

# Endometrium-limited endometrioid adenocarcinoma and lung metastasis with unusual hyaline globules

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## Summary

**Background:** Endometrium-limited endometrial cancer that metastasizes is rare, as is endometrioid adenocarcinoma that contains hyaline globules. **Case:** A 33-year-old woman was referred after lung cancer was detected upon a routine health screening. Video-assisted thoracic surgery was performed, and subsequent pathologic examination revealed a metastatic lung cancer that was positive for both estrogen receptor (ER) and progesterone receptor (PgR). A follow-up Papanicolaou (Pap) test indicated endometrial carcinoma. Grade 1 (G1) endometrioid adenocarcinoma was diagnosed upon endometrial biopsy. There was no muscular invasion and CT and positron emission tomography-CT (PET-CT) showed no other metastases. Hysterectomy and bilateral adnectomy were performed and the final diagnosis was endometrial carcinoma, pT1aNXM1. In both the lung and uterine specimens, especially in areas showing squamous differentiation, there were numerous unusual hyaline globules. The hyaline globules stained weakly with Mallory Azan but not with alcian blue or von Kossa, and the periodic acid-Schiff reaction was negative. Immunohistochemically, the hyaline globules were negative for cytokeratins, vimentin, desmin, muscle actin,  $\alpha$ -fetoprotein, transthyretin,  $\alpha$ -antitrypsin,  $\alpha$ 1-chymotrypsin, fibrinogen, laminin, and  $\beta$ -catenin. **Conclusion:** We conclude that the unique hyaline globules had some metastatic potential or that previous dilatation and curettage, thrice performed, might have been responsible for the metastasis of the endometrium-limited cancer to the lung.

**Key words:** Endometrium-limited endometrial cancer; G1 endometrioid adenocarcinoma; Lung metastasis; Hyaline globule.

## Introduction

We encountered a metastatic lung cancer that arose from an endometrial cancer. The original cancer was an endometrioid adenocarcinoma, Grade 1 (G1), with squamous differentiation and without muscle invasion. Cytologically and histologically, many unusual hyaline globules were seen in the area of squamous differentiation in both the metastatic lung cancer and the endometrial cancer.

Lung metastasis of an endometrium-limited G1 endometrioid cancer is quite rare, as is a cancer that produces hyaline globules at both the local and metastatic sites. The rarity of hyaline globules in an endometrioid adenocarcinoma necessitated differentiation of the nodules seen in the present case from other kinds of globules, such as psammoma bodies, and to rule out the possibility of contaminants in the cytology specimen. We attempted to uncover any role the hyaline globules might have played in the metastatic process.

## Case Report

A 33-year-old Japanese woman, gravida 0 para 0, was referred to our department under a suspicion of endometrial carcinoma. In March 2010, atypical polypoid adenomyoma had been diagnosed at another hospital. After three dilatations and curettage (D&C) treatments, in vitro fertilization and embryo transfer was

attempted because of the patient's desire for a child. In November 2012, chest X-ray examination performed during a routine health screening revealed lung cancer, and she was referred to the Department of Respiratory Surgery at our hospital, where video-assisted thoracic surgery was performed in February 2013. Pathologic examination of the surgical specimen revealed a metastatic lung cancer positive for both estrogen receptor (ER) and progesterone receptor (PgR).

The patient was thus referred to our department in March 2013. At that time, her uterus was a hen's egg in size, and the uterine adnexa appeared normal. Magnetic resonance imaging revealed a thickened endometrium. Her cervical Papanicolaou (Pap) smear was described as negative for intraepithelial lesion or malignancy, but her endometrial Pap smear was abnormal and indicative of endometrial carcinoma. A biopsy specimen was obtained, and G1 endometrioid adenocarcinoma was diagnosed. No other metastatic lesion was detected upon CT or positron emission tomography-CT (PET-CT), and we treated the cancer surgically by means of hysterectomy and bilateral adnectomy. The patient gave her written informed consent. The final diagnosis was endometrial carcinoma, pT1aNXM1.

The patient underwent six courses of adjuvant paclitaxel-plus-carboplatin chemotherapy. Five years have passed since the surgery, and the patient has been disease-free. Imprint cytology was performed on a smear obtained from the resected lung tumor (Figure 1). Squamoid cells containing orange hyaline globules were observed. These features were indicative of adenosquamous carcinoma.

Resected lung tissue was prepared for histologic examination (Figure 2). The tumor was composed of columnar cells, and the

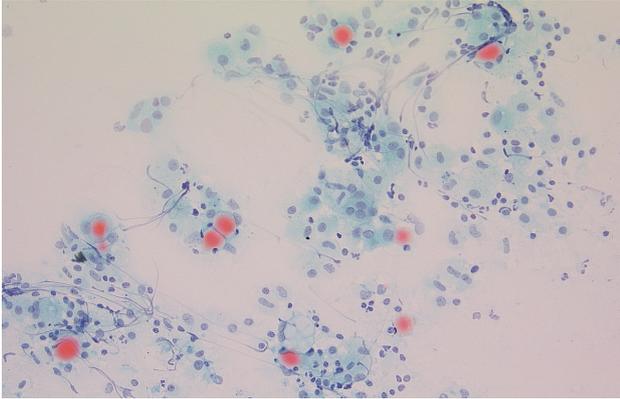
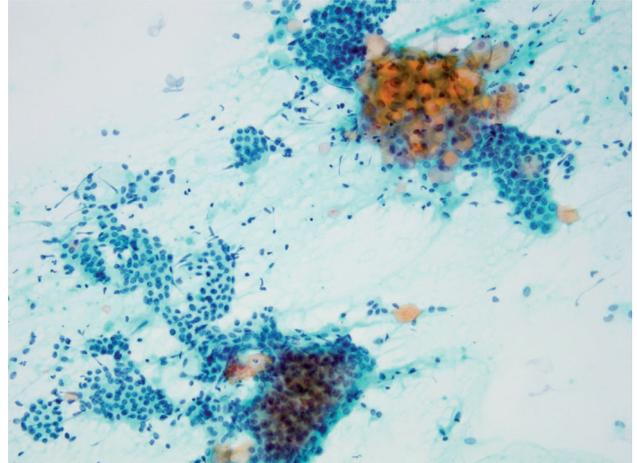
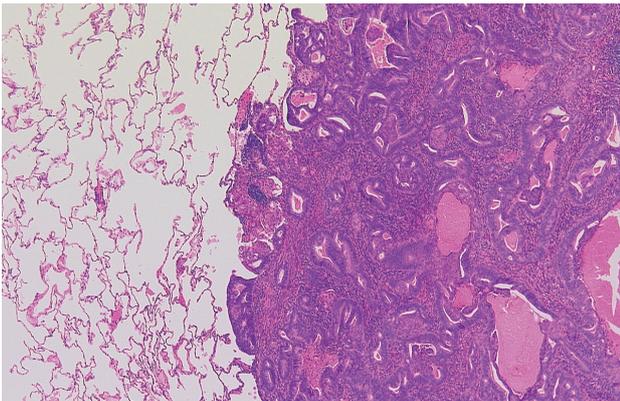


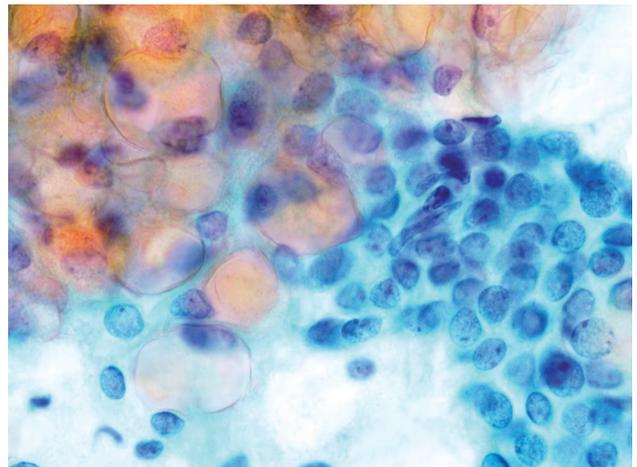
Figure 1. — Imprint cytology performed on the resected lung tumor reveals squamoid cells that contain orange hyaline globules. Papanicolaou staining ( $\times 20$  magnification).



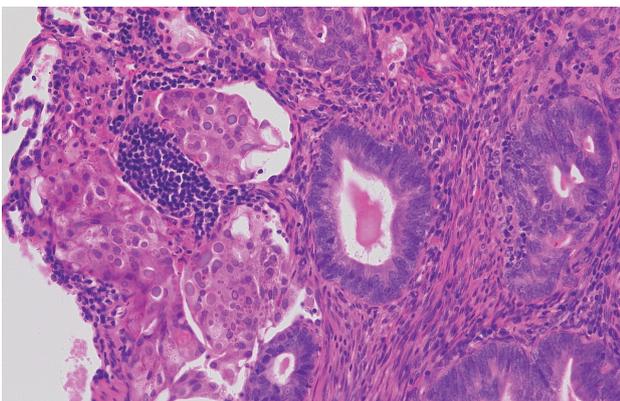
A



A



B



B

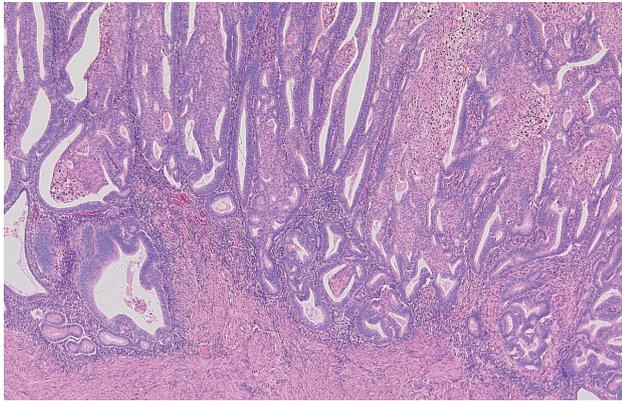
Figure 2. — The lung specimen is characterized by columnar cells with a mixed tubular and papillary growth pattern and numerous squamoid areas. Hyaline globules were seen in the squamoid areas. Hematoxylin and eosin staining. A:  $\times 4$  magnification. B:  $\times 20$  magnification.

Figure 3. — Endometrial cytology reveals atypical endometrial glandular cells. Pink to orange globules are seen in squamoid area. Papanicolaou staining. A:  $\times 20$  magnification. B:  $\times 100$  magnification.

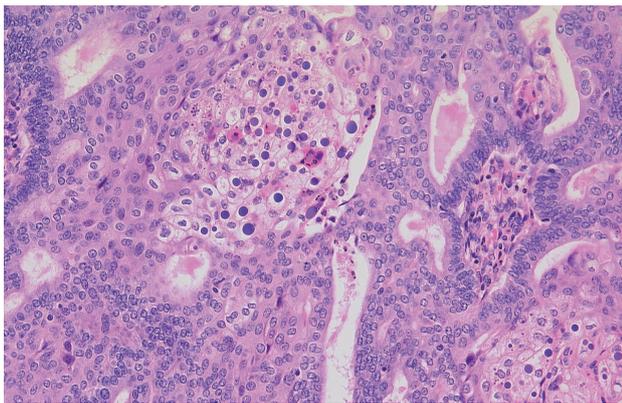
growth pattern was both tubular and papillary. Numerous squamoid areas were observed. Hyaline globules, pink to pale purple, were seen in the squamoid areas and varied in size. Some were contained within the cell cytoplasm, and some existed outside the cells. Immunohistochemically, the tumor cells were positive for cytokeratin7 (CK7), ER, PgR, and mammaglobin and negative for CK20, TTF1, ALK, p63, CDX-2, and napsin A.

An endometrial specimen (Figure 3) was examined cytologically. Clusters of atypical endometrial glandular cells with mild nuclear atypia were seen. Adjacent to endometrial glands were metaplastic lesions (squamous morules), the cells of which included pink to orange globules in the cytoplasm. These findings were indicative of endometrial adenocarcinoma.

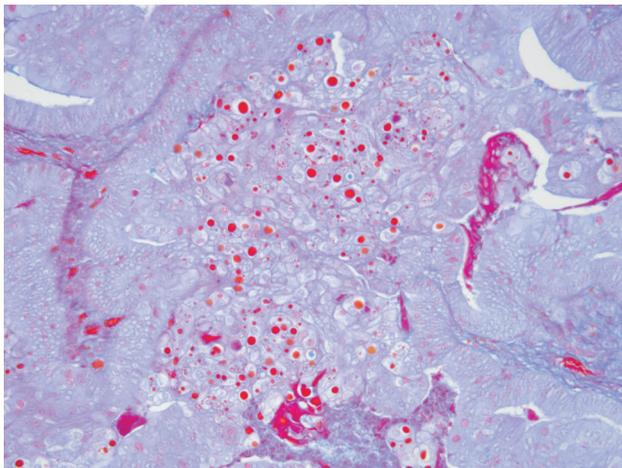
Upon macroscopic examination of the resected uterus, numerous small polypoid masses were seen throughout the uterine cavity. The entire uterus was cut into 21 step sections. Microscopically, the polypoid lesions were characterized by



A



B



C

Figure 4. — Histopathologic examination of the resected uterine tissue confirms the diagnosis of G1 endometrioid adenocarcinoma with squamous differentiation. Hyaline globules are scattered especially in the areas of squamous differentiation. The globules stained positively stained for Mallory Azan. A: Hematoxylin and eosin staining.  $\times 4$  magnification. B: Hematoxylin and eosin staining.  $\times 20$  magnification. C: Mallory Azan staining  $\times 20$  magnification.

marked glandular architectural complexity and marked epithelial stratification. Numerous areas of squamous differentiation were seen (Figure 4). There was no evidence of muscular invasion or lymphatic or vascular permeation. Hyaline globules were scattered about, especially in the areas showing squamous differentiation. The hyaline globules were classified by size ( $< 10$  vs.  $\geq 10$  micrometers) and counted accordingly in 10 high-power fields (HPFs). The mean numbers per HPF were recorded. The counts were 169.5/HPF and 28.2/HPF, respectively. The final histologic diagnosis was G1 endometrioid adenocarcinoma with squamous differentiation. Tumor cells were positive for ER and PgR. The hyaline globules stained weakly with Mallory Azan and did not stain with alcian blue or von Kossa. The periodic acid-Schiff reaction was negative. Immunohistochemically, the hyaline globules were negative for cytokeratins, vimentin, desmin, muscle actin,  $\alpha$ -fetoprotein, transthyretin,  $\alpha$ -antitrypsin,  $\alpha$ 1-chymotrypsin, fibrinogen, laminin, and  $\beta$ -catenin.

## Discussion

Endometrium-limited G1 endometrioid adenocarcinoma seldom metastasizes [1]. In a search of the literature for cases of lung metastasis of endometrioid adenocarcinoma (PubMed search with “endometrial cancer Stage IA” and “lung metastasis” used as keywords), we found no reports of such an entity. We found one report of metastatic lung disease that arose as a recurrence of a endometrium-limited G1 endometrioid adenocarcinoma [2], but the present case differed in that the lung lesion in the patient was not a recurrence.

The present case was also unusual in that hyaline globules were observed at both the local and metastatic site. There is one report of cytoplasmic inclusions in endometrial cancer cells, but the cancer in that case was a serous adenocarcinoma [3], and the inclusions were psammoma bodies. We seldom see hyaline globules in endometrioid adenocarcinoma. In the present case, small hyaline globules appeared in the cytoplasm of cells in the areas of squamous differentiation, and as these globules increased in size, they were excreted from the cells. This phenomenon was observed in both the endometrium and lung. In general, there are many kinds of inclusion bodies. Examples are hyaline bodies, psammoma bodies, sarcoma bodies, and Mallory bodies [4]. Mature squamous cells that contain hyaline globules are referred to as polka dot cells, but the appearance of the dots differs from the appearance of the globules in the present case [5]. In fact, the hyaline globules in this case were unique in that the only positive staining was the Mallory Azan staining, so we were unable to identify the globules. We speculate that the globules had some metastatic potential or that the repeated D&Cs led to metastasis via the circulation. Squamous differentiation should be suspected when such hyaline globules are discovered, and the possibility of metastatic potential should be kept in mind. The metastatic process in the present case will remain somewhat a mystery until similar cases can be thoroughly investigated.

## References

- [1] Labi F.L., Evangelista S., Di Miscia A., Stentella P.: "FIGO Stage I endometrial carcinoma: evaluation of lung metastases and follow-up". *Eur. J. Gynaecol. Oncol.*, 2008, 29, 65.
- [2] Oaknin A., Barretina M.P., Morilla I.: "Muscle metastasis of low-grade endometrial carcinoma seven years after diagnosis: a case report". *Eur. J. Gynaecol. Oncol.*, 2010, 31, 114.
- [3] Yamawaki T., Teshima H., Takeshima N., Yamauchi K., Hasumi K.: "A clinicopathological study in clear cell adenocarcinoma of the endometrium". *Nihon Sanka Fujinka Gakkai Zasshi*, 1996, 48, 328. [Article in Japanese]
- [4] Takahashi Y., Inoue T.: "Hepatoid carcinoma of the uterus that collided with carcinosarcoma". *Pathol. Int.*, 2003, 53, 323.
- [5] Shiffer J.D., Sandweiss L., Bose S.: "The "polka dot" cell". *Acta Cytol.*, 2001, 45, 903.

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