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## Clinical advances in musculoskeletal imaging: spondylodiscitis and pediatric oncology

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# **Chapter 1**

## **General introduction**

## **PART I. Spondylodiscitis**

### **General**

Spondylodiscitis is a relatively uncommon disease, but its incidence is on the rise, and it may result in considerable morbidity and even death if not treated in a timely manner. Early and accurate diagnosis are therefore crucial. Magnetic resonance imaging (MRI) and image-guided biopsy (usually under computed tomography [CT] guidance) are important tools in the diagnostic work-up of patients suspected of spondylodiscitis. However, the exact value of CT-guided biopsy in patients with MRI findings suggestive of spondylodiscitis, in terms of microbiological yield and clinical impact, are still unclear. This will be the topic of the first part of this thesis.

### **Pathophysiology**

Infection of the spine can have a wide spectrum of manifestations. Involvement of the vertebral body, disc, spinal canal and paravertebral soft tissue may be seen. Spondylodiscitis specifically refers to a condition in which there is infection of the intervertebral disc along with infection of the adjacent vertebrae [1]. It has a bimodal age distribution (pediatric and older populations), which are considered as separate entities. In the pediatric age group, infection often starts in the intervertebral disc itself because the discs are highly vascularised. In adults, the discs are avascular, and blood supply arises from capillaries terminating at the endplates. Consequently, infection in adulthood begins at the vertebral body endplate, extending into the intervertebral disc space and then into the adjacent vertebral body endplate [2].

Spondylodiscitis is often a result of hematogenous infection, direct introduction or contiguous contamination. It can be due to an infection at a distant site (genitourinary tract infection, respiratory tract or gastrointestinal tract infection, endocarditis, abscess). It can also arise after a surgical intervention in a distant site (vascular, pelvic, urinary, cardiac or gastrointestinal tract surgery) that is complicated by a local infection that eventually becomes systemic (hematogenous spread). IV use of illicit drugs is another cause. Infection by contiguous introduction from an adjacent structure (contiguous spread), such as an abscess or an aortic graft infection, is much rarer (<5%) [1]. Infections after direct introduction develop as a consequence of a local contaminating event affecting the discs or vertebrae, such as laminectomy, discectomy, or other surgery to the spinal column. Hematogenous spondylodiscitis preferentially affects the lumbar spine, whereas the thoracic and cervical spine are less frequently affected. The thoracic spine is more frequently

affected in patient with spinal tuberculosis. The cervical spine is relatively more commonly affected in IV drugs users [3].

### **Epidemiology**

The annual incidence of spondylodiscitis in the Western world ranges between 0.4-2.4 per 100,000. The age distribution is bimodal as mentioned before with the first peak in young childhood and a second peak around the fifth-sixth decade, though patients of all ages can be affected. Spondylodiscitis has a male predominance with a male to female ratio of 1.5 to 1, although this predominance is not observed below the age of 20 years [4, 5]. In the last decades, the incidence of spondylodiscitis has risen. This has been attributed to the increase in susceptible populations, including elderly populations, patients with diabetes, IV drugs users, alcoholics, spinal surgery patients, patients with HIV infection, and patients on immunosuppressants [5].

### **Clinical presentation, diagnosis and treatment**

Spondylodiscitis is a serious disease, causing paralysis or motor weakness in around 25% of patients, and requiring surgery in some patients. Clinical manifestations of spondylodiscitis are often non-specific and generally vague. Back pain is common, typically worsening at night. Fever is reported in about 50% of cases. Restricted spinal range of motion is observed during physical examination [6].

Serum infection parameters (CRP) are not always elevated, in only about 20-40% of cases [7, 8]. If the infection extends posteriorly to the epidural space, an abscess may form and back pain may be accompanied by radiculopathy, motor weakness and sensory disorders.

The diagnostic procedure can often be delayed and the condition of the patient may initially be misdiagnosed and mismanaged as a degenerative process, especially in cases in which the clinical presentation is non-specific. A delay of 6-8 weeks between the onset of symptoms and diagnosis is not unusual.

The primary goals of spondylodiscitis management are to establish an accurate diagnosis, identify the causative organism and apply an effective antibiotic therapy. Delay in diagnosis and therapy initiation are regarded as detrimental to outcome. Timely diagnosis and treatment initiation are essential. Non-operative treatment with antibiotic therapy is adequate in most cases if the spondylodiscitis is detected at early stage. Surgical treatment is usually reserved for patients with failed antibiotic therapy, epidural abscess, progressive spinal deformity or neurological disorders.

## 1 **Diagnosis: role of imaging**

Spondylodiscitis is a challenging diagnosis to make. Although plain film radiography is almost always the first examination that is ordered, it is insensitive for the early changes of discitis / osteomyelitis, with normal appearances being maintained for up to 2-4 weeks [1]. Thereafter disc space narrowing and irregularity or ill definition of the vertebral endplates can be seen. In untreated cases, bony sclerosis may begin to appear in 10-12 weeks.

CT offers cross-sectional views in multiple planes. It can demonstrate the extent of the affected area. Abnormalities such as areas of reduced bone density, osteolysis and bone erosion can be visualized, but these signs are only visible in late stages of spondylodiscitis. In addition, these signs are also nonspecific for spondylodiscitis.

MRI is generally regarded as the imaging modality of choice for suspected spondylodiscitis because of its high sensitivity, specificity and accuracy of >90% [9]. One of the first responses to infection in the vertebral body and disc is increased extracellular fluid, which is demonstrated as low signal intensity areas on T1-weighted and high signal intensity areas on T2-weighted sequences. MRI findings suggestive of spondylodiscitis are involvement of two consecutive vertebrae and the disc with T2 hyperintensity and/or contrast enhancement after gadolinium administration [9].

## **Diagnosis: role of intervention**

Once the diagnosis spondylodiscitis has been suggested based on MRI findings, attempts are to be made to confirm the diagnosis by identifying the causative microorganism. If blood culture or serologic tests remain negative, biopsy (percutaneous or open), could be considered to obtain a positive culture. Percutaneous CT-guided biopsy is less invasive and has fewer complications compared to open biopsy.

A CT-guided biopsy is performed on the CT table while the patient is lying in prone position. First, a pre-procedural CT scan of the area of interest is acquired. Subsequently, an approaching route and site of skin puncture will be determined. Biopsy is done under sterile conditions, and, depending on the patient's condition, under local or general anesthesia. Biopsy is performed by using a bone biopsy system which consist of an external cannula and an internal biopsy needle. The choice of the needle size depends on the preference of the attending radiologist as determined for each case individually. If possible, the radiologist will attempt to obtain an aspiration of the disc, or, when present, of a fluid collection. A core

sample of the vertebral endplate-disc complex will also be acquired. In most cases a sufficient sample core will be cut into two pieces to be sent for both microbiological and pathological examination.

Percutaneous endoscopic debridement and drainage (PEDD) is an alternative technique to CT-guided biopsy. It is a relatively new technique with reported higher accuracy rates than CT-guided biopsy in the detection of the causative organism [10]. It is a minimally invasive procedure and performed under local anaesthesia in the operating room. Under fluoroscopic guidance, a spinal needle is inserted into the targeted disc. A dilator and a cannulated sleeve are guided into the disc space as the working channel. An abscess is aspirated when present. A cutting tool is used to harvest a biopsy core. A discectomy forceps can also be used to extract tissue from the infected disc. Finally, a drainage tube can be inserted if necessary.

### **Guidelines for diagnostic imaging and intervention in spondylodiscitis**

Current Infectious Diseases Society of America (IDSA) guidelines recommend performing spine MRI and obtaining blood cultures in all patients with suspected spondylodiscitis. They also recommend an image-guided biopsy when a microbiological diagnosis has not been established by blood cultures or serologic tests [7, 11, 12]. The same guidelines recommend repeating image-guided biopsy if the initial biopsy remains negative or proceeding to open biopsy. Babic et al. reported that every effort should be made to establish a microbiological diagnosis [13]. However, these recommendations are mainly based on expert opinions rather than on supporting literature. Reported culture yield of CT-guided biopsy varies widely. Some studies reported percentages as low as 19% while others report percentages up to 91% [14-20]. A recent meta-analysis reported the cultural yield of initial image-guided biopsy in spondylodiscitis to be approximately 48% [21]. These studies show conflicting results because they suffer from methodological biases. A potential reason for the reported low culture-positive yield is data contamination with spondylodiscitis mimickers (such as Modic I degeneration and acute Schmorl node) and inclusion of patients with a previous history with spondylodiscitis (these patients have non-specific MRI findings after treatment which are known to frequently result in erroneous diagnosis of active spondylodiscitis) [1]. In addition, some studies with reported high cultural yields excluded all patient with negative blood cultures [17]. Furthermore, criteria used by clinicians for referral of patients for CT-guided biopsy are often unclear. Hence, further research is essential to determine both the actual positive cultural rate of CT-guided biopsies and its impact on antimicrobiological treatment. Another unknown important issue is

1 whether CT-guided biopsy results have any prognostic implications in terms of progressive neurologic and orthopedic complications, the need for surgery, and mortality. If CT-guided biopsy proves to have both a low pathogen detection rate with limited treatment implication and no prognostic implication, the use of this invasive procedure may be reconsidered. Therefore, in **Chapter 2** we investigate the value of CT-guided biopsy in patients with suspected spondylodiscitis. We determine the cultural yield in percentages, the impact on antimicrobial treatment and relationship with outcome.

When an initial CT-guided biopsy remains negative, it is unclear whether empirical antibiotic therapy should be started, if a repeat (second) image-guided biopsy should be performed, or if more invasive procedures such as PEDD or open surgical biopsy should be considered. IDSA guidelines recommend repeating image-guided biopsy or proceeding to open surgical biopsy, without indicating a preference for either method since evidence is lacking [7]. The cultural yield of a second CT-guided biopsy is still unclear because of the limited number of studies on this topic with relative small sample sizes and heterogeneous methodology. Theoretically, if both patient spectrum and technical factors related to the biopsy are the same for the first and second attempts, the cultural yield will also be the same. However, this is not necessarily a reflection of clinical practice. Therefore, information on the cultural yield of a second image-guided biopsy, as performed in clinical practice, is important for evidence-based clinical decision making. In **Chapter 3** we investigate the culture yield of repeated percutaneous image-guided biopsy after initial negative biopsy in suspected spondylodiscitis by performing a systemic review and meta-analysis

## **PART II. Pediatric oncology**

### **General**

Primary malignant bone tumors in children are rare, but should be diagnosed and differentiated from benign entities in a timely manner to facilitate (limb-sparing) treatment planning and patient outcome. Imaging and image-guided biopsy play important roles in the diagnostic work-up of patients with a suspected bone tumor. Imaging also plays an important role for staging and is used for the follow-up of these patients after treatment. The second part of this thesis will focus on some clinically relevant aspects of imaging and image-guided biopsy in pediatric bone tumors, with Ewing sarcoma being the main topic.

### **Epidemiology**

Incidence of cancer in pediatric patients is much lower compared with that in adults. Annually, approximately 130 children per million (around 1 out of 500 children) between 0 and 16 years are diagnosed with cancer [1]. The incidence of primary malignant bone tumors is noticeably lower than the incidence of benign bone tumors in children, with malignant bone tumors accounting for only 6% of all bone tumors [2]. More than 94% of primary malignant bone tumors in children are osteosarcomas or Ewing sarcomas [3]. Despite their low incidence, malignant bone tumors are a major cause of mortality and disability in pediatric patients due to their aggressive, invasive and rapid growth, and their potential to develop metastases.

After osteosarcoma, Ewing sarcoma is the second most common malignant bone tumor with an annual incidence of 2.9 per million. The incidence is highest in Caucasian populations, while it is particularly rare among Asians and black populations [4]. This disease was named after James Ewing, who was the first to describe this bone malignancy in 1921 [5]. Nowadays, because of their histologically and genetically shared characteristics, it is considered as a part of a spectrum of neoplastic diseases known as the Ewing sarcoma family of tumors. The Ewing sarcoma family of tumors encompasses skeletal Ewing sarcoma, extra-osseous Ewing sarcoma, Askin tumor, and peripheral neuro-ectodermal tumor. Histologically they are all described as “small blue round cell tumors”. Genetically, 85% of Ewing sarcoma family of tumors demonstrate a non-random reciprocal translocation between chromosomes 11 and 22  $t(11;22)(q24;q12)$  resulting in the formation of the EWS-ETS fusion gene [6, 7]. Ewing sarcoma is slightly more common in men than women (1.3-1.5:1). Its peak incidence is during the second decade of life, though 25% of cases are diagnosed in the first decade. The remainder



of this introduction will predominantly focus on Ewing sarcoma, because it is the main topic of the second part of this thesis.

### **Clinical presentation**

The most common sites of initial disease of Ewing sarcoma are the pelvis (26%), femur (20%), ribs (12%), tibia (8%), fibula (7%), spine (6%), and humerus (6%) [8, 9]. Ewing sarcoma typically presents with pain and swelling. Pain can be mild in the beginning but may intensify rapidly after exercise and is often worse at night. Sometimes a minor trauma or muscle strain calls attention to the lesion [10]. Pathologic fracture has been reported to occur in approximately 10% of cases [11]. A soft tissue mass can be present and is firmly attached to the bone (in case of primary osseous Ewing sarcoma) and is moderate to markedly tender to palpation. Juxta-articular location of the lesion may present with loss of motion. If the spine or pelvis are involved, spinal cord compression and cauda equine syndrome may occur. Less frequently, patients may develop systemic symptoms, such as fever, fatigue, weight loss, or anemia. These signs are present in approximately 10-20% of cases at presentation [12].

### **Diagnosis: role of imaging**

Plain radiography is the first examination that should be used to evaluate a (potential) malignant bone lesion. In Ewing sarcoma, the affected bone typically presents with a destructive lesion with poor margins ("described as moth-eaten"), and the diaphysis of the long bones are more commonly affected. In contrast, osteosarcoma usually occurs in the metaphysis and epiphysis. Adjacent soft tissue masses are common in both entities. Expansion of the cortex and periosteum displaced by the underlying tumor result in the appearance of Codman's triangle. As a result of periosteal reaction, layers may be formed which is described as an onion-peel appearance.

A standard plain radiograph can be supported by a CT scan. Bone destruction, intramedullary space and extraosseous involvement, and transarticular spread are better seen on CT than on plain radiography. However, MRI remains the gold standard for the non-invasive evaluation of Ewing sarcoma and other malignant bone tumors, because of its superior definition of tumor size, local intraosseous and extraosseous extent, and it can determine the relationship of the tumor with critical anatomic structures, such as nerves, vessels, and fascial planes [13].

The differential diagnosis of Ewing sarcoma includes both benign and malignant conditions. The most common benign possibility is subacute osteomyelitis, which

can have a similar clinical presentation such as, pain, fever and increased serum inflammatory markers. Besides similar clinical features, these entities may also have common imaging examination features such as aggressive periosteal reaction, cortical destruction, and articular involvement [14]. In fact, it has been reported that up to 50% of subacute osteomyelitis cases in children are confused with tumor [15]. Differentiation of these two entities is very important since treatment and outcome are completely different. In **Chapter 4** we investigate the value of several potentially useful MRI signs in differentiating Ewing sarcoma from osteomyelitis.

A common malignant bone tumor which should be included in the differential diagnosis is osteosarcoma. It can be challenging to distinguish it from Ewing sarcoma on imaging examinations, however osteosarcoma is usually located in the metaphysis and frequently has a rim of bone formation which is not usual in Ewing sarcoma.

### **Diagnosis: role of intervention**

Although imaging (including plain radiography, CT, and MRI) may narrow the differential diagnosis, for a definitive diagnosis a biopsy is inevitable. Biopsy of the tumor can be performed by a core needle biopsy or open surgical biopsy. To avoid haemorrhagic artefacts, biopsies should take place after the completion of imaging examinations of the primary site. In order to obtain sufficient diagnostic material, adequate amounts of tissue are necessary. If insufficient material is obtained such as only necrosis, a second (open) biopsy may be required. Additionally acquired specimens should be sent for microbiology to rule out osteomyelitis, since osteomyelitis is an important mimicker of Ewing sarcoma.

Acquired bone biopsy samples are evaluated by a pathologist. A diagnosis, at least in terms of benign or malignant origin of the lesion, is important in determining further diagnostic steps and patient counselling. A problem arises when the acquired tissue is reported to be inconclusive or indeterminate by the interpreting pathologist. Usually, an indeterminate result is a reason for a second biopsy (percutaneous or open). An alternative option is to follow-up these patients, although this may cause treatment delay and negatively affect outcome if the lesion of interest eventually proves to be a (primary) malignancy (time loss may result in local tumor growth which may even require amputation instead of limb salvage, and/or increase the risk of metastatic disease). Reported studies that investigated associated factors with indeterminate CT-guided biopsy in pediatric populations are lacking. Prior knowledge about these factors is important because patients with these characteristics may be referred immediately to open biopsy to

1 avoid time loss and unnecessary anesthesia. In **Chapter 5**, we assess the frequency of indeterminate percutaneous CT-guided bone biopsy results in a pediatric population, the subsequent management of these indeterminate biopsy results, and the factors associated with an indeterminate biopsy result.

### **Prognostic factors and staging of Ewing sarcoma**

Ewing sarcoma has a strong potential to metastasize. Metastasis generally occurs via the haematogenous pathway. The most common site for metastases are the lungs, bone and bone marrow. 25% of patients present with metastatic disease at the time of diagnosis. Despite the fact that approximately 75% of patients have only localized disease at time of initial presentation, it has been reported that without systemic therapy most of these patients go on to develop overt metastatic disease, from which they subsequently die.

Metastatic status at diagnosis is the strongest prognostic factor across different treatment strategies. Five-year survival rates of these patients remain <30% [16]. Some studies report that patients with isolated pulmonary metastasis have a better outcome than patients with metastases at other sites [17-19]. Primary tumor location, soft tissue extension, site of metastasis, and histological response to neoadjuvant chemotherapy are also well-known prognostic factors. In localized and disseminated Ewing sarcoma, primary tumor volume is another important and independent prognostic factor. The optimal cut-off value for prognostic stratification is still underinvestigated, although patients with primary tumor volume of more than 200 ml have been reported to have worse survival rates [16]. The imaging modality at which these volume measurements should be done nowadays is also unclear, although they are currently usually performed on MRI scans. Importantly, inter-observer and intra-observer variability of MRI-based primary tumor volume measurements in newly diagnosed Ewing sarcoma have never been investigated. This knowledge is crucial for reliable prognostic stratification and treatment decisions. In **Chapter 6** we investigate the inter- and intra-observer agreement of MRI-based primary tumor volume in newly diagnosed Ewing sarcoma patients and we compare these results with actual primary tumor volume at MRI and with metabolically active tumor volume (MATV) as measured on <sup>18</sup>F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/CT.

There is no universally accepted staging work-up scheme for Ewing sarcoma. In addition to primary site imaging with plain radiography and MRI, a chest CT is performed to detect lung metastases, combined with whole-body bone scintigraphy (99mTc-MDP) for the detection of osseous metastases and bilateral

bone marrow biopsies of the iliac crest for bone marrow assessment. A disadvantage of whole-body bone scintigraphy is its insensitivity for the detection of metastases that are exclusively located in the bone marrow without any osteoblastic reaction, whereas bone marrow biopsy is invasive (which usually requires general anesthesia in young children) and suffers from sampling errors. Recently, FDG-PET/CT has emerged as a potential “one-stop shop” staging alternative to chest CT, whole-body bone scintigraphy, and bone marrow biopsy. FDG-PET/CT can evaluate the whole-body, including the lungs and entire bone marrow[20]. In this setting, it may potentially replace blind bone marrow biopsies of the iliac crest. In **Chapter 7** we investigate the feasibility of replacing invasive blind bone marrow biopsy by non-invasive FDG-PET/CT.

### **Treatment and posttreatment follow-up**

There are three therapeutic options which are currently used in combination to treat Ewing sarcoma: systemic chemotherapy, local surgery and radiation therapy. Ewing sarcoma patients with only localized disease have a poor prognosis with only a 10% likelihood of cure if they were only treated with local surgery or radiation therapy. The majority of these patients die due to late metastasis, which demonstrates that Ewing sarcoma patients almost always have micro-metastases. For this reason, treatment of Ewing sarcoma should always include chemotherapy to treat distant metastases, regardless of their identification at initial staging [21]. Most recent studies report 5-year overall survival rates between 65-75% if intensive chemotherapy is applied. If pre-operative imaging suggests a possible resection with wide margins, surgery is preferred without radiation therapy. If surgical resection with wide margins seems impossible, pre-operative radiation therapy should be added to the treatment strategy.

After completion of therapy with curative intent, it is common practice to perform routine surveillance MRI of the location of the primary tumor site. MRI (with intravenously administered contrast agents) has reported high accuracy rates in detecting local recurrence of Ewing sarcoma [22]. However, despite second-line therapy after detection of locally recurrent Ewing sarcoma, 5-year event-free and overall survival rates are only 5.1% and 7.1%, respectively [23]. These numbers question the utility of routine surveillance MRI of the primary tumor location. Furthermore, besides patient outcome, MRI costs and potential side effects of gadolinium-containing contrast agents should also be taken into account when considering the utility of surveillance MRI. In **Chapter 8** we assess the frequency of locally recurrent Ewing sarcoma on surveillance MRI and the outcome of these patients.

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# **PART I**

## **Spondylodiscitis**