Chondroblastic Osteosarcoma of the Lower Tibia:

A case report

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The Foot and Ankle Online Journal 3 (2): 1

Osteosarcoma is the third most common cancer in adolescence, occurring less frequently than only lymphomas and brain tumors. It is thought to arise from a primitive mesenchymal bone-forming cell and is characterized by production of osteoid. The most common form of treatment is removal of the lesion. Limb-sparing procedures can often be used to preserve function. Chemotherapy is also required to treat micrometastatic disease, which is present, but not detectable in most patients at diagnosis. We present a chondroblastic osteosarcoma of the lower tibia in a 13 year-old boy. Diagnosis was confirmed by magnetic resonance imaging histopathology. Neo-adjuvant chemotherapy, en bloc resection of the tumor with ankle arthrodesis, fibular grafting and post-operative chemotherapy was performed. The patient made a full clinical and symptomatic recovery after 2 years of follow-up.

Key words: Chondroblastic osteosarcoma, bone cancer, chemotherapy.

Accepted: January, 2010

Published: February, 2010

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Osteosarcoma is a bone tumor that can occur in any bone. It most commonly occurs in the long bones of the extremities near metaphyseal growth plates. The most common sites are femur (42%), tibia (19%), and humerus (10%). Other locations include the skull or jaw (8%) and pelvis (8%). A number of variants of osteosarcoma include conventional types (i.e. osteoblastic, chondroblastic, fibroblastic types) and telangiectatic, multifocal, parosteal, and periosteal types.

Case Report

A 13 year-old boy came to our out-patient department with pain of the left ankle for 3 weeks duration. He was consulting a local practitioner for the same problem and got some relief after taking nonsteroidal anti-inflammatory drugs. There was no history of trauma, evening rise of temperature, weight loss, or loss of appetite. On examination, the left ankle had a mild to moderate swelling in the distal end of the tibia. It was not warm, but tender on palpation. There was no bony crepitus or abnormal mobility felt in the distal end of left tibia. His blood parameters including lactate dehydrogenase (LDH) and Alkaline Phosphatase were within normal limits. Radiographs showed a large sclerotic lesion, soft tissue permeation in the lower end of tibia with elevation of the periosteum (Codman triangle) and extension of the lesion through the periosteum resulting in a sunburst appearance. (Figs. 1 and 2)

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Figure 1 A large sclerotic lesion with soft tissue permeation in the lower end of tibia. Here, the tumor lifts the periosteum away from the bone (Codman's triangle).

Figure 2 Typical 'sunburst' appearance as the tumor penetrates soft tissue as it extends through the periosteum.

Magnetic resonance (MRI) clearly showed the intramedullary extent, nature of the lesion and the presence of sclerosis, soft tissue permeation, cortical breach, and skip lesions. Coronal short-tau inversion recovery (STIR) MRI and T1, T2 signal intensities noted abnormal signal intensity of the bone marrow in the metaphysis of the lower end tibia, the cortical destruction, and the prominent soft-tissue mass with the surrounding edema or reactive zone. Coronal T1-weighted MRI showed abnormal signal intensity in the metaphyseal marrow and T2 showed the extent of soft-tissue mass. It also showed ossified component of the tumor as low signal intensity, but superficially, hyperintense material.

This may be chondroblastic soft tissue extension of tumor, adjacent reactive edema, or a combination of both. Both high intensity and low intensity intramedullary signals were noted on T2 images, while all T1 weighted pulsing sequences showed intramedullary disease to have low signal intensity. Extraosseous tumor on T2 weighting image had a high signal and the disease extent was sharply demarcated from uninvolved muscle and vessels.

Figure 3 Lateral (A) and axial (B) MRI images shows extraosseous tumor on T2 weighting with high signal and the disease extent was sharply demarcated from uninvolved muscle and vessels.

Lateral and axial T1-weighted MRI of the medullary cavity of the tibia shows predominantly normal signal intensity, except anteriorly, where the slightly reduced signal intensity raises the possibility of early tumor invasion. (Figs. 3A and B)

CT scan of the chest was normal. The malignant nature of the lesion, site of the lesion, along with the findings of radiograph and MRI confirmed osteosarcoma. Neo-adjuvant chemotherapy was started accordingly. (Table 1)

Surgical Technique

The line of resection was planned with the pre-operative imaging studies. Coronal MRI was particularly useful to define the extent of marrow involvement of the lesion. A line of resection was chosen so that a cuff of normal tissue was removed with the tumor. This cuff of normal tissue was composed of both a bone (tibia) and a soft tissue margin.

With the protection of pre-operative chemotherapy and the more accurate intramedullary imaging available with MRI, it was acceptable to reduce the intramedullary bone margin 2 to 3 cm. One must be careful not to enter the pseudocapsule of the tumor. An arthrodesis is very durable and often will last a life time without the need for further surgery. It is an excellent option when the surgeon must resect the entire joint, as is necessary when tumor seeding has occurred. There are several different surgical techniques. Intramedullary nails are most commonly used for fixation.

Two operating teams were involved. Standard anterior-lateral approach to the distal end of tibia was performed by one team of surgeons. Extent of the tumor was visualized meticulously. En bloc resection of the tumor was carefully performed with a tumor free margin of 3 cm. Meanwhile, the second surgical team was ready with opposite side fibular graft of 10.5 cm length.

CHEMOTHERAPY	WEEK
Pre-operative	Radiographic diagnosis
Ifosfamide 1,800mg/m²/day for 5 days	0,5
Cisplatin 120mg/m²	10
Doxorubicin 25 mg/m²/day for three continious infusions	0,5,10
Methotrexate 12 gm/m²	3,4,8,9,13,14
Operation	15 th week
Post-operative	
Ifosfamide, Doxorubicin, Methotrexate, Cisplatin	Up to 25 th week post-operative phase

Table 1 Chemotherapy drugs were started accordingly. This table shows the relative start times, dosages and intervals of various neo-adjuvant chemotherapy agents specifically used to treat chondroblastic osteosarcoma in our patient.

Stabilization of the ankle was performed by arthrodesis using a long retrograde, intramedullary nail-like form into the talus using the fibular graft. The fibular graft was supplemented with a cancellous screw and washer in the ankle. (Figs. 4 and 5)

Sutures were removed after 2 weeks. Post-operative chemotherapy was started after suture removal. The skin at the site of the surgical scar was healthy. Non-weight-bearing ambulation began after 2 weeks. Serial blood testing was done to look for abnormalities. Repeat computed tomography (CT) scan of the chest was normal. The plaster of paris (POP) cast was removed after 6 weeks and a custom made above knee caliper with a hinge joint was worn for 3 months until signs of consolidation were seen on radiograph.

Three months after surgery, the ankle foot orthosis was dispensed and the patient was advised to start partial weight-bearing with a walker. He was then allowed to walk weight-bearing according to his tolerance after 6 months. Radiographs of the leg, taken 2 years after surgery, showed good consolidation of bone and the fibular graft. (Fig. 6) The patient is now walking full weight-bearing and doing all of his normal activities. (Fig. 7)

Biopsy of the tumor demonstrated chondromyxoid matrix and hypercellular neoplasm along with lobular configuration suggestive of chondroblastic type of osteosarcoma. (Fig. 8) An above knee POP cast was applied to the limb with a window cut in the distal end of leg.

Discussion

The incidence is 400 cases per year (4.8 cases per million persons <20 years of patients age). The overall 5-year survival rate for patients whose condition was diagnosed between 1974 and 1994 was 63% (59% for male patients, 70% for female patients). The incidence is slightly higher in African Americans than in Caucasians. Moreover, the incidence is slightly higher in male individuals than in female individuals. In male individuals, the incidence is 5.2 cases per million populations per year. Osteosarcoma is rare in children younger than 5 years and has an annual incidence of approximately 0.5 cases per million populations.^{3,20} The incidence increases steadily with age, and a relatively dramatic increase in adolescence corresponds with the growth spurt.^{2,13,17} The most common presenting symptom of osteosarcoma is pain, particularly with activity. Patients may complain of a sprain, arthritis, or so-called growing pains.

Figure 4 En bloc resection of the tumor, arthrodesis of the ankle with fibular grafting and cancellous screw fixation was performed.

Figure 5 Later radiograph shows fibular strut-graft and arthrodesis.

The patient often has a history of trauma, though pathologic fractures are not particularly common. The exception is the telangiectatic type of osteosarcoma, which is commonly associated with pathologic fractures.^{13,17,19} If pain affects a lower extremity, it may result in a limp.

The patient may have a history of swelling, depending on the size of the lesion and its location. Systemic symptoms, such as fever and night sweats are rare. Metastases to the lungs only rarely results in respiratory symptoms, and such symptoms usually indicate extensive lung involvement. Metastases to other sites are extremely rare; therefore, other symptoms are unusual.

Only 15-20% of patients present with metastases, which primarily affect the lungs, but they can also affect other bones. Manifestations at several bone sites at diagnosis may indicate multifocal sclerosing osteosarcoma.^{3,5,13} Physical findings are usually limited to those of the primary tumor site and they can be soft tissue mass, decreased range of motion, lymphadenopathy and respiratory findings. The exact cause of osteosarcoma is unknown. However, a number of risk factors are known.^{5,17,19} Rapid bone growth appears to predispose patients to osteosarcoma. This is suggested by the increased incidence during the adolescent growth spurt, the high incidence among large dogs and the typical location of osteosarcomas near the metaphyseal growth plate of long bones.³ Exposure to radiation is the only known environmental risk factor.⁸

Figure 6 Two years after surgery, there is good bone consolidation and arthrodesis without sign of recurrent tumor.

Figure 7 The patient is now full weight-bearing and back to his regular activity.

A genetic predisposition may also exist such as in Retinoblastoma, bone dysplasias, including Pagets disease, fibrous dysplasia, enchondromatosis, and hereditary multiple exostoses, Li-Fraumeni syndrome (germline TP53 mutation) and Rothmund-Thomson syndrome).^{3,13,17,19} The differential diagnosis includes Ewing' sarcoma and neuroectodermal primitive tumors, histiocytosis, osteomyelitis, rhabdomyosarcoma, stress fracture, hematoma, chondroblastoma, chondromyxoid fibroma, osteochondroma, osteoblastoma, bone cysts giant cell tumor, fibrosarcoma, chondrosarcoma. Most recommended laboratory studies are related to the use of chemotherapy. Therefore, assessing organ function before, during, and after chemotherapy is important.

The only blood tests with prognostic significance are measurements of lactate LDH and alkaline phosphatase levels.^{3,5,13,17,19}

No single feature on radiographs is diagnostic. Osteosarcomatous lesions can be purely osteolytic (about 30% of patients), purely osteoblastic (about 45% of patients), or a mixture of both. Elevation of the periosteum may appear as the characteristic Codman triangle.^{3,5,19} Extension of tumor through the periosteum may result in a so-called sunburst appearance (about 60% of patients).

Figure 8 Biopsy of the tumor demonstrated chondromyxoid matrix and hypercellular neoplasm along with lobular configuration suggestive of chondroblastic type of osteosarcoma.

The entire bone and adjacent joint should be imaged to assess for skip lesions and joint involvement. Telangiectatic osteosarcomas are often cystic and can be mistaken for an aneurysmal bone cyst. Chest radiographs (posteroanterior and lateral views) should be obtained to evaluate for pulmonary metastases. CT scan of the primary lesion and a high-resolution CT scan of the chest (at 3.75- to 7.5-mm intervals) should be obtained. CT scanning of the primary lesion helps in delineating the location and extent of the tumor and is critical for surgical planning. CT of the chest is more sensitive than plain radiography for assessing pulmonary metastases. In the ideal situation, the chest CT should be obtained before biopsy to avoid ambiguity that can arise from post anesthesia atelectasis.

MRI of the primary lesion is the best method for assessing the extent of intramedullary disease. MRI findings are best correlated with the extent of disease assessed at the time of definitive surgery. MRI should include joint-to-joint imaging to rule out skip lesions. Radionuclide bone scan evaluation with technetium-99m diphosphonate for the presence of metastatic or multifocal disease with bone scanning is imperative. Abnormal areas should subsequently be imaged by using CT or MRI.^{3,5,13}

On histologic examination of the tumor, two elements are most important. Firstly, the type of the tumor can be assessed by examining the biopsy specimen. Secondly, the response to treatment can be assessed only by evaluating the tissue resected after chemotherapy. The characteristic feature of osteosarcoma is the presence of osteoid in the lesion, even at sites distant from bone (e.g. the lung). Stromal cells may be spindle shaped and atypical with irregularly shaped nuclei. A number of distinct histologic types of osteosarcoma are described.^{3,5}

The conventional type is the most common in childhood and adolescence. This type has been subdivided on the basis of the predominant features of the cells (i.e. osteoblastic, chondroblastic, fibroblastic types), though the subtypes are clinically indistinguishable. Conventional osteosarcoma is generally a grade 3 or 4 tumor with nuclear atypia, hyperchromasia and a high mitotic rate. Osteoblastic osteosarcoma has abundant osteoid ranging from a lace like matrix to thickened trabecular bone. Chondroblastic osteosarcoma has cartilage production and the fibroblastic form has a spindle cell stroma with focal osteoid.

The purpose of staging tumors is to stratify risk groups. The conventional staging system Enneking devised is based on grade, extramedullary spread, and metastases.²¹ Other features of the tumor, though technically not used in staging, may affect the prognosis. These include the LDH and alkaline phosphatase levels, the site of primary tumor (mostly related to ease of complete resection), the histologic response to chemotherapy⁶, and the cause of disease.

Before the use of chemotherapy which began in the 1970s, osteosarcoma was treated primarily with surgical resection, usually amputation. Despite such good local control of their disease, more than 80% of patients subsequently developed recurrent disease that typically manifests as pulmonary metastases. The high recurrence rate indicates that most patients have micrometastatic disease at diagnosis.

Therefore, the use of adjuvant (postoperative) systemic chemotherapy is critical for the treatment of patients with osteosarcoma. Neo-adjuvant (preoperative) chemotherapy not only facilitates subsequent surgical removal by shrinking the tumor but also provides oncologists with an important risk parameter.^{5,6,9,10,11,12,13,14,15,17}

Patients who have a good histopathologic response to neo-adjuvant chemotherapy (>95% tumor cell kill or necrosis) have a prognosis better than those whose tumors do not respond favorably. Osteosarcomas are not particularly responsive to radiotherapy and surgery is the only option for definitive tumor removal (i.e. local control). The chemotherapeutic drugs most active in osteosarcoma are doxorubicin, cisplatin, and high-dose methotrexate (for which a low dose is ineffective). A number of pilot studies are currently being conducted to test the efficacy and safety of alkylator dose escalation; In addition, other therapies are being tested, such as the following: Anthracycline escalation by using a cardioprotectant Topoisomerase I inhibitors, Cyclosporin A to block the P-glycoprotein pump, which causes multi-drug resistance, Muramyl tripeptide phosphatidyl ethanolamine (MTP-PE) and other immune enhancers, Monoclonal antibody against the Her2/neu antigen, which is over expressed in some osteosarcomas and inhibitors of epidermal growth factor receptor, as based on its high rate of expression in osteosarcomas.^{5,6,9,13,15,17,19}

Cardiomyopathy is primarily a result of anthracycline (doxorubicin) use. Patients should receive routine follow-up echocardiography after they complete therapy. Secondary malignant neoplasms may arise as a result of chemotherapy, particularly with alkylating agents. Infertility is a nearly universal effect of the high-dose alkylating agents used to treat osteosarcoma. Emesis is a clinically significant adverse effect of chemotherapeutic drugs, particularly the drugs used to treat osteosarcoma.¹² Patients often require several antiemetics, and antiemetic regimens should be tailored for each patient.

Commonly used antiemetics include serotonin receptor antagonists (eg, dolasetron, granisetron, ondansetron, tropisetron), corticosteroids (eg, dexamethasone), and dopamine receptor antagonists (eg, metoclopramide, prochlorperazine).^{5,9,11,13,14,16,19} Perform a CBC twice each week for patients receiving G-CSF. Monitoring blood chemistries, including monitoring with renal and liver function tests, is important for patients receiving parenteral nutrition or for those who have a history of organ toxicity (especially if nephrotoxic or hepatotoxic antibiotics or other drugs are continued). After completing chemotherapy, patients should continue to undergo regular blood workup and radiographic scanning on an outpatient basis with the frequency decreasing over time. In general, these visits occur every 3 months for the first year, every 6 months for the second year and perhaps a third year, and yearly thereafter. Five years or longer after patients finish therapy, they are considered long-term survivors.^{5,9,18,19}

Open biopsy is preferred because it avoids sampling error and provides adequate tissue for biologic studies.^{3,5,13,17,18,19} The primary aim of definitive resection is the patient's survival. Margins on all sides of the tumor must contain normal tissue (ie, wide margin). The width of the margin is important only for the marrow, where an adequate margin is thought to be 5-7 cm from the edge of the abnormality, as shown on MRIs or bone scans. Radical margins, defined as removal of the entire compartment involved (joint to joint for bone and origin to insertion for muscle), are usually not required to achieve a cure. A marginal or intralesional margin may be functionally helpful as debulking therapy, but it is not locally curative. Amputation may be the treatment of choice.

Patients usually prefer limb-salvage reconstruction (if possible) over amputation, but recent studies of late effects show that patients with amputations may sustain long-term quality of life equivalent to that of patients undergoing limb salvage.

The reconstruction technique must be chosen on the basis of individual considerations, as described below.^{3,5,7,13,15,17,18,19}

1. Autologous bone graft: This form of graft has no rejection and a low rate of infection. This technique should be used only in skeletally mature patients because periosteal infusion inhibits epiphyseal growth.

2. Allografting: Graft healing and infection can be problematic with this technique, particularly during chemotherapy. Rejection can also occur. Prosthetic joints can be solitary or expandable. They are usually expensive, and their longevity is unknown.

3. Rotationplasty: This technique is suitable for tumors of the distal femur or proximal tibia when the knee cannot be spared and particularly for large tumors for which high amputation is the only alternative. Young or athletic patients may functionally benefit from this procedure.

4. Metastatic lung nodules: Can be cured by means of complete surgical resection, most often wedge resection. Lobar resection or pneumonectomy is occasionally required to achieve clear margins.

5. Restrictions on activity: This will vary with the location of the tumor and on the type of surgical procedure required for treatment.

The prognosis for patients with osteosarcoma primarily depends on whether metastases are detectable at diagnosis.^{3,5,6,14,18,19,20} Patients who present with metastases or with multifocal disease have a poor prognosis, with long-term survival rates of less than 25%. For patients with initially localized disease; the prognosis depends mainly on 2 variables: resectability and the response to chemotherapy. Those who have completely resectable disease and those whose tumors have an excellent histologic response to neo-adjuvant chemotherapy, have the best likelihood for a cure. Before the 1970s, the 5-year survival rate of patients with nonmetastatic osteosarcoma was <20%, even with aggressive surgery (mostly amputations).

The fact that most relapses occurred at metastatic sites (primarily the lung) attests to the fact that most patients have undetectable metastatic disease at diagnosis (i.e. micrometastatic disease). With the introduction of postoperative (adjuvant) chemotherapy, survival rates began to improve. According to data from the NCI SEER program, the 5-year survival rate from 1975-1984 was 49% and from 1985-1994 was 63%. For the latter period, female patients fared slightly better than male patients (5-year survival rates of 70% vs. 59%).^{6,14,19,20} Our patient came with pain, swelling in the left ankle with no constitutional symptoms, showed malignant features in radiographs, MRI and gold standard biopsy. Neo-adjuvant chemotherapy, surgical resection of the tumor and post-operative chemotherapy resulted in a favorable outcome. Our patient is symptom free with good consolidation and is walking and doing normal activities. Chondroblastic type of osteosarcoma has a better survival rate than any other type. The facts of our diagnosis, presentation, management and prognosis of chondroblastic osteosarcoma has not been extensively described and does contribute a base for our observation.

Conclusions

Limb salvage has become the accepted standard of care for patients with sarcomas of the extremities. The goals of treatment of chondroblastic type of osteosarcoma are the complete eradication of the tumor with minimal complications while maintaining acceptable function, durability, and cosmesis of the limb. Achieving a surgical margin that will ensure a low rate of local recurrence is paramount. The selection of the surgical technique for reconstruction depends on the wishes of the patient, the location of the tumor, and the extent of the surgical defect created by the resection.

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