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Osteosarcoma: Clinical Priorities for Recognition and Treatment

### Medical Breakthroughs from Penn Medicine

#### Advancing Medicine through Provision Diagnostics and Novel Therapies

Narrator:

Welcome to **Medical Breakthroughs** from Penn Medicine, Advancing Medicine through Provision Diagnostics and Novel Therapies. Your host is Dr. Lee Freedman.

Dr. Freedman:

Osteosarcoma is a relatively rare but feared diagnosis. What exactly is an osteosarcoma, and how should this be worked up and treated? I am your host, Dr. Lee Freedman, and with me today is Dr. Kristy Weber, Chief of Orthopedic Oncology in the Department of Orthopedic Surgery at the Perelman School of Medicine at the University of Pennsylvania and also President of the Musculoskeletal Tumor Society.

Dr. Weber, thank you so much for being with us.

Dr. Weber:

Thank you, Dr. Freedman. It's a pleasure to be here.

Dr. Freedman:

Well, I'm interested to hear about osteosarcoma. I have not seen one in my practice of 25 years or so, but I carry a lot of trepidation when I just hear the word. What exactly is osteosarcoma?

Dr. Weber:

An osteosarcoma is a bone-forming malignancy that occurs primarily in the skeleton, and it's not likely that you would see an osteosarcoma in your long practice because they are incredibly rare. So, the American Cancer Society estimates that a little over 3,000 new bone tumors, that's primary bone tumors, that are malignant will be diagnosed in 2014, and of those, a little over 1,000 will be osteosarcomas, so it's quite rare.

Dr. Freedman:

So, only 1,000 in the country per year.

Dr. Weber:

That's correct.

Dr. Freedman:

And you mention that it's usually in the bone. Do we sometimes see this in other sites?

Dr. Weber:

We occasionally see what's called a soft tissue or extraosseous osteosarcoma, but that's not the main presentation, so I think we'll focus our comments today on the primary presentation in the skeleton.

Dr. Freedman:

Okay, that seems very fair. And it's very rare, but what is the epidemiology? When should we at least have this in mind?

Dr. Weber:

This is the number one malignant bone tumor in children, the most common. The second most condition is Ewing's sarcoma. Osteosarcoma occurs primarily in the second decade. I've seen it in children as young as 4 years old. I've seen it in people in their 90s. There is a bimodal curve where there is a smaller jump in the curve in an older age group. We also can see it as a secondary problem in people with Paget's disease or postradiation sarcoma, but primarily, this is a disease of the adolescent, equal incidence in females and males.

Dr. Freedman:

Is this a situation where a child will present with bone pain?

Dr. Weber:

Yes, absolutely. Destructive tumors that involve the bone are almost always painful, as in contrast to soft tissue sarcomas which can grow to very large sizes and be completely asymptomatic other than the mass. So, a typical presentation of an osteosarcoma is the young adolescent, 14-year-old boy or girl who plays soccer and begins having pain in their knee. So, I don't want the practitioners to get nervous out there that every time they have a patient come in with pain after playing sports that it's an osteosarcoma, but it does present that way, and there are a few features to watch for that should heighten your concern. One, lots of adolescents and young adults have pain in their extremities because they are quite active, and in general, when someone presents with knee pain or hip pain or some other extremity pain, it's perfectly reasonable to treat them symptomatically with anti-inflammatory medications, rest, ice, modification of their activity, and see if it gets better, because the majority of time that's going to happen. The times that you should be concerned is when the patient does not get better and when their pain continues to worsen despite those treatment options. If a patient is now starting to have pain at rest, starting to have pain at night, requiring additional medications, moving on to narcotic medications, those should be very big warning signs that this is not a strain or a sprain but this is, in fact, something more ominous.

Dr. Freedman:

And I would think, in general, a couple of weeks with some rest and ice and an NSAID, we should see this settling down in children. Is that a reasonable time period?

Dr. Weber:

I think that is reasonable. If the child truly is settling down, and that may be difficult to ascertain, then the pain should get better, especially if it's a stress fracture or a strain or a sprain. If it is getting worse, it's reasonable to see them again and get an image, and the image I would get is a plain radiograph. So, I don't think that patients need an x-ray every time they have pain on the sports field, but after several weeks of no improvement or worsening of symptoms, just a plain x-ray in 2 planes, so AP and lateral of the knee, of the hip, of the femur, whatever seems to be the localizing area of concern.

Dr. Freedman:

And I take it then that there isn't too much on physical exam that is going to differentiate an osteosarcoma from a typical sprain or strain.

Dr. Weber:

Well, certainly, if there's a mass, that would obviously raise your concern, but many times at the earliest outset, there may not be a big soft tissue mass. There may not be a joint contracture. If those things are present, I would move the workup along more quickly and have an imaging study more quickly, but if those are not present, then I think you can wait, and I think you just have to be listening for that escalation of symptoms and not ignore it.

Dr. Freedman:

And then on the radiograph, are there particular signs that indicate osteosarcoma? Is it very straightforward just from the plain film, or does it just prompt additional imaging?

Dr. Weber:

Well, it can be very straightforward. It's a bone-forming tumor so, in general, if you're looking at an x-ray and the bones are standard density, this is going to be an increased density. The majority of osteosarcomas occur in the metaphysis of the bone, so at either end of the bone near the growth plate, so not in the epiphysis or right next to the joint but in the metaphysis on the other side of the growth plate. That's the most common site. And you may see bone formation or a more dense area. You may see a soft tissue mass that's more dense. It can be a mixed appearance where you see some destruction of bone or more lytic areas combined with a more dense region of bone formation. You may just see something that looks unusual. If there is heightened concern on your part, then I would proceed to an MRI scan with contrast of the involved area of the bone. If for some reason you are not interested in obtaining an MRI scan, you can always get a bone scan. A bone scan is going to be hot or have increased uptake in an area of active bone turnover. It will be quite obvious in the case of an osteosarcoma. An MRI scan, however, in this case is going to define the extent of the disease within the marrow, so it's going to give a very sharp demarcation of where it is in the bone, and it's also going to allow an understanding of the soft tissue extension, which we frequently see, and it may extend near neovascular structures, so the MRI scan is going to give a better overall picture if you have a suspicion of a tumor osteosarcoma on plain radiographs.

Dr. Freedman:

If you are just tuning in, you are listening to Medical Breakthroughs from Penn Medicine on ReachMD. I am your host, Dr. Lee Freedman, and joining me today is Dr. Kristy Weber, President of the Musculoskeletal Tumor Society and Chief of Orthopedic Oncology at the University of Pennsylvania.

Dr. Weber, when you do have this abnormal finding, is excision next? Is biopsy next? How do we further work this up?

Dr. Weber:

So, if you're a practitioner and you have seen a patient that you're concerned about an osteosarcoma, you have got an x-ray which is concerning and, perhaps, you then moved on to get an MRI scan, which is also concerning, I would stop there and I would refer the patient to someone practicing orthopedic oncology. Usually, that's at a major center. And the next steps in the workup will be a biopsy.

Biopsies can be done in numerous ways. The standard years gone by is on open biopsy where the patient is taken to the operating room and a small incision is made over the tumor and a piece of the tissue is taken in the operating room. More frequently these days we've moved to image-guided needle biopsies where either the surgeon or a musculoskeletal radiologist will use fluoroscopy or CT scan or ultrasound to localize the area of biopsy and just use a small needle for both fine needle aspiration and core biopsies. The pathologists now are able to identify an osteosarcoma on this small amount of tissue, and that allows less contamination and quicker recovery and cheaper cost to the patient than an open biopsy.

Dr. Freedman:

If the biopsy is osteosarcoma in pathology, how do you next determine the extent of the disease—is it local or has it spread?

Dr. Weber:

Right, the next step is staging, so if we know the patient has an osteosarcoma, we've probably already gotten the plain radiographs and the MRI scan of the local area, and that's sufficient. The next step is to stage the patient with a CT scan of the chest, because that is the primary location of metastasis for osteosarcoma. A bone scan is also performed to look for bone metastases, which are much less likely than lung metastases. Assuming the staging studies are negative, or even if they are positive, the next step in management is referral to a pediatric or adult oncologist. The standard treatment for a patient, whether they're young or old, with osteosarcoma is chemotherapy. The chemotherapy is done first, and it's done for, usually, approximately 2½ to 3 months of chemotherapy with alternating 3 drugs. After the initial chemotherapy, surgical resection is performed to remove the local primary tumor. Patient recovers from the surgery for several weeks and then goes back into systemic chemotherapy for what could be an additional 6 months.

Dr. Freedman:

And the initial chemotherapy starting with that, does that improve surgical cure rates?

Dr. Weber:

Well, historically, we used the chemotherapy because we had to fashion a custom prosthesis in many cases, and we needed time to do that. It had to be built in the factory. Nowadays, we don't need that. We have modular prosthetic reconstructions that we can put together for all sizes in the operating room. However, our standard practice remains to start with the chemotherapy, and when we do the surgical resection, we actually study the resected specimen very carefully and look at the percent necrosis, so how much of the tumor is dead presumably from the chemotherapy, and we're looking for greater than 90%. Greater than 90% necrosis in an osteosarcoma is a prognostic factor for a better overall survival. If the percent necrosis is less, it does not mean that the patient is going to die from the disease. It just means that it's less good prognosis.

Dr. Freedman:

And it sounds like the surgeries are rather radical. The involved extremity needs to be excised, I would imagine.

Dr. Weber:

Well, again, in the 1960s and '70s, patients with osteosarcoma, almost all of them had an amputation. And because the disease kills by micrometastases, patients had an amputation and then they frequently died of their disease anyway. Nowadays, with the advent of more sophisticated imaging techniques such as higher resolution MRI scans, we're better able to see the extent of the tumor. With better chemotherapy, we're able to provide a higher necrosis rate in these patients, and we can become more effective in resecting the tumor and saving the limb or the extremity. So, in 90% of the cases, limb salvage surgeries are possible. And we can use any number of different reconstructive techniques to get the patient back on his or her feet. We can use metal prostheses, because I've already mentioned that these occur in the metaphysis of the bone, so they're close to a joint, so that's probably the most common method of reconstruction after the tumor is removed. A metal prosthesis will generally get the patient back on their feet immediately so they don't lose time on crutches while they're going through additional chemotherapy. Other options, depending on the location of the tumor, may

be to use a cadaveric allograft, cadaver bone, fill in a structural segment, perhaps, between the joints, and in that case they may be secured with plates, screws or rods. Vascularized tissue in the form of a vascularized fibula may be harvested by a microvascular surgeon or plastic surgeon to supplement a bony reconstruction. We still use amputation in certain cases where the tumor is incredibly large or surrounding a neurovascular bundle, but it is in the minority of cases.

Dr. Freedman:

That's very good. And it sounds like in terms of the chemotherapy, there's a standard 3-drug regimen before the surgery. Does that get modified based on the amount of necrosis found in the surgical specimen?

Dr. Weber:

That's a great question. Currently, the drugs that are used are methotrexate, Adriamycin and cisplatin. If the necrosis rate is low, there have been national trials looking at whether adding in different combinations of different drugs will allow them a better overall prognosis, and that has not borne out, so changing the chemotherapy based on necrosis has not been effective in overall survival. So, right now, although the drugs may be changed per the specific oncologist, we do not have a great solution for this.

One other comment I wanted to make is that radiation, which is focused and standard treatment for soft tissue sarcoma, is not generally used for osteosarcoma.

Dr. Freedman:

Just not effective?

Dr. Weber:

It's not effective and, therefore, not used, and radiation given to children has other side effects, such as growth arrest, contractures, and the potential for a second cancer down the line.

Dr. Freedman:

And overall prognosis, generally positive?

Dr. Weber:

Overall prognosis has, unfortunately, not moved very far in the last 20 to 25 years. With a patient who has an extremity osteosarcoma with no metastasis at the time of diagnosis, the 5-year survival is approximately 70%. Though we cure many more than we don't cure, but we'd like to see that number increase so that we're curing more children and adults.

Dr. Freedman:

Absolutely. And if there are metastases, I imagine much lower 5-year survival?

Dr. Weber:

If there are metastases at the time of diagnosis, yes, the survival rate is less than 50%, or if the patient has a tumor in the pelvis—there are varying reports in the literature—but that is also a poor prognostic factor, likely because of the large size that these tumors grow to prior to identifying them. If a patient does have metastases to the lung and they are still present after the chemotherapy, we can aggressively remove the lung metastases with thoracotomy and actually save many patients with aggressive treatment, so that's not an

indication that we don't have anything else to add.

Dr. Freedman:

Very interesting, so sometimes the metastases themselves will be resected from the lung.

Dr. Weber:

Exactly. And with children, I think most people want to be as aggressive as is reasonable because they are young, and we want to do everything we can to cure them.

Dr. Freedman:

Dr. Weber, as you look to the future, the next 5 to 10 years, do you see some additional avenues of treatment that are on the horizon?

Dr. Weber:

Well, I think in the future we may have more reconstructive options from a local perspective, so we may be coming up with better biologic alternatives so we don't have to use metal and plastic that wear out over time and over the life of the patient. In a much more important aspect, the treatment of the metastasis or prevention of metastasis is really what everyone is searching for, so there are so many laboratories working on specific biologic options to target pathways in osteosarcoma that will allow us to treat these patients more specifically. If they do have an aberration of a specific signaling pathway, we can target that individually. So, I think right now the focus is on specific targeted treatments, something that will allow us to give less toxic chemotherapy and have a better overall cure rate. We still haven't found it, but there's active work in this area.

Dr. Freedman:

Dr. Kristy Weber has outlined for us when we need to be thinking about osteosarcoma as a possible etiology for, particularly, an adolescent with persistent bone pain, and she has talked about the workup and treatment for this relatively rare but important tumor.

Dr. Weber, again, I thank you so much for being with us.

Dr. Weber:

Thank you, Dr. Freedman. I enjoyed being here.

Narrator:

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