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CASE REPORT

Clear Cell Sarcoma-Like Tumor of the Gastrointestinal Tract

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Introduction

Clear cell sarcoma-like tumor of the gastrointestinal tract (CCSLGT) is a relatively recently described neoplasm usually arising from wall of the small intestine [1–6]. Because of the rarity of CCSLGT as well as its overlapping histomorphologic and genetic features (*EWSR1* rearrangement) with other gastrointestinal mesenchymal neoplasms, especially with clear cell sarcoma of soft tissue, rendering a diagnosis of CCSLGT might be challenging.

We herein report an ileal CCSLGT and discuss clinicopathological, immunohistochemical, and molecular features as well as differential diagnoses of CCSLGTs.

Case Report

A 28-year-old male patient presented with 20-lb weight loss, over the past 18 months, as well as occasional night sweat and fatigue. Upper and lower endoscopies did not reveal any lesions. However, CT scan showed wall thickening and a soft tissue mass in a loop of small intestine. The small intestine proximal to the lesion was fluid-filled and dilated, consistent with obstruction. There were also multiple enlarged lymph nodes and multiple liver lesions consistent with metastases. Resection of the small intestine segment and liver biopsy were performed for pathologic evaluation.

Gross examination revealed a 4.2 × 2.7 × 0.8-cm tan-white, firm, centrally ulcerated mass within the small intestinal wall, extending to the serosa. Microscopically, the tumor was cellular and showed predominantly nested growth pattern separated by thin fibrous septa (Fig. 1). The tumor cells were mostly uniform, small epithelioid or spindle cells with eosinophilic cytoplasm and round, vesicular nucleus with single prominent nucleolus (Fig. 2a). Mitotic count revealed up to 12 mitoses per 10 high-power fields (Fig. 2b). Scattered multinucleated, osteoclast-type giant cells as well as cells with clear cytoplasm were also noted (Figs. 3 and 4). Lymphovascular and perineural invasions were present. Two out of eight lymph nodes and liver were involved by the tumor.

Performed immunohistochemical stains revealed that the tumor cells were positive for SOX10 (diffuse) and S100 (patchy) (Fig. 5a, b), while negative for HMB-45, A103, CD117, DOG-1, SMA, desmin, Cam 5.2, chromogranin, and synaptophysin. Additionally, expression of retinoblastoma protein is retained in the tumor cells, and the Ki-67/Mib-1 proliferative index was approximately 50%.

Fluorescence in situ hybridization (FISH) analysis detected rearrangement of *EWSR1* (22q12) gene in 82% of the cells (Fig. 6), and targeted next-generation sequencing revealed *EWSR1-ATF1* fusion (EWSR1 exons 1–9 fused to ATF1 exons 4–7): t(12;22) (q13.12;q12.2) (chr12:g.51190862:chr22:g.9687109).

The patient received systemic chemotherapy and is alive after 8 months. However, follow-up CT scan revealed that the hepatic and mesenteric lymph node metastases remain unchanged in size with decreased vascularity, likely representing posttreatment effect.

Discussion

Gastrointestinal mesenchymal neoplasm that shows similar histomorphologic, immunohistochemical, and molecular features with clear cell sarcoma of soft tissue but lacks of melanocytic differentiation recently has been described as clear cell sarcoma-like tumor of the gastrointestinal tract (CCSLGT) [2–4, 7–24].

CCSLGTs mostly affect young adults and children without a sex predilection [1, 25]. These often arise from the wall of

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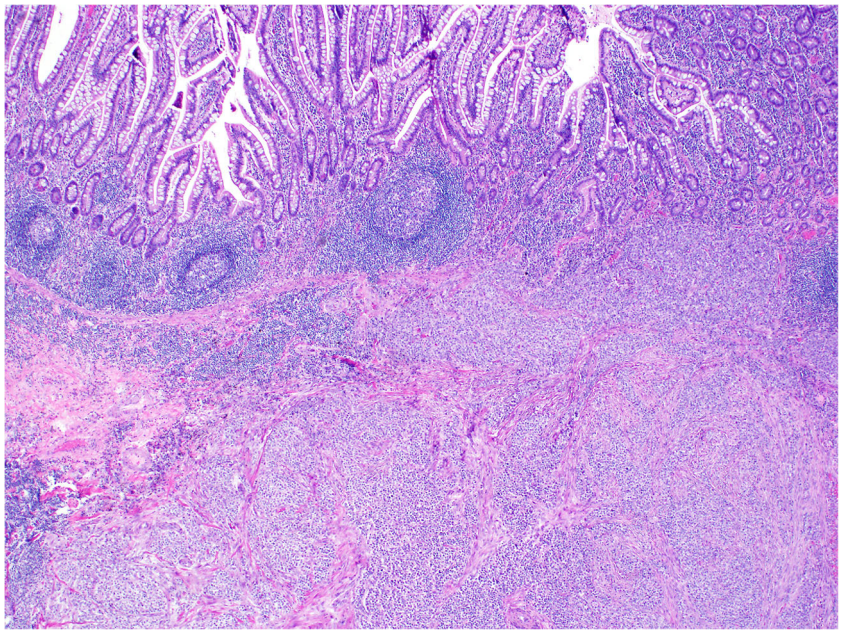

Fig. 1 Diffuse infiltration of the small intestinal wall by cellular tumor (× 40)

the small intestine, rarely from the wall of stomach, colon, and peritoneum. Patients generally present with non-specific symptoms such as abdominal pain, weight loss, fever, fatigue, or nausea [11, 18, 26]. Most have local regional lymph node or distant metastasis at the time of presentation [2, 4, 8]. Thus, the clinical course of CCSLGT appears to be more aggressive than that of clear cell sarcoma of soft tissue [13, 19, 27].

Macroscopically, CCSLGT is a multinodular, infiltrative tumor with a median size of 4.5 cm [12]. Microscopically, it is centered within the muscularis propria, often with extensions to the submucosa and subserosa [27]. The tumor is characterized by nests or sheets of mostly epithelioid or occasionally spindle cells separated by thin fibrous septa. The tumor cells have eosinophilic to clear cytoplasm and round, vesicular nuclei with prominent nucleoli [8, 12, 15]. Characteristic feature of CCSLGT is the lack of melanin pigment. Another clue, which might also be useful in distinguishing it from other clear cell neoplasms, is the presence of CD68-positive, multinucleated osteoclast-like giant cells. Unfortunately, these are seen in only 50% of the cases [1, 3, 18, 19]. Thus, immunohistochemical work-up is essential for diagnosis. Diffuse and strong nuclear expression of S100, coupled with the absence of melanocyte-specific markers, such as HMB-45 and Melan-A, is a key feature for CCSLGT. Similarly, no melanosomes or melanosome-like structures have been reported ultrastructurally. Although there is now increasing evidence that many CCSLGTs may also express neuroendocrine markers [2, 3, 7, 8, 12, 18, 23], cytokeratins, myoid differentiation, or gastrointestinal stromal tumor markers are consistently negative [8]. More importantly, most CCSLGTs have been found to

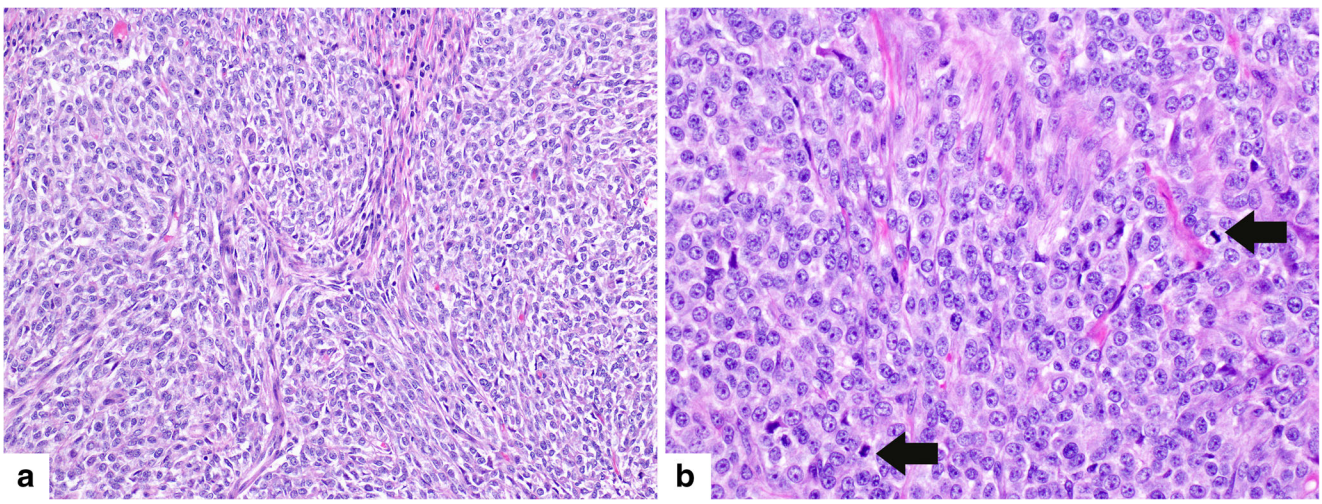

Fig. 2 **a** The tumor composed of nests and separated by thin fibrous septa. Tumor cells were mostly uniform, spindle cells with eosinophilic cytoplasm and round, vesicular nucleus (× 200). **b** Note the frequent mitotic figures (arrows) (× 400)

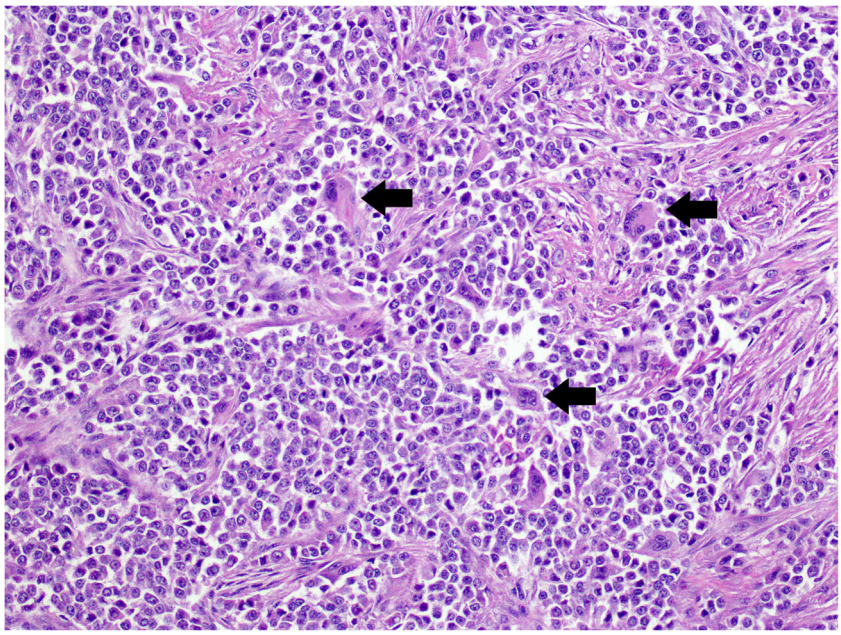

Fig. 3 Scattered multinucleated, osteoclast-type giant cells were also present (arrows) (× 200)

harbor *EWSR1-CREB1* fusions or *EWSR1-ATF1* fusions; the latter are also associated with conventional clear cell sarcoma of soft tissue.

Because of these morphologic, immunohistochemical, and genetic features, the main differential diagnosis of CCSLGT is clear cell sarcoma of soft tissue. Although lack of melanin pigment and the presence of osteoclast-like giant cells are important features [28], it should be kept in mind that the lack of melanin pigment does not exclude clear cell sarcoma of soft tissue as amelanotic variant of this tumor can occur [1]. Similarly, SOX10 expression has been described both in CCSLGT and clear cell sarcomas of soft tissue and does not help in differential diagnosis [8, 29]. Malignant melanoma is another important differential diagnosis. These two tumors are distinct entities at genetic level as CCSLGTs are characterized by *EWSR1* rearrangements; in contrast, malignant melanomas usually have *BRAF* mutations. However, considering the 30–50% of clear cell sarcomas does not exhibit the novel *EWSR1* rearrangement, and mucosal melanomas may not have *BRAF* mutations; thorough clinical investigation comes to the forefront.

Our case was arising from the wall of the ileum with predominantly epitheloid and focal clear cell features. Metastatic melanoma and clear cell sarcoma of soft tissue were our first

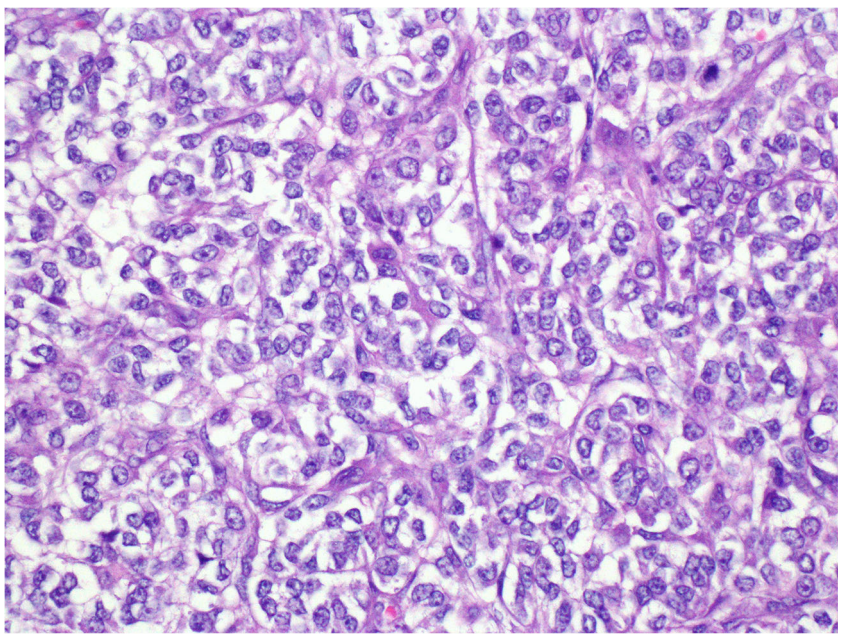

Fig. 4 In some foci, tumor cells revealed clear cytoplasm (× 400)

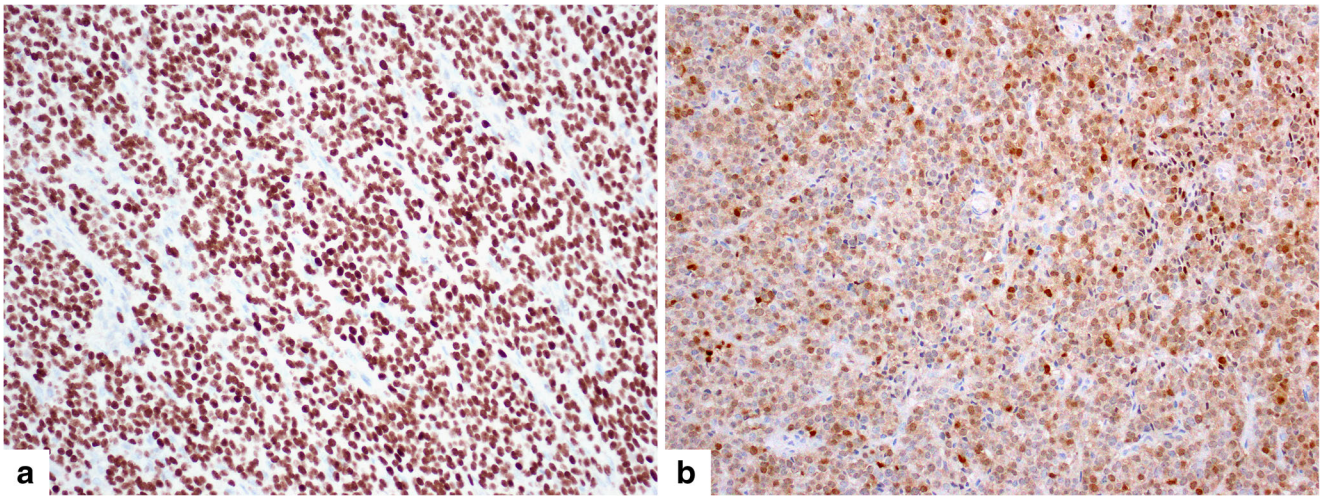

Fig. 5 **a** Strong and diffuse SOX10 expression (× 200). **b** Cytoplasmic and nuclear S100 expression (× 200)

differential diagnoses; however, due to lack of melanin pigment and specific melanocytic differentiation markers (HMB-45 and Melan-A), these were ruled out. Other differential diagnoses including poorly differentiated neuroendocrine carcinoma (no cytokeratin and neuroendocrine marker expression) [30], gastrointestinal stromal tumor (no CD117, DOG-1 expression) [31–33], leiomyosarcoma (no smooth muscle marker expression) [34], synovial sarcoma (no cytokeratin or CD99 expression) [35], and malignant peripheral nerve sheet tumor (no diffuse and strong S100 expression) [36] were also ruled out based on the results of additional immunohistochemical work-up. Malignant peripheral nerve sheet tumor was also excluded on molecular basis, which is known to exhibit *IGF1R* amplification [37] and chromosomal translocation t(X;18) [38]; the latter is detected only in a subset of cases along with synovial sarcomas. Moreover, FISH analysis revealed characteristic *EWSR1* rearrangement in our case, confirming the diagnosis of CCSLGT.

In summary, CCSLGT is a rare and distinct subtype of clear cell sarcoma of soft tissue and should be kept in mind for any tumor arising from the wall of the gastrointestinal tract with epitheloid or spindle cell population that shows S100 expression and lack of melanocytic differentiation [8, 19].

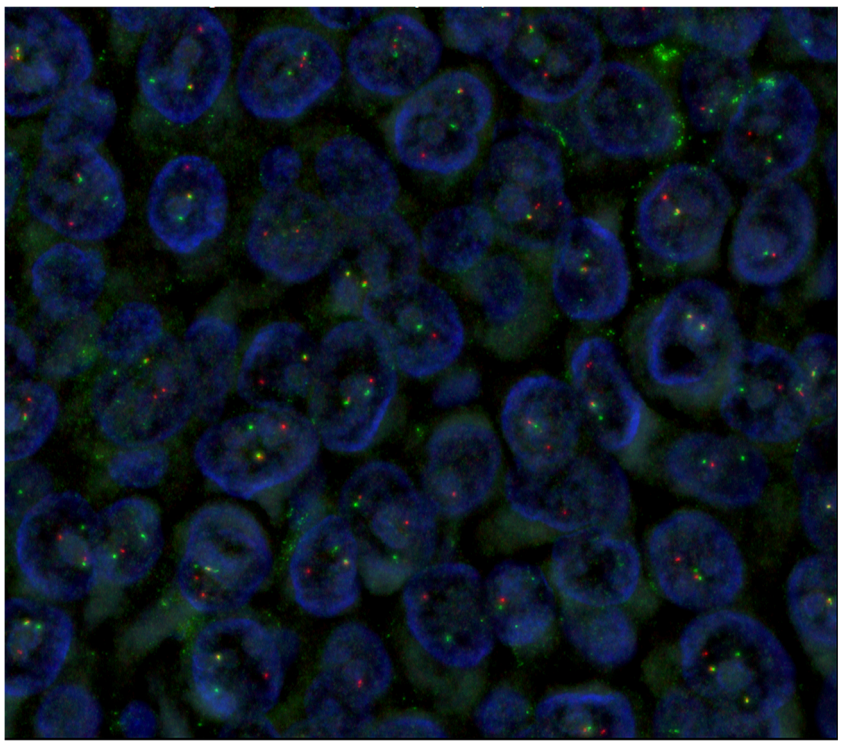

Fig. 6 Representative image of *EWSR* gene rearrangement with a *EWSR1* dual color break-apart probe exhibiting separate green and red signals, characteristic feature of CCSLGT

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study

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