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Clear cell sarcoma of lumbar vertebra: A case report on how imaging improved diagnostics after initial suspicions

Christina Natalia Ramoh[1], Yuefen Zou[1], Felix Hamzah[1], Lipeng Yu[2], Yan Zhu[3]

[1]Department of Radiology, Jiangsu Province Hospital, the first affiliated hospital with Nanjing Medical University, Nanjing, China
[2]Department of Orthopedic, Jiangsu Province Hospital, the first affiliated hospital with Nanjing Medical University, Nanjing, China
[3]Department of Pathology, Jiangsu Province Hospital, the first affiliated hospital with Nanjing Medical University, Nanjing, China

ABSTRACT

Clear cell sarcoma is a rare malignant soft tissue neoplasm with a predilection for arising deep soft tissues adjacent to tendons and aponeuroses and fascial structures. This report presents a 32-year-old woman with low back pain and swelling, night sweat, and lateral numbness in her right thigh for 3 months. Magnetic resonance imaging revealed a 4.0 × 5.8 cm vertebral lesion on the right lumbar region, without characteristics of a melanin rich tumor. Immunohistochemistry and fluorescence *in situ* hybridization confirmed the diagnosis of clear cell sarcoma. The patient underwent a chemotherapy protocol. At 4-month post-surgery, CT revealed a soft tissue lesion in the right L3, suspected to be either a cancer relapse or harmless post-surgery lesion. Radiotherapy was performed in precaution of a relapse. At 11-month post-surgery, tumor relapse and multiple bone metastasis were observed. Combination of imaging methods improves diagnostics and subsequently differentiates clear cell sarcoma from other pathologies.

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Introduction

Clear cell sarcoma of tendon and aponeurosis (CCSTA) or soft parts is a rare malignant melanin-producing tumor entity that is derived from the neural crest cells originating from soft tissues displaying melanocytic differentiation. Enzinger first discovered CCS in 1965 [1–3]. It was formerly known as malignant melanoma of soft tissue due to the presence of melanin pigmentation and (pre-) melanosomes in a significant percentage of these tumors [4]. CCS cannot be distinguished from malignant melanoma by immunohistochemistry as both will be immunoreactive for HMB-45, S100, and Melanin A. Despite this similarity, fluorescence *in situ* hybridization (FISH) and polymerase chain reaction (RT-PCR) technique can show that CCS has a specific cytogenetic feature: t (12;22) (q13;q12) chromosome translocations [5]. Generally, CCS affects predominantly young adults aged from 20 to 40 years old, with a slight predilection for women [6]. It has a predilection for arising in deep soft tissues adjacent to tendons and aponeuroses and fascial structures, commonly found in lower extremities, particularly the foot and ankle. CCS is characteristically a slow-growing, firm mass with an aggressive growth pattern, infiltrating adjacent adipose tissue and muscle [7]. These tumors have a very poor prognosis with a survival rate of 5–10 years because of local recurrence, early to late metastasis to lymph nodes, lungs, bones, and liver [8,9].

We present a 32-year-old female patient with primary CCS of the right lumbar vertebrae, who was referred to our hospital a week after her initial visit to a local hospital.

Case Presentation

Patient information

A 32-year-old woman had a history of waist, lower back pain for 3 months. She had excision of thoracodorsal cyst 1 year prior. She initially noted back pain aggravated by extended activity and relieved by rest. She experienced night sweat and lateral numbness in her right thigh without bowel movement disorder. The pain had increased during the last 2 weeks,

Contact Yuefen Zou ✉ zouyuefendc@126.com Department of Radiology, Jiangsu Province Hospital, the first affiliated hospital with Nanjing Medical University, Nanjing, China.

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so she consulted a local doctor. Magnetic resonance imaging (MRI) of her lumbar spine in a local hospital revealed abnormal signal intensity in the L3 vertebral body and right psoas muscle. She was misdiagnosed as spinal tuberculosis with the formation of cold abscess. A week later she was referred to our hospital. Initial physical examination revealed tenderness, percussion pain, palpable mass arising from the lumbar region. There were no signs of any superficial skin lesions. The patient had no history of melanoma or other skin tumors. Imaging studies were requested for further investigation.

Imaging and histological examination

Chest X-ray showed no abnormalities. Lumbar spine X-ray revealed some cortical bone destruction, osteolytic lesions on the body of the L3 vertebra (Fig. 1). Abdominal computed tomography (CT) and MRI revealed a vertebral lesion measuring 4.0 × 5.8 cm in diameter, with an enhancing, solid paraspinal component and epidural extension, compressing the spinal cord (Fig. 1). These findings indicated the presence of malignant tumor. There was also metastasis found at the right iliac bone, and 1st sacrum (Fig. 2). For better sensitivity, specificity, and accuracy in detecting lymph nodes and distant metastasis of sarcomas, whole body ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET)/CT was requested.

PET-CT (Fig. 1) revealed a hypermetabolic mass in the right side L3 vertebra, anterior to the right psoas major muscle, involving the L3 vertebral

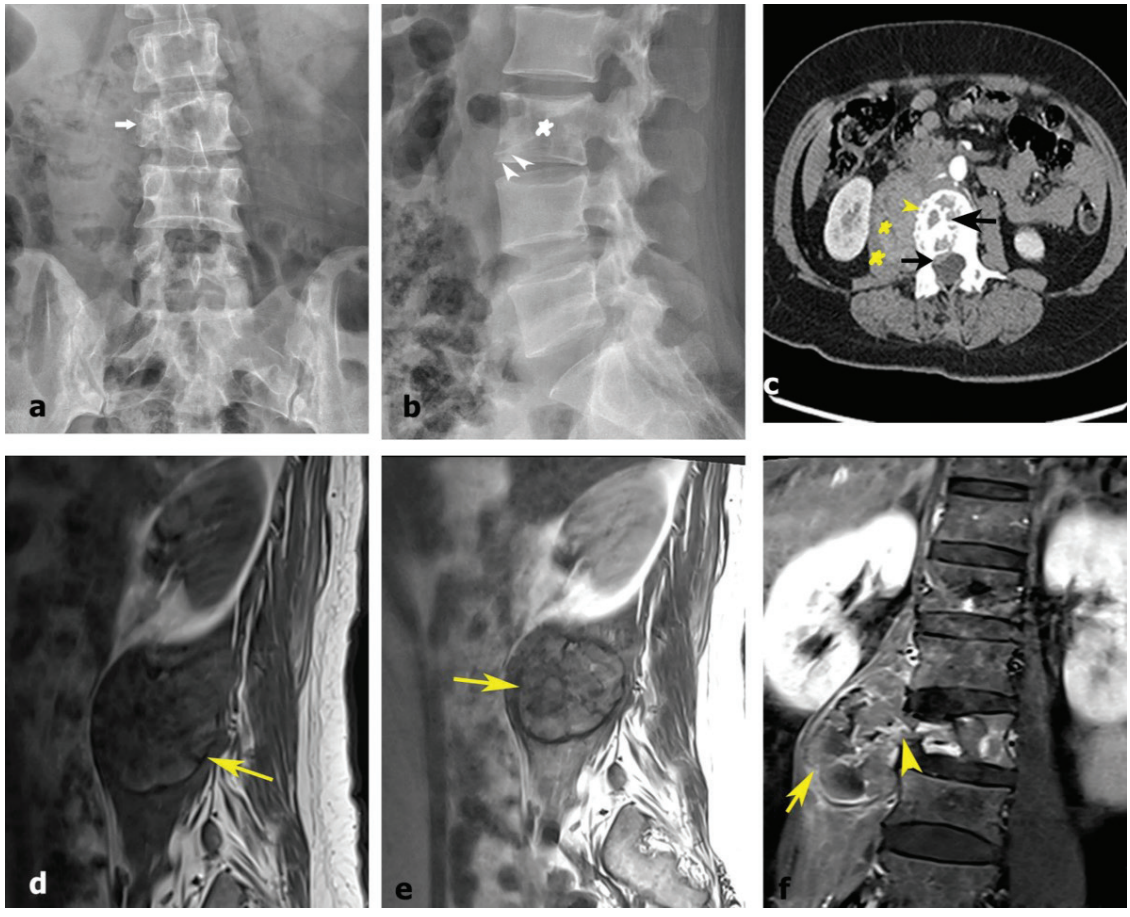


Figure 1. Frontal (a) and lateral view (b) plain radiography of right lumbar vertebra showed right cortical destruction (white arrow) and osteolytic lesions (white star) on the L3 vertebral body. Local, inferior cortical discontinuity was seen (b) due to a one-sided collapse (white arrowhead). Contrast axial view abdominal CT (c) revealed a large enhancing necrotic soft tissue mass (yellow star) infiltrating vertebral body, spinal canal (black arrow) with L3 vertebral cortex destruction (yellow arrowhead). (d) MRI showed an irregular, well-defined soft tissue mass (yellow arrow), connecting to an enhanced L3 vertebral body lesion with bone destruction (f) (yellow arrowhead). Heterogeneously hypointense in T1WI (d), heterogeneous, slightly hyperintense in T2WI compared to the muscle (e), and heterogeneously strong enhancement on contrast (f).

body and spinal canal. Maximum standardized uptake value (SUV) was 8.3. There was an oval-shaped low-density lesion on the right iliac bone, measuring 1.02 by 0.7 cm. It contained a circular high-density shadow within, with a maximum SUV of 5.5. It is the same right iliac bone metastasis seen on CT and MRI. No additional metastatic lesion was discovered. CT guided biopsy was requested to confirm malignancy of mass, as FDG PET modality is not specific for the diagnosis of cancer. Inflammation and infection are also associated with increased FDG uptake. Thus, the tuberculin skin test was also requested to rule out tuberculosis.

Tuberculin skin test result was negative, so tuberculosis was excluded. Preoperative six serum tumor biomarkers revealed increased CA724 and NSE. On immunohistochemical (IHC) staining, the tumor cells were positive for HMB45, melanin-A, S-100, and Sox10 (Fig. 3c and d). This result could not differentiate CCS from malignant melanoma, which was why FISH was requested. FISH revealed the EWSR1 gene fragmented and recombined, which would be present in CCS but not malignant melanoma (Fig. 5). On the basis of these findings, the diagnosis was confirmed to be the primary CCS of the lumbar spine.

Treatment and Follow-up

Treatment plan for this high malignancy tumor was margin-free surgery combined with chemotherapy. The surgery consisted of selective intra-arterial embolization, spinal decompression, lumbar laminectomy, adnexal tumor resection, discectomy of adjacent upper and lower intervertebral disk, and lumbar vertebral body artificial replacement (Fig. 4). During the operation, the surgeons noticed that the tumor was partially encapsulated and hard texture.

Three courses of chemotherapy were administered, which included temozolomide, doxorubicin, and ifosfamide. At 4 months post-surgery, she noted low back pain, 5 kg weight loss, and right thigh numbness. Abdominal CT (Fig. 4b) revealed a 16 mm diameter soft tissue lesion in the right L3 vertebra, which we suspect to be either a cancer relapse or harmless post-surgery lesion. Radiotherapy with 30 Gy/10f was given in precaution of a relapse. Patient did not attend the next routine follow-up in 3 months due to personal reasons. At 11 months post-surgery, a patient's relative followed up, revealing that the patient continued her care in another hospital. We obtained CT images from the hospital, which revealed tumor relapse and multiple bone metastasis (Fig. 4c–g). The patient is still alive.

Discussion

CCS is a rare malignant tumor, and primary CCS of bone is even less common. Foot and leg are the most common sites of CCS, followed by

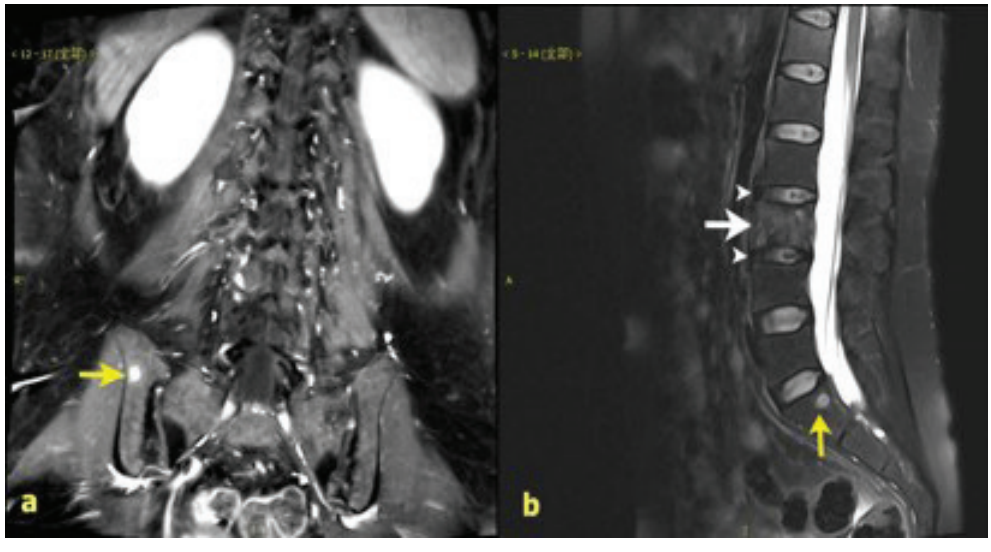


Figure 2. MRI T2 fat-suppressed sequence, the S1 vertebral body (b) and right iliac bone (a) showed enhancing, hyperintense nodular lesion, suggestive of the metastatic tumor (yellow arrow). L3 vertebral body tumor was involved wholly on this sagittal view, showing moderately high signal intensity (white Arrow) with normal adjacent intervertebral disk (white arrowhead).

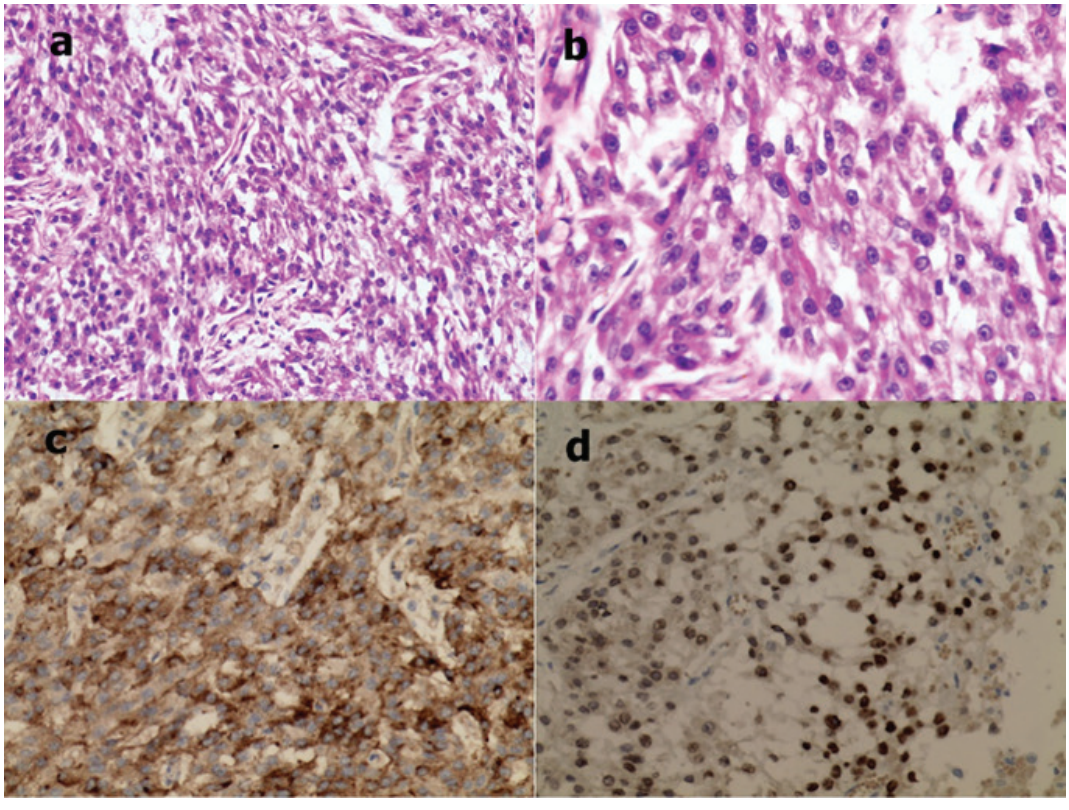


Figure 3. HE staining Magnified 200× (a) and Magnified 400× (b) showed tumor cells with nest-like distribution, abundant eosinophilic cytoplasm. Cytoplasm of local tumor cells was transparent with vesicular nuclei and prominent nucleoli. Immunohistochemical staining for SOX10 (c) showed nucleic positivity in tumor cells. Immunohistochemical staining Magnified 200× for HMB45 (d) showed cytoplasmic positivity.

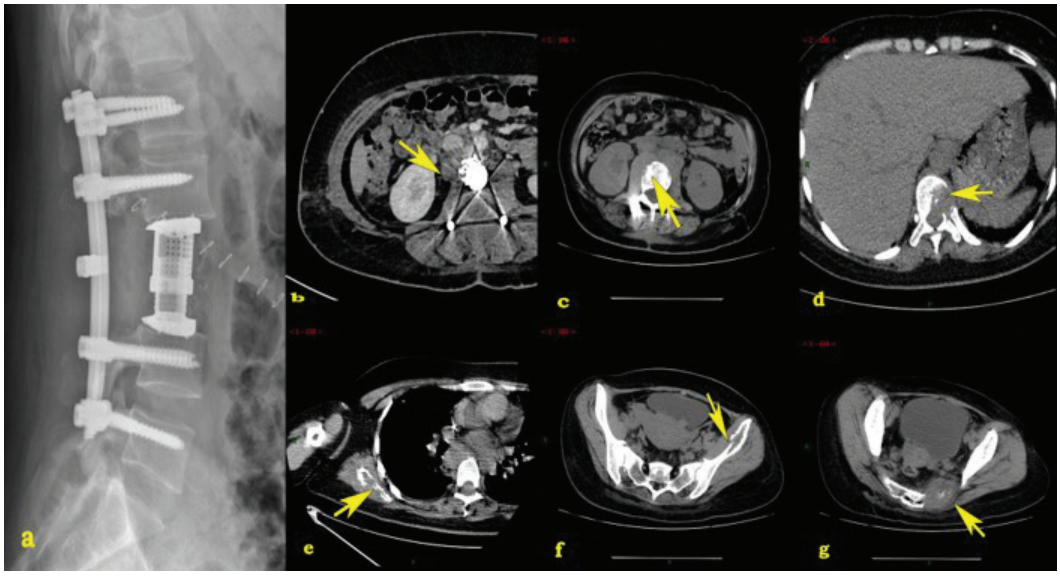


Figure 4. (a) Lateral plain radiograph images taken 7 days after surgery. Complete removal of the L3 vertebral body and adjacent soft tissue mass, replaced with an artificial vertebral body and internal fixation were in place. (b) Abdominal Contrast CT images taken 4 months after surgery. Nodular soft tissue density was seen on the right side of the L3 vertebral body, measuring 16 mm in diameter. Multiple bone destruction with soft tissue invasion on vertebral bodies, right scapula, left iliac bone, sacrum, suggesting metastasis (c–g).

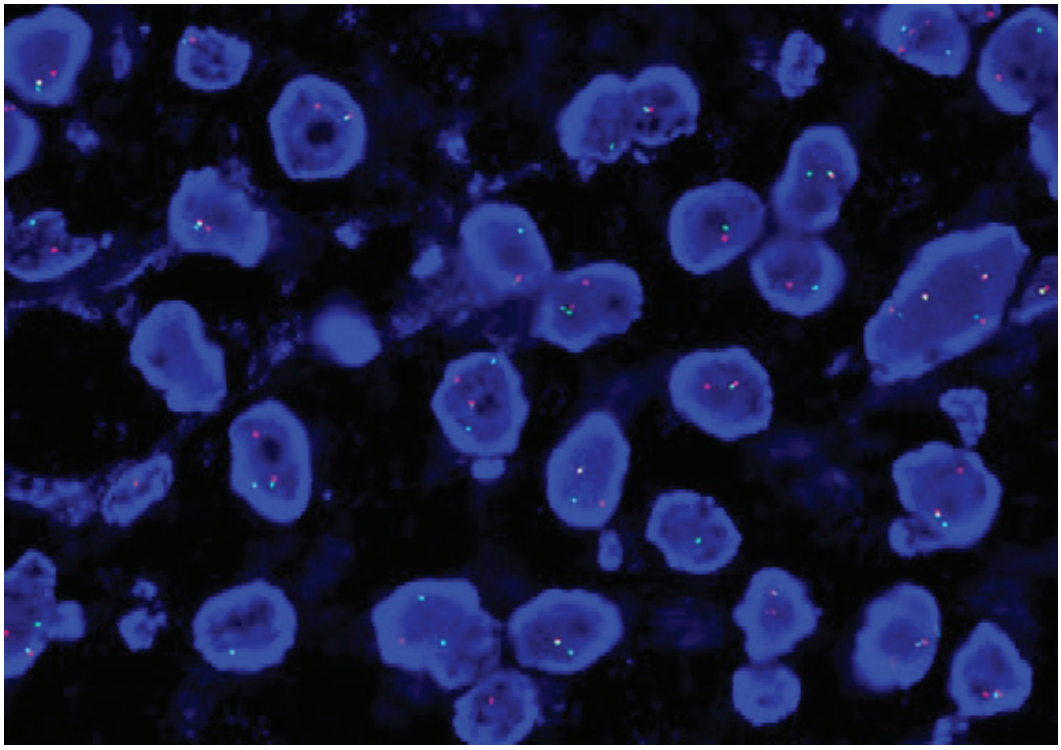


Figure 5. Using GLP EWSR1 probe: Microscopically, more than 10% of the cells showed red, green, and yellow signals, suggesting that the EWSR1 gene was fragmented and recombined. This would be present in CCS but not malignant melanoma.

hand, arm, and shoulder [10]. Recent literature also described CCS arising from the mediastinum, parapharyngeal space, gastrointestinal organs, and kidney [2,11,12,13]. CCS patients often complained of local pain, palpable mass with claudication [6]. Clinical manifestations are due to local compression and invasion of organ, nerve, major blood vessels [14]. CCS is characteristically a slow-growing, firm mass with an aggressive growth pattern, infiltrating adjacent adipose tissue and muscle. Tumor size ranges from 0.4 up to 14.5 cm in diameter. Generally, CCS patients do not possess a history of trauma [6]. Macroscopically, clear cell sarcoma is a tan-gray, firm, circumscribed mass [15,16]. Microscopically, tumor cells were epithelioid, with palely eosinophilic cytoplasm, arranged in sheets [13]. Approximately two-thirds of all CCS contain melanin, and therefore are S-100 positive, whereas the immunological profile for CCS is typically positive for melan-A, HMB-45, and microphthalmia transcription factor [5]. Polymerase chain reaction (PCR) and FISH can detach the translocation (t[12; 22] [q13;q12]) or a resultant EWSR1-ATF1 fusion gene, which is unique to CCS and sufficiently differentiate it from malignant melanoma [12].

Although the final diagnosis of CCS requires histopathological assessment, a combination of imaging methods improves diagnostics by assessing primary and secondary soft tissue tumors and subsequently differentiates CCSTA from other pathologies.

Imaging

Plain radiograph

Plain radiography has a very little role in CCS, as the findings are non-specific. It will either show no abnormalities [17] or the presence of osteolytic lesions, and soft tissue shadow in some cases [18]. In our case, osteolytic lesion and irregular cortical disruption on the right side were observed. Plain radiography may be used as first-line imaging for patients with pain and swelling in areas such as metatarsal, scapula, and ankle [1,7,19].

CT

CT is often used as supplementary or even primary imaging for suspected CCS patients with MRI contraindications [4]. Based on the literature we read, contrast CT can depict CCS mass clearly: size, tumor composition, margin, bone destruction, and infiltrating nature [14]. CCSTA on a CT shows only homogeneous density soft tissue mass lesion but

heterogeneous when necrosis is involved, significant bone destruction can be appreciated [7,15]. Calcification is unusual in CCS [20], with only one case reporting intratumor calcification on CT [11]. In our case, post-contrast abdominal CT showed big round soft tissue mass at the right side of the L3 vertebral, with a clear margin and bone destruction, infiltrating spinal canal. The mass was heterogeneous and necrotic.

MRI

MRI is the best imaging modality for CCS diagnosis prior to biopsy. It produces a clear image of the tumor and its relations to local structures, e.g., nerves and major blood vessels, which may result in reduced per operative morbidity due to better planning [4]. Therefore, it is important to consider obtaining the best preoperative MR-imaging simultaneously. Delay in radical pre-surgery planning may worsen prognosis [4].

The melanin-containing tumor typically appears hyperintense in T1 and hypointense in T2, due to paramagnetic properties of melanin causing the shortening of T1 and T2 relaxation time [7]. Lesions containing less or no melanin will appear isointense, as observed in our case. A study of 21 CCS cases reported that on non-contrast T1WI, 50% would appear slight hyperintense, 33% hypointense, and 14% isointense. On T2WI, 42% would appear hyperintense, 9.5% hypointense, and 28.6% isointense. CCSTA containing less melanin would appear iso-intense in T1WI. Post-contrast CCS generally shows intermediate to strong enhancement. The study also reported 67% were well defined, 10% bone destruction, and 5% intratumor necrosis. 86% of CCS mass were homogenous in T1 & T2 [20]. In our case, the tumor appeared heterogeneous in all sequences. CCS would usually appear homogenous in T1, but heterogeneous in T2WI [21].

PET-CT

PET/CT is the most accurate imaging modality in screening for distant metastases, with both sensitivity and specificity higher than 95% [14]. In our case, PET/CT detected a lesion in the right iliac bone, with maximum SUV of 5.5. Functional imaging of PET-CT has some advantages over its static imaging counterparts, capable of evaluating tumor response to therapy [22]. Marcrom et.al reported [22] a decrease of SUV from 9.5 to 3.0 in 1 month after radiotherapy, demonstrating good response. As CCS typically disseminate by hematogenous spread to the lungs or via the lymphatic system, PET-CT scan may be used to evaluate patients' status in terms of radical surgery [4]. Five cases on mediastinum CCS reported SUV ranging from 8.5 to 16.8 [3,11,14,22,23], while in our case maximum SUV was 8.3. Although the FDG PET scan is a useful imaging method to evaluate various primary masses and distant metastases, diagnosis is rarely established prior to biopsy or surgery. Therefore, percutaneous or surgical biopsy should be done to confirm the diagnosis [11].

Differential diagnosis

The main differential diagnosis of CCS is cutaneous malignant melanoma, as both of them share the same IHC features. The main differential diagnosis tests are the FISH and RT-PCR techniques [2].

Parameters such as age, size, location, presence of skin lesions, necrosis, calcifications, cystic degeneration, invasiveness, and metastatic deposits must be considered when diagnosing CCS [7].

Cortical and vertebral body destruction, paraspinal soft tissue mass in our patient made us suspect this is a case of CCS in the spine. Other spinal lesions that must be excluded are spinal TB, spinal metastatic diseases, and chondrosarcoma.

Spinal tuberculosis

Spinal TB is a common extrapulmonary form of the disease, with a peak age of 45–60 years old [24]. Backache is the most common clinical symptom. CCS and spinal TB would both show bony destruction. On plain radiography, spinal TB typically shows intravertebral disk space narrowing accompanied with rarefaction of adjacent vertebral end plates, which will lead to bony deformity (kyphosis). This is not seen in CCS. On Chest X-ray, spinal TB frequently show active pulmonary lesion, while CCS would show no significant abnormality. On CT, spinal TB would reveal paraspinal multilocular abscess with a clear, smooth inner margin. CCS would instead reveal a soft-tissue tumor with an irregular inner margin of intratumor necrosis if present. On post-contrast MRI, the paraspinal collection is well-circumscribed, with fluid centers, marginal enhancement. CCS usually shows heterogeneous enhancement in the entire tumor. Diagnosis of spinal TB is confirmed either with culture and sensitivity, Gene Xpert PCR test, or by histopathological evidence [24,25].

Spinal metastasis disease

Over half of all systemic cancer patients will have spinal metastasis. Most spinal metastasis patients had known primary malignancy history and multiple vertebrae are involved. CCS patients would not have primary malignancy history and involve single vertebrae only. Common clinical symptom is backache. On plain radiography, spinal metastasis would either show osteolysis with or without osteosclerotic. CCS would usually display osteolysis only. On CT, both spinal metastasis and CCS may show cortical destruction (absent pedicle sign) of vertebral body with epidural soft tissue mass displacing the thecal sac or filling the neural foramen. On MRI, T1WI spinal metastasis appears as diffuse marrow hypointensity. On sagittal T2WI, spinal metastasis depicts a hypointense lesion and a surrounding hyperintense rim (Halo sign). The lesion may extend into the ventral epidural space, compressing the spinal cord with intact disk space. On post-contrast MRI, spinal metastasis demonstrates multiple heterogeneously enhancing lesions [26], while CCS would only show a single heterogeneously enhancing lesion.

Chondrosarcoma

Chondrosarcoma arises from a muscle tendon or synovial sheath. This mesenchymal, cartilage-forming neoplasms, rarely affect the vertebral body. Men are twice more likely to have a chondroma than women, with a peak age of 30–50 years old. Clinical manifestation is local tenderness at the site of the tumor, with possible palpable mass due to tumor expanding into surrounding paraspinous tissues. Plain radiography would show a well-circumscribed, lytic lesion without reactive sclerosis. On CT, a lytic, destructive lesion of varying density will be seen. Alternatively, focal expansion of the bone could occur. A peripheral chondrosarcoma may produce thickening of the vertebral cortex with exophytic extension into the soft tissue. Stippled patterns of calcification are common. On the contrary, calcification is rare in CCS, with our case showing no calcification. On MRI, an extra osseous extension of lobulated cartilage mass which appear hypointense in T1WI, hyperintense in T2WI. Post-contrast MR would reveal a peripheral ring of enhancement or heterogeneous enhancement of the entire tumor [27].

Treatment

Generally, the treatment of CCS is margin-free surgery. In addition to this, our patient also underwent postoperative chemotherapy and radiotherapy, common supplements to prevent local recurrence and metastasis. Benefits of chemotherapy on CCS metastasis are debatable across studies [4,14,15]. Marcrom et al. [22] suggested synergy between concurrent radiotherapy and PD1 blockade in CCS after complete response of a recurrent, unresectable mediastinal CCS. Pembrolizumab with radiation was used. Significant reduction in tumor bulk was observed after just two radiation fractions, with standard fractionation of 2 Gy per day. Complete radiographic response was observed at 50 Gy.

Conclusion

CCSTA is a rare, slow-growing, high malignancy producing melanin. Symptoms are caused by tumor compression and invasion to local structures such as nerve, major blood vessels. MRI is the best imaging modality, and critical to preoperative planning. PET/CT has very high sensitivity and specificity in screening for distant metastases. After imaging studies, IHC and FISH must be requested to confirm the diagnosis of CCS, as the latter sufficiently differentiates CCS from malignant melanoma. CCS with less melanin content is atypical, making it more difficult to suspect this rare malignancy. Increased awareness in CCS radiological characteristics dan the differential diagnosis of CCS may quicken diagnosis and management. Despite its rarity, CCSTA needs to be ruled out with every suspected case of malignant melanoma or any soft tissue tumor.

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