Cytological-Pathological Correlation

Low-grade endometrial stromal sarcoma presenting as multiple pulmonary nodules: A potential pitfall in fine needle aspiration and core biopsy specimens - A Cytological - Pathological Correlation

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ABSTRACT

Low-grade endometrial stromal sarcoma (LGESS) is the second most common malignant mesenchymal tumor of the uterus. The most common location is the uterine corpus, but it can also primarily arise in a variety of extraterine locations such as pelvis, ovary, abdominal cavity, vagina, and vulva. We are reporting a case of a 47-year-old female with no significant medical history who presented with multiple pulmonary nodules. Fine needle aspiration (FNA) specimen revealed spindle cell neoplasm consistent with the diagnosis of LGESS. The differential diagnosis included neuroendocrine tumor, synovial sarcoma, solitary fibrous tumor, smooth muscle tumors, and peripheral nerve sheath tumors. The clinical, cytological, and histopathologic details of this case, as well as a discussion of the potential pitfalls and differential diagnosis of spindle cell lesions of the lung are described.

1. Introduction

Low-grade endometrial stromal sarcoma (LGESS) is the second most common malignant mesenchymal tumor of the uterus with majority occurring in the perimenopausal period [1]. The differential diagnosis would have to include a number of monomorphic spindle cell neoplasms. These may include, depending on the site of FNA, endometriosis, ovarian stromal tumors, smooth muscle tumors, peripheral nerve sheath tumors, synovial sarcoma, and solitary fibrous tumor, among others.

2. Case report

A 47-year-old female who never smoked, presented with abdominal pain at an outside institution. A CT scan revealed multiple bilateral lung nodules and therefore a CT-guided fine needle aspiration (FNA) and a core biopsy of the largest 1.0 cm solid lung nodule was performed at the outside institution (OI #1) in June 2015. The diagnosis of “Atypical cells present, consistent with carcinoma” was made. The patient was then referred to New York-Presbyterian Hospital/Weill Cornell Medicine for further evaluation. The pathology slides were reviewed within the Weill Cornell Medical College (WCMC) Department of Pathology and Laboratory Medicine.

The FNA smears revealed singly scattered and loosely cohesive groups of relatively uniform spindled tumor cells with scant to moderate delicate cytoplasm (Fig. 1A–C). The neoplastic cells exhibited round to oval nuclei with fine chromatin and inconspicuous nucleoli. Naked nuclei of tumor cells were noted and no mitoses were observed. Clusters of tumor cells attached to delicate blood vessels were also seen. The background was clean and no significant stromal matrix component was noted. The concomitant core biopsy specimen showed proliferation of bland spindle cells with mild cytologic atypia. (Fig. 2A)

Immunohistochemistry stains performed on the core biopsy specimen, by the outside institution, showed the lesional cells to be positive for CD56 (Fig. 2B) and negative for chromogranin, synaptophysin, AE1/AE3, CK20, CD117, CAM5.2, CD45 Leukocyte Common Antigen (LCA), and TTF-1. At WCMC, we performed additional immunostains on de-stained immunoslides. The lesional cells were positive for CD10 (Fig. 2C) and negative for PAX8. Ki-67 showed a proliferative index of 1–2%. Based on the immunohistochemical profile, the diagnosis of a neuroendocrine tumor (NET) was unlikely and we were favoring a diagnosis of metastatic endometrial stromal sarcoma. However, a precise diagnosis could not be rendered on the limited tissue material, and additional tissue sampling for further characterization of the lesion was necessary.

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Repeat CT chest showed 10 nodules in each lung, some of which increased in size while others decreased in size. The previously recommended.

Fig. 1. FNA showing singly scattered and loosely cohesive groups of relatively uniform spindled tumor cells with scant to moderate delicate cytoplasm. The neoplastic cells exhibited round to oval nuclei with fine chromatin and inconspicuous nucleoli. Occasional “comet cells” and naked nuclei of tumor cells were noted. Clusters of tumor cells attached to delicate blood vessels were also seen. (A–B) DQ stain and (C) PAP stain; A ×10, B–C ×40.

Fig. 2. The core biopsy specimen showed proliferation of bland spindle cells with mild cytologic atypia. (A) H&E stain (B) Immunostain for CD56 is positive in the lesional cells. (C) Immunohistochemistry CD10 performed on the de-stained slides is positive in the lesional cells. A–C ×40.
aspirated largest right lung nodule increased in size to 1.4 cm and now was mostly cystic. The largest left lung nodule now measured 1.0 cm (previously it was 0.8 cm). The nodules that increased in size were more cystic with no definite increase in solid component. In November 2015, repeat FNA was performed at WCMC which showed tumor cells with a similar morphology to the first FNA (Fig. 3A). A single strap cell consistent with rhabdomyoblastic differentiation was also present. Additional immunostains performed on the cell block preparations demonstrated positive immunoreactivity of the tumor cells for CD56, desmin, myoD1 (focal), CD10, ER (> 50%), and PR (rare cells) (Fig. 3B–D). WT1 showed cytoplasmic uptake, while Ki-67 demonstrated low proliferation index (2–3%). The lesional cells were negative for the following immunohistochemistry stains: CK(AE1/AE3), CAM5.2, CK7, synaptophysin, chromogranin, TTF-1, CD99, S100, SMA, CD34, CD31, PAX-8, and inhibin. The final diagnosis rendered was “Malignant spindle cell neoplasm with heterologous differentiation" with the following comment: “Tumors of this type can be seen in the gynecologic tract and the possibility of uterine origin should be considered”.

In December 2015, a wedge resection of the two largest nodules in the right lower and middle lobes was performed at WCMC. The resection showed a well circumscribed tumor composed of bland spindle cells (Fig. 4A–B). The immunostains showed positive immunoreactivity of the tumor cells for ER, PR (Fig. 4C), ERG, and focally for desmin. Ki67 proliferative index was 10%. Immunostains for CAM5.2, cytokeratin AE1/AE3 and TTF-1 highlighted type 2 pneumocytes and the interstitial growth pattern of the tumor cells (Fig. 4D). PAX8, WT-1, CD34, CD31, GATA3, and inhibin immunostains were negative. Beta-catenin showed cytoplasmic staining and the immunostain for MyoD1 was noncontributory. The diagnosis of metastatic low-grade endometrial stromal sarcoma (LGESS) with focal smooth muscle differentiation was made. In addition, it was noted in the surgical pathology report that the patient had a recent hysterectomy in August 2015 at another institution, different than the first institution where the patient first presented. Subsequently, the pathology slides from the morcellated uterine hysterectomy specimen were requested for review at WCMC. One slide demonstrated a myxoid and paucicellular low-grade spindle cell neoplasm within the myometrium, similar to that seen in the lung metastasis (Fig. 5A–B).

3. Discussion

The differential diagnosis of spindle cell lesions in the lung is broad. It may include both primary and metastatic tumors with spindle cell features, such as neuroendocrine tumors (NET), synovial sarcomas, and various other benign and malignant soft tissue neoplasms [2].

Multiple bilateral pulmonary nodules are due to metastatic disease in about 70% of cases. In the absence of previous history of malignancy, the main differential diagnosis in our case was a NET, including typical/ atypical carcinoid. In the setting of multiple bilateral pulmonary nodules, consideration should be given to diffuse idiopathic

Fig. 3. Repeat FNA on the right lower lobe nodule showed same features as the first FNA. (A) H&E stain (B) Immunostain for Desmin is positive in the lesional cells. Immunohistochemistry shows (C) focal positivity for MyoD1, (D) and > 50% positive for ER. A–D ×40.
neuroendocrine cell hyperplasia (DIPNECH). The cytology smears of carcinoid tumors would also demonstrate singly scattered and loosely cohesive fragments of bland monomorphic cells with round to oval nuclei. An “organoid” growth pattern which includes nested, rosette-like, papillary-like, islands and/or trabecular arrangements of tumor cells can also be observed, particularly in cell block preparations. Atypical carcinoid tumors may show nuclear molding, more frequent mitoses and/or necrosis. Carcinoid tumor cells typically show strong immunoreactivity to one or more neuroendocrine markers (chromogranin, synaptophysin, and CD56), strong positivity to cytokeratins in > 80% of cases, and staining for TTF-1 in around 40% of cases. The diagnosis of carcinoid tumor in this case was highly unlikely due to the absence of typical NET growth pattern and the absence of immunoreactivity of the tumor cells to chromogranin, synaptophysin, and multiple cytokeratins.

Both primary pulmonary and metastatic synovial sarcomas can show monophasic or biphasic morphologic growth patterns. The cytology smears are highly cellular and typically are composed of dyscohesive, singly scattered monotonous tumor cells and large cohesive complex clusters of morphologically similar tumor cells. The cell clusters may demonstrate a fascicular growth pattern with irregular borders and branches of delicate capillaries [3]. The tumor cells are predominantly small or medium-sized with high nuclear to cytoplasmic ratio, scant to moderate delicate cytoplasm, oval or spindled-shaped nuclei, finely granular chromatin, and inconspicuous nucleoli. Stripped nuclei of tumor cells may also be observed. Mitotic activity is usually

Fig. 4. Wedge resection of the lung showed a well circumscribed tumor composed of bland spindle cells (A-B) H&E stain. The immunostain showed positive immunoreactivity of the tumor cells for (C) PR. (ED) Immunostains for cytokeratin AE1/AE3 highlighted type 2 pneumocytes and the interstitial growth pattern of the tumor cells.; A ×2, B-D ×40.
entification. Useful immunomarkers to support the diagnosis of synovial sarcoma include cytokeratins, CD99, Bcl-2, EMA, and CD56. Bcl-2 and CD56 are very sensitive markers. Cytokeratins CK7 and CK19 immunopositivity is more common in synovial sarcomas than in other spindle cell sarcomas [5, 6]. Positive TLE-1 nuclear staining is a more specific marker for synovial sarcoma, has a strong correlation with the t(X;18)(p11.2;q11.2) chromosomal translocation, and can be seen in 96%–97% of cases [3]. The molecular test for t(X;18)(p11.2;q11.2) chromosomal translocation can help to confirm the diagnosis of synovial sarcoma [5, 7].

Solitary fibrous tumor (SFT) classically presents as a single pleural-based nodule but can also occur as a primary parenchymal neoplasm. Cytology smears may show variable cellularity. Loosely cohesive syncytiotubular tissue fragments composed of spindle cells may be surrounded by bland singly dispersed blunted spindle cell nuclei and/or intact fusiform cells with ill-defined cytoplasm and uniformly bland nuclei with fine granular chromatin. Irregular loose aggregates of tumor cells intimately admixed with ropy collagenous stroma can be also seen [8, 9]. Scattered inflammatory cells and mast cells can be noted in the background. Malignant SFT may present with multiple pulmonary nodules and cytologically will show more pronounced nuclear pleomorphism, increased mitotic activity, and necrosis [8]. SFT is typically immunoreactive for CD34, Bcl-2, and CD99, but is negative for epithelial markers. Almost all SFT harbor an NAB2-STAT6 fusion gene. Nuclear expression of STAT-6 has been recently reported as a highly sensitive and specific surrogate immunomarker for confirming the diagnosis of SFT [10].

Cytology smears of benign metastasizing leiomyoma (BML), metastatic leiomyosarcoma, and lymphangioleiomyomatosis (LAM) may demonstrate singly scattered and cohesive tissue fragments of neoplastic smooth muscles cells. In most cases, parallel arrays and interlacing fascicles of tumor cells in tight clusters are present. The tumor cells in low-grade lesions have an oval or spindle shape with elongated or cigar-shaped nuclei. The cytoplasm is often scant, however tumor cells with abundant eosinophilic cytoplasm, elongated bipolar wispy cytoplasmic processes, and multinucleated tumor cells with abundant cytoplasm can also be seen. Smears obtained from leiomyomas are usually hypocellular with no mitotic figures or necrosis observed. Low-grade leiomyosarcomas may morphologically resemble leiomyomas. High-grade tumors show more nuclear pleomorphism, mitotic figures and areas of necrosis are more commonly seen. Smooth muscle tumors are immunoreactive for desmin, smooth muscle actin, muscle-specific actin, calponin, h-caldesmon, smooth muscle myosin heavy chain, and are typically negative for CD10. Cytologic distinction between BML and LAM may be difficult. However, LAM will be immunoreactive for HMB45, melan-A, estrogen receptor (ER), and progesterone receptor (PR). The typical clinical presentation of LAM is a young patient with spontaneous pneumothorax, chylous pleural effusions and progressive dyspnea. Cytologic findings of well-organized globular structured in chylous effusions which display characteristic immunoprofile can be also helpful in establishing the diagnosis of LAM.

Schwannomas are rarely seen in lung FNA specimens. They show typical cytomorphologic features which include large fascicular or syncytiotubular tissue fragments of spindle cells, rare singly scattered spindle cells, and sometimes “old-fishnet/twisted rope” pattern of growth of spindle cells [8]. The individual tumor cells generally show bipolar cytoplasmic processes, bent, fishhook or, wavy nuclear morphology, with uniform chromatin and occasional intranuclear pseudo-inclusions [11]. Degenerative nuclear changes such as nuclear enlargement, nuclear membrane irregularities, and hyperchromasia (so-called “ancient change”) may be observed and should not be interpreted as a feature of malignancy. Myxomatous and metachromatic stroma may be evident in the background. Mitoses are not seen. The tumor is strongly immunoreactive for S100 and negative for CD117 and DOG1.

Malignant peripheral nerve sheath tumors will show a greater degree of nuclear pleomorphism. The tumor cells are mostly loosely cohesive or singly scattered and do not demonstrate the well-formed “old

Fig. 5. One slide of the uterine hysterectomy specimen demonstrated a myxoid and paucicellular low-grade spindle cell neoplasm within the myometrium, similar to that seen in the lung metastasis. (A–B) H&E stain; A ×10, B ×20.
fishnet” growth pattern. Mitotic figures and atypical mitoses can be seen. Fibrillary or myxoid background is seen in some of the cases. The tumor cells will show only focal weak immunoreactivity for S-100, but can show positivity for CD34, GFAP, and focal staining for EMA [8].

Lastly, metastatic melanoma should always be in the differential diagnosis of pulmonary spindle cell neoplasms. A clinical history of previous melanoma and an IHC panel that includes multiple melanoma markers will be helpful in confirming the diagnosis.

Endometrial stromal tumors are the second most common pure mesenchymal neoplasm of the uterus, accounting for < 10% of all such tumors [12]. The current WHO classification divides them into four categories: endometrial stromal nodule, low-grade endometrial stromal sarcoma (LGESS), high grade endometrial stromal sarcoma, and undifferentiated sarcoma. [13]

LGESS accounts for 0.2% of female genital tract malignancies. The age range of the patients is between 40 and 58 years old. Rare cases have been reported in younger women or young adolescents [13]. Patients typically present with abnormal uterine bleeding, pelvic pain and dysmenorrhea, however about 25% of patients can be asymptomatic [14]. About 30–50% of patients have extraterrorine spread at the time of diagnosis. LGESS rarely presents initially at an extraterrorine site, including metastatic disease involving the ovary and lung, causing diagnostic challenges [13, 15].

Morphologically, LGESS tumors are composed of cells that resemble endometrial stromal cells of proliferative endometrium and therefore the diagnosis of typical LGESS is straightforward. However, diagnostic difficulties may arise when the tumor displays secondary differentiation or heterologous components [16]. Metastatic LGESS demonstrates the same range of histologic features as primary uterine tumors. Diagnostic difficulties may also occur when the tumor presents initially at an extraterrorine site, as in our case [15]. Aubry et al. reported that features complicating recognition of pulmonary metastasis include cystic change, a “biphasic pattern” due to incorporated non-neoplastic epithelium, and a prominence of histologic features such as secondary differentiation or heterologous components that may not have been demonstrated in the primary tumor. [2]

Cytomorphologic features of LGESS have been described in a small number of case reports and small series [17]. These features include moderate to marked cellularity, clean background, and relatively equal amounts of stromal fragments and bland cells scattered singly and in small clusters. Some of the stromal fragments may demonstrate interposed blood vessels and occasional hylial stromal matrix. The neoplastic cells have scant cytoplasm, round to oval nuclei, fine chromatin, and occasional prominent nucleoli. Epithelioid and spindled “comet” cells may also be observed. Scattered mitoses can be seen. In their largest series of LGESS sampled with fine needle aspiration, Policarpio-Nicolas et al. noted that in cases of previously undiagnosed tumor, the differential diagnosis would have to include a slew of monomorphic spindle cell neoplasms [17]. These may include, depending on the site of FNA, endometriosis, ovarian stromal tumors, smooth muscle tumors, peripheral nerve sheath tumors, synovial sarcoma, and solitary fibrous tumor, among others. The authors comment that it is doubtful that one would be able to distinguish these lesions without the assistance of ancillary studies.

LGESS are typically immunoreactive for CD10, vimentin, muscle-specific actin, smooth muscle actin, desmin, Bcl-2, and frequently keratin. Endometrial stromal tumors frequently express ER and PR and beta-catenin. A useful initial immunopanel for diagnosing LGESS is reported to be CD10, ER, and PR and at least two smooth muscle markers (such as desmin, h-Caldesmon, smooth muscle heavy chain myosin). Not uncommonly, LGESS may exhibit immunoreactivity for smooth muscle markers, especially at foci of muscle differentiation. In rare cases, CD10 can be negative in LGESS, and conversely smooth muscle tumors may be immunoreactive to CD10. Foci of sex-cord differentiation in LGESS can be immunoreactive for inhibin, calretinin, WT1, Melan-A, and CD99. Therefore, it is important to consider the relative intensity and distribution of these immunostains and interpret them in view of morphologic and clinical findings while entertaining the diagnosis of LGESS [1]. In addition, as it was in our case, occasional CD56 expression in LGESS has also been reported, causing diagnostic pitfalls.

Most LGESS harbor the translocation t(7;17) with involvement of two zinc finger genes, JAZF1 and JAZA1. Currently, molecular testing for diagnosis of LGESS is not routinely performed. However, it may be helpful in cases with unusual clinical presentation or morphologic findings [1].

In our patient, the diagnosis of metastatic LGESS was made following morphologic and immunohistochemical evaluation of pulmonary nodules. More importantly, the primary tumor was misdiagnosed as leiomyoma in the morcellated hysterectomy specimen after the diagnosis of pulmonary metastasis was rendered in a different institution. This highlights the value of clinical care continuity. The clinical scenario was likely also complicated by limited sampling of the tumor following uterine morcellation.

In summary, this case is presented to illustrate potential pitfalls in the diagnosis of metastatic LGESS in a patient without clinical history of a gynecologic neoplasm. It also highlights the significance of compiling all clinical data and correlating various surgical pathology specimens from different institutions. Judicious use of ancillary studies and remembering their limitations is important to obtain a correct diagnosis, especially while evaluating cytology and small biopsy specimens.

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References