Problem Cases in Surgical Pathology

XXV Congreso de la Sociedad Española de Patología (SEAP) - Zaragoza, Mayo 18-21, 2011.

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Case - 2

Clinical History:

A 43 year old man with no significant past history was seen for right chest pain and shortness of breath. A chest X-ray showed right pleural effusion and consolidation of the right lower lobe of lung. A CT scan showed an infiltrative mass extensively involving the diaphragmatic and costal margin of the pleura.
Other Stains:

CEA – negative
MOC31 – negative
TTF1 – negative
S-100 – negative
HMB45 – negative
Bcl-2 – negative
CD31 – negative
CD34 – negative
P63 – negative
WT1 – negative
EMA - negative
Diagnosis:

1) Metastatic sarcomatoid renal cell carcinoma
2) Pleomorphic leiomyosarcoma
3) Sarcomatoid malignant mesothelioma
4) Pleural invasion by sarcomatoid carcinoma of lung
5) Pleuropulmonary blastoma
6) Malignant solitary fibrous tumor
Additional History:

- Extensive clinical studies and radiographic evaluation failed to identify any evidence of tumor elsewhere.
- Additional history indicated that the patient had worked in his youth in a factory where he had been exposed to asbestos.
- The patient died of progressive local disease 8 months after the operation.
Diagnosis:

SARCOMATOID MALIGNANT MESOTHELIOMA
Sarcomatoid Mesothelioma – a New Paradigm?

- Diagnosis of exclusion
- Necessitates extensive clinical evaluation and imaging studies to rule out the possibility of a tumor elsewhere
- Immunohistochemical studies and electron microscopy are non-specific and serve mostly to rule out other diagnostic possibilities
- Often abused diagnosis in clinical practice
Sarcomatoid Mesothelioma

- Spindle cells arranged in fascicles or having a haphazard distribution that resemble fibrosarcoma or MFH
- The differentiation from sarcomatoid carcinoma of the lung or metastatic sarcomatoid renal cell carcinoma can be exceedingly difficult
- Immunostains do not reliably differentiate between these possibilities
- In such cases, gross and clinical features may be helpful.

WHO Pathology and Genetics of Lung, Pleura, Thymus and Heart, 2004.
Assumptions Regarding the Diagnosis of Mesothelioma

- Any history of asbestos exposure is adequate proof that the patient has malignant mesothelioma
- Any diffuse plaque-like tumor growth involving the pleura is evidence of malignant mesothelioma
- There are specific and distinctive IHC markers that permit a reliable diagnosis of pleural mesothelioma
History of Asbestos Exposure

- Not all mesotheliomas are related to asbestos exposure
- Not all exposure to asbestos automatically leads to the development of malignant mesothelioma
- The vast majority of individuals exposed to asbestos do NOT develop mesothelioma
- Trivial or brief exposure to asbestos is highly unlikely to cause malignant mesothelioma
- An appropriate latency period (15-30 years) between exposure and development of mesothelioma should exist
Diffuse Pleural Spread of Tumor

- Malignant mesothelioma
- Metastatic adenocarcinoma
- Pseudomesotheliomatous adenocarcinoma of lung
- Synovial sarcoma
- Angiosarcoma
- Leiomyosarcoma
- Metastatic malignant melanoma
- Thymoma
- Others
IHC Diagnosis of Mesothelioma

- Numerous studies and markers reported in the literature during past 20 years
- There is no “specific” marker so far for malignant mesothelioma
- IHC represents a diagnosis of EXCLUSION
- Panel of “positive” and “negative” markers
- Many exceptions to the rules; diagnosis must be adapted to specific clinical and pathological circumstances
IHC – Limitations in the DD with Adenocarcinoma

- The “positive” marker, CK5/6, is only of utility in the differential diagnosis between lung adenocarcinoma and epithelioid mesothelioma, but not for discriminating adenocarcinomas from other organs.
- Calretinin can also be expressed in a large variety of other epithelial neoplasms, including lung, breast, ovarian and thymic carcinoma, in addition to spindle cell carcinoma, synovial sarcoma, sex-cord stromal tumors and malignant melanoma.
- WT1 is also seen in ovarian serous carcinoma, renal cell carcinoma, ovarian stromal tumors, Sertoli cell tumor and malignant melanoma.
- The “negative” markers can also be positive in mesothelioma.
Role of IHC for the Diagnosis of Sarcomatoid Mesothelioma

- The percentage of reactivity of the currently available “positive” markers in sarcomatoid mesothelioma is significantly lower than for conventional epithelioid tumors, indicating very poor sensitivity.

- There is a great deal of overlap in the expression of markers between mesothelioma and other primary and metastatic malignant spindle cell tumors of the pleura, such as synovial sarcoma, leiomyosarcoma, spindle cell carcinoma, etc.
IHC in Sarcomatoid Mesothelioma

- Calretinin was positive in 17% of spindle cell sarcomas and in 60% of sarcomatoid carcinomas
- Thrombomodulin was positive in 38% of sarcomas and in 40% of sarcomatoid mesotheliomas
- Smooth muscle actin was positive in 60% of sarcomatoid mesotheliomas

# IHC in Sarcomatoid Mesothelioma

<table>
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<tr>
<th>Study</th>
<th>CK</th>
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<td>(75%)</td>
<td>(58%)</td>
<td>(39%)</td>
<td>(20%)</td>
<td>(19%)</td>
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</table>
IHC in Sarcomatoid Mesothelioma

- The same number of cases of sarcomatoid mesothelioma stained positive for calretinin than did sarcomatoid carcinomas metastatic to the pleura and sarcomas.
- The same number of cases of sarcomatoid mesothelioma stained positive for pan-keratin and vimentin than other non-mesotheliomatous spindle cell tumors of the pleura.
- In the pleura, cytokeratin staining is only of value in the setting of malignant solitary fibrous tumors, but of no help with the rest of the tumors involved in the differential diagnosis.
Spindle Cell Tumors of the Pleura

- Metastatic spindle cell carcinoma
- Synovial sarcoma
- Malignant solitary fibrous tumor
- Other primary or metastatic spindle cell sarcomas of the pleura (leiomyosarcoma, angiosarcoma, etc)
- Spindle cell thymoma
- Metastatic spindle cell melanoma
Conclusions:

- Sarcomatoid mesothelioma is a *diagnosis of exclusion* and should not be automatically rendered on just any spindle cell tumor of the pleura.
- Immunohistochemical stains are of limited value for the diagnosis of sarcomatoid mesothelioma, and the usual panel of stains used for conventional epithelioid mesothelioma cannot be applied with similar results.
- Ruling out alternative conditions, such as sarcomatoid carcinoma, synovial sarcoma, and metastases of other spindle cell neoplasms, is always indicated.
Case 4

Clinical History:
A 45 year old man with no significant past history was seen for the development of a palpable right thyroid nodule. An FNA showed “follicular cells consistent with follicular process”. A right thyroid lobectomy was done. The resected specimen showed a tan-brown, well-circumscribed nodule that measured 5.0 cm. in greatest diameter and was surrounded by a thin rim of normal thyroid parenchyma.
Diagnosis:

1. Follicular tumor with artifactual clearing of the nuclei
2. Follicular variant of papillary thyroid carcinoma
3. “Macrofollicular” variant of papillary carcinoma
4. Hyperplastic nodule with degenerative changes secondary to poor fixation
5. Benign follicular adenoma with “pseudoclear” nuclei of Haepke and Dehner
Diagnosis:

THYROID FOLLICULAR ADENOMA WITH PSEUDOCLEAR NUCLEI
Diagnosis of PTC:

- Is based on a *constellation* of findings not on a single feature:
  - Typical nuclear features
  - Architectural changes, including papillation, invasion and stromal desmoplasia
  - Invasive properties
  - Other findings: psammoma bodies, multinucleated giant cells, scalloping of dense-staining colloid, etc.
Nuclear Features of Papillary Carcinoma

- “Optically clear” (Orphan Annie) nuclei
- Longitudinal nuclear grooves
- Cytoplasmic pseudonuclear inclusions
- Overlapping of nuclei (“shingling”)
The Optically Clear Nucleus

(a) Optically clear nucleus of papillary carcinoma
(b) "Pseudoclear" nucleus of Hapke and Dehner
(c) Nucleus in follicular adenoma/carcinoma

Other Thyroid Conditions with Clear Nuclear Changes

- Follicular adenoma
- Hyperplastic nodules
- Hashimoto’s thyroiditis
Thyroid intrafollicular neoplasia: A spectrum of morphological appearances from benign cytologic precursors to microscopic papillary carcinoma

N. Pennelli
University of Padova, Italy

J Postgrad Med 53:5-6, 2007
Follicular Variant of Papillary Thyroid Carcinoma (FVPTC)

- Definition: a tumor with a predominant or exclusive follicular growth pattern displaying the characteristic nuclear features of PTC
- First described by Lindsay in 1960
- Same prognosis and behavior as conventional PTC
- Two histologic types:
  - Encapsulated FVPTC
  - Widely invasive FVPTC
Follicular Variant of Papillary Carcinoma: The Diagnostic Limitations of Preoperative Fine-Needle Aspiration and Intraoperative Frozen Section Evaluation

Ho-Sheng Lin, MD; Arnold Komisar, MD, DDS; Elana Opher, MD; Stanley M. Blaugrund, MD

Follicular Variant of Papillary Carcinoma: The Diagnostic Limitations of Preoperative Fine-Needle Aspiration and Intraoperative Frozen Section Evaluation

- 47 patients with PTC studied who had both FNA and FS done
- 24/47 patients had a final diagnosis of FVPTC
- Sensitivity for FNA in cases of FVPTC was 25%
- Sensitivity of FS in cases of FVPTC was 29%
- Sensitivity of conventional PTC for FNA was 74%
- Sensitivity of conventional PTC for FS was 87%

CONCLUSION: “The thyroid surgeon needs to realize that, like follicular carcinoma, FVPTC is often diagnosed only on final pathological examination”

Problem Areas in the Diagnosis of Follicular Variant of PTC:

- Wide variation in pathologist’s perception of what constitutes the “nuclear features of PTC”
- Tumors in which the nuclear features of PTC are only seen focally within the tumor
- Tumors in which multiple microscopic foci with nuclear features suggestive of PTC are present
- Tumors in which the nuclei adopt a “pseudoclear” appearance, but no other features of FVPTC are present
Observer Variation in the Diagnosis of Follicular Variant of Papillary Thyroid Carcinoma

Ricardo V. Lloyd, MD,* Lori A. Erickson, MD,* Mary B. Casey, MD,* King Y. Lam, MBBS, FRCPA,* Christine M. Lohse, BS,* Sylvia L. Asa, MD, PhD,† John K. C. Chan, MBBS, FRCPA,† Ronald A. DeLellis, MD,§ H. Ruben Harach, MD, PhD,¶ Kennichi Kakudo, MD, PhD,|| Virginia A. LiVolsi, MD,** Juan Rosai, MD,†† Thomas J. Sebo, MD, PhD,* Manuel Sobrinho-Simoes, MD, PhD,‡‡ Bruce M. Wenig, MD,§§ and Marick E. Lae, MD*
Percentage of Diagnoses by 10 Reviewers in 87 Follicular Tumors

<table>
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<th>Reviewer</th>
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<th>FA</th>
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<td>10</td>
<td>60.9%</td>
<td>11.5%</td>
<td>1.2%</td>
<td>26.4%</td>
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Observer Variation in the Diagnosis of Follicular Variant of Papillary Thyroid Carcinoma

- All 10 experts agreed on the diagnosis in only 39% of all cases.
- All 10 experts agreed on the diagnosis in 66.7% of cases that were widely invasive and metastasized.
- The lowest concordance was for well-circumscribed, non-invasive and encapsulated tumors.

CONCLUSION: “Since most cases with metastatic disease had obvious invasion, caution should be used in making a diagnosis of FVPTC in the absence of the major histopathologic features of clear-cut invasive growth.”

There are a small number of follicular tumors in which there is no vascular invasion and genuine doubt exists about capsular invasion.

Since follicular tumors with only capsular invasion carry an extremely good prognosis, as do encapsulated FVPTC, these cases should not be subjected to further treatment (i.e., total thyroidectomy + radioactive iodine); lobectomy with clear margins is generally curative.

The term “Well-differentiated tumor of uncertain malignant potential” or “Follicular tumor of uncertain malignant potential” is proposed for these lesions to avoid overtreatment and overdiagnosis.
Nomenclature for Encapsulated Follicular Tumors by the Chernobyl Group

PTC

Nuclear Features of PTC

- Obvious
  - Definite capsular or vasc. invasion
  - Well-differentiated Ca
    - Not otherwise specified
- Equivocal
  - None or questionable caps/vasc invasion
  - Well-differentiated tumor of uncertain malignant potential
Architectural and Stromal Changes in Papillary Thyroid Carcinoma

- Papillary architecture
- Stromal desmoplasia
- Infiltrative growth pattern
- Capsular invasion
- Vascular invasion
- Psammoma bodies

These changes in and of themselves are not pathognomonic for papillary thyroid carcinoma but their absence in a thyroid process with clear nuclear features should challenge a diagnosis of PTC
CONCLUSIONS:

- It may be better to err on the benign side than to overdiagnose FVPTC, because lobectomy or nodulectomy is curative in most instances.
- A diagnosis of carcinoma should be avoided in tumors with only focal, partial or equivocal features of invasion or nuclear features of PTC.
- “Well-differentiated tumor of uncertain malignant potential” or “Follicular tumor of uncertain malignant potential” may be a preferable designations for such cases.
Conclusions:

- Clear nuclear features in thyroid nodules *per se* and in isolation are not diagnostic of papillary thyroid carcinoma
- Focal clear nuclear changes can be seen in a variety of conditions other than papillary carcinoma, including nodular hyperplasia, follicular adenoma and Hashimoto’s thyroiditis
- The diagnosis of papillary thyroid carcinoma is established based on a *constellation* of findings including nuclear features, architecture, and stromal changes, not on the basis of any given single feature
Case - 6

Clinical History:
A 43 year old woman without any significant past medical history was seen for symptoms of abdominal pain and cramps. Upper endoscopy showed luminal obstruction of the duodenum by a mass lesion infiltrating the wall of the bowel. A biopsy was read as a high-grade malignant neoplasm. A small bowel resection was done.
Round/polygonal  Spindle/oval
Diagnosis:

1) GIST
2) GANT
3) Metastatic malignant melanoma
4) Clear cell sarcoma-like tumor of the GI tract
5) Epithelioid sarcoma
6) Anaplastic carcinoma
<table>
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<th>Positive:</th>
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<td>S-100</td>
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<td>CD99</td>
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Ultrastructure
Splitting of fluorescent signal with break apart probe for chromosomal translocation
Additional Molecular Findings:

- Break-apart FISH for partner fusion genes showed involvement of the activating transcription factor \((ATF1)\) gene
Diagnosis:

Gastrointestinal Neuroectodermal Tumor (GNET)
Clinicopathological, Immunohistochemical, Ultrastructural and Molecular Analysis of Clear Cell Sarcoma (CCS)-Like Tumor of the GI Tract.

DL Stockman, M Miettinen, D Spagnolo, H Dominguez, V Adsay, P Chou, P van Tien, B Arman, S Suster, EY Zambrano. Medical College of Wisconsin, Milwaukee; Armed Forces Institute of Pathology, Washington, DC; QEII Medical Centre, Nedlands, Western Australia, Australia; Cancer Institute of Mexico, Mexico City, Mexico; Emory University Hospital, Atlanta, GA; Children’s Memorial Hospital, Chicago, IL.

Background: CCS of soft parts is a rare soft tissue tumor, defined by S100 positivity, melanocytic markers, ultrastructural melanosomes and specific chromosomal abnormalities. A GI tumor, possessing the same chromosomal abnormalities, but with different morphologic, immunophenotypic, ultrastructural and behavioral characteristics, has been described and designated CCS of GI tract (CCS-GI).

Design: 15 cases of CCS-GI were analyzed for the clinical, histopathological, immunohistochemical and molecular features.

Results: 8 female and 7 male patients (mean age: 43; range: 17–77); all de novo neoplasms involving small intestine (10), stomach (3), and colon (2), with solid, nested, trabecular/ribbon-like, pseudoalveolar, pseudoglandular, pseudopapillary, and fascicular patterns featuring predominantly epithelioid cytologic features, ranging from small to fusiform. Nucleoli were prominent. Mitotic activity was high. Osteoclast-like giant cells were identified in most cases. All cases showed vimentin, S100, and SOX10 expression. Synaptophysin was detected in 7/13, CD56 in 4/7, NSE in 4/8. All cases were negative for GIST (DOG1, CD117, CD34) and melanocytic (HMB45, MelanA, Tyrosinase) markers. MiTF showed focal (<1%) weak positivity in 2 cases. AE1/AE3, SMA and desmin were negative in all cases. Ultrastructural analysis of 3 cases yielded synapsis-like structures, primitive gap junctions, dense core granules and no identifiable melanosomes or premelanosomes. Ewing sarcoma breakpoint region 1 (EWSR1), CREB1 and ATF1, were studied by break-apart FISH in 10 cases showing EWSR1-ATF1 t(12;22) (6), EWSR1-CREB1 t(2;22) (1), extra EWSR1 copies (1), and EWSR1-7 t(?;32) (2). Follow-up data showed death 3-108 months (mean: 37) after initial surgery (7), alive with disease (2), and no evidence of disease (1).

Conclusions: This study shows that CCS-GI follows a neuroectodermal line of differentiation, displaying S100, SOX10, Synaptophysin, and NSE positivity, with synapsis-like structures and dense core granules at the ultrastructural level, for which we propose the term gastrointestinal neuroectodermal tumor (GNET).
16 cases of primary malignant neoplasms of the GI tract with features reminiscent of so-called “Clear cell sarcoma-like tumor of the GIT”

All cases were studied by histology, IHC, molecular pathology, and in 5 cases by electron microscopy

A large panel of IHC stains was utilized: DOG1, SMA, desmin, vimentin, S-100, CD34, CD56, CD99, CD117, HMB45, Melan-A, tyrosinase, MiTF, neurofilament, MSE, synaptophysin, chromogranin, NB84, NeuN, SOX10, GFAP, CK AE1/AE3, CAM5.2 and Ki-67.

FISH for EWSR1 and FUS was done using dual-color break-apart probes

FISH rearrangement of ATF1 on chromosome 12q13 and for CREB1 on chromosome 2q34 was performed on paraffin sections
Clinical Findings:

- 8 women and 8 men, aged 17-77 years (mean: 42 years)
- Abdominal pain, obstruction and abdominal mass discovered on imaging studies
- No history or evidence of similar tumor elsewhere
- Location: small intestine (10), stomach (4), colon (2)
- Size: 2.5 – 15 cm in greatest diameter (mean: 5 cm)
- Gross: solid, firm, tan white and lobulated
- Treatment: surgery; chemotherapy
- Follow-up: 6/12 died of tumor before 2 yrs; 4/12 are alive but with regional metastases; 2 pts A&W at 3 years
Histologic Findings:

- All tumors involved the wall of the GI tract (submucosa and muscularis propria)
- Solid population of uniform, small epithelioid or oval to spindled tumor cells forming sheets or nests
- Pseudoalveolar, pseudopapillary, pseudoglandular, trabecular, microcystic patterns of growth were observed focally
- 6/16 cases showed clear cytoplasmic features
- 12/16 cases showed osteoclast-type giant cells
- 2/3 of cases showed ulceration of the overlying mucosa and areas of necrosis
- Significant mitotic activity (average: 6 mitoses per 10 HPF)
Clear cell features

Pseudorosettes
Osteoclast-type giant cells
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

Eduardo Zambrano, MD,* Miguel Reyes-Mugica,* Alessandro Franchi, MD,† and Juan Rosai, MD‡

Six cases are reported of an osteoclast-rich tumor of the gastrointestinal tract that should be segregated from GIST. Five of the cases were located in the small bowel and one in the stomach. The age of the patients ranged from 13 to 37 years. The tumors behaved aggressively, with metastases to regional lymph nodes, liver, and other intra-abdominal sites. Microscopically, the tumor cells were medium-sized, predominantly oval, relatively monomorphic, diffusely immunoreactive for S-100-protein, and negative for CD117, CD34, HMB-45, and Mart-1. They were admixed with scattered osteoclast-like multinucleated giant cells which were S-100-protein negative and KP1-positive. One case studied cytogenetically had the karyotype 46XX t(12;22)(q13;q12). The cases here reported are interpreted as examples of a distinctive type of gastrointestinal neoplasm which shares some features with clear cell sarcoma of soft parts (melanoma of soft parts), including in one case the chromosomal translocation that is characteristically associated with that entity. *Int J Surg Pathol 11(2):75–81, 2003

**Key words**: clear cell sarcoma of soft parts, malignant melanoma of soft parts, GIST, osteoclasts.
Immunohistochemical Findings:

- S-100, SOX10 and Vimentin + in ALL cases
- Melanocytic-associated markers (HMB45, Melan-A, MiTF) were negative in ALL cases
- GIST markers (DOG-1, CD34, C-Kit) were negative in ALL
- Epithelial markers (AE1/AE3, CAM5.2) were negative in ALL
- Glial, neuronal (NeuN) and muscle markers were negative
- CD99 negative in ALL cases
- Neural and neuroendocrine markers, including synaptophysin, chromogranin, CD56, NB84 and NSE showed variable degrees of positivity ranging from 45-62% of cases
Ultrastructural Findings:

- EM was done in 5 cases:
- Polygonal cells with multiple interdigitating cell processes joined by macula adherens type junctions
- Slender and bulbous cytoplasmic processes
- In 2 cases, scattered cytoplasmic dense-core neurosecretory granules could be identified
- No evidence of muscle, nerve sheath, or melanocytic differentiation could be identified on extensive search (no premelanosomes or intracysternal tubules seen)
Molecular Studies:

- Ewing sarcoma breakpoint region 1 (EWSR1) was studied in 14 cases by break-apart FISH
- 12 cases showed involvement of EWSR1
- 11 cases showed splitting of the fluorescent probe consistent with chromosomal translocation involving EWSR1
- 1 case showed extra copies of the EWSR1 gene
- 5/11 cases showed involvement of ATF1 partner fusion gene with EWSR1 by break-apart FISH
- 3/11 cases showed involvement of CREB1 partner fusion gene with EWSR1 by break-apart FISH
- All cases were negative for FUS gene rearrangements
Clear Cell Sarcoma-Like Tumors of the Gastrointestinal Tract

- Six cases reported by Zambrano et al in 2003 characterized by S-100+ and multinucleated osteoclastic giant cells
- Tumors have been felt to represent the GI counterpart of “clear cell sarcoma of tendons and aponeurosis” arising in soft tissues
- Unlike most other “clear cell sarcoma-like” tumors, our cases did not reveal any immunohistochemical or ultrastructural features of melanogenesis or melanocytic differentiation
- Ultrastructural and IHC features are more in keeping with a primitive neuroectodermal tumor with autonomic nerve differentiation (similar to GANT)
Molecular Profile:

- Precise significance of the molecular genetic abnormality is unknown.
- The translocation $EWSR1$-$ATF1$ is shared with:
  - Clear cell sarcoma of tendons and aponeurosis
  - Small round blue cell tumor of the intraosseous membrane
  - Polyphenotypical round cell sarcoma of bone
  - Angiomatoid fibrous histiocytoma
- The sharing of this common rearrangement with other related and unrelated neoplasms may be an indication that the different phenotypes are not a direct result of the molecular alteration but rather of the cell types in which the chimeric gene is expressed.
# Molecular Promiscuity

<table>
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<th>Translocation/Fusion Genes</th>
<th>Tumor</th>
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| **T(12,22)** EWSR1-ATF1    | Clear cell carcinoma of salivary gland  
|                            | Clear cell sarcoma of tendons and aponeurosis  
|                            | Small round desmoplastic tumor of bone  
|                            | Angiomatoid fibrous histiocytoma  |
| **T(X,17)** TFE3-ASPS      | Translocation-associated renal cell carcinoma  
|                            | Alveolar soft parts sarcoma  |
| **T(12,16)** ETV6-TRK-C    | Congenital fibrosarcoma  
|                            | Cellular mesoblastic nephroma  
|                            | Acute myeloid leukemia  
|                            | Secretory breast carcinoma  
|                            | Mammary-type secretory skin CA  |
Summary:

- We believe these tumors correspond to a distinct, previously unrecognized entity that is closely related to clear cell sarcoma of tendons and aponeurosis but that possess distinctive features that set them apart; namely, lack of melanocytic differentiation and evidence of autonomic nerve features.

- The tumors may be part of a family of neurocristomas that are derived from neural crest progenitor cells and that may give rise to a spectrum of phenotypes, including melanocytic and neural (autonomic nerve differentiation).

- We propose the designation of gastrointestinal neuroectodermal tumor (GNET) to distinguish them from other similar and related lesions.
David Stockman, M.D.
Medical College of Wisconsin

Eduardo Zambrano, MD
Medical College of Wisconsin

Markku Miettinen, M.D.
Armed Forces Institute of Pathology

Volkan Adsay, M.D.
Emory University

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