Gastrointestinal Neuroectodermal Tumor(GNET): A rare entity

Case of the month-November

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Introduction

- Malignant gastrointestinal neuroectodermal tumor (GNET) is rare tumor.
- Because of its rarity, it poses a diagnostic challenge to pathologists.
- It is associated with poor prognosis.
- We present one case of GNET in a 58 year old male
  - with a jejunal mass and mesenteric nodes.

Case presentation

- 58 yr old male
- Presented with c/o abdominal pain and constipation since last one week.
- There were no other symptoms like vomiting, malena or haematochezia.

- For evaluation computed tomography(CT) of whole abdomen was done and that showed a jejunal mass with mesenteric lymph nodes.

- Resection of jejunal mass with mesenteric nodes was done.

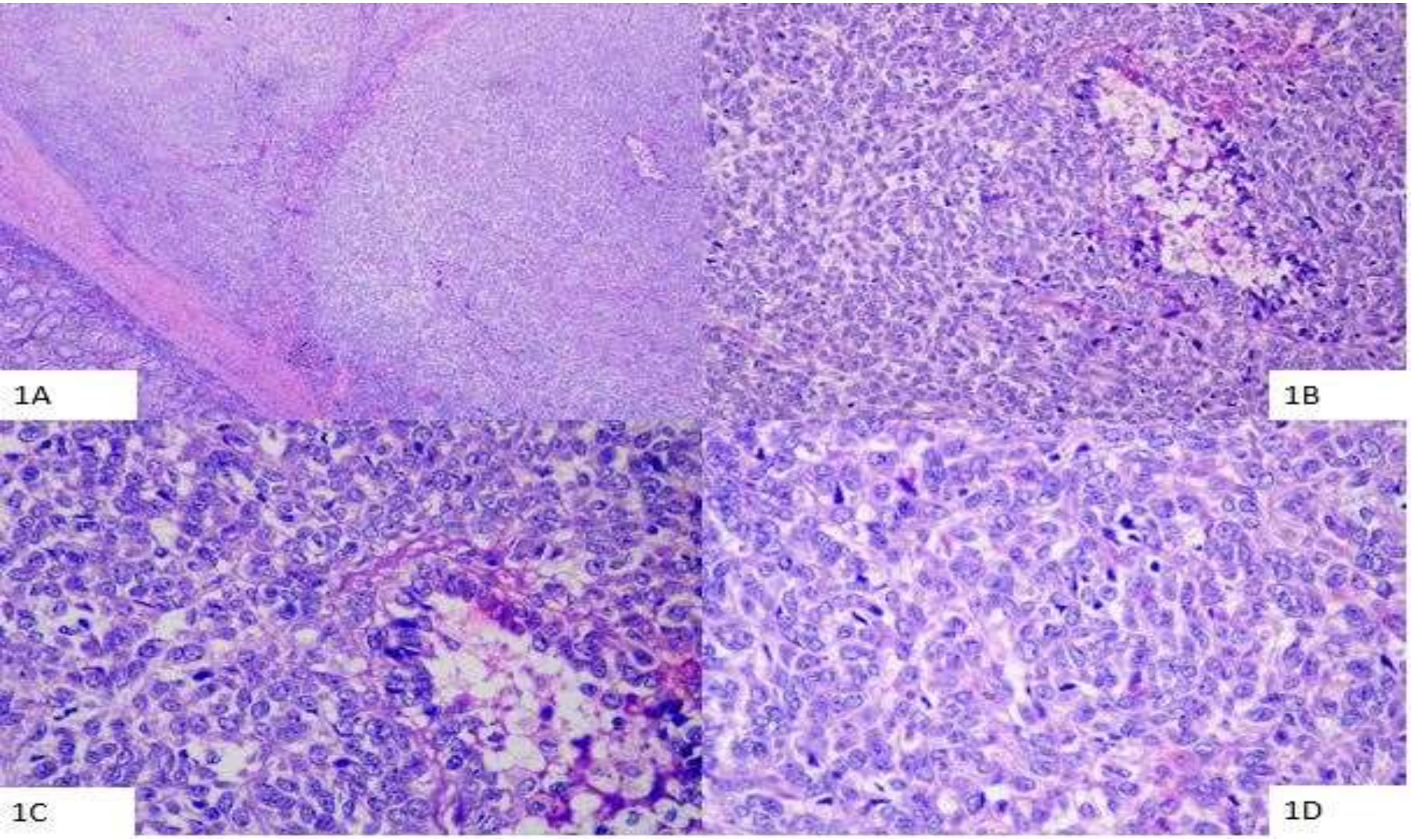
MICROSCOPY

- Section showed diffuse patternless sheets of round to oval tumor cells arranged in vague nodules at places.

  The individual tumor cells had large round to ovoid nuclei, with vesicular chromatin, inconspicuous nucleoli and clear cytoplasm.

- Mitosis was brisk (~ 20 per 10 hpf).
- Focal areas of necrosis were seen.
- Tumor was reaching up to submucosa of jejunum.
- Vascular emboli were present.
- Perineural invasion was not identified.

- Two lymph nodes were identified and both were involved by tumor of similar morphology. Extra nodal extension was positive.



1A. H&E 4X magnification revealing a tumor in submucosa in sheets and lobules separated by fibrous septa
1B. H&E 20X magnification revealing ovoid cells in sheets and nests with fine chromatin ,inconspicuous nucleoli
1C.&D 40 x magnification revealing brisk mitotic activity

IHC

- Tumor cells were positive for
  - S100,
  - SOX10 and
  - synaptophysin,
- while were negative for
  - panCK,
  - DOG1,
  - HMB45,
  - NKX2.2
- Retained expression for INI-1.

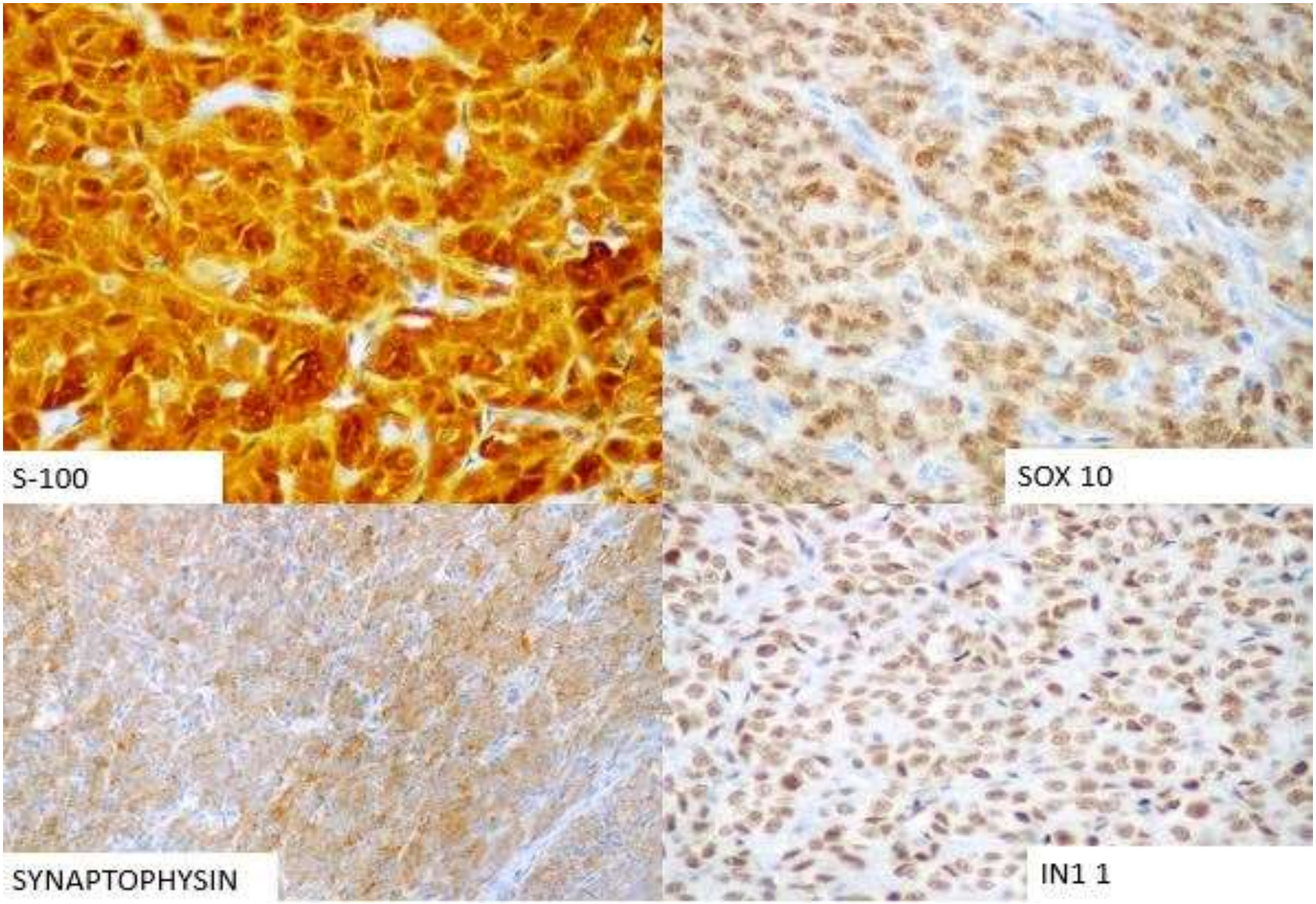


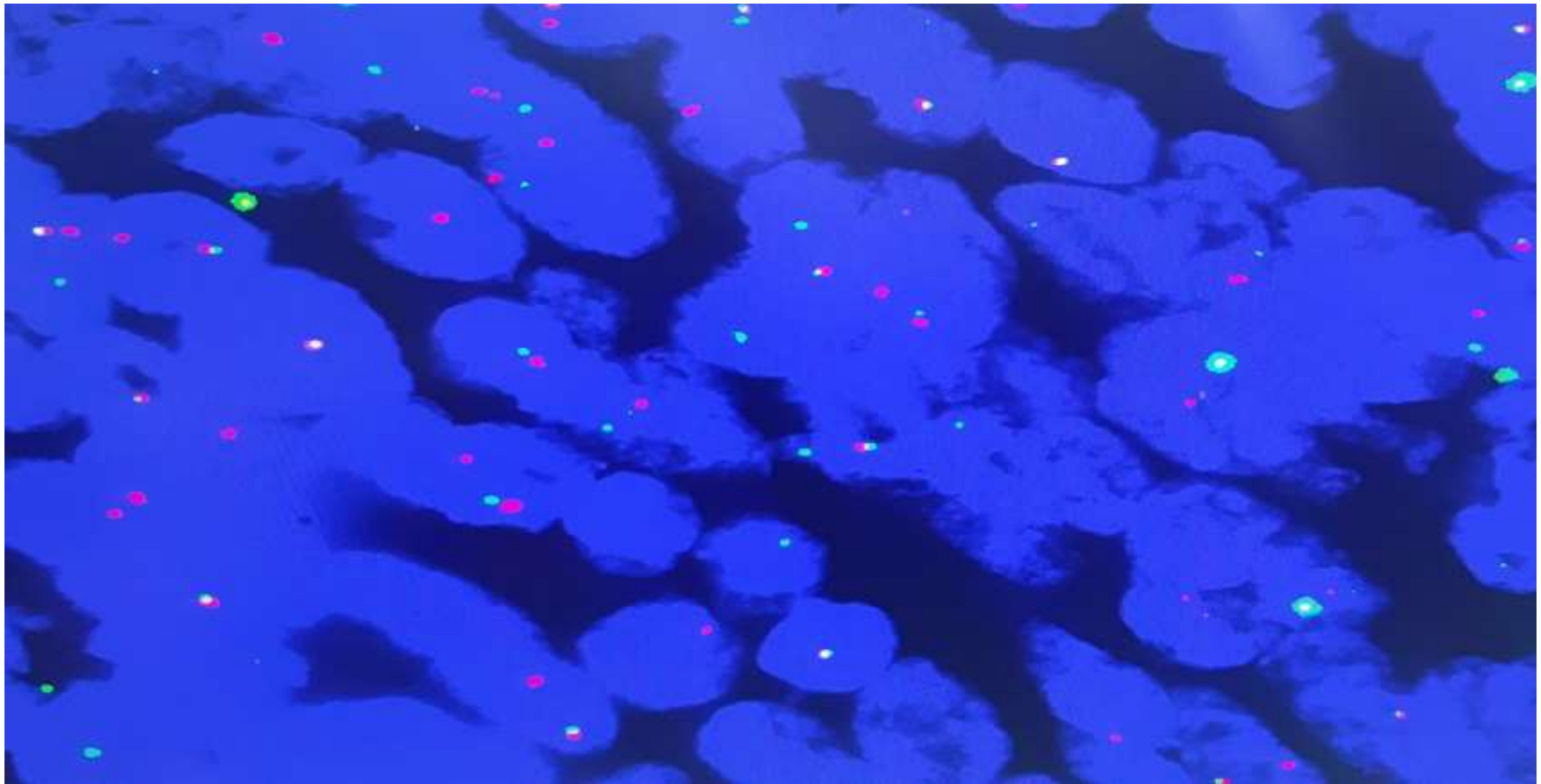
FIGURE : On IHC, the tumor cells are positive for S-100 ,SOX10 and synaptophysin. INI1 was retained

- Final impression of Gastrointestinal clear cell sarcoma/ malignant gastrointestinal neuroectodermal tumor was made.

- EWSR-1 gene rearrangement testing was advised.

- FISH testing was done using Vysis directly labeled LSI EWSR1 22q12 Dual Color Break Apart DNA probe.

- EWSR1 Gene Rearrangement was seen in 90% cells with a pattern of one fused allele and one broken apart allele.
- So, there were one fused, one green and orange signals per cell as shown in figure below.



FURTHER WORKUP

- Serum chromogranin levels were in normal range.
- DOTANOC scan was done and there was no avid lesion noted.
- Post op FDG avid PET scan showed residual mesenteric deposits and mesenteric lymph nodes.
- Patient was planned for palliative VAC-IE based chemotherapy.

Discussion

- Malignant gastrointestinal neuroectodermal tumor (GNET) also termed as clear cell sarcoma-like tumor of the gastrointestinal tract (CCSLTGT).
- very rare tumor type
- usually arise from small intestine, stomach and colon (1).
- Commonly presents in adolescents and young adults
  - no sex preponderance.
- Common presenting symptoms
  - weight loss,
  - abdominal pain
  - intestinal obstruction
  - abdominal mass.

  metastatic disease at presentation.
- very aggressive behaviour and poor prognosis (2)

This entity was first described in 2003 by Zambrano et al. (3), who described six cases of a biologically-aggressive neoplasm

- affecting sites exclusively within the gastrointestinal tract

- showed similarities to soft tissue clear cell sarcoma (CCS), also referred to as clear cell sarcoma of soft parts or conventional-type clear cell sarcoma.

- GNET arises from muscularis propria of GI tract with extension into the mucosa and/or serosa forming a well-circumscribed border .(4).

- The tumor cells grow as sheets or nests of oval / spindled mesenchymal cells with clear or eosinophilic cytoplasm, oval or round nuclei, visible nucleoli and often mitoses.

- Patterns of growth- pseudoalveolar, fascicular

  uncommon patterns- microcystic, pseudopapillary or rosette-like architecture.

  Osteoclast-like giant cells may be seen

Immunohistochemistry

- Tumor cells characteristically shows strong and diffuse staining for S100.
- also stain with SOX10
- variable positivity with synaptophysin, CD56 and neuron-specific enolase.
- negative for HMB-45, Melan-A, tyrosinase, MiTF and GIST markers (CD117, DOG-1 and CD34). Desmin and SMA were also negative.
- Epithelial markers are also usually negative.

Ultrastructural features

- melanosomes or melanosome-like structures were not identified in tumor cells.

- clear secretory vesicles, dense-core secretory granules or multiple interdigitating cell processes may be seen in tumor cells. (5)

Genetics

- Commonly EWSR1 (22q12.2) gene rearrangement seen.

- However, Stockman et al (6) and Joo et al (8) have reported that in their cases EWSR1 gene rearrangement was not present, indicating that other genetic events may also be associated with GNET tumorigenesis.

- Other tumors where EWSR1 gene rearrangement may be present
  - Ewing sarcoma
  - extraskeletal myxoid chondrosarcoma,
  - hyalinizing clear cell carcinoma of the salivary gland
  - fibrous histiocytoma
  - myoepithelial carcinoma
  - myxoid liposarcoma
  - angiomatoid and desmoplastic small round cell tumors [7]

- Therefore, EWSR1 gene rearrangement is not a specific criterion for GNETs, but can aid in diagnosing GNET.

Differential diagnosis

- GIST
- CCS
- Melanoma
- MPNST
- Synovial sarcoma.

- GISTs also feature spindle and/or epithelioid cells making distinction from GNET very difficult.
  - However, GIST is not characterized by osteoclast-like multinucleated giant cells and
  - GNET don’t expresses GIST markers i.e. CD117, DOG-1 and CD34 immunohistochemically.

- For differentiating CCS and melanoma from GNET,
  - electron microscopy may help by revealing melanocytic differentiation which is absent in GNET.

- MPNST usually doesn’t show strong and diffuse reactivity for S100 protein as seen in GNET [6].

- To differentiate monophasic synovial sarcoma from GNET can be difficult based on morphology alone.
  - Synovial sarcoma may show S100 protein expression but it also characterized by epithelial markers expression.
  - In difficult cases, SYT gene rearrangement t(X;18) detection can help in the distinction.

- Rarely malignant granular cell tumor may be kept as differential diagnosis in view of unusual finding of oncocytic cytoplasm in GNET.
  - Both tumors express S100 protein and SOX10.

- To confirm the diagnosis of GNET assessment of EWSR1 gene status is necessary [8].

CONCLUSION

- GNET is an extremely rare and very aggressive malignant tumor of the GI tract.
- Because of its rarity, it is frequently misdiagnosed.
- Awareness of its existence and diagnostic criteria by the pathologist is necessary to avoid misdiagnosis, particularly as GIST, CCS or MPNST.

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