Mesenchymal Chondrosarcoma

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MESENCHYMAL CHONDROSARCOMA

An ESUN Article

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WHAT IS MESENCHYMAL CHONDROSARCOMA?
Mesenchymal chondrosarcoma is a malignant type of chondrosarcoma, or cancer of cartilage. Approximately two thirds of cases of mesenchymal chondrosarcoma occur in bone while the rest occur in places outside of the bone—i.e., in extra-skeletal locations. Unlike other types of malignant chondrosarcoma, which have a tendency to grow more slowly and rarely develop metastases, mesenchymal chondrosarcoma is a fast growing tumor that spreads more often. At the same time, it can remain dormant for long periods of time. It tends to affect children and young adults, but is a rare tumor, accounting for less than 1% of all sarcomas (Weis and Huvos).

Mesenchymal Chondrosarcoma was originally described by Lichtenstein and Bernstein in 1959 in "Unusual benign and malignant chondroid tumors of bone: a survey of some mesenchymal cartilage tumors and malignant chondroblastic tumors including a few multicentric ones and chondromyxoid fibromas."

Cartilage is a type of connective tissue that forms at the ends of growing bones before mineralization makes the new bone hard and strong. It is also found as padding and supportive tissue in joints such as the knee and the shoulder in adults and children. Mesenchymal chondrosarcoma is thought to originate from cartilage precursor cells, or chondroblasts, that have failed to develop into mature chondrocytes. Chondrocytes are the cells found in normal cartilage. The designation mesenchymal refers to the appearance of the tumor cells as primitive looking connective tissue cells.

WHY DOES MESENCHYMAL CHONDROSARCOMA OCCUR?
Cancer arises in cells that have undergone several genetic mutations that cause their growth to become abnormal. In healthy cells, complex molecular mechanisms prevent cells from growing when they are not supposed to grow. It is thought that a series of genetic events occur wherein these molecular mechanisms are thrown off. The initial genetic event probably does not cause the cancer in its full-blown form, but rather throws the cell off-guard enough so that it will be certain to develop further genetic mutations and turn into a malignant tumor. The entire sequence of genetic changes in the cell is unknown for most cancers, including sarcomas. For some tumors, translocations are important in the early development of the tumor (Hanahan). Translocations are events in which one piece of a chromosome breaks off and becomes stuck to another chromosome. This disrupts genes, turning off important "anti-growth" or tumor suppressor genes in some cases and turning on important "pro-growth" genes, also called oncogenes, in other cases. Regardless of what the initial event is that leads to mesenchymal chondrosarcoma, there are no studies that have demonstrated why a patient suffers such an "initial" event and no investigators have been able to uncover whether there are any risk factors that increase a person’s risk for developing this rare tumor (Weis).
In most cases of mesenchymal chondrosarcoma, no specific translocations are found. There have been a few cases described with identifiable changes. These changes may lead to the dysregulation of certain genes; these changes are associated with the cells inability to grow into a specialized cartilage cell and proliferating without control. Investigators found a piece of chromosome 13 attached to a piece of chromosome 21 in two cases of mesenchymal chondrosarcoma. These rearrangements were found in a case of both skeletal and extraskeletal tumor, suggesting that the two entities are the same (Naumann). Other authors have described a translocation that is typically found in some cases of Ewing’s sarcoma between chromosomes 11 and 22, underscoring the similarities between the tumor types despite the fact that their appearance under the microscope and response to therapy is slightly different (Sainati). This suggests that the development of these two types of sarcoma may involve at least several genetic alterations, as the same translocation appears capable of causing two distinct cancer types. Another patient has been described with a translocation between chromosomes 4 and 19 (Richkind). In most cases of mesenchymal chondrosarcoma, where no translocation or other signature genetic mutation that has been found, researchers presume that there is something mutated in these tumors which has just not yet been discovered.

**Presentation — What does mesenchymal chondrosarcoma feel like?**

Mesenchymal chondrosarcoma tends to present with some type of swelling or pain, either in a limb or another part of the body. It may be diagnosed when it causes these symptoms related to the physical location of the tumor. At times, the tumor may be detected early because it is seen on an x-ray that is done for other reasons, such as a minor, unrelated injury. The tumor can occur almost anywhere in the body, and is known to spread to the lungs, soft tissues, and other major organs. Mesenchymal chondrosarcoma may occur near the spinal cord, also known as a parameningeal presentation. Patients with tumors in such a location can present with diffuse pain or even paralysis due to compression of the spinal cord by the tumor. The severity of the symptoms and the type of nerve problems associated with the tumor depend on how big the tumor is, how forcibly it compresses the spinal cord, and where on the spinal cord it is compressing the nerves (Weis, Platania, and Kruse). Figure 1 demonstrates such a tumor occurring near the spinal cord. Parameningeal tumors can occur inside the skull as well (La Spina), or even in the ear canal (Antonio). A patient has been described who suffered from congenital mesenchymal chondrosarcoma of the orbit, meaning the patient had a tumor around the eye at birth. This case also illustrates the fact that the tumor can occur in very young patients (Tuncer). Such cases of orbital mesenchymal chondrosarcoma typically present with eye pain, eye swelling, visual disturbances and exophthalmos, or protrusion of the eyeball (Weis and Tuncer). Mesenchymal chondrosarcoma can present with metastases, or tumor that has spread to other parts of the body through the blood stream. Usually, patients feel symptoms from their primary tumor before they feel anything from their metastases. The most common site to which the tumor spreads is the lungs. Many patients will not develop metastases until after their initial presentation. Table 1 shows a list of some of the anatomic locations in the body where mesenchymal chondrosarcoma has presented.
Table 1: Anatomic location of tumors in selected series

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Extremities</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Lower Extremities</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>Orbit</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Trunk</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Dura/meninges</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Head and neck</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>51</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

*Table 1 adapted from Weis*

**PATHOLOGY – WHAT DOES IT LOOK LIKE UNDER THE MICROSCOPE?**

If this diagnosis is suspected, it is important that the biopsy be done either as an open procedure by a surgeon or as a needle guided biopsy by an experienced interventional radiologist, with the consultation of a surgeon familiar with oncologic procedures (Trembath).

There are cases when mesenchymal chondrosarcoma of the bone will appear similar to osteosarcoma, which is a malignant tumor of the bone that also occurs in children and young adults. Osteosarcoma is slightly more common than Ewing’s sarcoma, but it generally requires the presence of bone or bone formation somewhere in the tumor specimen for the diagnosis. Generally speaking, a pathologist should be able to distinguish osteosarcoma from mesenchymal chondrosarcoma (Aigner).
Mesenchymal chondrosarcoma has a bimorphic **histological appearance**. Under the microscope, it appears to have both highly cellular areas composed mostly of only cancer cells and other composed of well-differentiated cartilage. Mesenchymal chondrosarcoma can have distinct areas of these two appearances or the areas can be relatively mixed up. To make the diagnosis of mesenchymal chondrosarcoma, the pathologist needs to see a combination of these two appearances on the biopsy specimen. A difficulty in making the diagnosis of mesenchymal chondrosarcoma arises when the two areas are not well mixed up and the surgeon obtaining the diagnostic biopsy samples only the “cellular” part of the tumor. Under the microscope, the cellular part of the tumor looks like a "small round blue cell tumor". Given that the tumor tends to occur in bone, a small biopsy sample showing only tumor cells can appear to be Ewing’s sarcoma. The key is to have adequate sampling showing both parts of the tumor and an experienced pathologist to review the sample (Weis).

**Epidemiology – Who Gets It?**
This tumor affects children and young adults, usually between the ages of 15-35 years, although in some case series patients up to 74 years in age have been diagnosed with mesenchymal chondrosarcoma. It is quite rare; for instance, a series of only 111 cases were documented as patients or outside consultations at the Mayo Clinic from the initial description of the tumor in 1959 through 1985 (Weis and Nakashima). The occurrence may be slightly higher in females than in males. No identifiable risk factors have been found for the development of this tumor. It is thought that mesenchymal chondrosarcoma tends to occur in extra-skeletal locations in younger patients (mean age 23.5 years) and in bone in older patients (Weis and Louvet).

**Initial Work up**
When a patient with mesenchymal chondrosarcoma presents to medical attention, this diagnosis is usually not the first diagnosis the physicians consider. In a young adult or a child, Ewing’s sarcoma or osteosarcoma, or potentially even rhabdomyosarcoma in certain parts of the body, are much more common and more likely. Regardless, when a patient presents with symptoms attributable to a tumor, like swelling or pain, the evaluating physicians will obtain certain studies. First and foremost, the physician should take a complete history and perform a thorough physical exam. If the tumor is near a bone, then plain x-rays should be done of the area. Tumors should be evaluated with either CT or MRI, or both, depending on their location.

Additionally, because sarcomas tend to metastasize to the lungs, a CT scan of the lungs should be performed. The appearance of the tumor on x-rays is that of a well-defined soft tissue or bony mass with small areas of calcification apparent in some extra-skeletal tumors. Subsequently, a bone scan should be performed to evaluate for the possibility of further dissemination of the tumor to these bones, although this would be unusual based on the available data, as described below (Nakashima). A case has been described in which the patient had symptoms on presentation attributable to a soft tissue mass that may have been a metastasis from a skeletal primary, which was only revealed when the whole skeleton was x-rayed (Weis). Some of these tests will be done after some type of initial biopsy, explained below, as the correct diagnosis based on tissue sampling is necessary to perform the correct work up.

The initial work up must include some type of biopsy—either an open biopsy in which a surgeon removes a small piece of tumor through an incision, a needle guided biopsy by which a radiologist specializing in such procedures removes a small piece of the tumor with a needle, or even through a full resection if the surgeon feels that such a procedure is appropriate. These procedures should yield tissue that the pathologist will be able to use to make a diagnosis. Such procedures and the initial work up should be performed with the involvement of an oncologist and a surgeon so that the correct tests are ordered and the correct procedure is done the first time (Weis).
Some physicians may recommend a bone marrow test with the initial work up, to evaluate for the possibility of bone marrow metastases. There is no standard for whether or not evaluating the bone marrow for mesenchymal chondrosarcoma at diagnosis is necessary. The tumor is so rare that little evidence exists for or against testing the bone marrow initially. Some oncologists will recommend initial bone marrow testing because of the biological similarity between mesenchymal chondrosarcoma to Ewing’s sarcoma. Ewing’s sarcoma is known to have an appreciable incidence of bone marrow involvement at diagnosis. Such involvement of the bone marrow is associated with a worse treatment outcome than Ewing’s sarcoma without bone marrow metastases at diagnosis, regardless of the application of more intensive chemotherapy (Miser). Certainly, any patient presenting initially with mesenchymal chondrosarcoma and blood counts that are lower than expected should have their bone marrow evaluated. Otherwise, it is a decision which patients and physicians need to consider together, based on the entire clinical picture at the time of presentation.

These initial studies matter because they help to determine therapy and the follow up plan for the patient. Patients with local disease only, without evidence of any cancer spread beyond the original site of their tumor, generally have a better prognosis than other patients, particularly when their original tumor can be fully resected. Therefore, a surgeon may choose to pursue a more aggressive surgery, with the potential for more long-term side effects, in patients with only localized disease, in the hopes of curing the patient. A patient known to have widely spread disease would not be a good candidate for very aggressive surgery with the chance for post-operative morbidity, as they will need effective chemotherapy and perhaps radiation therapy to be cured of their cancer if this is at all possible (Huvos).

**TREATMENT**

*Surgical resection* is the optimal first treatment. Generally, *chemotherapy* is administered after surgery – this is known as adjuvant chemotherapy. The advantage of this approach is that chemotherapy can work to kill tumor cells when the tumor cells are at their lowest numbers. Chemotherapy tends to be more effective under such circumstances (Balis). Sometimes, tumors that are wrapped around important anatomic structures such as veins, arteries or nerves, are difficult for the surgeon to remove completely without causing excessive morbidity. Such tumors may respond to chemotherapy and shrink enough for the surgeon to remove them after a few rounds of treatment (Shamberger). This approach is known as neo-adjuvant chemotherapy. Regardless of whether or not the tumor can be removed completely at surgery, medical oncologists generally recommend involving a radiation oncologist to plan treatment for this tumor. *Radiation* may be used to treat patients known to have tumor left behind after surgery – for instance when the surgeon cannot remove the entire tumor because it involves a vital anatomic structure such as the spinal cord. For other patients, radiation is used to treat the tumor cells which oncologists presume are still in the area of the original tumor, even when the resection appears to have removed the entire tumor. Most oncologists will recommend surgery, chemotherapy and radiation therapy if they are possible for all patients with mesenchymal chondrosarcoma (Platania, Kruse, La Spina, Antonio, Tuncer, and Huvos).

Most physicians recommend an initial chemotherapy strategy similar to Ewing’s sarcoma and other soft tissue sarcomas. This involves alternating cycles of etoposide with ifosfamide and Adriamycin with vincristine plus cyclophosphamide. These are standard chemotherapy agents that are known to be active against most sarcomas.

It is controversial whether to use chemotherapy for patients who do not have metastases at presentation and whose primary tumors can be treated adequately with surgery and radiation therapy. However, there are some studies suggesting that the tumor is responsive to chemotherapy. Moreover, the biological similarities between Ewing’s sarcoma and mesenchymal chondrosarcoma suggest that it may respond like Ewing’s sarcoma to treatment (Huvos). Certainly, the high relapse rate of mesenchymal chondrosarcoma, described below, suggests that
maximal therapy could be employed to control it as long as physicians and patients understand the lack of evidence for or against such a strategy. The number of cycles of chemotherapy depends somewhat on individual factors such as the quality of the response of the tumor to the chemotherapy, the toxicities that the patient suffers from the chemotherapy and the aggressiveness of planned radiation therapy and surgery. Sometimes, it is prudent to cut back on the number of cycles of chemotherapy if it is more important to give high doses of radiation that could be toxic with higher numbers of cycles of chemotherapy.

Patients with mesenchymal chondrosarcoma generally do not have metastatic disease at presentation, although the literature on the subject is sparse due to the rarity of the tumor (Nakashima). For patients who develop metastatic disease during or after therapy, the prognosis is poor. There are no specific mesenchymal chondrosarcoma research protocols available at this time. If the tumor is metastatic at presentation, or if it comes back locally or systemically after standard treatment, one can consider experimental protocols for sarcomas in general (see, for example, the Liddy Shriver Sarcoma Initiative’s Clinical Trials section). Even patients with relapsed disease can sometimes have good responses and quality of life from a combination of surgery, radiation therapy and chemotherapy, as described in case studies and in retrospective series (Kruse, Nakashima, and Huvos).

PROGNOSIS
In the large pathologic review conducted at the Mayo Clinic, it was noted that the overall prognosis for this tumor was poor. Of the 23 patients followed clinically at the Mayo, 73.9% died of the disease between 6 months and 23 years after initial diagnosis, with an average time of 6.7 years after diagnosis. The 5- and 10-year survival rates for the tumor were 54.6 and 27.3 percent respectively. Thus, there is a protracted period during which these patients remain at risk for relapse and disease progression after initial diagnosis. Others found benefit to the addition of chemotherapy and radiation therapy to survival, although there was still a substantial incidence of disease recurrence. Among 35 patients with an average age of 26 years, follow-up analysis revealed a 37.9 months median survival, and 28% to be alive at ten years (Huvos). In retrospective reviews such as these two studies, it is difficult to assess the relative value of the treatment modalities used.

Others attempted to correlate signs of rapid growth and lack of similarity to mature cartilage on pathological examination under the microscope with prognosis and found perhaps a slight correlation. Patients with less proliferative tumors, they suggest, had a slightly better outcome (Nussbeck). However, they found that mesenchymal chondrosarcoma tumors had a wide variation in the amount of differentiation seen on microscopic examination, and were thus difficult to characterize as low or high risk based on pathology alone.

FOLLOW UP
As evidenced by the Mayo study, patients remain at some risk for relapse despite treatment. Most physicians recommend that patients undergo scans of the area of the original tumor and lung CT scans every 3 months for the first year. After the first year, it is difficult to extrapolate how often scans should be done. Patients are known to relapse late in this disease – and yet there is no way to know if scanning patients every 3 months for 6-10 years after treatment ends will pick up recurrence of disease while it is still treatable. Most patients are left to determine a follow up schedule for scans with which both they and their physician are comfortable. The key is for both patient and oncologists to be cognizant of the long-term risk for relapse in this disease, and the risks and benefits of frequent scanning. New symptoms should be taken seriously in patients even several years out from diagnosis.
**LABORATORY RESEARCH**

Laboratory based cancer investigators are constantly looking for new clues to the origin and progression of cancer, even for diseases as rare as mesenchymal chondrosarcoma. One group of cancer pathology researchers has found that an antibody directed against Sox 9, a gene important in the development of cartilage, stains mesenchymal chondrosarcoma. These pathologists took an antibody, which is a specific molecule that can bind directly to a known gene, directed against the Sox 9 gene and found that the test was a reliable indicator of the diagnosis of mesenchymal chondrosarcoma (Wehrli). While these results are preliminary, and this type of testing is not currently thought to be necessary for the diagnosis of mesenchymal chondrosarcoma, the implication is that understanding the biology of this genetic pathway could lead to a better understanding of the tumor and perhaps a cure. This kind of gene makes a protein that is called a transcription factor – meaning it acts by binding to certain other genes and causes them to be expressed. Transcription factors are notoriously difficult molecules to target with anti-cancer medications because of their chemical properties – they bind to other molecules weakly even in their normal function. Sox 9 may not be a target that researchers will use to destroy the cancer cells. However, it is possible that Sox 9 could trigger other changes in the cancer cell that would leave the tumor vulnerable to certain medications. The search is on for such vulnerabilities through groups that are using large-scale technologies looking for up-regulated genes and their protein products.

In one such attempt to catalog the tumors potential vulnerabilities, other researchers have found that using a wide variety of antibody molecules to highlight proteins known to be important in other types of cancer has suggested that some of these classes of proteins could be potential drug targets in mesenchymal chondrosarcoma. For instance, the tyrosine kinase PDGFR was found to have increased intensity in these tumor cells. Kinase molecules act as cellular "switches" – they turn on and off in response to other molecules released into the blood stream which bind to the part of the molecule which is outside the cell. In some cancers, there are too many of these kinases and they end up turning on without the proper signal. In other cancers, they are mutated or "broken" and are therefore stuck in the "on" position all the time. Kinases make much better targets for chemotherapy than transcription factors. They are on the outside of the cell and they are easier to block with medications. Gefitinib and imitinab are the two most commonly used kinase inhibitors, effective in some, but not all, patients with lung cancer and chronic myelogenous leukemia, among other things (Paez and Lydon). Efforts are underway to catalog kinase mutations in many tumors in a variety of ways. Pharmaceutical industry researchers also know that such medications are potentially very effective in the right patients, and are designing new molecules to target broken kinases that have yet to be discovered.

**CONCLUSION**

Mesenchymal chondrosarcoma is a rare tumor of soft tissues and bone characterized by a bimorphic appearance on histopathology. It occurs in both young and old people and is more aggressive on initial presentation than other types of cartilaginous tumors. Even after treatment, mesenchymal chondrosarcoma can relapse years later. Researchers are exploring ways to evaluate the tumor in a systematic fashion looking for vulnerabilities of the tumor to new therapeutic strategies.

**REFERENCES**


The Electronic Sarcoma Update Newsletter

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ESUN was first published in 2003, and each issue is accessed by thousands of readers worldwide.

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