Clear cell sarcoma of tendons and aponeuroses, and osteoclast-rich tumour of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: a review and update

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ABSTRACT
Clear cell sarcoma (CCS) is a rare, distinctive soft tissue neoplasm, typically occurring in the distal extremities of young adult patients. Although CCS shows melanocytic differentiation, it is now clear that it is clinicopathologically and genetically distinct from conventional malignant melanoma. The ‘osteoclast-rich tumour of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts’ is an extraordinarily rare gastrointestinal neoplasm that shares some features of CCS, but differs from it in other ways. The historical, histopathological, ultrastructural, immunohistochemical and genetic aspects of these two tumours are reviewed in this article.

INTRODUCTION
Clear cell sarcoma (CCS) of tendons and aponeuroses is a rare translocation-associated sarcoma showing melanocytic differentiation at the light microscopic, ultrastructural and protein levels. Osteoclast-rich tumour of the gastrointestinal tract with features resembling CCS of soft parts is a very rare, recently described tumour of uncertain differentiation; it shares some morphological, immunohistochemical and genetic features with CCS. This article reviews the historical, histopathological, ultrastructural, immunohistochemical and genetic features of these two entities.

CLEAR CELL SARCOMA
Historical and ‘histogenetic’ aspects
CCS was first recognised in 1965 by Dr Franz Enzinger in a series of 21 cases culled from the archives of the Armed Forces Institute of Pathology over a 25-year period. The introduction of that seminal paper is notable for the observation that ‘While benign tumours of tendons and aponeurosis are observed commonly and have been defined adequately, malignant tumours originating from these tissues are rare…Nearly all have been classified as synovial sarcoma or fibrosarcoma’. 1 Indeed, two of the 21 cases in Enzinger’s series had been previously reported by Bennet in a series of malignant neoplasms involving the synovium (‘synoviomata’), as examples of a ‘more solid and simplified type of sarcoma derived from synovial tissues’. 2 The term ‘clear cell sarcoma of tendons and aponeuroses’ was chosen purely as a descriptive term, reflecting Enzinger’s uncertainty as to its histogenesis. Interestingly, although Enzinger noted the presence of Fontana-positive pigment in CCS, he initially regarded this as a potential diagnostic pitfall, rather than a clue to the line of differentiation taken by this enigmatic sarcoma. Credit for recognition of melanocytic differentiation in CCS thus belongs to Hoffman and Carter who documented the presence of intracytoplasmic melanosomes in 1975, in an ultrastructural study. 3 Melanocytic differentiation in CCS was subsequently confirmed by a small number of investigators over the next several years, 4,5 although as late as 1979 the existence of CCS as a discrete entity, rather than simply a morphological variant of so-called ‘tendosynovial sarcoma’ (a term that encompassed synovial sarcoma, epithelioid sarcoma, extraskeletal myxoid chondrosarcoma, and CCS) was questioned in a major textbook of soft tissue pathology. 6

In 1983, Chung and Enzinger reported what remains the largest series to date of CCS (141 cases), and proposed the new name ‘malignant melanoma of soft parts’ for this entity, noting ‘…clear cell sarcoma represents a malignant neuroectodermal tumour derived from potentially melanogenic cells that have migrated from the neural crest during embryonal life’ and ‘…the tumour is in many aspects akin to malignant melanoma and malignant blue nevus’. 7 However, as has been noted by Rosai, 8 Chung and Enzinger clearly recognised that CCS was clinically distinct from conventional melanoma, an observation that has been amply supported by our evolving understanding of the genetic underpinnings of CCS and melanoma. As is discussed below, it is now abundantly clear that CCS is a soft tissue sarcoma showing melanocytic differentiation, in almost all instances as a result of the translocation t(12;22) (q13;q12)(EWS-ATF1), a genetic event not seen in melanoma. 9–11

Clinical features
CCS is quite rare, comprising <1% of all soft tissue tumours. 12 Approximately 500 cases have been reported, including a number of relatively large series from cancer centres and consultation practices 1,3–5,7,13–24 CCS most often occurs in young to middle-aged adults of either sex, although it has been reported in very young children and in elderly adults. The tumour most often involves the foot and ankle, with less common sites of involvement including the knee, thigh, hand, elbow and forearm. Isolated cases of CCS occurring in the head/neck, 25

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trunk,\textsuperscript{26} penis,\textsuperscript{27} retroperitoneum,\textsuperscript{28} bone,\textsuperscript{29} kidney\textsuperscript{17} and gastrointestinal tract\textsuperscript{30} have been reported. CCS is typically a deeply situated lesion that often appears to arise from or in association with the tendons and aponeuroses, involving the skin only in long-standing or larger lesions. Most tumours are relatively small (<5 cm) at the time of diagnosis, and a long prebiopsy duration is present in many instances.

Histopathological features
The histological features of CCS are illustrated in figure 1. As described by Enzinger, CCS is composed of compact nests and fasciciles of pale fusiform or epithelioid cells, surrounded by a delicate framework of fibrocollagenous tissue contiguous with the adjacent tendons and aponeurosis, forming a vaguely organoid (‘neuroendocrine-like’) pattern. In addition to this organoid pattern, CCS may grow in a more diffuse or sheet-like pattern, and occasionally shows a pseudoalveolar pattern, reminiscent of alveolar soft part sarcoma, a myxoid/microcystic pattern, or a prominent chronic inflammatory cell infiltrate, similar to seminoma. The cells of CCS range from epithelioid to spindled, and most often contain lightly eosinophilic to amphophilic cytoplasm, with truly clear cells typically comprising only a minority of the neoplastic cell population. The cells have indistinct cell borders, and generally uniform round nuclei with prominent macronucleoli, similar to conventional malignant melanoma. Multinucleated, Touton-like tumour giant cells are frequently present and may be a valuable diagnostic clue. Cellular pleomorphism is uncommon, but may rarely be seen in genetically confirmed CCS;\textsuperscript{11} this feature may become more prominent in recurrent and/or metastatic lesions. Mitotic figures are typically few in number and necrosis is uncommon. Melanin pigment may occasionally be identified in CCS, typically only in scattered cells.

Ultrastructural features
The first ultrastructural study of CCS was that of Kubo and colleagues, who perpetuated the idea that it was a variant of synovial sarcoma, based on their finding of basement membrane material, a ‘biphasic’ pattern of cells and the presence of pseudoglandular structures with filopodia.\textsuperscript{31} However, following this report, a small number of subsequent ultrastructural studies suggested a closer relationship to melanoma and nerve sheath tumours, based on the presence of melanosomes, basement membrane material and the presence of interdigitating cellular processes, wrapping around neighbouring cells and extracellular structures.\textsuperscript{13} 19 The cells of CCS have also been reported to contain moderate numbers of organelles, aggregates of glycogen, and inclusions composed of multilayered membrane structures forming myelin-like figures.\textsuperscript{13} 19

Immunohistochemical features
By immunohistochemistry, CCS shows a phenotype identical to that of conventional malignant melanoma (figure 2A–C). Overall, prior studies of CCS have documented expression of S100 protein in approximately 75% of reported cases, and expression of more specific melanocytic markers, such as HMB-45, Melan-A and microphthalmia transcription factor (MiTF), in a smaller percentage of cases.\textsuperscript{1 7 13–16 21 22 32–34} However, these results include many cases studied before the use of modern immunohistochemical techniques. A very recent study of 33 genetically confirmed CCS by Hisaoka et al showed strong S100 protein expression in 100% of cases, with expression of HMB-45, Melan-A and MiTF in 97%, 71% and 81% of cases, respectively.\textsuperscript{18} These results are in accordance with our own experience with CCS in the modern immunohistochemical era. CCS may also express neuroendocrine and/or nerve sheath-related markers in a significant percentage of cases, with Hisaoka et al documenting expression of synaptophysin, CD56 and CD57 in 45%, 21% and 75% of studied cases, respectively.\textsuperscript{18} CCS is negative for markers of myogenous differentiation, but may rarely show anomalous expression of epithelial markers, including cytokeratins and epithelial membrane antigen. CD34 is generally negative, and Bcl-2 expression is common.\textsuperscript{19} Although it has been suggested by some investigators that differential expression of CD117 (c-Kit) may be useful in the distinction of CCS (usually negative) from conventional malignant melanoma (frequently positive), other studies have not validated this hypothesis.\textsuperscript{18} 35

Cyto genetic and molecular genetic features
Early cytogenetic analyses of CCS identified multiple structural and numerical abnormalities, involving chromosomes 2, 3, 7, 8, 12, 15, 14, 15, 17, 21 and 22.\textsuperscript{36} 37 It has subsequently become clear that in >90% of cases CCS is associated with the reciprocal translocation t(12;22)(q13;q12), resulting in fusion of the EWSR1 gene located at 22q12 and the ATFi gene located at 12q13\textsuperscript{38} (figure 2D). This gene fusion results in production of a chimeric protein containing the N-terminal domain of EWSR1 linked to the basic leucine zipper (bZIP) domain of ATFi, with loss of the regulatory PKA domain of ATFi and the RNA-binding domain of the EWSR1 gene.\textsuperscript{10} Four types of EWSR1–ATFi fusion transcripts have been identified to date, with fusions between exon 8 of EWSR1 and exon 4 of ATFi representing the most common transcript.\textsuperscript{39} More recently, Antonescu et al have identified EWSR1–CREB1 gene fusions (presumably representing the translocation t(2;22)(q32.5;q12)) in three CCS-like gastrointestinal tumours (see below), and this same gene fusion has been identified in a small number of otherwise conventional soft tissue CCS.\textsuperscript{40} To date, fusion type does not appear to be related to prognosis in CCS.\textsuperscript{33}

Rearrangements involving the EWSR1 gene, a member of the TET family of transcription factors, have been implicated in a number of sarcomas, including Ewing sarcoma/primitive neuroectodermal tumour, extraskeletal myxoid chondrosarcoma, myxoid liposarcoma, angiomatoid (malignant) fibrous histiocytoma, and desmoplastic small round cell tumour.\textsuperscript{41} ATFi is a member of the CREB transcription factor family, whose activity is normally regulated by phosphorylation of the kinase-inducible domain.\textsuperscript{42} In CCS, an activating domain derived from EWSR1 replaces the kinase-inducible domain of ATFi, resulting in a chimeric protein that transactivates in a cAMP-independent manner.\textsuperscript{43} In normal melanocytes, CREB and ATFi are crucially involved in driving expression of MiTF (a critical regulator of melanocyte differentiation), in combination with the neural crest restricted transcription factor SOX10.\textsuperscript{42} Recently, Davis et al have shown that the EWSR1–ATFi fusion protein is capable of binding to and activating melanocyte-specific MiTF, and in the presence of SOX10 this results in expression of the melanocytic phenotype and the growth/survival of CCS cells.\textsuperscript{42} Gene expression profiling studies have shown CCS to cluster with melanomas, with expression of a variety of genes associated with melanocytic differentiation, including MiTF, SOX10, ERBB3 and FGFR1.\textsuperscript{44}

Prognosis and therapy
The clinical course of CCS is usually protracted with multiple local recurrences and late metastases. However, up to 30% of patients with CCS in some series have presented with...
metastases. In Enzinger’s original series, local recurrences, distant metastases and death from disease were seen in 84%, 63% and 74% of patients, respectively. The follow-up study of Chung and Enzinger noted local recurrence, distant metastasis and mortality rates of 39%, 50% and 50%, respectively. Other large series of CCS have reported 5-year, 10-year and 20-year survival rates of 47%, 33%, and 10%, respectively. Similar survival rates have been reported in paediatric patients with CCS. Although some studies have reported an association between worse outcome and histopathological parameters such as mitotic activity and necrosis, this has not been confirmed in other studies. There is general agreement that the prognosis is worse for larger (>5 cm) tumours. CCS are not formally graded under either the French Federation of Cancer Centers or the National Cancer Institute soft tissue sarcoma grading schema, but should be considered ‘high grade’ for purposes of staging and therapy. CCS metastasises most often to lung and bone, as well as to lymph nodes in approximately 15% of cases. Therapy for CCS typically includes wide surgical excision and adjuvant radiotherapy. It is unclear whether chemotherapy and/or immunotherapy have any role in the treatment of patients with CCS. Elective lymph node dissection and sentinel lymph node biopsy have been advocated by some investigators for staging of patients with CCS. Essentially indefinite clinical follow-up is mandatory for patients with CCS, owing to this tumour’s propensity for late metastases.

**OSTEOCLAST-RICH TUMOUR OF THE GASTROINTESTINAL TRACT WITH FEATURES RESEMBLING CCS OF SOFT PARTS**

Clinical features and prognosis

Osteoclast-rich tumour of the gastrointestinal tract with features resembling CCS of soft parts (referred to hereafter as ‘clear cell sarcoma-like gastrointestinal tumour,’ CCSLGT) and true soft-tissue-type CCS of the gastrointestinal tract are extremely rare. Table 1 summarises the clinicopathological features of all 20 reported cases, 13 of which appear to represent CCSLGT, and seven of which correspond to soft tissue-type CCS. The term ‘osteoclast-rich tumour of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts’ was coined in 2003 by Zambrano et al, in a report of six distinctive tumours of the gastrointestinal tract. A case morphologically corresponding to this entity had been previously published by Alpers and Beckwith as a ‘malignant neuroendocrine tumour of the jejunum with osteoclast-like tumour giant cells.’ Since the description of this tumour by Zambrano et al, only two definite and four probable additional examples have been reported.

The clinical behaviour of CCSLGT appears to be highly aggressive, with aggressive local recurrence, lymph node or
visceral metastases, or death from disease in 12 of 12 (100%) reported cases, generally in <36 months. This behaviour is in contrast to the more indolent behaviour of classical CCS of soft tissue. There are no data on the possible role of adjuvant therapies in the treatment of CCSLGT.

Histopathological, ultrastructural and immunohistochemical features

The morphological features of CCSLGT are illustrated in figure 3A–E. CCSLGT is typically centered within the wall of the bowel, with secondary involvement of the mucosa and serosa. The tumours grow in solid sheets, pseudopapillary formations and alveolar formations, generally without the well-formed nests that characterise soft-tissue-type CCS. The neoplastic cells are usually round to oval, with only infrequent spindling, and contain a moderate amount of clear to lightly eosinophilic cytoplasm. The nuclei of CCSLGT are centrally located and round, with irregularly dispersed chromatin, and either inapparent or small nucleoli, in most instances. Macronucleoli of the type seen in conventional melanoma and soft-tissue-type CCS are only infrequently identified. Mitotic activity may be brisk and necrosis is frequently present. Perhaps the most distinctive feature of CCSLGT is the presence of osteoclast-like multinucleated giant cells admixed with the neoplastic cells. The number of osteoclast-like giant cells varies greatly from field to field within a given CCSLGT, with some areas containing large numbers of such cells, and other areas lacking them entirely. Neoplastic giant cells, of the type seen in soft tissue CCS, are absent.

Ultrastructurally, the cells of CCSLGT are poorly differentiated, with primitive cell junctions, scarce intracellular filaments and variable amounts of glycerogen. Melanosomes have not been identified in any case studied to date, although occasional dense core granules have been reported to be present. The morphology of CCSLGT can be compared with that of soft tissue CCS, with expression of S100 protein and absent expression of markers of melanocytic differentiation, such as HMB-45, Melan-A and tyrosinase (figure 3F and G). All cases studied to date have been CD117 (c-Kit) negative. Occasional cases have been reported to express CD57 and/or neuron-specific enolase.

Soft-tissue-type CCS involving the gastrointestinal tract have shown the same morphological, ultrastructural, and immunohistochemical features as their somatic soft tissue counterparts.

Cytogenetic and molecular genetic features

Traditional karyotyping, reverse transcription PCR analysis and/or fluorescence in situ hybridisation (FISH) study have been performed on six CCSLGTs and six soft-tissue-type CCS of the gastrointestinal tract (table 1). Of the CCSLGTs, three cases contained EWS–CREB1 fusions, two cases contained EWS–ATF1 fusions, and one case contained a EWS rearrangement by FISH, with an unknown partner. The soft-tissue-type CCS involving the gastrointestinal tract contained EWS–ATF1 fusions in five cases, and a EWS rearrangement with an unknown partner in one case.

Relationship of CCSLGT and CCS

Although some investigators have regarded CCSLGT as simply a variant of CCS lacking melanocytic differentiation, others have questioned whether CCSLGT may represent an entirely distinct entity. In our opinion, the preponderance of evidence suggests that CCSLGT represents a distinct entity. From a clinical perspective, CCSLGT shows much more aggressive behaviour than does soft tissue CCS, with metastatic disease in <36 months in almost all reported cases, as compared with the much more protracted survival of patients with CCS. However, it should be noted that the behaviour of reported soft-tissue-type CCS of the gastrointestinal tract appears to be more aggressive than that of its somatic soft tissue counterpart (table 1). Morphologically, CCSLGT shares some features with CCS, such as clear to lightly eosinophilic cytoplasm and
a tendency towards nested growth, but more often shows dissimilar features, including sheetlike, pseudoalveolar and pseudopapillary growth, inapparent or small nucleoli, and, perhaps most notably, osteoclast-like giant cells, instead of pseudopapillary growth, inapparent or small nucleoli, and, perhaps most notably, osteoclast-like giant cells, instead of

dissimilar features, including sheetlike, pseudoalveolar and pseudopapillary growth, inapparent or small nucleoli, and, perhaps most notably, osteoclast-like giant cells, instead of

We share the viewpoint advanced by Barr and Zhang in a recent editorial,60 who suggested that ‘...these differing phenotypes are not due to the fusion subtypes but rather to the cell types in which the fusion is expressed.’ Barr and Zhang go on to hypothesise the existence of three distinct cell types in which the fusion is expressed.

<table>
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<th>Report</th>
<th>Age (years)/sex</th>
<th>Location</th>
<th>Soft tissue CCS histology</th>
<th>CCSLGT histology</th>
<th>S100</th>
<th>HMB-45</th>
<th>Melan-A</th>
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AWD, alive with disease; CCS, clear cell sarcoma; CCSLGT, clear cell sarcoma-like gastrointestinal tumour; DOD, dead of disease; EM, electron microscopy; FISH, fluorescence in situ hybridisation; LN, lymph node; Mets, metastases; ND, not done; NED, no evidence of disease; RT, reverse transcription.
The differential diagnosis of CCS centres around S100 protein and/or melanocytic-marker-positive neoplasms, including malignant melanoma, epithelioid malignant peripheral nerve sheath tumour (MPNST), melanotic schwannoma, perivascular epithelioid cell neoplasm (PEComa), cellular blue naevus and granular cell tumour, but may also include other epithelioid tumours and/or nested tumours, such as synovial sarcoma, alveolar soft part sarcoma, paraganglioma, epithelioid sarcoma and carcinoma. Conventional malignant melanoma is often extremely difficult (if not impossible) to distinguish from CCS on morphological grounds. In general, CCS occurs in much younger patients, lacks epidermal involvement, tends to display less cellular pleomorphism, and may contain Touton-type neoplastic giant cells, an unusual feature in melanoma. There are no immunohistochemical markers that reliably differentiate CCS and melanoma, and molecular genetic study for the EWS-ATF1 or EWS-CREB1 fusion may be required for definitive diagnosis. Epithelioid MPNST may arise in patients with neurofibromatosis type 1, and it often contains intermixed areas of more conventional spindled MPNST, lacks expression of melanocytic markers such as HMB-45 and Melan-A, and is negative for EWS rearrangements. Melanotic schwannoma most often occurs in patients with Carney

**Figure 3** (A) Clear cell sarcoma-like gastrointestinal tumour (CCSLGT), consisting of a highly infiltrative sheet-like proliferation of clear to lightly eosinophilic epithelioid cells. (B) Pseudoalveolar pattern in CCSLGT, reminiscent of alveolar soft part sarcoma. (C) Pseudopapillary growth pattern in CCSLGT. (D) The most characteristic morphological feature of CCSLGT is the presence of admixed osteoclast-like giant cells. Such cells are not seen in CCS of soft tissue. Multinucleated neoplastic giant cells, a feature of CCS, are not seen in CCSLGT. (E) At higher-power magnification, the cells of CCSLGT tend to lack the prominent macronucleoli that are seen in CCS. (F) CCSLGT, positive for S100 protein. (G) CCSLGT, negative for HMB-45.
syndrome, in a paraspinal or nerve plexus-related location, frequently contains psammomatous calcifications, contains very abundant melanin pigment, and grows in a non-nested, syncytiotidal pattern. PEComas may closely mimic CCS by virtue of their nested arrangement and admixture of spindled and epithelioid cells. However, PEComas have less prominent nuclei than do CCS, and Touton-type giant cells are absent. By immunohistochemistry, PEComas show a ‘myomelanocytic’ phenotype, with co-expression of smooth muscle actins and melanocytic markers, most often in the absence of S100 protein expression. Cellular blue naevi lack cytological atypia, frequently grow in a ‘dumbbell-shaped’ configuration and are negative for the EWS–ATF1 gene fusion. Granular cell tumours generally lack cytological atypia, contain abundant coarsely granular cytoplasm and lack expression of melanocytic markers. Finally, synovial sarcomas, epithelioid sarcomas and carcinomas all lack the distinctive nested growth pattern of CCS, and express cytokeratins, but not S100 protein.

CCSLGT may be distinguished from CCS involving the gastrointestinal tract and metastatic melanoma by virtue of its distinctive morphological features, including the presence of osteoclast-like giant cells, and absent expression of specific melanocytic markers. Gastrointestinal stromal tumours differ morphologically from CCSLGT and express CD117, protein melanocytic markers. Gastrointestinal stromal tumours differ gastrointestinally from CCS and express CD117, protein melanocytic markers. Gastrointestinal stromal tumours differ gastrointestinally from CCSLGT and express CD117, protein melanocytic markers. Gastrointestinal stromal tumours differ gastrointestinally from CCSLGT and express CD117, protein melanocytic markers. Gastrointestinal stromal tumours differ gastrointestinally from CCSLGT and express CD117, protein melanocytic markers. Gastrointestinal stromal tumours differ gastrointestinally from CCSLGT and express CD117, protein melanocytic markers. Gastrointestinal stromal tumours differ gastrointestinally from CCSLGT and express CD117, protein melanocytic markers.

CONCLUSIONS
CCSs is a rare soft tissue tumour with distinctive morphological features and melanocytic differentiation. It is now clear that CCS is caused by fusions of the EWS gene with either the ATF1 gene or the CREB1 gene. CCSLGT is an extraordinarily rare neoplasm of the gastrointestinal tract, and it shares some morphological, immunohistochemical and genetic features with soft tissue CCS, but differs from it significantly in a number of important ways. At the present time, CCS and CCSLGT should be regarded as distinct entities, rather than site-specific manifestations of a single entity.

Competing interests None.

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REFERENCES
Clear cell sarcoma of tendons and aponeuroses, and osteoclast-rich tumour of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: a review and update

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