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REVIEW – CLINICAL ONCOLOGY

Endocervical adenocarcinoma in situ (AIS) with ovarian and pulmonary involvement: report of a case and review of the literature suggesting a "seed and soil hypothesis"

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Abstract

Purpose Cervical cancer metastases to the ovary may occur with advanced tumor stage, deep cervical stromal involvement and corpus involvement. Endocervical adenocarcinoma in situ (AIS) with ovarian involvement is exceptionally rare with about twelve reported cases.

Methods Here we present a case of endocervical AIS with ovarian and pulmonary involvement 39 months after the initial diagnosis. The characteristics of that case were compared and summarized with the eleven previously published cases.

Results The patients' age ranged between 30 and 40 years (median 37.4 years). The time interval between the diagnosis of AIS and ovarian involvement was 26.7 months (range 2–84 months). Majority of the patients are alive without evidence of disease after a median time of 63.4 months (range 9–156 months). All reported cases were positive for high-risk HPV which was associated with strong p16 expression on immunohistochemistry.

Conclusions The ovarian involvement by endocervical AIS suggests the concept of a transtubal spread of the neoplastic cervical cells with or without previous colonization within the endometrium without evidence of invasive growth, suggesting a seed and soil spread of the disease. In cases with ovarian involvement by the AIS and without additional extragenital spread, the prognosis may be favorable.

Keywords Adenocarcinoma in situ · Cervix · Ovarian metastases · p16 · HPV

Introduction

Ovarian metastases of an invasive carcinoma of the uterine cervix are rare, and their reported frequency ranges between 0.7 and 3.3% (Yamamoto et al. 2001; Sutton et al. 1992; Landoni et al. 2007). The incidence of ovarian involvement depends on tumor stage, histological tumor type and tumor extension within the uterus (Shimada et al. 2006; Landoni et al. 2007). More recently, rare cases of endocervical adenocarcinoma in situ (AIS) with ovarian involvement have been reported (Ronnett et al. 2008; Chang et al. 2009; Ashton et al. 2015; Turashvili et al. 2015). We present a case of cervical AIS with ovarian and pulmonary involvement.

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Case report

A 48-year-old gravida 2 para 2 presented 7 years after a cervical cone biopsy was initially performed because of a high-grade squamous intraepithelial lesion (CIN 3) that was completely resected. 3 years after the cone biopsy, a follow-up pap smear showed atypical glandular cells of undetermined significance (AGUS). After a colposcopically guided biopsy and cervical curetting, a cone biopsy was performed. That specimen revealed an adenocarcinoma in situ of the endocervical glands (AIS) with broad vertical extension and 0.2 cm thickness, extending up to the isthmic endometrium (Fig. 1a, b) with clear margins. The Pap smear, obtained 2.5 months after the biopsy, showed abnormal cells, suspicious for adenocarcinoma in situ. Therefore, a laparoscopically assisted vaginal hysterectomy (LAVH) and bilateral prophylactic salpingectomy were performed and it again showed AIS of the endocervical glands (extension 0.8×0.1 cm) and a proliferative endometrium. 15 months after the LAVH, the patient presented with back pain and a mild increase in abdominal circumference. The gynecologic examination revealed an ovarian mass. Transvaginal ultrasound showed a cystic tumor cephalad of the vaginal cuff of about $10.5 \times 6.6 \times 11$ cm with solid areas of $6.0 \times 2.6 \times 4.5$ cm. CT imaging showed a solid-cystic ovarian mass (Fig. 2a). Additionally, bilateral pulmonary lesions of up to 1.1 cm in largest dimension were detected (Fig. 2b). Tumor markers (CA 12-5, CA 15-3, CA 19-9 and CEA) were within normal limits.

A moderately differentiated adenocarcinoma was diagnosed in the transbronchial biopsy (Fig. 3a, b). The ovarian specimen showed a solid papillary tumor (450 g and $12 \times 10 \times 7$ cm) with an intact capsule. Histopathologically, the growth pattern was similar to an ovarian borderline tumor (Fig. 3c, d). Peritoneal and omental biopsies revealed no tumor involvement. The histopathological and

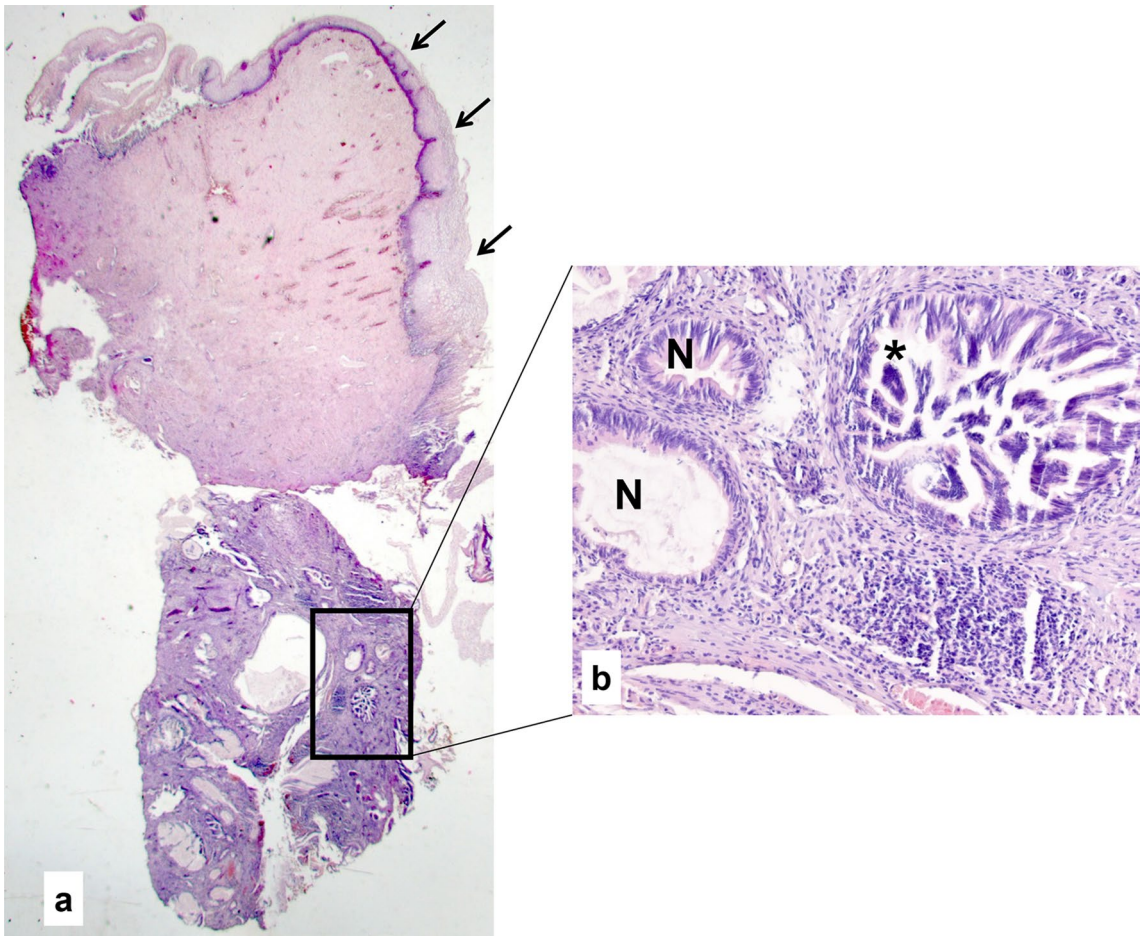

Fig. 1 Adenocarcinoma in situ (AIS) of the uterine cervix in the cone biopsy. **a** Low magnification of the cone biopsy with regular squamous epithelium of the ectocervix (arrow), endocervical mucosa shows heavy cauterisation artifacts (asterisk). **b** Higher magnification of the endocervical mucosa showing glands of the adenocarcinoma in situ (asterisk) and regular endocervical glands (N)

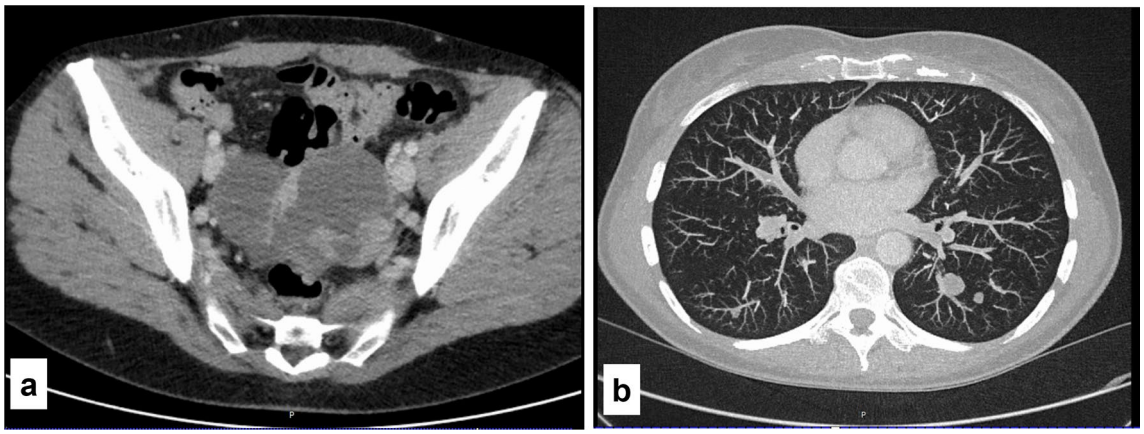

Fig. 2 Ovarian and pulmonary involvement by the cervical adenocarcinomatous lesion. **a** CT imaging showing the pelvic lesion with solid-cystic appearance and marginal contrast medium enhancement. **b** CT imaging showing bilateral pulmonary lesions with spiculated and round appearance (arrows)

immunohistochemical patterns of the glandular lesions of the lung and the ovary were identical, with immunohistochemical positivity for CK 7, PAX-8, P-504-S (α-racemase), MUC-1, CA 12-5 (apical cytoplasmic staining) and negative staining for CK 20, CDX-2, CEA, TTF-1, WT-1, p53 represented a wild-type staining pattern (Fig. 3e–h). p16 showed a diffuse and strong staining of about 90% of the cells in both lesions (block staining; Fig. 3b, g). The PCR-based chip analysis of the above-mentioned adenocarcinoma in situ, the pulmonary and the ovarian lesion showed DNA for HPV 16 on analysis with the DNA-based liquid–crystal display [LCD-Array kit (Chipron GmbH, Berlin, Germany) according to the manufacturer's protocol]. The re-examination of the hysterectomy specimen with p16 immunohistochemistry showed glands of the AIS between the endometrial glands of the isthmic endometrium (Fig. 4a–c), at the surface and within the glands of the endometrium of the uterine corpus (Fig. 4d), indicating an endometrial involvement (seeding). Additionally, the re-examination of the conisation as well as the hysterectomy specimen showed no evidence of invasive disease.

Re-examination of the fallopian tubal mucosa including the fimbriated ends by H&E staining and immunohistochemistry for p16 was inconspicuous.

The final diagnosis of an adenocarcinoma in situ of the endocervix with ovarian and pulmonary involvement was made. The patient was treated with paclitaxel and cisplatin which were added by antiangiogenetic treatment by bevacizumab. The patient refused further treatment by chemotherapy but maintained antiangiogenetic therapy. The patient is alive with evidence of disease representing a slight progression in size (but not in number) of the pulmonary lesions 18 months after starting antiangiogenetic treatment. The patient's clinical course is summarized in Fig. 5.

Discussion

The overall incidence of ovarian involvement for invasive cervical carcinoma in the largest reported studies ranges between 0.7 and 1.5% (Sutton et al. 1992; Shimada et al. 2006, Landoni et al. 2007). Ovarian involvement increases with increasing tumor stage from 0.4 to 0.8% in FIGO stage IB up to 3.3% in FIGO stage IIB (Yamamoto et al. 2001; Shimada et al. 2006). Other risk factors for ovarian spread may be deep cervical stromal invasion, blood vessel involvement, pelvic lymph node disease and involvement of the uterine corpus (Yamamoto et al. 2001; Shimada et al. 2006; Landoni et al. 2007). Cervical adenocarcinomas are more frequently associated with ovarian involvement than squamous cell cancers (0.4% vs. 8.2%; Yamamoto et al. 2001, 0.8% vs. 5.3%; Shimada et al. 2006, 0.5% vs. 1.7%; Sutton et al. 1992). More recently, adenocarcinomas in situ (AIS) without evidence of stromal invasion have been reported to show ovarian involvement (Ronnett et al. 2008; Chang et al. 2009; Ashton et al. 2015; Turashvili et al. 2015). Clinicopathologic characteristics of the cases in the literature as well as the present care are summarized in Table 1.

Ovarian involvement by AIS may cause some diagnostic challenges. Generally, bilaterality, a tumor size lower than 12–13 cm and the presence of extraovarian disease are considered hallmarks of metastatic ovarian involvement (Pinto et al. 2012; Leen and Singh 2012; Horn et al. 2014; Hu et al. 2018). However, in about two-thirds of the reported cases, the metastatic tumors associated with AIS were unilateral and measuring 12–13 cm or larger (Elishaev et al. 2005; Ronnett et al. 2008; Ashton et al. 2015; Turashvili et al. 2015; Hu et al. 2018). Almost all cases showed a smooth external ovarian surface and a solid-cystic appearance on the cutting surface. On histopathology, the tumors exhibited features comparable with borderline ovarian tumors

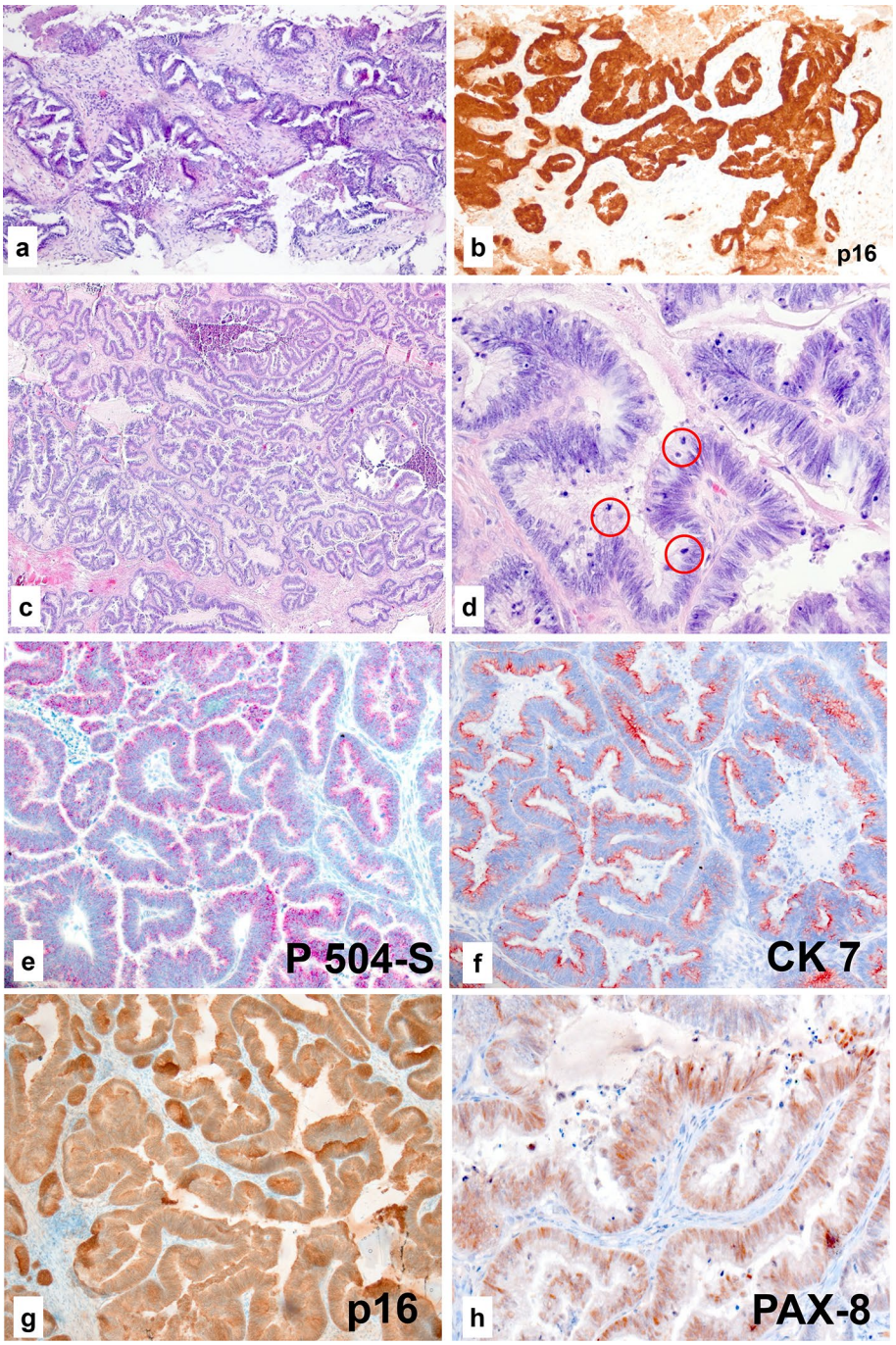

Fig. 3 Histopathological findings of the pulmonary and ovarian lesion. **a**, **b** Pulmonary lesion: core needle biopsy with a moderately differentiated adenocarcinoma with strong immunohistochemical staining for p16. **c** Ovarian lesion: microscopic low power view showing a growth pattern similar to an ovarian borderline tumor. **d** On high power, the tumor cells show a mucinous morphology with an apical cytoplasmic localization of aptotic and mitotic figures (encircled). **e**–**h** Immunohistochemical staining results of the ovarian lesion, note the strong and diffuse staining for p16 and nuclear positivity for PAX-8, indicating a Müllerian origin of the lesion

(borderline like; Chang et al. 2009; Ronnett et al. 2008; Ashton et al. 2015; Turashvili et al. 2015). An ovarian involvement of AIS may therefore be clinically and histopathologically misinterpreted as AIS in conjunction with a borderline ovarian tumor. In the present case, neither CA 12-5 nor CA 15-3 was elevated. Tumor markers were not mentioned in all other cases reported in the literature. The time interval between the detection of AIS and of the ovarian involvement ranges between 2 and 84 months (median 26.7 months; see Table 1). Only rare cases present with AIS and a synchronous ovarian tumor. The patient age varies between 30 and 49 years (median 37.4 years).

The reported outcome for patients with ovarian metastases in invasive cervical carcinomas is associated with a high rate of distant failures independent of pelvic lymph node involvement and parametrial spread and may therefore be poor (Shimada et al. 2006). The prognostic information for AIS with ovarian involvement is limited. In majority of the cases, the patients are alive without evidence of disease after a median of 63.4 months (range 9–156 months; see

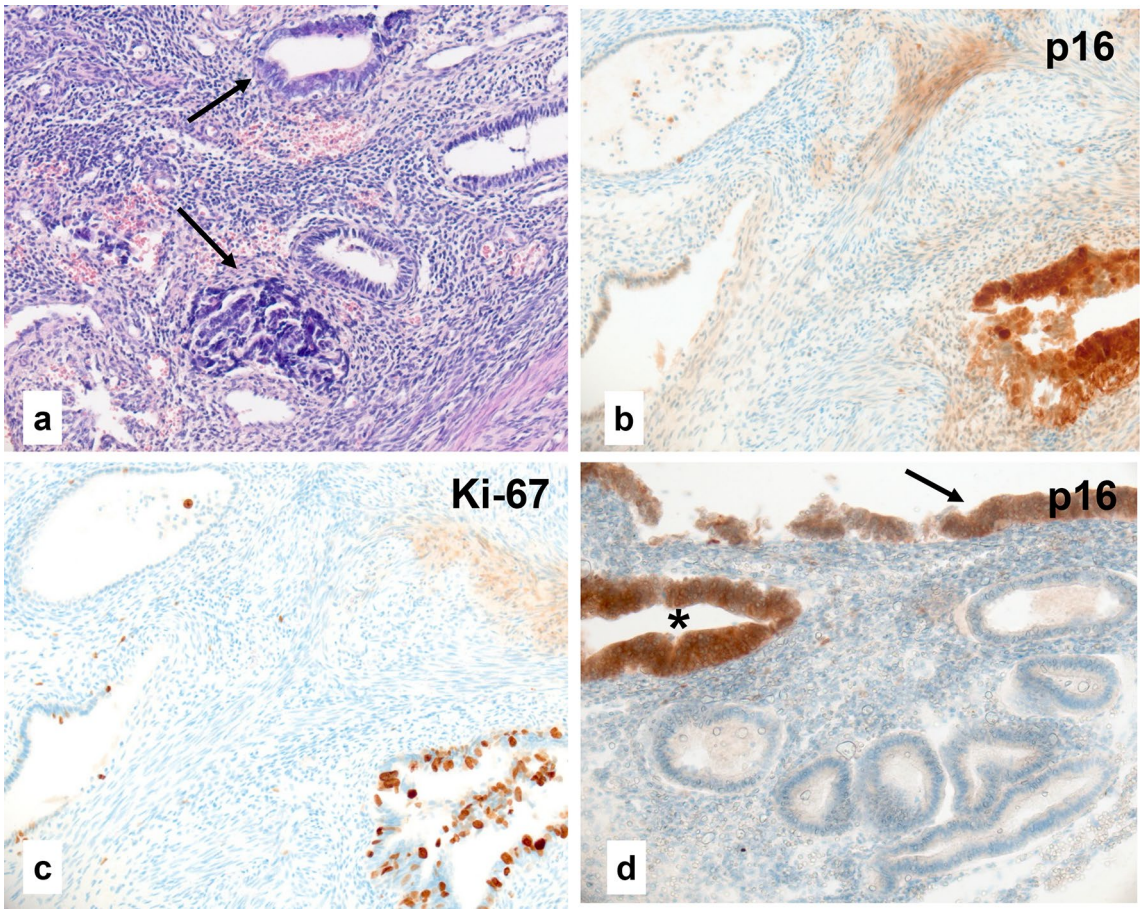

Fig. 4 Re-examination of the isthmic and corporal endometrium of the hysterectomy specimen. **a–c** Extension of the AIS to the isthmic endometrium, note malignant glands within the endometrial stroma (arrow) close to normal endometrial glands (**a**), representing severe cauterisation artifacts. The glands of the AIS represent a strong positivity for p16 (**b**) and a high proliferative activity, highlighted by MIB-1 staining (**c**). **d** Re-examined endometrium of the uterine corpus with p16-positive glands at the endometrial surface (arrow) and within the endometrial stroma (asterisk)

Table 1; Ronnett et al. 2008; Chang et al. 2009; Turashvili et al. 2015). One patient in the report of Ronnett et al. (2008) died of the disease 35 months after the diagnosis of ovarian involvement. She presented with additional extrauterine involvement within the pelvis. In the present case, bilateral pulmonary lesions were diagnosed. The patient is alive with pulmonary disease after 18 months after the antiangionetic treatment was started (see Fig. 4). Although there is very limited data, extrauterine disease in addition to the ovarian involvement appears to worsen the prognosis (Table 2). In the present case, it can be hypothesized that pulmonary disease is based on the ovarian tumor where the invasive component was missed during the histopathological workup of the ovarian lesion.

Large tumor size, deep cervical stromal invasion, blood vessel involvement, involvement of the uterine corpus and higher tumor stage are risk factors for ovarian involvement in invasive cervical carcinoma (Ronnett et al. 2008; Yamamoto et al. 2001; Shimada et al. 2006). The mechanisms of spread to the ovary in patients with cervical carcinoma are controversial. In invasive disease, lymphatic and hematogeneous spread may be responsible for ovarian involvement (Wu et al. 1997; Yamamoto et al. 2001; Chang et al. 2009). AIS represent a non-invasive lesion with intramucosal growth only. Therefore, spread via lymphatics or blood vessel is unlikely, and other routes of spread must be explored. Some of the reported AIS with ovarian involvement showed a wide horizontal extension (Ronnett et al. 2008; Ashton et al. 2015; Chang et al. 2009; Yemelyanova et al. 2009; present case). Rarely, there was involvement of the endometrium of the uterine isthmus and corpus (Chang et al. 2009; Yemelyanova et al. 2009; Reyes et al. 2015). In the present case, the endometrium of the lower uterine segment and uterine corpus was involved (Fig. 4a–d). These data support the concept of direct (non-lymphovascular and non-hematogeneous) spread of endocervical neoplastic lesions to the upper genital tract through the fallopian tubes (Chang et al. 2009; Ashton et al. 2015; Reyes et al. 2015; Gungor et al. 2011; present case).

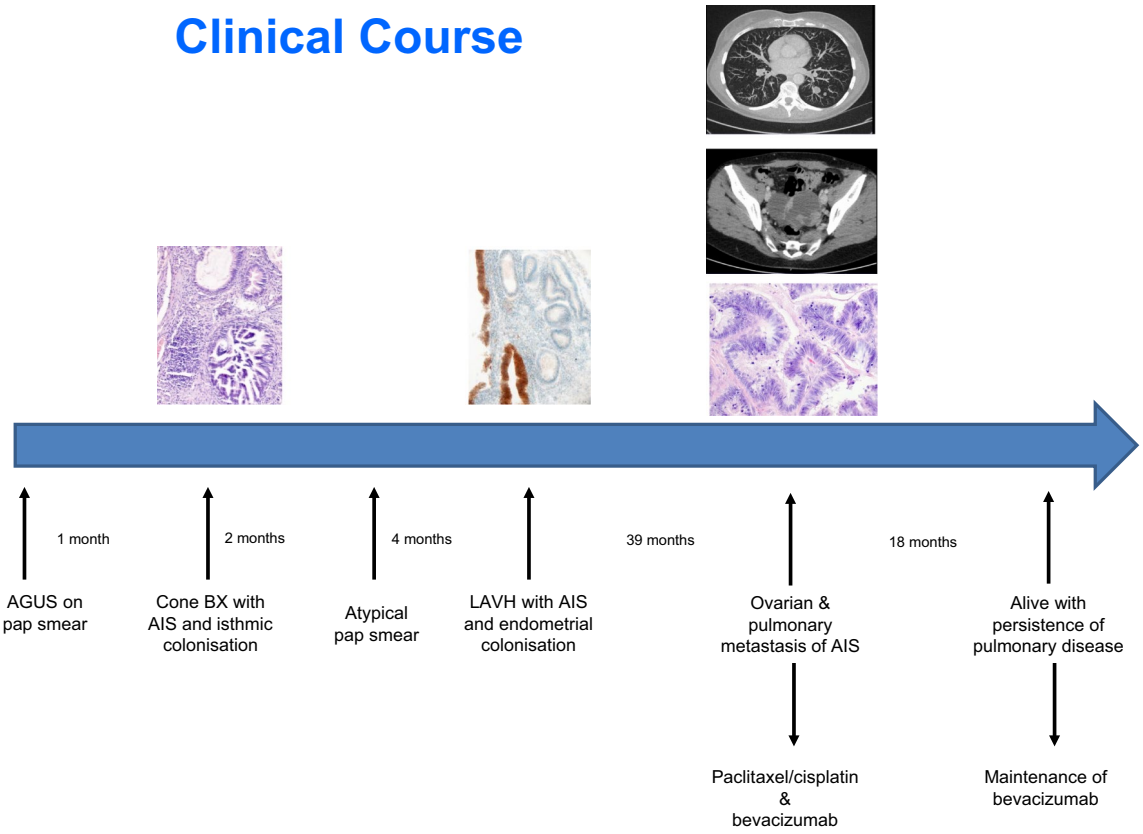

Fig. 5 Summary of the clinical course of the patient

The concept of transtubal spread may be indirectly supported by the occurrence of non-invasive, intramucosal involvement of the tubal mucosa by cervical and endometrial carcinomas (Rabban et al. 2015; Agashe et al. 2007; Singh and Cho 2017). Surface defects (e.g., ruptured corpus luteum) along with the transtubal retrograde spread of neoplastic endocervical cells allows access to the ovarian stroma, analogous to endometrial tissue from retrograde menstruation. This route may be indirectly supported by the development of tubal inclusion cysts within the ovary, potentially associated with the development of serous ovarian cancer (Banet and Kurman 2015). The concept of transtubal spread ("seed and soil hypothesis") is summarized in Fig. 6.

Clinically and on histopathology, ovarian involvement by AIS of the uterine cervix may mimic ovarian borderline tumors (BOT) because of its solid-cystic appearance on ultrasound and macroscopy. Additionally, the microscopic growth pattern is borderline like in the majority of cases (Elishaev et al. 2005; Ronnett et al. 2008; Chang et al. 2009; Turashvili et al. 2015), as well as in the present case (Fig. 3c, d). The borderline-like growth pattern may be challenging in the histopathological workup and may mimic an ovarian primary (Elishaev et al. 2005; Turashvili et al. 2015). An apical localisation of apoptotic and mitotic figures within the stratified epithelium within the ovarian involvement can be detected in Figs. 2–5 of the paper of Ronnett et al. (2008) and is also seen in Fig. 3d of the present case.

Additionally, immunohistochemical stains for p16 may be helpful (Elishaev et al. 2005; Chang et al. 2009; Ashton et al. 2015; Turashvili et al. 2015). It has been reported that diffuse (> 75% positive tumor cells) moderate to strong p16 expression is a sensitive (100%) and specific (97%) marker that can be used to identify HPV-related endocervical adenocarcinomas that metastasized to the ovary (Vang et al. 2007). In the present case, the endocervical AIS and ovarian involvement as well as the pulmonal lesion exhibited strong p16 staining (see Fig. 3b, g). HPV testing may also be very valuable in this setting. The paired analysis of the endocervical and ovarian lesions showed identical HPV types in more than 96% of the HPV-related cases (Ronnett et al. 2008; Chang et al. 2009; Ashton et al. 2015; Turashvili et al. 2015), with HPV 16 and 18 being the most prevalent types (Ronnett et al. 2008; Elishaev et al. 2005; Turashvili et al. 2015; present case). Some difficulties may occur within the recently described gastric variant of mucinous adenocarcinomas of the uterine cervix, because that type of adenocarcinoma is not HPV related and p16 staining may therefore be negative or only focally positive (Park et al.

Table 1 Clinicopathologic features of adenocarcinoma in situ (AIS) of the uterine cervix with ovarian involvement

Case number	Age (years)	Clinical presentation	History of AIS	Status of the disease
Ronnett et al. (2008)				
1	49	Ovarian tumor at hysterectomy for AIS	Cone biopsy for AIS with margin involvement 2 months before	NA
2	34	Ovarian mass	Hysterectomy for AIS 13 months before	ANED 51 months
3	44	Ovarian mass	Cone biopsy for AIS with margin involvement 2 months before	ANED 83 months
4	38	Adnexal mass	Vaginal Hysterectomy for AIS 6 years before	DOD 35 months
5	43	Pelvic mass	Vaginal hysterectomy for AIS 7 years before	ANED 38 months
6	42	Right pelvic mass	Cone biopsy for AIS with margin involvement 14 months before, simple hysterectomy 12 months before without malignancy	ANED 47 months (pelvic and abdominal recurrency 13 and 16 months before)
7	42	Pelvic mass	Cone biopsy for AIS 3 years before	NA
8	42	Bilateral adnexal mass	Vaginal hysterectomy for AIS 9 months before	NA
Chang et al. (2009)				
1	34	Pelvic mass	CONE biopsy for AIS 14 months before, simple hysterectomy with AIS 9 months before	ANED 156 months
2	30	Uneventful	Simple hysterectomy for AIS, concurrent ovarian involvement	ANED 9 months
Turashvili et al. (2015)				
1	~45	Abdominal fullness and pain	Cone biopsy 4 years before with clear margins and AIS within the TAH and BSO for surgical treatment of the ovarian tumor	ANED 60 months
Present case				
1	48	Pelvic mass and pulmonary lesions	Cone biopsy 39 months before with clear margins, LAVH for AIS 15 months before	Alive with pulmonary disease 18 months

AIS adenocarcinoma in situ, *ANED* alive, no evidence of disease, *DOD* dead of disease, *NA* not available, *TAH and BSO* total abdominal hysterectomy with bilateral salpingo-oophorectomy

Table 2 Key points of cervical adenocarcinoma (AIS) with ovarian involvement

Frequency of ovarian metastases in invasive cervical carcinomas range between 0.7 and 3.3%
The risk of ovarian involvement in invasive cervical carcinoma correlates with tumor stage, deep cervical stromal invasion, involvement of the uterine corpus, blood vessel involvement and may be more frequent in adenocarcinomas
Ovarian involvement by adenocarcinoma in situ of the uterine cervix (AIS) is exceptionally rare with about 12 reported cases
Ovarian involvement by AIS may mimic borderline ovarian tumors (BOT) clinically and on histopathology
Ovarian involvement by AIS occur in a time interval between AIS and ovarian lesion of 2–84 months (median 26.7 months) in the majority of cases; simultaneous involvement is rare
Ovarian involvement by AIS is associated with excellent prognosis with no evidence of the disease (NED) after a median of 63.4 months (range 9–156 months) in the reported cases
Additional extrauterine (pelvic) spread of AIS may be an indicator for poor prognostic outcome
Abstracting the reported cases a "seed and soil hypothesis" with colonization of the isthmic/corpus endometrium by the AIS with transtubal spread to the ovary may be suggested
Occurrence of ovarian mass after a history of (endo-) cervical AIS may prompt the paired analyses for p16 and/or HPV typing for metastatic lesion or, just in case, whole genomic profiling
Awareness of ovarian involvement by AIS or invasive adenocarcinoma of the uterine cervix should be made in all patients with the history of malignant glandular lesion of the uterine cervix

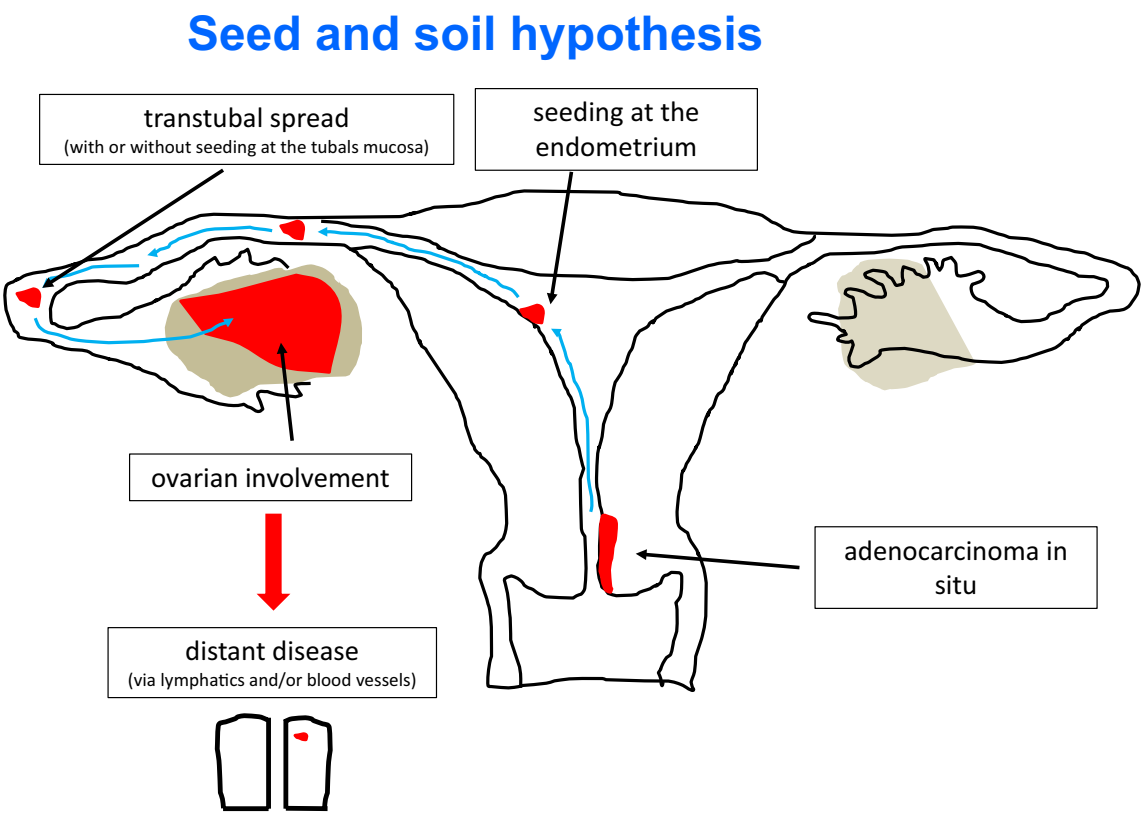

Fig. 6 Schematic illustration of the transtubal spread of neoplastic cells of cervical AIS to the adnexae ("seed and soil hypothesis"; see text)

2011). In these cases, whole genomic copy number analyses may confirm the cervical origin of the ovarian involvement (Ashton et al. 2015).

In summary, the involvement of the ovaries by AIS is very rare and represents a distinct pattern of spread, in contrast to ovarian metastases in invasive cervical (adeno-) carcinomas. While the latter represents advanced stage disease with poor prognostic outcome, patients with AIS and ovarian involvement typically have favorable follow-ups which may, however, be impaired if additional extrauterine/-pelvic disease besides ovarian involvement is present. The occurrence of an unusual borderline-like ovarian tumor and the history of a cervical glandular neoplastic lesion may prompt further analyses to establish or exclude metastatic involvement of the ovary by cervical glandular lesions.

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Compliance with ethical standards

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

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent from the patient was obtained by presenting the data in the case report.

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