

# Clear Cell Sarcoma–like Tumor of the Gastrointestinal Tract

## An Evolving Entity

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• **Clear cell sarcoma–like tumor of the gastrointestinal tract (CCSLGT) is a rare malignant neoplasm that occurs in the wall of the small bowel, stomach, or large bowel, predominantly in young adults. It is an aggressive neoplasm that frequently presents with metastatic disease and has a high mortality rate. Histologically, it is usually composed of medium-sized primitive ovoid or epithelioid cells with pale or clear cytoplasm that are arranged in sheets or in papillary or alveolar architectures. Clear cell sarcoma–like tumor of the gastrointestinal tract is positive for S100 protein, invariably negative for melanocyte-specific markers and is often also positive for neuroendocrine markers. The etiology of CCSLGT is unknown, but many studies have shown associations with *EWSR1-CREB1* gene fusions and, less frequently, with *EWSR1-ATF1* fusions. Here, we discuss the current status of CCSLGT, including histologic, immunophenotypic, and molecular findings.**

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**C**lear cell sarcoma–like tumor of the gastrointestinal tract (CCSLGT; osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma [CCS] of soft parts) is a rare malignant neoplasm that arises within the wall of the small bowel, stomach, or large bowel, and predominantly occurs in young adults.<sup>1–3</sup> Clear cell sarcoma–like tumor of the gastrointestinal tract was first described as a distinct entity in 2003 in a series of 6 cases by Zambrano et al.<sup>3</sup> However, cases that may be morphologically similar to CCSLGT have been reported previously, including by Alpers and Beckstead,<sup>4</sup> who reported a “malignant neuroendocrine tumor of the jejunum with osteoclast-like tumor giant cells” in 1985. To our knowledge, only 38 cases have been published,<sup>1,2,5–14</sup> of which 9

are single case reports and 5 are cases series, with the largest describing a cohort of 16 patients.

Clear cell sarcoma–like tumor of the gastrointestinal tract is often difficult to distinguish from conventional CCS (of soft tissue or of tendons and aponeuroses) because their morphologic features overlap, they both express S100 protein, and they both can harbor identical genetic abnormalities, but in contrast to CCS, CCSLGTs lack immunohistochemical or ultrastructural evidence of melanocytic differentiation. Clear cell sarcoma (previously known as melanoma of soft parts) is a longer-established and better-recognized entity that was first described in 1965 by Enzinger.<sup>15</sup> Clear cell sarcoma occurs in young to middle-aged adults, but typically in the deep soft tissues of the lower extremities. Ekfors et al<sup>16</sup> first described a case of CCS arising in the duodenum, and there have since been even fewer reports of CCS arising in the gastrointestinal tract, compared with CCSLGT (n = 13).

Because of the similarities between the two entities, it is often difficult to be certain whether cases reported represent one or the other, and it has been debated as to whether they might represent variants of the same entity.<sup>17</sup> However, more recent evidence points to CCSLGT and CCS representing two distinct tumor types, as discussed below.

### CLINICAL FEATURES

Clear cell sarcoma–like tumor of the gastrointestinal tract is an extremely rare neoplasm that occurs predominantly in younger adults, with a median age of 35 years, although the age distribution is wide (ranging from 10 to 81 years), and no particular sex preponderance has been noted. Clear cell sarcoma–like tumor of the gastrointestinal tract has been described exclusively within the abdominal cavity. Most CCSLGTs have arisen in the wall of the small bowel (including ileum and jejunum), with other documented sites including the stomach, colon, and peritoneum. Most patients present with abdominal pain, with intestinal obstruction, or with an incidental finding of an abdominal mass on imaging. Some patients have nonspecific symptoms of anorexia, weight loss, anemia, lethargy, or pyrexia, and occasionally presentation is with vomiting or hematemesis. The etiology of CCSLGT is unknown, although 2 reported cases have occurred as second malignancies following irradiation for neuroblastoma in infancy,<sup>14,18</sup> suggesting radiotherapy as a possible precipitating factor for its development later in life. One patient was reported to

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have a synchronous colonic adenocarcinoma, which was excised at the same time as the CCSLGT,<sup>1</sup> whereas another neoplasm was described to coexist with peritumoral immunoglobulin G4 (IgG4)-associated sclerosing inflammation in the abdomen.<sup>9</sup>

### Prognosis and Treatment

A large proportion of patients with CCSLGT have metastases at presentation, mainly to lymph nodes or liver. Of 25 patients with follow-up data, 8 developed recurrences, of whom 2 had hepatic metastasis<sup>1,3,13</sup>; 8 patients subsequently died of their disease, with a median survival of 18.5 months (range, 3–106 months).<sup>3,13</sup> There are currently no reliable clinical or pathologic parameters helpful in predicting biologic behavior, and optimum management remains to be fully established. The usual management is resection of tumor with the corresponding bowel segment followed by close monitoring for locally recurrent and metastatic disease, including regular imaging. There have been no reports of postoperative radiotherapy or chemotherapy in any of the patients described to date. Only 1 patient, who had a synchronous colonic adenocarcinoma, proceeded to receive adjuvant chemotherapy with 5-fluorouracil<sup>1</sup>; she subsequently developed liver metastasis from CCSLGT and underwent a partial hepatectomy.

## PATHOLOGIC FEATURES OF CCSLGT

### Morphology

Macroscopically, CCSLGT is typically found in the bowel or stomach wall, centered within the muscularis propria but often with extension into the submucosa and subserosa.<sup>13</sup> Some tumors grow as polypoid masses extending into the lumen with mucosal ulceration, whereas others are circumferential stenosing lesions. The median size of primary neoplasms is 4.5 cm, with a range of 2.4 to 15 cm. Grossly, these are multinodular, infiltrative lesions with a solid, tan-white surface, with variable hemorrhage and necrosis and sometimes secondary cystic change. Microscopically, CCSLGTs are highly infiltrative cellular tumors that frequently obliterate the bowel or gastric wall (Figure 1), with mucosal ulceration and serosal extension. There is a morphologic spectrum. Most CCSLGTs are composed of relatively monomorphic medium-sized to relatively large ovoid or epithelioid cells that have variable amounts of pale eosinophilic or, less frequently, clear cytoplasm (Figure 2). The nuclei are centrally located and polygonal, with vesicular chromatin. Nucleoli are most often small and inconspicuous, although occasionally there are macronucleoli. Spindling of cells is a rarer feature, as are large epithelioid cells<sup>5</sup> and pleomorphism (Figure 3),<sup>19</sup> which can also occur in gastrointestinal CCS with *EWSR1-ATF1* fusion transcripts.<sup>20</sup> Architecturally, cells are most often arranged in diffuse sheets or more ill-defined nests (Figures 2 through 4), without the well-formed nests typical of CCS. Clear cell sarcoma-like tumors of the gastrointestinal tract often also show, at least focally, pseudoalveolar (Figure 5), pseudopapillary, microcystic, fascicular, or trabecular growth patterns, and abortive rosettelike structures have been described.<sup>13</sup> The spindle cell areas can show a fascicular pattern, and there is often surrounding desmoplastic stroma or, less frequently, myxoid stromal change. Recurrent or metastatic neoplasms generally retain the morphology of the primary tumor, although they may display greater pleomorphism (Figure 6).<sup>13</sup> A characteristic feature of CCSLGT, which

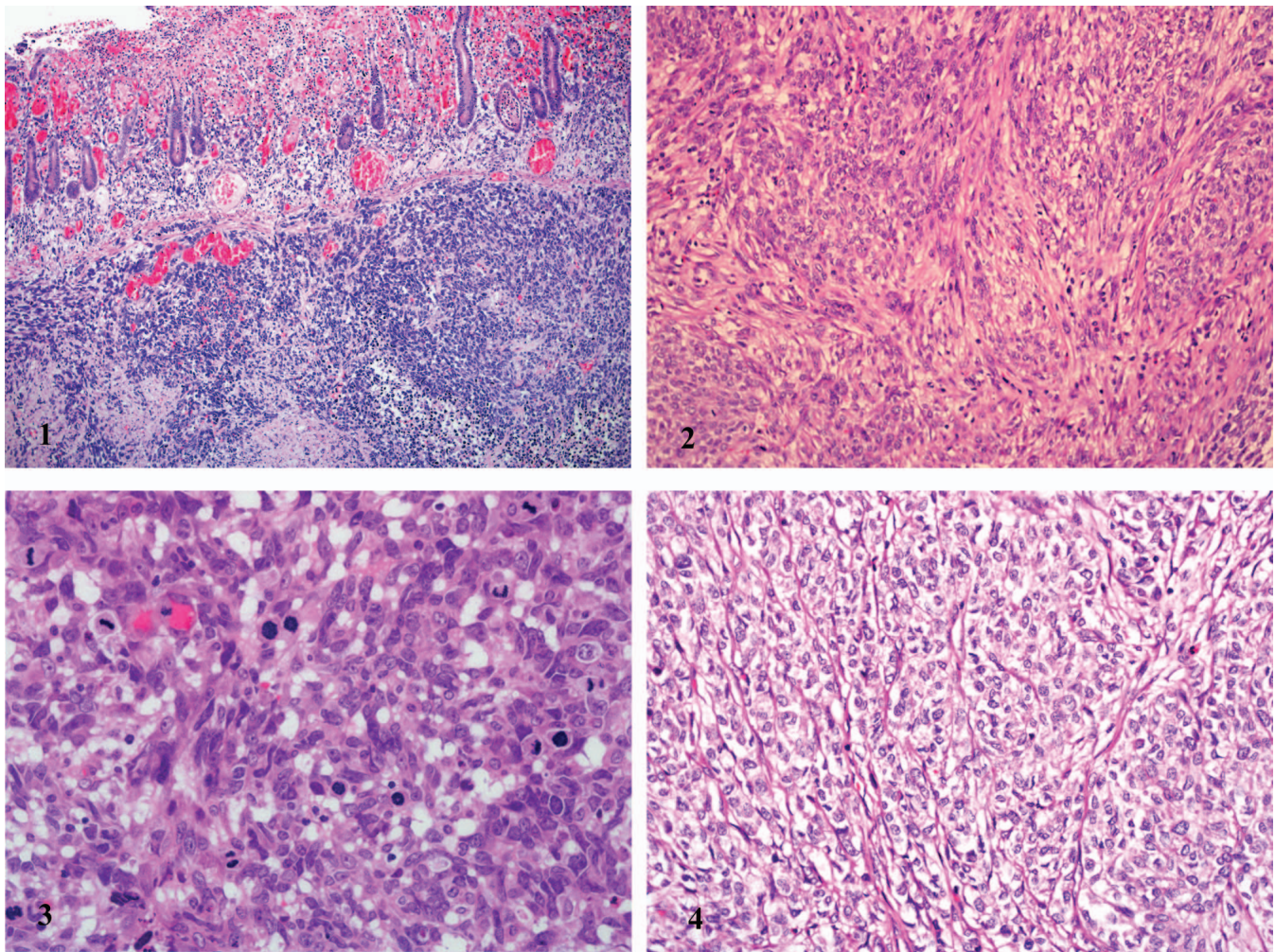
often distinguishes it from other clear cell neoplasms, is the presence of CD68-positive, multinucleated osteoclast-like giant cells (Figure 7),<sup>3</sup> distinct from the tumoral giant cells of conventional CCS, which are not seen. The number of osteoclast-like giant cells varies markedly between tumors and from field to field within a tumor, and not all CCSLGTs have this feature. Another feature distinguishing CCSLGT from CCS and melanomas affecting the gastrointestinal tract is the absence of melanin pigment in all cases reported.<sup>1,2,8,13</sup> The lack of melanin pigmentation does not preclude diagnosis of CCS or melanoma, because amelanotic variants of these can occur. However, 6 of 7 cases of conventional CCS of the gastrointestinal tract were found to contain melanin where there was an active search for pigmentation.<sup>20–23</sup> Most CCSLGTs show extensive areas of tumor necrosis and often show high mitotic activity.<sup>13</sup>

## ANCILLARY STUDIES

### Immunohistochemistry and Electron Microscopy

A key distinguishing feature of CCSLGT is the expression of S100 protein (Figure 8), which varies from diffuse to patchy, coupled with the absence of melanocyte-specific markers, such as HMB-45, Melan-A, tyrosinase, and microphthalmia transcription factor. S100 protein positivity has been seen in all 38 CCSLGTs where it was performed, whereas the melanocyte-specific markers were negative in all CCSLGTs studied.<sup>1,2,5–14</sup> This is in contrast to conventional-type CCSs occurring in the gastrointestinal tract, most of which are positive for S100 protein as well as melanocyte-specific antigens. There is now increasing evidence that many CCSLGTs also express neuroendocrine markers (Figure 9). Of 25 cases in the literature that involved assessment for the presence of at least one neuroendocrine marker (including chromogranin-A, synaptophysin, neuron-specific enolase, and CD56) immunohistochemically, 19 (76%) were shown to express at least one of these markers.<sup>1,2,6,8–10,13</sup> In the series by Stockman et al,<sup>13</sup> all cases expressed SOX10 (further supporting evidence of a primitive neural phenotype for CCSLGT) and vimentin. Markers associated with gastrointestinal stromal tumor (GIST)—CD117, DOG1, CD34—are universally negative, and CCSLGT is also negative for desmin, smooth muscle actin, pancytokeratin AE1/AE3 (although 1 of 8 cases has shown focal patchy positivity for Cam5.2), and CD99.<sup>13</sup>

Electron microscopy studies have been reported in 16 CCSLGTs.<sup>1,3,13</sup> Ultrastructurally, cells are described as polygonal shaped, with multiple interdigitating cell processes that are joined by either macula adherens-type or primitive junctions. Some studies report slender or bulbous cytoplasmic processes, scarce fine intracellular filaments, scattered microtubules, clear secretory vesicles, and variable amounts of glycogen. No melanosomes or melanosome-like structures have been identified, although premelanosomes were very occasionally seen in one case.<sup>7</sup> Stockman et al<sup>13</sup> performed electron microscopy on 5 CCSLGTs, of which 4 contained dense-core secretory granules, consistent with neuroendocrine differentiation. Some also showed synapse-like structures, and one showed neuroaxonal and Schwannian-like features. In view of the ultrastructural and immunohistochemical features supporting neural/neuroectodermal differentiation, their group has proposed that CCSLGT be designated “malignant gastrointestinal neuroectodermal tumor.” In contrast, Antonescu et al<sup>1</sup> did not identify dense-core neuroendocrine secretory granules or



**Figure 1.** Clear cell sarcoma-like tumor of the gastrointestinal tract. Low-power view shows diffuse infiltration and extensive effacement of the small bowel wall, completely destroying the muscularis propria (hematoxylin-eosin, original magnification  $\times 40$ ).

**Figure 2.** The tumor is composed of sheets and vague nests of epithelioid or ovoid cells that show moderate nuclear atypia, and amphophilic or clear cytoplasm. The cells contain medium-sized ovoid to occasionally spindled vesicular nuclei, and often small nucleoli (hematoxylin-eosin, original magnification  $\times 100$ ).

**Figure 3.** Tumors can show marked pleomorphism and striking mitotic activity (hematoxylin-eosin, original magnification  $\times 400$ ).

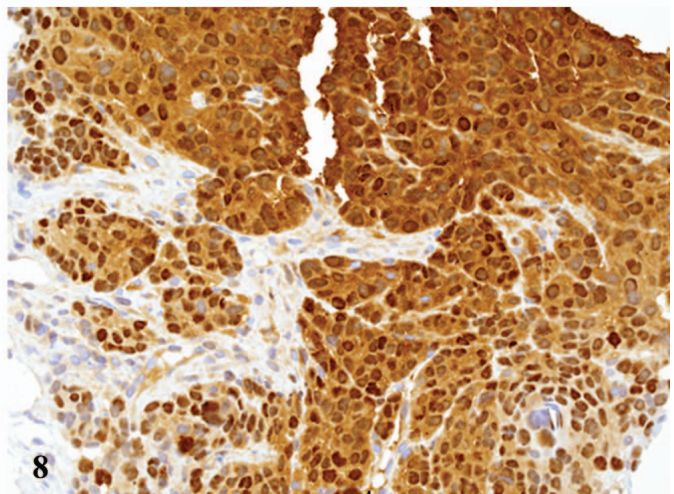
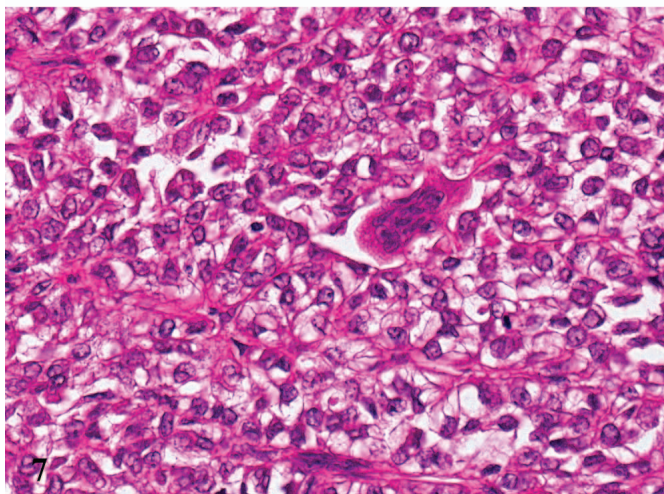
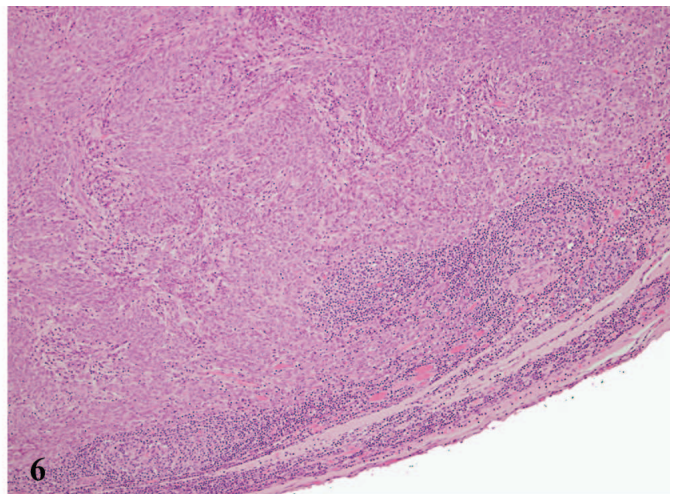
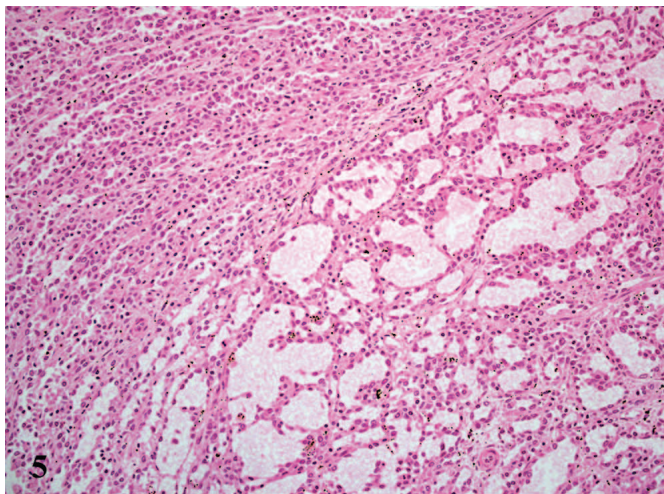
**Figure 4.** The nested pattern can be striking, although it is usually more ill-defined than those seen in conventional soft tissue clear cell sarcoma of tendons and aponeuroses (hematoxylin-eosin, original magnification  $\times 200$ ).

melanosomes in their 3 CCSLGTs, although there were electron-dense granules of varying sizes and shapes.

### Genetics and Differentiation

Cases described in the literature as gastrointestinal CCSs comprise a mixed group; because much of the literature focuses on the detailing of molecular features of tumors that share a general characteristic morphologic and immunophenotypic pattern, rather than on precise detailing of tumor histology, it is often difficult to accurately separate true CCSLGT from conventional-type CCS occurring in the gastrointestinal tract. However, many of the molecularly characterized gastrointestinal CCSs are neoplasms with the morphologic and immunophenotypic features of conventional (soft tissue) CCS, many of which also have *EWSR1-ATF1* fusions most commonly associated with soft tissue CCS.<sup>20</sup> Although the numbers of CCSLGTs reported are small, most to date have shown *EWSR1-CREB1* fusions,

although some harbor *EWSR1-ATF1* associated with conventional CCS. Although Zambrano et al<sup>3</sup> first defined CCSLGT in 2003, cytogenetic analysis was performed on only 1 of 5 cases, and it showed a translocation between chromosomes 22 and 12, in keeping with rearrangement of *EWSR1* and *ATF1* genes. In 2006, Antonescu et al<sup>1</sup> reported 3 of 3 cases of CCSLGT as showing translocations involving chromosomes 22 and 2 instead, resulting in fusions between *EWSR1* and the *CREB1* gene. Stockman et al<sup>13</sup> studied 14 cases by fluorescence in situ hybridization, of which 12 harbored a split *EWSR1* signal, 6 showed rearrangement of *ATF1*, 3 showed rearrangement of *CREB1*, and the remaining 3 showed no *ATF1*, *CREB1*, or *FUS* rearrangements. Of the 2 cases that lacked *EWSR1* split signals, 1 showed extra intact *EWSR1* signals, indicating possible *EWSR1* amplification. Shenjere et al<sup>12</sup> have reported 3 cases conforming to CCSLGT: 1 with *EWSR1-ATF1* fusion, and 2 with *EWSR1-CREB1* fusions. Other cases with convincing



**Figure 5.** Different architectural patterns that may be focally present include pseudoalveolar, pseudopapillary, microcystic, fascicular, or trabecular growth patterns. Here, there are areas of myxoid change (right of field), giving a pseudoalveolar architecture (hematoxylin-eosin, original magnification  $\times 100$ ).

**Figure 6.** Clear cell sarcoma-like tumors of the gastrointestinal tract (CCSLGTs) are highly aggressive neoplasms that have frequently metastasized at the time of presentation. This shows diffuse infiltration of a regional lymph node by a small bowel CCSLGT. This metastatic tumor had morphology similar to that of the primary neoplasm, although recurrent and metastatic lesions may exhibit a greater degree of pleomorphism (hematoxylin-eosin, original magnification  $\times 40$ ).

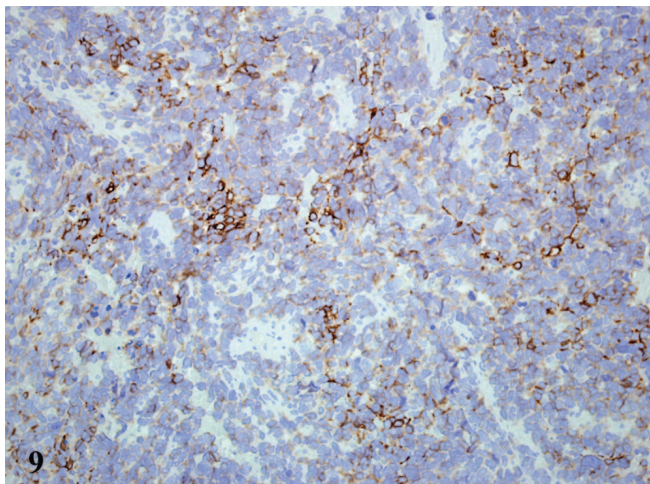
**Figure 7.** A characteristic feature of clear cell sarcoma-like tumor of the gastrointestinal tract (CCSLGT) is the presence of CD68-positive, multinucleated osteoclast-like giant cells, which are distinct from the tumoral giant cells of conventional clear cell sarcoma. The number of osteoclast-like giant cells varies markedly between tumors, and not all CCSLGTs have this feature. Photo kindly provided by Dr Patrick Shenjere, The Christie Hospital, Manchester, United Kingdom (hematoxylin-eosin, original magnification  $\times 200$ ).

**Figure 8.** Clear cell sarcoma-like tumors of the gastrointestinal tract (CCSLGTs) are invariably positive for S100 protein. This example shows diffuse nuclear and cytoplasmic expression, but in some cases this is seen only focally. Expression of S100 protein without staining for melanocytic markers, such as HMB-45 and Melan-A, is typical for CCSLGT (immunohistochemistry, original magnification  $\times 100$ ).

histology and immunoprofile for CCSLGT have had fluorescence in situ hybridization with probes flanking *EWSR1* only, and in these cases rearrangements were identified but the fusion partner was not assessed.<sup>8,9</sup>

Apart from aiding in the diagnosis of CCSLGT, the presence of *EWSR1-ATF1* and *EWSR1-CREB1* gene fusions also provides possible insight into the pathogenesis of these neoplasms.<sup>24</sup> The *EWSR1* gene, located at 22q12.2, encodes the eponymous Ewing sarcoma breakpoint region 1 (*EWSR1*) protein, which is a member of the TET family of transcription factors. It is a multifunctional protein that is involved in various cellular processes, including gene expression, cell signaling, and RNA processing and trans-

port. The protein includes an N-terminal transcriptional activation domain and a C-terminal RNA-binding domain. The *EWSR1* gene is a “promiscuous gene” with a propensity for fusing with many different partner genes, and it is involved in other neoplasms, including Ewing sarcoma, desmoplastic small round cell tumor, and myxoid/round cell liposarcoma. The *ATF1* gene, located at 12q13.12, encodes activating transcription factor 1 (ATF1) protein, which belongs to the ATF subfamily and basic-region leucine zipper (bZIP) family. It is a cAMP response element-binding protein, which binds to cAMP-inducible promoter regions and influences cellular physiologic processes by regulating the expression of downstream target genes, which are



**Figure 9.** Many clear cell sarcoma-like tumors of the gastrointestinal tract also show patchy expression of one or several neural or neuroendocrine markers. This case shows focal positivity for CD56 (hematoxylin-eosin, original magnification  $\times 100$ ).

related to growth, survival, and other cellular activities. The *CREB1* gene, located at 2q33.3, also encodes a member of the leucine zipper family. It has been seen to have similar functions to *ATF1*, and DNA sequencing has shown extensive similarities between *ATF1* and *CREB1*. It has been suggested that, at least for *EWSR1-ATF1*, the fusion protein binds to the promoter region of *MITF*, a regulator of melanocytic differentiation.<sup>25</sup> This results in the melanocytic phenotype seen in CCS, but it remains to be established how *EWSR1-ATF1* and *EWSR1-CREB1* contribute to the development of CCSLGT. In addition to CCSLGT and CCS, *EWSR1-ATF1* and *EWSR1-CREB1* fusions are also found in other rare neoplasms: angiomatoid fibrous histiocytoma, hyalinizing clear cell carcinoma of salivary gland, and primary pulmonary myxoid sarcoma.<sup>24</sup> The frequencies of these translocations vary between tumors; *EWSR1-CREB1* is the most frequent gene fusion in angiomatoid fibrous histiocytoma (compared with *EWSR1-ATF1* or *FUS-ATF1*),<sup>26</sup> whereas most conventional CCSs display *EWSR1-ATF1* fusions, with only a subset harboring *EWSR1-CREB1*.<sup>27</sup> Hyalinizing clear cell carcinoma of salivary gland appears to consistently show *EWSR1-ATF1* fusions, whereas primary pulmonary myxoid sarcoma is characterized by *EWSR1-CREB1* fusions.<sup>28</sup>

The etiology of CCSLGT is unknown, and although it is of uncertain histogenesis, the presence of at least focal expression of neural or neuroectodermal markers by immunohistochemistry and findings of neural differentiation by electron microscopy have led to the suggestion that CCSLGT may arise from gastrointestinal neuroectodermal precursor cells that have lost the potential to differentiate along the melanocytic lineage.<sup>1</sup>

### DIFFERENTIAL DIAGNOSIS

Clinically and radiologically, CCSLGTs present as masses in the gastric or intestinal wall, often giving rise to intestinal obstruction. In these contexts, the list of differential diagnoses is extensive and includes adenocarcinoma, GIST, leiomyosarcoma, neuroendocrine tumor (including carcinoid tumor), and lymphoma. Microscopically, however, the

appearances of CCSLGTs are those of a polygonal or spindle cell tumor, and the histologic differential includes CCS of the gastrointestinal tract, metastatic melanoma, GIST, synovial sarcoma, malignant perivascular epithelioid cell tumor, granular cell tumor, epithelioid malignant peripheral nerve sheath tumor, and clear cell carcinomas of the kidney or ovary. Although CCSLGT and CCS frequently have similar morphologic features, CCS has a more uniform appearance, with cells that are in defined nests separated by thin fibrous septa, are relatively monotonous, and often contain macronucleoli. Clear cell sarcomas frequently display tumoral giant cells but lack the osteoclast-like giant cells of CCSLGT, and up to two-thirds contain melanin pigment. Immunophenotypically, more than 90% of CCSs are also positive for either HMB-45 or Melan-A, whereas CCSLGT is invariably negative for these. Expression of neuroendocrine markers, often found in CCSLGT, may be helpful, but SOX10 less so, because the latter has been described in 57% of CCSs.<sup>29</sup> Electron microscopy showing melanosomes rather than neurosecretory granules also helps exclude CCSLGT. Melanomas tend to occur in older patients who may have a synchronous or previous history of a primary skin or acral melanoma, are mostly also positive for HMB-45 or Melan-A, and lack *EWSR1* rearrangements. Although GIST can display a variety of morphologies, including epithelioid and pleomorphic variants and, very rarely, osteoclast-like giant cells, most are composed of fascicles of relatively uniform spindle cells with little pleomorphism, and that sometimes have paranuclear vacuolations or palisading. Routine immunohistochemistry should make CCSLGT easy to exclude, because more than 90% of GISTs express DOG1, CD117, or CD34,<sup>30</sup> whereas CCSLGT is negative for these markers. Most KIT-negative GISTs will express DOG1 and/or CD34. Synovial sarcoma, malignant granular cell tumor, and perivascular epithelioid cell tumor can have epithelioid or spindle cell morphologies that overlap with CCSLGT, and again, immunohistochemistry is vital in distinguishing these entities. Perivascular epithelioid cell tumor, for example, shows a “reverse” expression pattern of S100 protein, HMB-45, and Melan-A, being negative for S100 protein and positive for the others. Granular cell tumor is positive for S100 protein, carcinoembryonic antigen, and periodic acid-Schiff, but it is negative for HMB-45 and Melan-A. Up to 30% of synovial sarcomas can express S100 protein, but they are also positive for TLE-1,<sup>31</sup> focally so for cytokeratins and epithelial membrane antigen (EMA), and also express bcl2 and CD99 while CCSLGT is negative for these. Synovial sarcoma also has a specific translocation, t(X;18), resulting in *SS18-SSX* fusion genes, which are absent in all other neoplasms. Epithelioid malignant peripheral nerve sheath tumor may be associated with a nerve or preexisting neurofibroma or schwannoma, and it can occur in patients with NF1 (although more rarely so than for patients with classical malignant peripheral nerve sheath tumor). It typically comprises vague nodules of cords, strands, or clusters of large, rounded cells with prominent nucleoli, and it often contains spindled areas that merge with the epithelioid cells. It tends to show strong and diffuse expression of S100 protein (in contrast to CCSLGT, which often shows patchier staining). Clear cell carcinomas from the kidney and ovary can usually be distinguished from CCSLGT by their more nested or alveolar cellular patterns, as well as the lack of spindle cells. Sarcomatoid change can occur in both neoplasms, but immunoreactivity for epithelial

markers such as cytokeratins and epithelial membrane antigen will exclude CCSLGT.

## CONCLUSION

CCSLGT is a rare soft tissue sarcoma occurring exclusively in or near the gastrointestinal tract, and is characterized by sheets of medium to large epithelioid and polygonal cells with pale or clear cytoplasm. Its constellation of features, including morphology, expression of S100 protein, and presence of *EWSR1* rearrangements, makes it difficult to distinguish from CCSs that are seen in the deep soft tissues and can rarely occur in the gastrointestinal tract. Clear cell sarcoma-like tumor of the gastrointestinal tract is a highly aggressive neoplasm, with a high rate of local recurrence, metastases, and early death from disease. Features that distinguish CCSLGTs from CCSs and other differential diagnoses include the presence of osteoclast-like giant cells, lack of reactivity for melanocyte-specific markers, the immunohistochemical or ultrastructural evidence of neuroendocrine or neuroectodermal differentiation, and the presence of *EWSR1-CREB1* fusion genes. Authors have proposed that this entity be redesignated "malignant gastrointestinal neuroectodermal tumor,"<sup>13</sup> and it remains to be seen whether this will replace the term CCSLGT in the future. The lack of familiarity of surgical pathologists with the features of this neoplasm may have previously contributed to its underrecognition, but the finding of an epithelioid or spindle cell neoplasm in or around the gastrointestinal tract with S100 protein expression but a lack of melanocyte-specific markers should always warrant molecular assessment for *EWSR1* rearrangement and for *EWSR1-CREB1* and *EWSR1-ATF1* fusion transcripts.

## References

1. Antonescu CR, Nafa K, Segal NH, Dal Cin P, Ladanyi M. *EWS-CREB1*: a recurrent variant fusion in clear cell sarcoma—association with gastrointestinal location and absence of melanocytic differentiation. *Clin Cancer Res*. 2006;12(18):5356–5362.
2. Huang W, Zhang X, Li D, Chen J, Meng K, Wang Y, et al. Osteoclast-rich tumor of the gastrointestinal tract with features resembling those of clear cell sarcoma of soft parts. *Virchows Arch*. 2006;448(2):200–203.
3. Zambrano E, Reyes-Mugica M, Franchi A, Rosai J. An osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: reports of 6 cases of a GIST simulator. *Int J Surg Pathol*. 2003;11(2):75–81.
4. Alpers CE, Beckstead JH. Malignant neuroendocrine tumor of the jejunum with osteoclast-like giant cells: enzyme histochemistry distinguishes tumor cells from giant cells. *Am J Surg Pathol*. 1985;9(1):57–64.
5. Friedrichs N, Testi MA, Moiraghi L, Modena P, Paggen E, Plötner A, et al. Clear cell sarcoma-like tumor with osteoclast-like giant cells in the small bowel: further evidence for a new tumor entity. *Int J Surg Pathol*. 2005;13(4):313–318.
6. Venkataraman G, Quinn AM, Williams J, Hammadeh R. Clear cell sarcoma of the small bowel: a potential pitfall: case report. *APMIS*. 2005;113(10):716–719.
7. Granville L, Hicks J, Popek E, Dishop M, Tateviian N, Lopez-Terrada D. Visceral clear cell sarcoma of soft tissue with confirmation by *EWS-ATF1* fusion detection. *Ultrastruct Pathol*. 2006;30(1):111–118.
8. Comin CE, Novelli L, Tornaboni D, Messerini L. Clear cell sarcoma of the ileum: report of a case and review of literature. *Virchows Arch*. 2007;451(4):839–845.
9. Joo M, Chang SH, Kim H, Gardner JM, Ro JY. Primary gastrointestinal clear cell sarcoma: report of 2 cases, one case associated with IgG4-related sclerosing disease, and review of literature. *Ann Diagn Pathol*. 2009;13(1):30–35.

10. Lagmay JP, Ranalli M, Arcila M, Baker P. Clear cell sarcoma of the stomach. *Pediatr Blood Cancer*. 2009;53(2):214–216.
11. Terazawa K, Otsuka H, Morita N, Yamashita K, Nishitani H. Clear-cell sarcoma of the small intestine detected by FDG-PET/CT during comprehensive examination of an inflammatory reaction. *J Med Invest*. 2009;56(1–2):70–75.
12. Shenjere P, Salman WD, Singh M, Mangham DC, Williams A, Eyden BP, et al. Intra-abdominal clear-cell sarcoma: a report of 3 cases, including 1 case with unusual morphological features, and review of the literature. *Int J Surg Pathol*. 2012;20(4):378–385.
13. Stockman DL, Miettinen M, Suster S, Spagnolo D, Dominguez-Malagon H, Hornick JL, et al. Malignant gastrointestinal neuroectodermal tumor: clinicopathologic, immunohistochemical, ultrastructural, and molecular analysis of 16 cases with a reappraisal of clear cell sarcoma-like tumors of the gastrointestinal tract. *Am J Surg Pathol*. 2012;36(6):857–868.
14. Balkarasingh P, Saad SA, Govil SC, Thind PK, Ballance CM, Weiss AR. Clear cell sarcoma of the gastrointestinal tract presenting as a second malignant neoplasm following neuroblastoma in infancy. *Pediatr Blood Cancer*. 2012(3);58:481–482.
15. Enzinger FM. Clear-cell sarcoma of tendons and aponeuroses: an analysis of 21 cases. *Cancer*. 1965;18:1163–1174.
16. Ekfors TO, Kujari H, Isomaki M. Clear cell sarcoma of tendons and aponeuroses (malignant melanoma of soft parts) in the duodenum: the first visceral case. *Histopathology*. 1993;22(3):255–259.
17. Rosai J. Editorial: clear cell sarcoma and osteoclast-rich clear cell sarcoma-like tumor of the gastrointestinal tract: one tumor type or two?: melanoma or sarcoma? *Int J Surg Pathol*. 2005;13:309–311.
18. Yang JC, Chou AJ, Oeffinger KC, La Quaglia MP, Wolden SL. Clear cell sarcoma of the gastrointestinal tract after very low-dose therapeutic radiation therapy: a case report. *J Pediatr Surg*. 2012;47(10):1943–1945.
19. Shenjere P, Salman WD, Singh M, Mangham DC, Williams A, Eyden BP, et al. Intra-abdominal clear-cell sarcoma: a report of 3 cases, including 1 case with unusual morphological features, and review of the literature. *Int J Surg Pathol*. 2012;20(4):378–385.
20. Lyle PL, Amato CM, Fitzpatrick JE, Robinson WA. Gastrointestinal melanoma or clear cell sarcoma?: molecular evaluation of 7 cases previously diagnosed as malignant melanoma. *Am J Surg Pathol*. 2008;32(6):858–866.
21. Covinsky M, Gong S, Rajaram V, Perry A, Pfeifer J. *EWS-ATF1* fusion transcripts in gastrointestinal tumors previously diagnosed as malignant melanoma. *Hum Pathol*. 2005;36(1):74–81.
22. Pauwels P, Debiec-Rychter M, Sciort R, Vlasveld T, den Butter B, Hagemeijer A, et al. Clear cell sarcoma of the stomach. *Histopathology*. 2002;41(6):526–530.
23. Fukuda T, Kakihara T, Baba K, Yamaki T, Yamaguchi T, Suzuki T. Clear cell sarcoma arising in the transverse colon. *Pathol Int*. 2000;50(5):412–416.
24. Thway K, Fisher C. Tumors with *EWSR1-CREB1* and *EWSR1-ATF1* fusions: the current status. *Am J Surg Pathol*. 2012;36(7):e1–e11.
25. Schaefer KL, Brachwitz K, Wai DH, Braun Y, Diallo R, Korsching E, et al. Expression profiling of t(12;22) positive clear cell sarcoma of soft tissue cell lines reveals characteristic up-regulation of potential new marker genes including *ERBB3*. *Cancer Res*. 2004;64(10):3395–3405.
26. Antonescu CR, Dal Cin P, Nafa K, Teot LA, Surti U, Fletcher CD, et al. *EWSR1-CREB1* is the predominant gene fusion in angiomatoid fibrous histiocytoma. *Genes Chromosomes Cancer*. 2007;46(12):1051–1060.
27. Hisaoka M, Ishida T, Kuo T, Matsuyama A, Imamura T, Nishida K, et al. Clear cell sarcoma of soft tissue: a clinicopathologic, immunohistochemical, and molecular analysis of 33 cases. *Am J Surg Pathol*. 2008;32(3):452–460.
28. Thway K, Nicholson AG, Lawson K, Gonzalez D, Rice A, Balzer B, et al. Primary pulmonary myxoid sarcoma with *EWSR1-CREB1* fusion: a new tumor entity. *Am J Surg Pathol*. 2011;35(11):1722–1732.
29. Karamchandani JR, Nielsen TO, van de Rijn M, West RB. *Sox10* and *S100* in the diagnosis of soft-tissue neoplasms. *Appl Immunohistochem Mol Morphol*. 2012;20(5):445–450.
30. West RB, Corless CL, Chen X, Rubin BP, Subramanian S, Montgomery K, et al. The novel marker, *DOG1*, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of *KIT* or *PDGFRA* mutation status. *Am J Pathol*. 2004;165(1):107–113.
31. Knosel T, Heretsch S, Altendorf-Hofmann A, Richter P, Katenkamp K, Katenkamp D, et al. *TLE1* is a robust diagnostic biomarker for synovial sarcomas and correlates with t(X;18): analysis of 319 cases. *Eur J Cancer*. 2010;46(6):1170–1176.