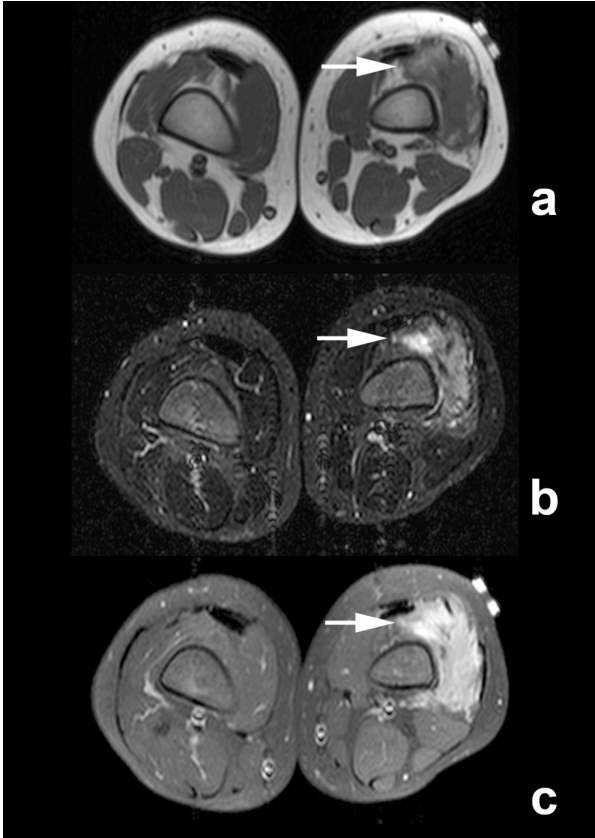
Figure 2. Axial MR images obtained at initial presentation show an ill-defined mass (arrows) in the vastus lateralis muscle. Axial T1-weighted MR image (a) shows the mass to be predominantly isointense to muscle with peripheral areas of high signal, potentially due to fat or hemorrhage. Axial STIR MR image (b) shows the mass to have heterogeneously high signal. Axial T1-weighted, fat-suppressed MR image post IV gadolinium (c) shows the mass to have intense heterogeneous enhancement.

cases are documented in the literature. As with other overgrowth syndromes, patients with Sotos syndrome have a moderately increased risk of malignancy (3-5). Increased malignancy risk is estimated to be 2% to 7%. However, a patient with Sotos syndrome less than fifteen years old has a cancer risk 150 times greater than normal patients of the same age in the United States. Malignancy in these patients usually occurs before the age of ten.

Case report

A two-year-old female presented to an outside institution for evaluation of a tender distal left-thigh mass. Her symptoms began two months before the initial evaluation. At that time, her parents noticed an egg-sized mass on her lateral distal left thigh. Her parents denied any history of trauma or systemic symptoms such as fever, chills, emesis, or abdominal pain. The patient's perinatal history and family history were unremarkable. The patient had a known history of reactive airway disease.

The patient underwent an MRI during initial evaluation that showed an ill-defined, intensely enhancing mass in the vastus lateralis muscle (Figs. 2-3). This was felt to most likely represent a vascular malformation. The patient then underwent three sclerotherapy treatments. These were done at three, five, and seven months from initial diagnosis. The sclerotherapies resulted in significant pain relief, and possible reduction in size of the thigh mass. During this time, the patient also underwent a punch biopsy whose contents were interpreted to be a spindle-cell epithelioid lesion with local nuclear pleomorphism. An incisional biopsy was also obtained, and its contents were interpreted to be focal myxoid and lymphoid nodules with prominent adipose tissue and possible vascular malformation.

The patient's pain initially improved following the sclerotherapies; however, she began to experience worsening left distal thigh pain and increasing size of the mass over the
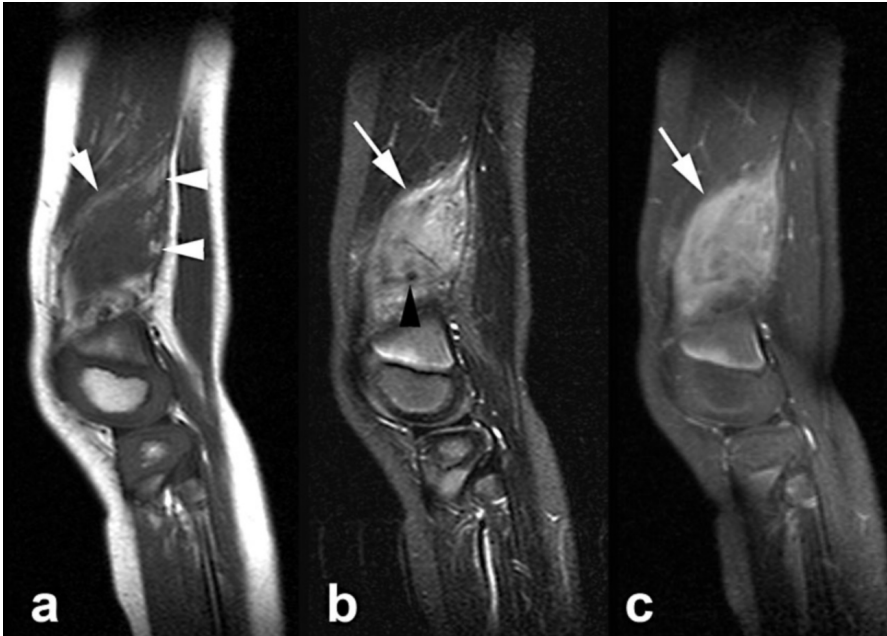

Figure 3. Sagittal MR images obtained at initial presentation show an ill-defined soft tissue mass (arrows). Sagittal T1-weighted MR image (a) shows the mass to be predominantly isointense to muscle with peripheral areas of high signal (white arrowheads). Sagittal STIR MR image (b) shows the mass to be heterogeneously high in signal with a rounded low signal focus (black arrowhead). Sagittal T1-weighted, fat-suppressed MR image post IV gadolinium (c) again demonstrates heterogeneous enhancement.
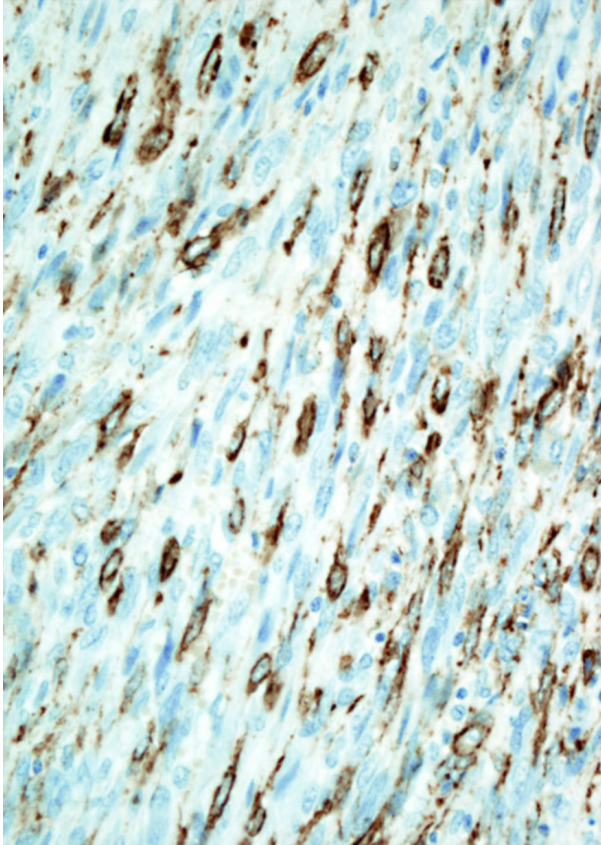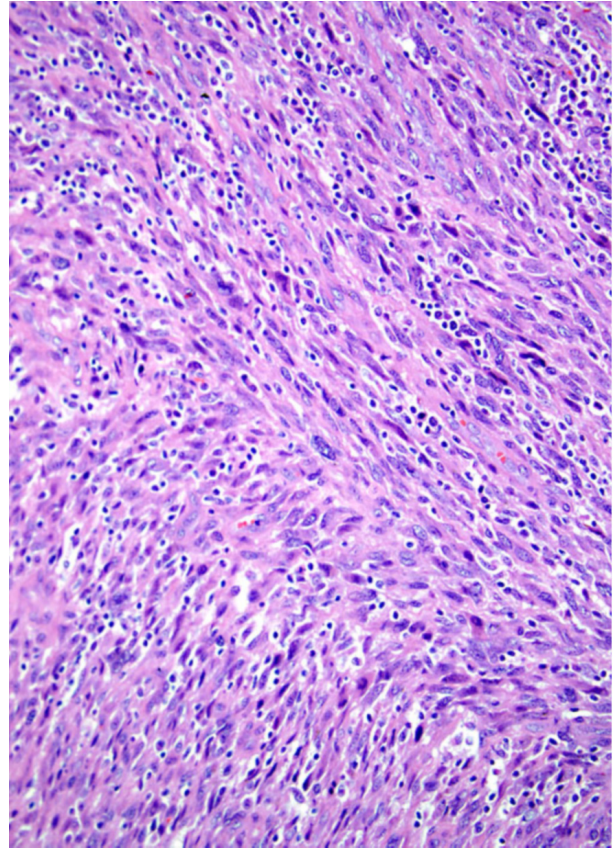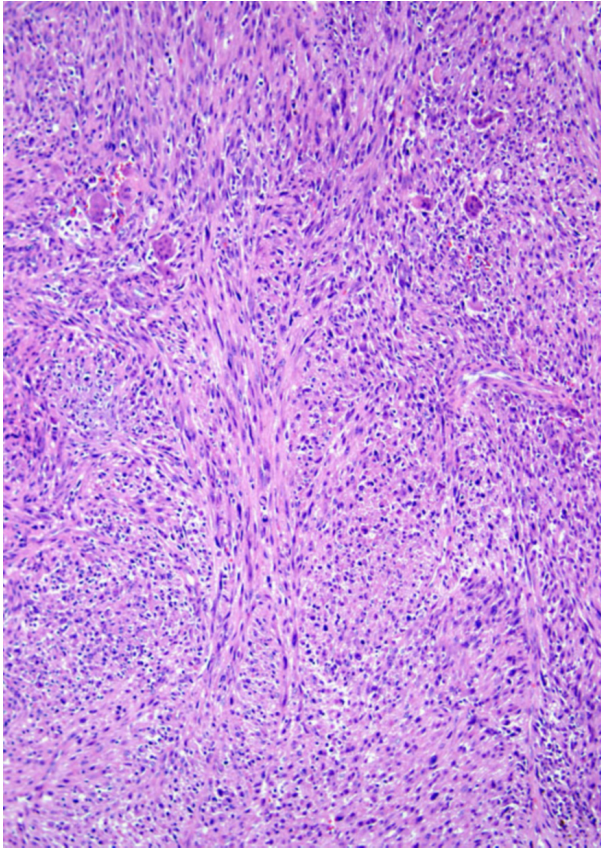
Figure 4. Hematoxylin- and eosin-stained sections of tissue from the initial surgical excision at low (upper left) and high (upper right) magnification show a high-grade spindle-cell sarcoma with nuclear pleomorphism. Immunostain for smooth muscle actin is positive (lower left), indicating myo-fibroblastic differentiation.

next year. She was subsequently evaluated by a plastic surgeon who recommended resection of the presumed vascular malformation. Surgical excision was undertaken 17 months after initial evaluation. The mass was incompletely resected, with some residual mass left around the iliotibial band. Histological evaluation revealed high-grade spindle-cell sarcoma (Fig. 4). Immunohistochemistry tests revealed that the tumor cells were positive for smooth-muscle actin and S-100 (weak focal). The tumor cells were negative for ALK-1, myogenin, desmin, CD34, and keratin. This immunoprofile indicates myofibroblastic differentiation.

The patient was subsequently referred to an oncologic orthopaedic surgeon for further evaluation and definitive treatment. During this period, the patient was also evaluated by a pediatric specialist and diagnosed with Sotos syndrome. Radiographs at the time of orthopaedic evaluation showed a large, nonspecific soft-tissue mass in the distal thigh with a small area of calcification (Fig. 5). MR imaging demonstrated a heterogeneous, hemorrhagic seroma in the surgical bed with irregular peripheral enhancement suggesting residual tumor (Fig. 6). The MRI also showed fluid
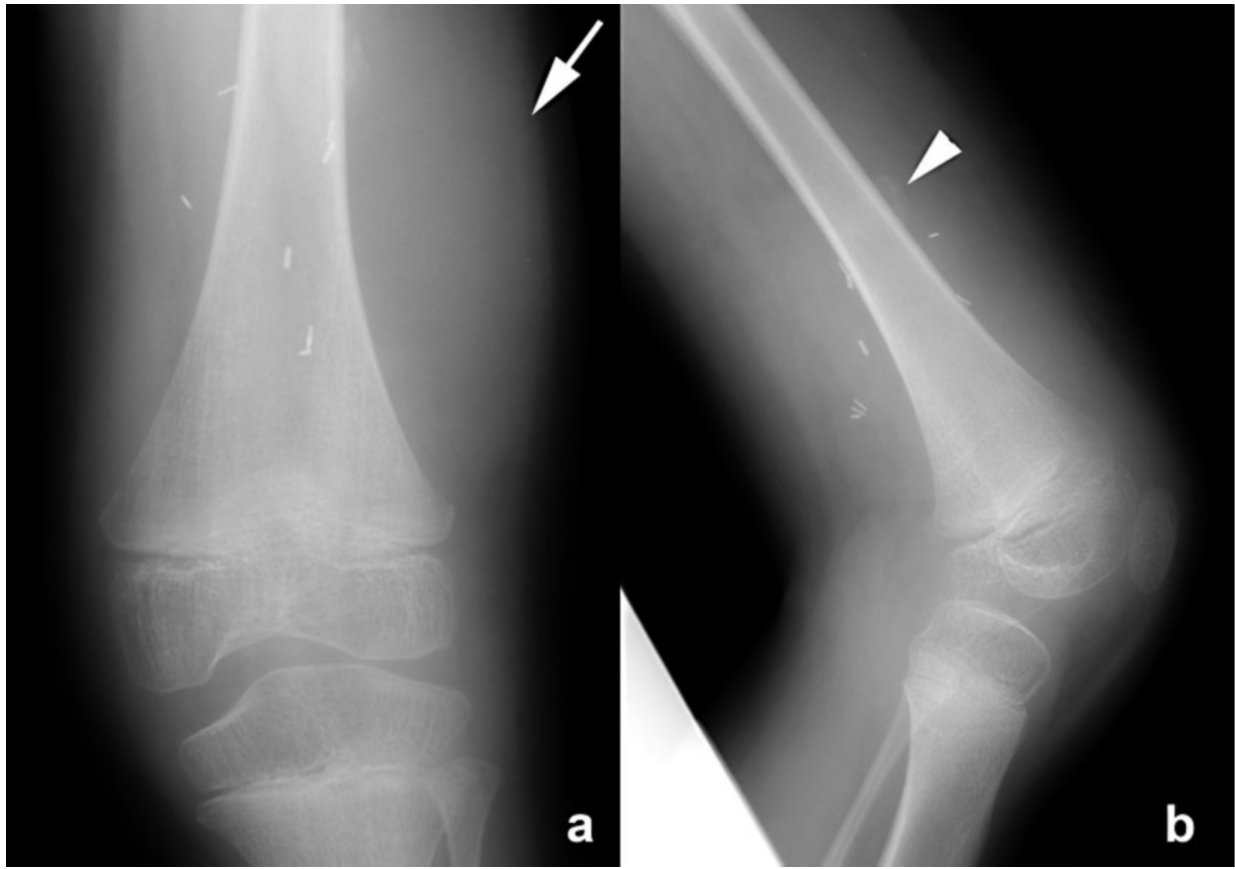
Figure 5. AP (a) and lateral (b) radiographs of the knee obtained after the initial, incomplete excision demonstrate a nonspecific soft-tissue mass (arrow) in the distal thigh with a small area of calcification or periosteal reaction (arrowhead).
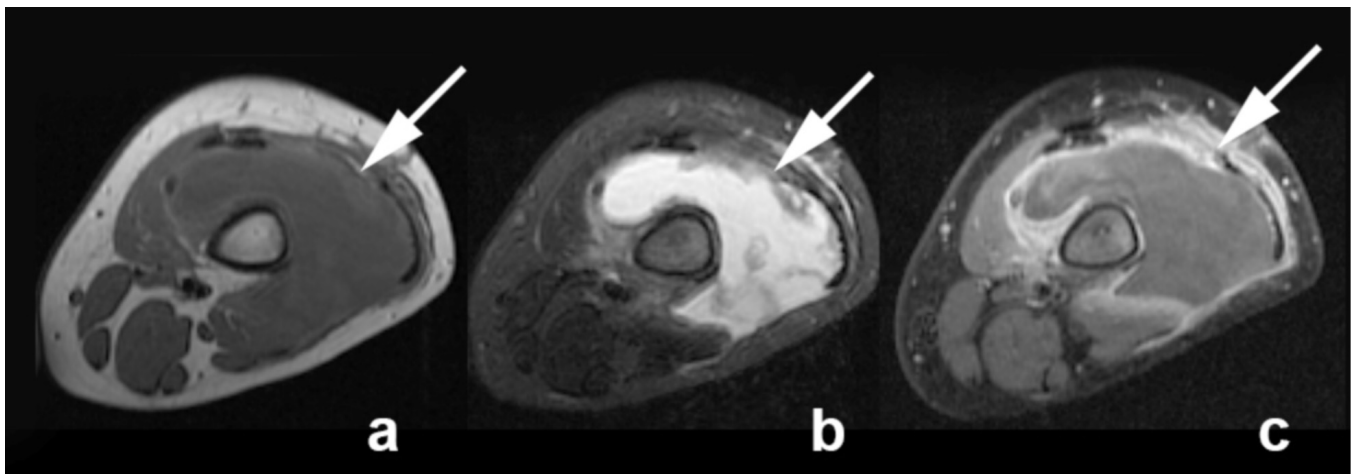
Figure 6. Axial MR images obtained after the initial excision show a complex, predominantly fluid signal mass (arrows) in the operative bed. Axial T1-weighted MR image (a) shows the mass to be hypointense to muscle with peripheral, mildly increased signal. Axial STIR MR image (b) shows hyperintense fluid centrally with irregular, peripheral, intermediate signal intensity. Axial T1-weighted, fat-suppressed MR image post IV gadolinium (c) shows irregular peripheral enhancement suggesting that residual tumor may be present.

Figure 7. Coronal T2-weighted, fat-suppressed MR image of the thighs from the initial resection shows a mass (arrow) of complex fluid in the surgical site that was contiguous with the suprapatellar bursa, indicating contamination of the knee joint.

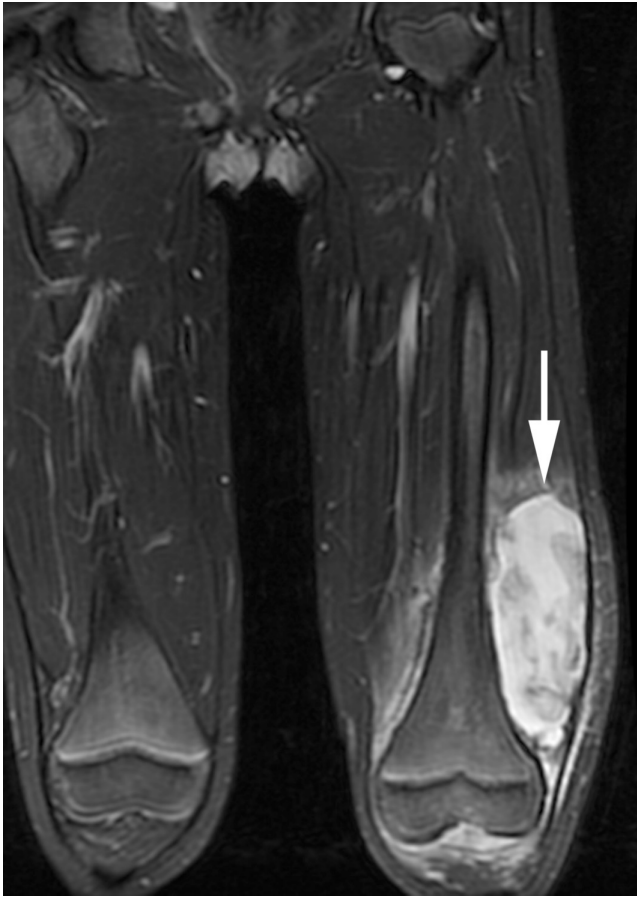in the surgical site to be contiguous with the suprapatellar bursa and knee-joint space (Fig. 7). Additional imaging performed for staging demonstrated ipsilateral enlarged iliac and inguinal lymph nodes (Fig. 8) and an indeterminant 4-mm pulmonary nodule (Fig. 9). An outside PET scan demonstrated abnormal activity limited to the region of the primary tumor in her thigh.

The patient's clinical course was reviewed by a team of physicians. Surgical treatment options, including a rotationplasty versus an above-the-knee amputation, were discussed with the patient's parents. At that time, it was felt that a rotationplasty would result in an increased risk for tumor recurrence, due to the proximity of the tumor to the peroneal nerve and a resultant lack of reasonable tumor-free margins. Because of this risk, the patient's parents preferred an above-the-knee amputation. The patient subsequently underwent the amputation for definitive treatment (Fig. 10). Histologic examination revealed a small area of residual tumor in a background of cystic necrosis (Fig. 11). The enlarged lymph nodes were sampled and tested nega-

tive for malignancy. Chemotherapy was not recommended due to the unclassifiable nature of the sarcoma. Radiotherapy was also not recommended due to the risk of inducing
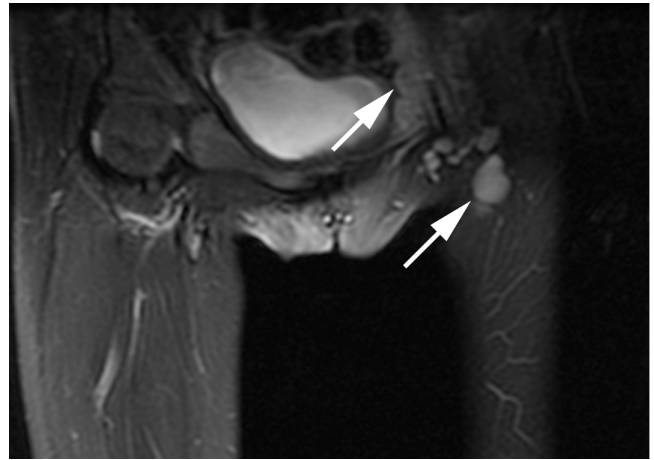
Figure 8. Coronal T2-weighted, fat-suppressed MR image through the low pelvis shows enlarged left internal iliac and inguinal lymph nodes (arrows).

an additional malignancy in this child with a genetic predisposition toward developing tumors.

The patient has been carefully monitored since the amputation. The three-year clinical followup revealed no evidence of local recurrence or metastatic disease. The pulmonary nodule was stable. The incision and stump were

Figure 9. Axial unenhanced CT of the lungs shows an indeterminant 4-mm nodule (arrow) in the left lower lobe. This study is degraded by patient motion.

Figure 10. AP radiograph of the femur shows an uncomplicated above-knee amputation.

well healed. The patient was able to walk approximately ten city blocks at a time, swim, and walk up and down stairs; however, the patient was unable to run at that time. The patient continues to be monitored closely.

Discussion

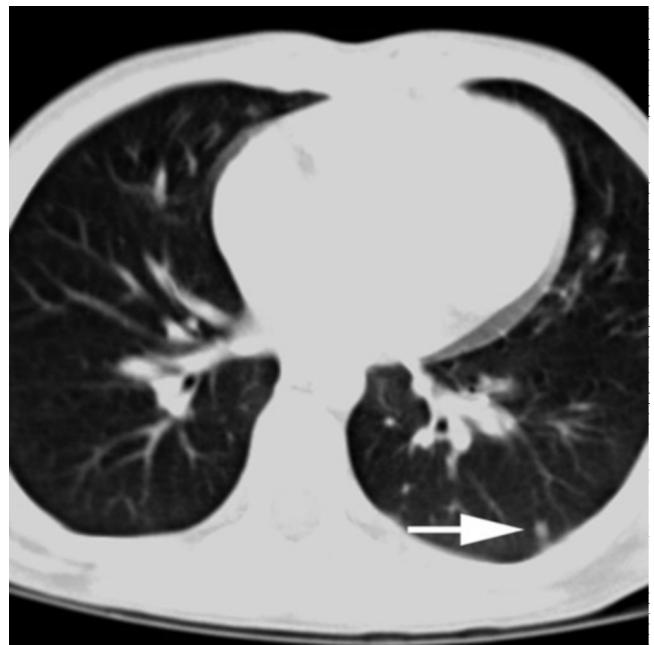Sotos syndrome is a rare congenital disorder. A mutation of the NSD1 gene, located on the 5q35 locus, has been identified in nearly 75% of individuals with Sotos syndrome (1, 3-4, 6). The NSD1 gene is felt to act as a tumor suppressor, and therefore a mutation in this gene may confer an increased risk of malignancies (1). A recent publication showed that a haploinsufficiency of the NSD1 gene in addition to an NSD1 mutation causes Sotos syndrome (6). Sotos syndrome is currently thought to arise both sporadically and to have an autosomal dominant inheritance pattern. It is known that patients under the age of 15 with Sotos syndrome are at an estimated 150% increased risk of developing a malignancy when compared to their healthy counterparts. Malignancies that have been associated with Sotos syndrome include Wilms tumor, neuroblastoma, hepatocellular carcinoma, gastric carcinoma, neuroectodermal tumors, small-cell lung carcinoma, acute lymphoblastic

and myeloid leukemias, B-cell lymphoblastic and other non-Hodgkin lymphomas, vaginal carcinoma, sacrococcygeal teratoma, and pulmonary blastoma metastatic to bone. Our case shows an example of a high-grade soft-tissue sarcoma with myofibroblastic differentiation associated with Sotos syndrome.

Imaging: There are no imaging findings in adults or children that are specific for Sotos syndrome. Sotos syndrome can be suggested on perinatal imaging in the proper clinical context. Suggestive findings on prenatal ultrasound include overgrowth, macrocephaly, ventriculomegaly, unilateral hydronephrosis, and polyhydramnios (7).

The initial imaging findings in this case were equivocal with respect to identifying the extremity tumor as a sarcoma. At the time of the first MRI, the clinical history of Sotos syndrome was not known; thus, the interpreting radiologist would not be likely to place sarcoma high in the differential diagnosis of a soft-tissue mass in a child. In general, for children less than five years of age, lower-extremity soft-tissue tumors are most likely to be granuloma annulare, hemangioma and myofibromatosis for benign lesions and fibrosarcoma, rhabdomyosarcoma, giant-cell fibroblastoma, and malignant schwannoma for malignant lesions (8-9).

The initial MR images shown in Figures 2 and 3 are that of an ill-defined, intensely enhancing soft-tissue mass involving the deep musculature of the thigh. An imaging finding that likely confounded the initial interpretation, although the original report was not available for review, was the presence of peripherally located foci of high T1-weighted signal. If these high-signal foci were presumed to represent fat, then the diagnosis of a hemangioma would be consistent with this finding. However, these areas of high signal did not show signal suppression on the corresponding STIR and fat-suppressed postgadolinium sequences, raising the possibility of this high signal being due to hemorrhage. Additionally, a round focus of low signal demonstrated on Figure 3b could have simulated a phlebolith, as would be seen in a vascular malformation. However, review of this region on additional sequences does not demonstrate a phlebolith, which would have been visible as a persistently low-signal focus.

The MRI performed after the initial, incomplete excision, shown in Figures 6-8, demonstrated a complex, hemorrhagic seroma involving the operative bed. The irregular peripheral enhancement of the operative site suggested the presence of residual tumor. Important findings to report in cases such as this include the entire anatomic extent of the prior resection, involvement of neurovascular structures or joints, and any evidence of regional metastasis. Lymph nodes involving the left iliac and inguinal regions were felt to be suspicious for potential tumor spread and helped direct lymph-node sampling. Inguinal lymph nodes can normally be up to 3 cm in long-axis dimension, but it was the rounded contour, lack of fatty hilum, and location draining the ipsilateral lower extremity that made these lymph nodes suspicious on imaging. There was no evidence of tumor within these lymph nodes upon histologic examination. Their enlarged size was likely inflammatory in nature.
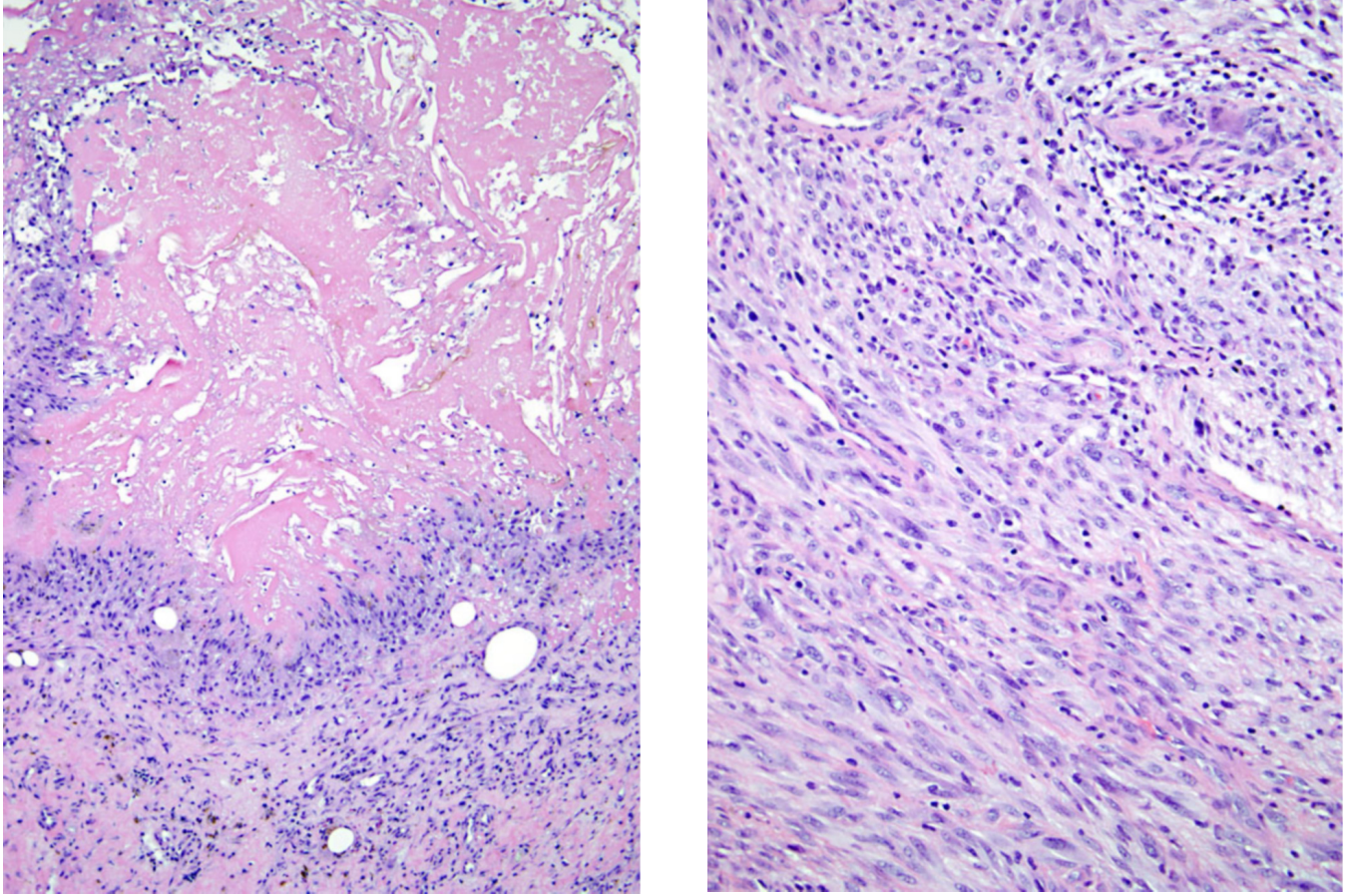
Figure 11. Hematoxylin- and eosin-stained tissue from the above-knee amputation at low (left) and higher (right) magnification shows diffuse cystic necrosis (left) and focal residual tumor (right).

A staging CT of the chest demonstrated a nonspecific 4-mm pulmonary nodule. In the setting of sarcoma, this lesion was considered a potential small metastasis. This finding necessitated serial imaging of the chest, which ultimately excluded this lesion being related to tumor spread.

Pathology: Before the initial incomplete surgical excision, both a punch biopsy and an incisional biopsy had been performed. Those tissue samples were not available for review and thus cannot be commented on. Tissue from the initial surgical excision demonstrated a high-grade spindle-cell sarcoma with nuclear pleomorphism and myofibroblastic differentiation. This lesion had no unusual features. Examination of the tissue from the above-knee amputation revealed predominantly diffuse cystic necrosis and only a small focus of residual tumor.

Surveillance: Once the diagnosis of Sotos syndrome has been made, it is vitally important to maintain proper surveillance of these patients. In the past, it has been recommended that patients younger than four years old with Sotos syndrome have a physical exam every three months and a complete blood-cell count every four months. It is also recommended that patients in this age group have biannual alpha-fetoprotein, beta-HCG, and abdominal ultrasound in addition to yearly urinalysis, urine catecholamines, and chest radiographs (10). These recommendations lessen somewhat in patients between the ages of four and ten. In this age group, it is recommended that patients be evaluated in the clinic every four months and that a complete blood count be performed. The recommendations also continue to include biannual laboratory tests including alpha-fetoprotein, beta-HCG, abdominal ultrasound, and yearly urinalysis, urine catecholamines, and chest radiograph (10). Once a patient with Sotos syndrome reaches ten years old, their risk of malignancy begins to approach normal risk levels. Therefore, the surveillance recommendations include a yearly physical exam with complete blood-cell count, alpha-fetoprotein, beta-HCG, abdominal ultrasound, urinalysis, urine catecholamines, and chest radiograph.

However, recent literature suggests that young children (less than five years old), need only a yearly physical exam and urinalysis. Children older than five years would need a physical exam and urinalysis every two years. No dedicated cancer testing is recommended for either age group by these new surveillance recommendations (11).

There is a large discrepancy in current recommendations for examination, which range from several times yearly to every other year. While we are unable to comment on surveillance recommendations due to the relatively few cases seen at our institution, we feel that potential symptoms of malignancy in a patient with Sotos syndrome should be aggressively investigated, preferably with the use of imaging that does not require ionizing radiation, such as MRI or ultrasound.

Treatment: A pediatric patient with a soft-tissue sarcoma would first undergo proper staging of the tumor. The most commonly used staging systems are the American Joint Committee on Cancer (AJCC) Staging System (12) and the Surgical Staging System of the Musculoskeletal Tumor Society, also known as the Enneking Staging System (13). Soft-tissue sarcoma treatment is largely on a case-to-case basis, but general treatment options include wide surgical excision, radiotherapy, and chemotherapy (14). Our patient would likely have undergone wide surgical excision had the diagnosis been discovered during the initial investigation. Unfortunately, the diagnosis was not elucidated initially, which resulted in our patient's above-the-knee amputation as the treatment option with the best chance for disease-free survival.

Conclusion

Sotos syndrome is a rare overgrowth syndrome that confers a significantly higher risk of malignancy compared to children of the same age. Patients have characteristic facies and are usually above the 97th percentile in height and head circumference for their age. Sotos syndrome can be autosomal-dominant, so clinicians should take careful note of family members' facies and medical history when examining a child. Clinicians should also have an elevated level of suspicion for malignancy when a child with Sotos syndrome presents with pain or a mass. At this time, malignancy surveillance recommendations are controversial, but with continued research and clinical correlation, our hope is that definitive recommendations will soon be available to guide clinical surveillance for malignancy in these children.

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