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Clear cell sarcoma-A review

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ABSTRACT

Clear cell sarcoma (CCS) previously known as malignant melanoma (MM) of the soft tissue, although, similar in morphology to MM, contemporary histopathologic and cytogenetic techniques have made this diagnosis obsolete, as it is now possible to distinguish between CCS and MM. CCS is often diagnosed in young adults with median age of 25 years. Overall mortality is generally poor, and the 5-year survival is between 40 and 60%. Hence, early diagnosis and radical surgery are key in the treatment of this extremely rare malignancy of the soft tissue comprising only about 1% of all sarcomas. This article present an overview of this rare malignancy.

Introduction

Clear cell sarcoma (CCS) is an extremely rare and aggressive subtype of sarcoma with melanocytic differentiation both immunohistochemically, ultrastructural and genomic.[1,2] It comprises approximately 1% of all diagnosed sarcomas.[3] Furthermore, the prognosis is poor due to predilection for metastasis at an early stage to the lymphatic system and the lungs.[4] CCS is thought to derive from the neural crest cells.[5] As a whole, sarcomas arises from the mesenchymal tissues, such as bone, muscle, fat, connective tissue, blood vessels and nerves.[5] Hence, corresponding tissue origin of clear cell sarcoma, which was first described by Enzinger et al in 1965.[6] The name CCS originates from the initial histopathological findings of clear cells, as the cytoplasm of the tumor cells may appear clear.[6] The term malignant melanoma of the soft tissue was previously used, however, contemporary histopathologic and cytogenetic techniques have made this diagnosis obsolete, as pathologist are able to distinguish between CCS and malignant melanoma today.[7] In 95% of the cases, the CCS arises in the lower extremities, particularly the foot and ankle. It presents as an indolent, growing and painless mass situated in the deep soft tissue or beneath the fascia.[4,8–10] CCS occur at all ages, but is most often observed in the third decade.[11–14] The mean age at the time of diagnosis is approximately 25 years and CCS is more common in Caucasians than in African Americans or Asians, without any gender predilection.[11–14] The aetiology of CCS is virtually unknown, and the exact cause and the mechanisms of formation remains to be elucidated. Genetic defects occurring on account of certain chromosomal exchanges is thought to play a key role in the formation. Hence, CCS is repeatedly seen in relation to specific genetic transformations. Only a few known risk factors are described *e.g.* exposure to chemicals (vinyl chloride, arsenic), chronic tissue irritation (lymphedema, foreign body implants) and radiation.[5]

Diagnosis

Compared to the aforementioned, identifying and diagnosing CCS is challenging. Quick and accurate diagnosis is dependent on the level of experience of the doctor at the initial examination and fast referral to specialized units with relevant experience, such as tertiary sarcoma centres are imperative. The mean time from onset of symptoms to confirmation of the diagnosis is often several months, which could be the result of an initial suspicion of a benign tumor.[13,14] This prolonged time to relevant examinations and to diagnosis may lead to a more advanced disease at the time of diagnosis and therefore a more sinister prognosis.[5,14,15]

Radiological examination

Hitherto, the most relevant initial investigation in the diagnosis of CCS is magnetic resonance imaging (MRI). Currently, no exact radiological criteria to differentiate between malignant and benign tumors in the soft tissue exist.[7,16–18] However, today a combination of different imaging tools is used to provide a tentative diagnosis, while the final diagnosis of CCS is made, based on the resulting or concomitant pathological examination.

MRI is the leading and most established modality to identify the primary tumor and its relations to adjacent structures.[17] In addition,

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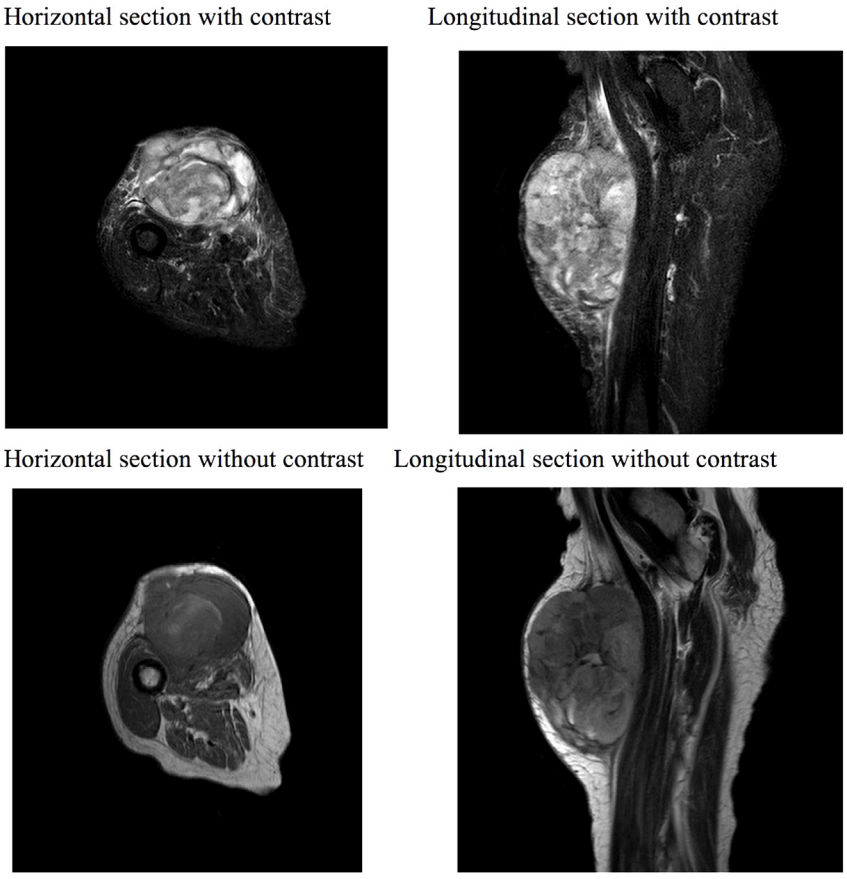

Figure 1. MRI scan: An 80-year-old woman with subcutaneous soft tissue tumor in the lower extremities with relation to both tendons, skin and vital blood vessels. Primary differential diagnosis was sarcoma. A biopsy was performed. Histopathological examinations raised doubt regarding the diagnosis; was it malignant melanoma or clear cell sarcoma. Subsequently verified as a metastasis of malignant melanoma.

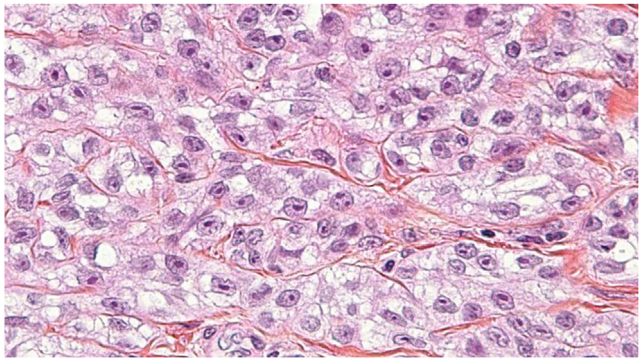

Figure 2. CCS, hematoxylin-eosin stain: There are irregular nests of cells separated by fibrous septa. Cells are fusiform and not pleomorphic. They have regular vesicular nuclei and prominent nucleoli with moderate to abundant eosinophilic or clear cytoplasm.

conventional ultrasound and computed tomography (CT) may be utilized as supplements and primary investigation in the few cases of contraindications to the MRI or because these modalities are more widely available.

When diagnosing CCS, it is important to consider obtaining the best possible preoperative imaging simultaneously, as surgery is the primary and possible curative treatment and further delays in terms of planning radical surgery, may render the prognosis even worse. As such the MRI 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 (Fig. 1).

As CCS typically disseminate by haematogenous spread to the lungs or via the lymphatic system, Positron emission tomography–computed tomography (PET-CT) scan may be used to evaluate patients' status in terms of radical surgery.

Pathological examination

The final diagnosis of CCS is pathological. Macroscopically the CCS appears to be well-defined solid tumors, with mat grey color that frequently infiltrate tendons and aponeuroses. Microscopically findings are small compact nests with uniform neoplastic cells divided into variable sized clusters by fibrous septa along the tendons and aponeuroses.[2,6] The tumor cells typically appear with a clear eosinophilic cytoplasm and a basophilic nucleolus (Fig. 2). The eosinophilic cytoplasm is due to the accumulation of glycogen, which can be visualized using periodic (PAS) stain method. The tumor cells show none or a minimal rate of mitosis in concordance with the slow growth rate of CCS. Scattered giant cells with 10–16 nucleoli and scattered necrosis may also be identified in CCS.[2]

Immunohistochemical studies of CCS show great similarity to the characteristics of malignant melanoma, including a strong expression of S-100, HMB-45, Melan-A and microphthalmia-associated transcription factor (MITF) in 81–97% of the cases.[2,19] Clear cell sarcoma is associated the chromosomal fusion of the Ewing's Sarcoma oncogene (EWS) and the cellular transcription factor (ATF1) into EWS/ATF1 oncogene.[20] This chromosomal fusion due to (t[12; 22] [q13; q12]) can be detected with cytogenetic investigations, *e.g.* polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) in 90% of the cases.[20] In addition, to the before mentioned translocation, a fusion between Ewing Sarcoma Breakpoint Region 1(EWSR1) and Camp Responsive Element Binding Protein 1 (CREB1) is also known to give rise to CCS.[21] Studies have shown that EWSR1/ATFI fusion protein is able to bind and activate melanocyte specific MITF via SRY-related HMG-box 10 (SOX10) transcription factor, which results in the expression of the melanocytic phenotype, thus the malignant melanoma is a differential diagnosis.[22,23]