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Mesonephric-Like Adenocarcinoma of the Endometrium Mimicking Advanced Tubo-Ovarian Cancer - A Literature Review Based on a Special Case

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Abstract: Mesonephric-like adenocarcinoma of the endometrium (ML-AC) is a rare variant of endometrial adenocarcinoma with aggressive clinical behavior and unusual metastatic spread. Because of its rarity, the diagnosis may be challenging but needs to be accurate due to the mostly poor prognostic outcome of these tumors. To aid in the understanding and recognition of this entity we present the detailed histopathological, immunohistochemical and molecular analysis of a case of ML-AC clinically mimicking advanced ovarian cancer in a 55-year-old woman and put it in the context of literature research on ovarian and endometrial carcinomas. In the present case the patient revealed abdominal distension, ascites and a moderately elevated CA-125 level (504.8 U/ml) with widespread peritoneal carcinomatosis and an endometrial lesion confined to the endometrium with the presence of free-floating tumor cells within the tubal lumen, suggesting transtubal peritoneal spread of the endometrial primary. All tumor sites shared various architectural patterns on histology with negative staining for p16, WT-1 and estrogen receptor and positivity for TTF-1. Matched pair molecular analysis revealed an identic clonal *KRAS*-mutation (p.G12C) within the endometrial, peritoneal and lymph node involvement as well as in the recurrent tumor. There was retained mismatch repair protein staining and p53 wild type pattern without any additional mutational alterations, including *POLE*. A hepatic recurrence was diagnosed after 11 months. Literature study confirms our findings and the suggestion of a morphomolecular diagnostic approach additional to the fact that *KRAS*-mutation may represent a targetable alteration within a specialized therapeutic approach for this entity.

Keywords: Endometrium, Cancer, Mesonephric, Adenocarcinoma, TTF-1, Prognosis, *KRAS*-Mutation, Ovarian

1. Introduction

Mesonephric-like adenocarcinomas (ML-AC) of the endometrium are rare tumors with a reported incidence of < 1% in large cohorts with combined morphologic and molecular analyses [1-3]. It might be associated with an unusual clinical

presentation and an aggressive clinical course.

Because of its rarity, the diagnosis of ML-AC may be challenging [4-6], but the accurate diagnosis is important because of the relatively poor prognostic outcome of these tumors [4, 5, 7]. There is considerable risk to spread beyond the pelvis with an increased frequency of pulmonary involvement [1, 8], including cases with very unusual metastatic sites [7, 9].

To aid in the understanding and recognition of this entity we report a case of ML-AC arising in the endometrium with extensive peritoneal spread, clinically and histopathologically mimicking tubo-ovarian carcinoma and analysed the detailed histopathological, immunohistochemical and molecular findings by comparison to other cases and cohorts described in literature. Also it is of interest if the molecular characterization of these tumors offers opportunities to a targeted therapy.

2. Case Presentation

Case history and clinical presentation: A 55-year-old postmenopausal woman, gravida I, para I with a last menstrual period six years prior to presentation was referred to our hospital because of abdominal distension and symptomatic ascites. Her clinical history included a laparoscopic resection of a uterine fibroid years ago. The serum CA-125 level was moderately elevated at 504.8 U/ml.

A diagnostic CT-scan revealed a diffuse peritoneal carcinomatosis, suggestive of an advanced tubo-ovarian carcinoma (Figure 1a, b). Cytologic examination of the ascites showed malignant cells indicative for adenocarcinoma (Figure 2a). As a result, cytoreductive surgery was performed. Frozen section examination of omental implants was consistent with (poorly differentiated) adenocarcinoma of Müllerian origin (Figure 2b, c).

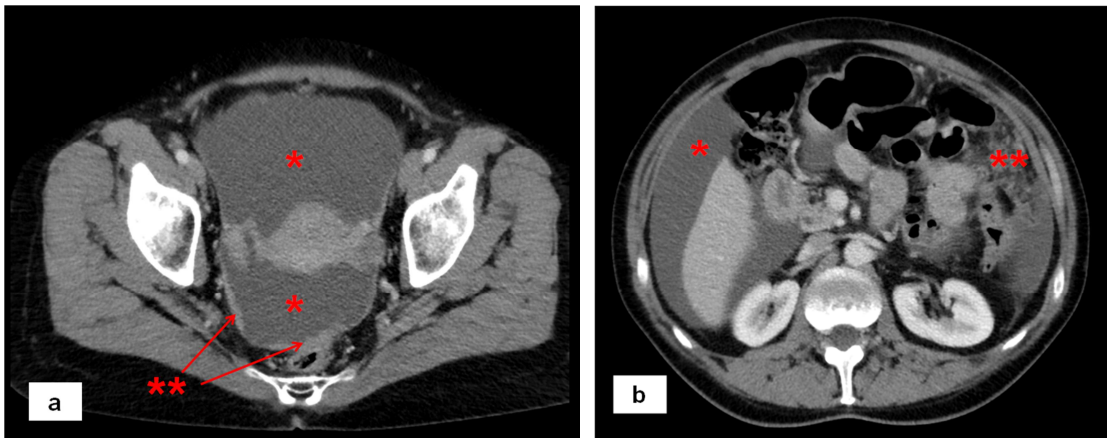

Figure 1. *Contrast-enhanced computertomographic scan with transverse slice guidance representing peritoneal involvement with ascites (*) and peritoneal seeding (**): a) at the level of the pelvis, b) within the omentum majus.*

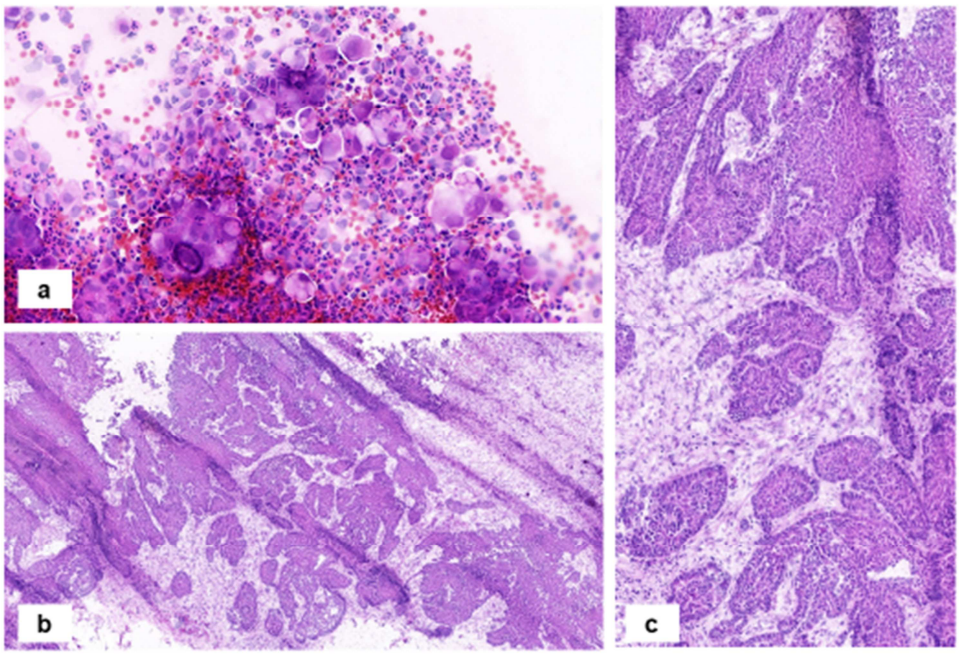

Figure 2. *Initial diagnostic findings: a) ascitic fluid with papillary architecture of highly polymorphic cells, b) and c) frozen section of omental spread, initially misdiagnosed as high-grade tubo-ovarian cancer.*

Macroscopical, histopathological and immunohistochemical findings: Macroscopic evaluation of the specimen showed widespread multinodular peritoneal disease involving the whole abdominal peritoneum, including the peritoneal diaphragm on both sides. Omental disease consisted of multinodular involvement up to 1.5cm in the largest dimension. The fallopian tubes including the fimbriated ends were clearly visible. Both the tubal and ovarian surface were affected by the tumor.

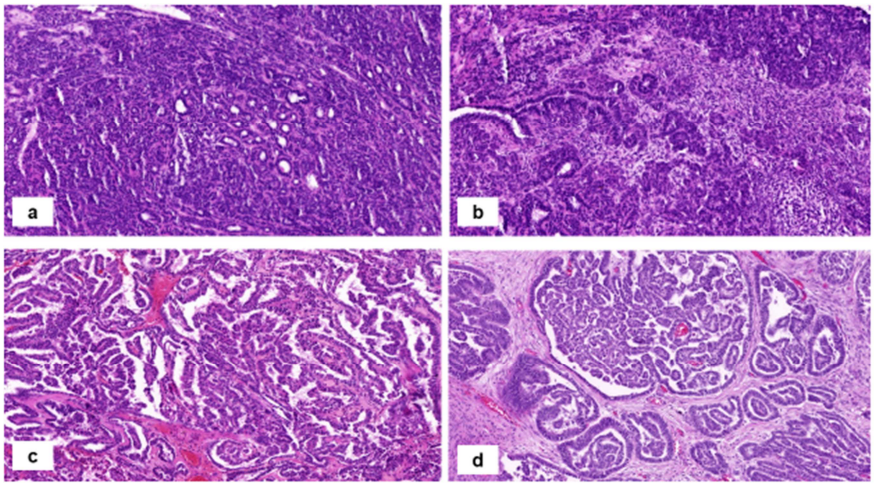

Figure 3. *Different morphologic patterns within the tumor: a) solid tumor growth, b) endometrioid-like, c) micropapillary features, d) tubular features mixed with a spindle cell pattern.*

Microscopically, the tumor showed various architectural patterns (Figure 3a-d). There was a plaque-like ovarian surface involvement (Figure 4a, b). The tubal mucosa on both sides revealed no epithelial serous precursor lesions nor invasive tumor (Figure 4c-f). Immunostainings for p53, p16 and Ki-67 were negative for serous tubal in situ carcinoma (STIC) or lesion in transition (STIL). The uterine endometrium was atrophic but an adenocarcinoma with a maximum dimension of 1.1cm, confined to the endometrium was seen (Figure 5a, b). Within the tubal lumen on the right side, free-floating tumor cells were observed (Figure 5c). Immunohistochemical evaluation of the endometrial and peritoneal tumor (including adnexal involvement) revealed identical findings, which have previously been described for a mesonephric differentiation [6, 10-12] (Figure 5d-l). The tumor cells showed retained expression of mismatch repair proteins (MLH-1, PMS-2, MSH-2, MSH-6).

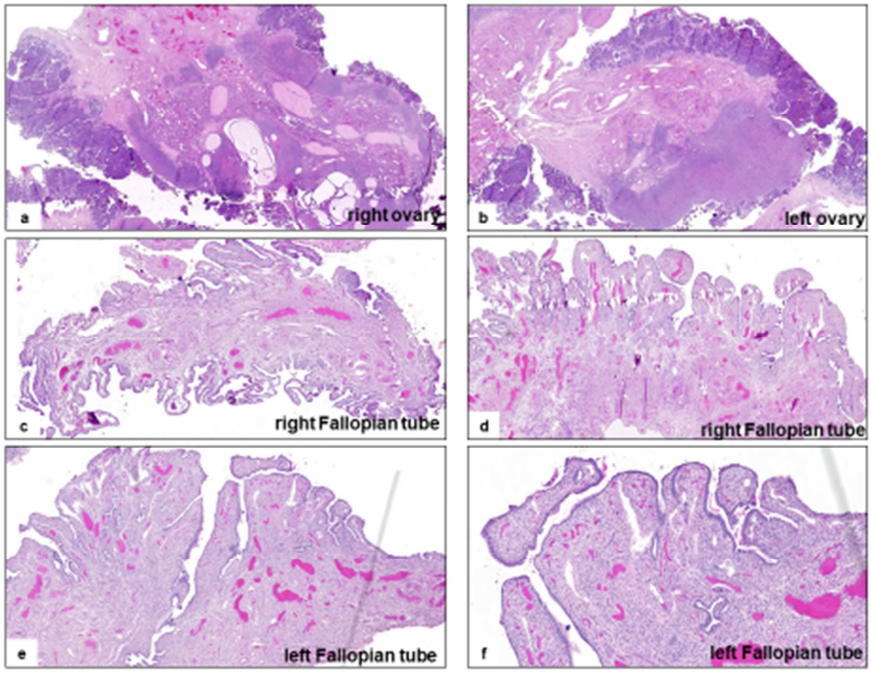

Figure 4. *Adnexal morphology: a) and b) plaque-like surface involvement of both ovaries, c) and d) fimbriated end of the right fallopian tube and e) and f) fimbriated end of the left fallopian tube without any serous precursor lesions.*

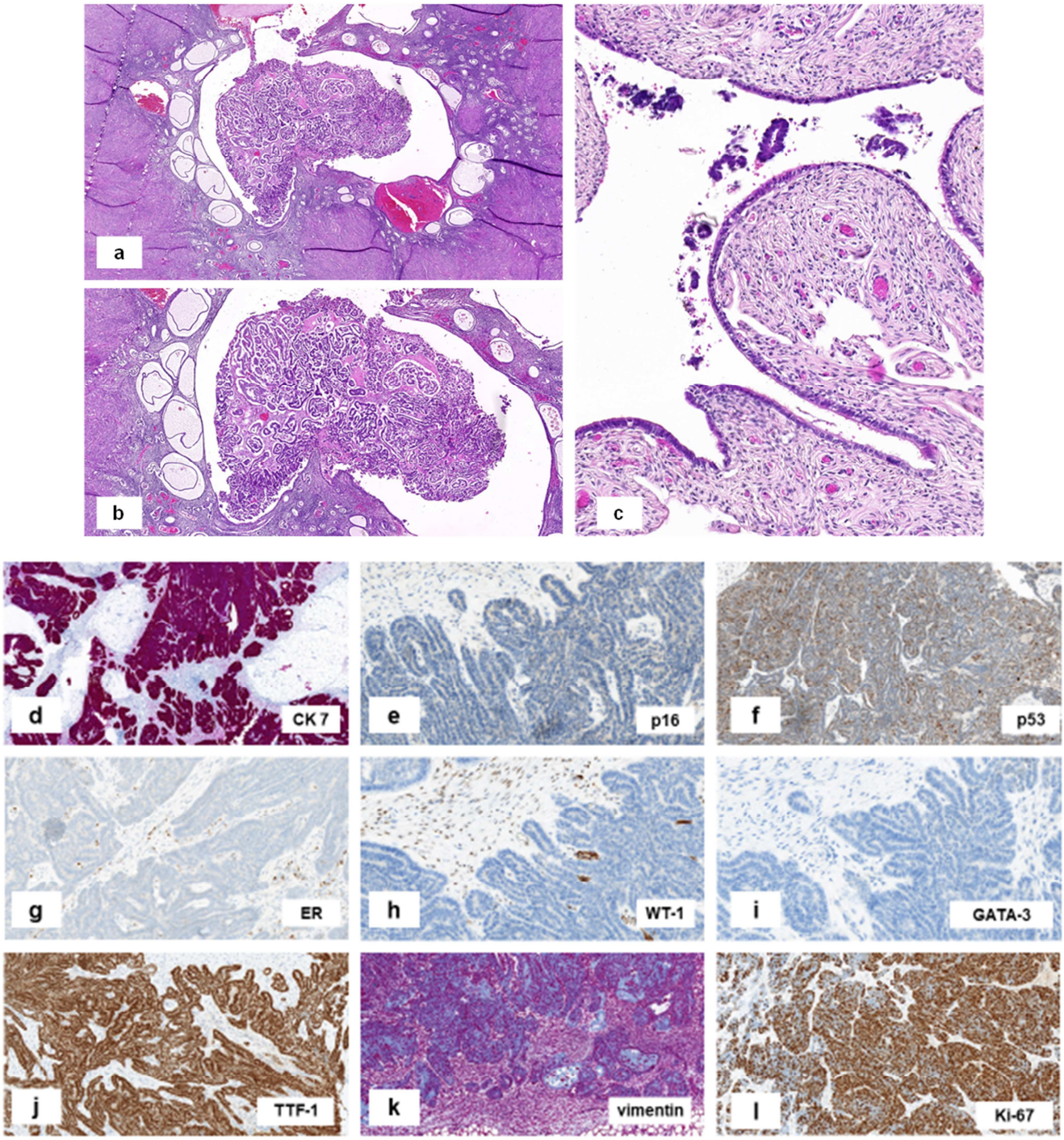

Figure 5. *Histopathologic and immunohistochemical findings of the endometrial primary, a) and b) endometrial tumor, confined to the endometrium with exophytic growth, surrounded by an atrophic endometrium, c) free-floating tumor cells within the lumen of the right fallopian tube, d) strong and diffuse staining for CK 7, e) p16-negativity, f) p53-wild type expression, g) negative staining for estrogen receptor, h) WT-1, i) GATA-3, j) diffuse and strong nuclear positivity for TTF-1, k) cytoplasmic staining for vimentin and l) high proliferative activity.*

Molecular results: NGS-based molecular analysis showed a *KRAS*-mutation (p.G12C) within the endometrial tumor. Therefore, the final diagnosis of an endometrial mesonephric-like adenocarcinoma with diffuse peritoneal involvement and a lymph node metastasis within one of 14 perirecto-sigmoidal nodes (pT3a, NX, pM1 LYM (1/14)) was made. Additional matched NGS-analysis of the peritoneal and lymph node involvement harbored a *KRAS*-mutation identical to the mutation found in the endometrial primary (Figure 6). NGS-analysis showed no additional mutational events within the tumor, *POLE* represented wild type status.

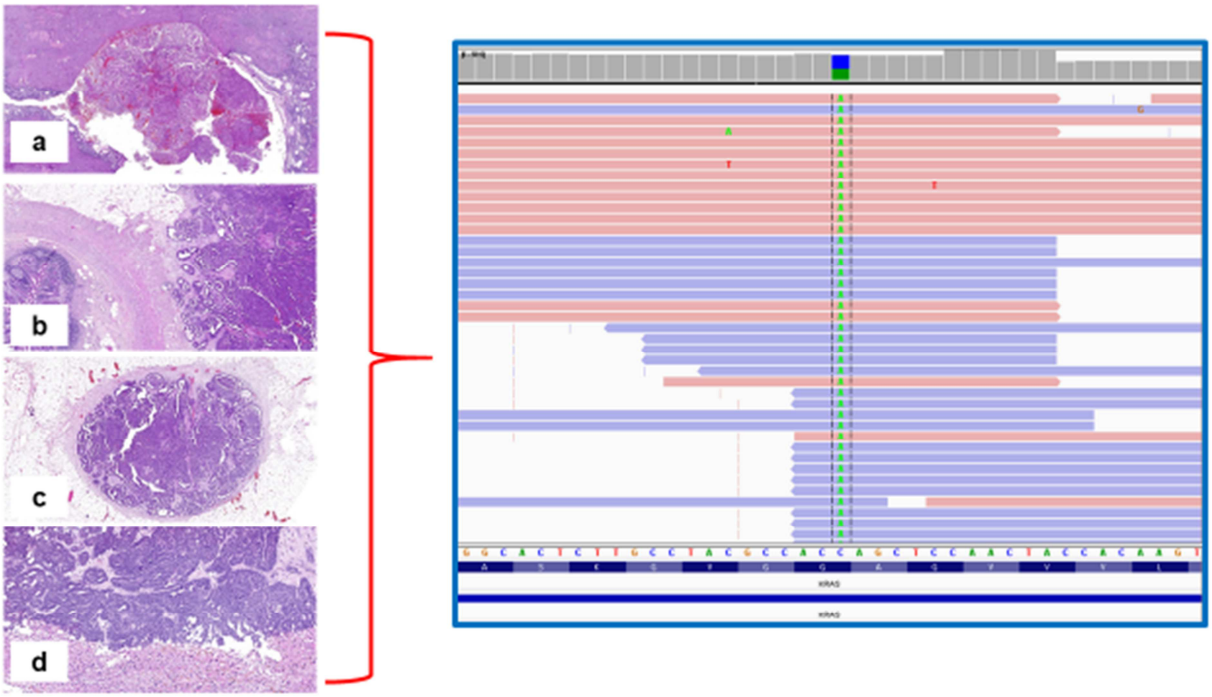

Figure 6. *Matched pair mutational analysis of KRAS with detection of identic clonal p.G12C-alteration within the a) endometrial primary, b) involvement of the fatty tissue of the appendix, c) involvement of lymph nodes, d) metastatic spread to the liver during follow-up.*

Adjuvant treatment and follow up: After cytoreductive surgery with optimal tumor debulking to no residual disease, clinically R0, the patient received systemic therapy with carboplatinum and paclitaxel for six cycles. Postoperatively, the CA-125 level decreased to 25.6 U/ml. Eleven months after surgery, the patient developed recurrent disease with hepatic metastases and tumor growth at the site of the ascites aspiration (Figure 7a, b). The patient is alive with disease after a follow-up of 14 months from initial diagnosis.

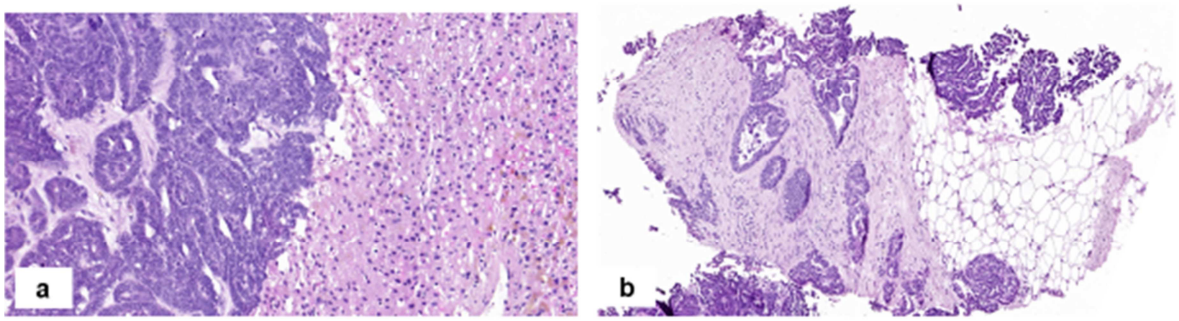

Figure 7. *Findings within the recurrent tumor: a) hepatic spread with tubulo-papillary tumor growth, b) tumor within the fatty tissue of the ascites puncture site.*

3. Discussion

Endometrial mesonephric-like adenocarcinomas (ML-AC) represent a rare but distinct clinical and morphological entity with a recently reported prevalence of 0.7% (4/585) [2], 0.7% (4/579) [1], 1.0% (4/398) [3], 2.9% (7/237) [6] and 1.0% (12/1239) [13].

Consistent with other histopathological subtypes of endometrial cancer, the most common symptom of endometrial ML-AC is abnormal vaginal bleeding [3, 5, 14, 15]. Very rarely, patients present with unusual symptoms, e.g. an ocular metastasis [9]. The presented patient showed clinical signs suspicious for ovarian cancer (see above), including a moderately elevated CA-125 value of 504.8 U/ml. Within a study of 432 endometrial cancers with various types, CA-125 was preoperatively elevated in 26.3% with a median of 66 U/ml (range 35-1.200 U/ml) and strongly associated with extrauterine spread [16]. Serum CA-125 values have rarely been reported for endometrial ML-AC in the literature [3, 5, 7, 14]. In the patient who presented with an ocular metastasis, the CA-125 was elevated to 215 U/ml [9]. Kim et al. [6] identified three of seven patients with endometrial ML-AC with a slightly elevated serum CA-125 (54; 68 and 50.8 U/ml). For *ovarian* ML-AC, serum CA-125 levels were also moderately elevated (206.7 U/ml by Kim et al. [7]; 72.5 U/ml and 108.8 U/ml by Koh et al. [17]).

About one fifth of the patients with serous endometrial

carcinomas will present with extrauterine spread [18]. In contrast, the vast majority of endometrioid endometrial carcinomas are diagnosed in FIGO stages I or II without peritoneal involvement [19]. Most patients with uterine ML-AC will also not present with peritoneal spread at the time of first diagnosis [4, 7, 8, 10, 11]. However, focal peritoneal spread has been reported in 14.3% patients (1/7, pelvic peritoneum [6]), 25% (1/4, cul de sac [14]) and 50% (2/4 [2]).

In the reported cases with initial peritoneal involvement, peritoneal disease was seen only focally [6, 14]. As far as we know the present case is the first case of an endometrial ML-CA mimicking advanced ovarian cancer because of its diffuse peritoneal spread. The diagnosis of the endometrial origin in our case was based on the following morphologic features: absence of any (serous) precursor lesion within both fallopian tubes [Figure 4c-f], plaque-like ovarian surface involvement [Figure 4a, b], presence of an endometrial tumor [Figure 5a, b], occurrence of free-floating tumor cells within the lumen of the right fallopian tube [Figure 5c] showing similar cytologic morphology to the cells within the ascites [Figure 2a], suggesting a transtubal spread from the endometrial lesion.

It may be argued that mesonephric-like ovarian carcinomas are in fact endometrial carcinomas with wide peritoneal spread. Although endometrial findings were not reported in all published cases of *ovarian* ML-AC, several ovarian tumors were associated either with ovarian endometriosis [8, 17, 20], other epithelial ovarian tumors [21, 22] or the ovarian tumor was the only malignant lesion within the genital tract [5, 17, 23].

Endometrial ML-AC share histomorphologic, immunophenotypic as well as molecular characteristics of mesonephric carcinomas but are not associated with mesonephric remnants [5, 14, 24]. The majority of reported endometrial ML-AC were initially diagnosed as FIGO low grade (G1 or G2) endometrioid carcinomas [4-6, 10, 11, 25]. On immunohistochemistry, endometrial ML-AC showed negative staining or only limited positivity for estrogen receptor and positive staining for TTF-1 and GATA-3 as well as for CD 10 in most cases [1, 2, 4, 6, 8, 11, 12, 14, 17]. Although the immunoprofile TTF-1^{+}/$ER^{-/low}$ is not specific for ML-AC, this finding should raise the suspicion for that tumor type [11, 25]. Euscher et al. [10] suggest TTF-1, GATA-3 and receptors for estrogen and progesterone as first-line markers, with CD 10 and calretinin as supplementary immunostains to establish the diagnosis for endometrial ML-AC. The final diagnosis should be made recognizing a mixed morphology on H&E-staining [2, 8, 10, 11, 14, 25] combined with the above-mentioned immunostaining in line with molecular features, representing a morphomolecular diagnostic approach.

The histopathological features, the immunoprofile as well as the molecular findings (see below) support the pathogenetic concept that endometrial ML-AC are Müllerian-derived, show mesonephric differentiation, suggesting a process of transdifferentiation [8, 10, 12, 25].

About 80% of endometrial ML-AC harbor *KRAS*-mutations [3, 6-8, 10, 11, 14]. Only a very small subset of cases with mesonephric features and the immunohistochemical profile suggestive for mesonephric-like differentiation does not harbor a *KRAS*-hotspot mutation [2, 6, 7, 10].

About 25% to one third of the reported cases display additional mutational alterations often seen in endometrial carcinomas, including *PTEN*, *CTTNB1* and *ARID1A* in decreasing frequency [1, 3, 8, 10-12]. Additional *TP53*-mutations are uncommon in endometrial mesonephric-like *carcinomas* but may occur in mesonephric-like *carcinosarcomas* of the uterus [26].

Al Nabhani et al. [9] reported a case of a 58-year-old woman presenting with an ocular metastasis as the first clinical sign of ML-AC of the endometrium. Morphologically, both the endometrial and ocular tumors showed a mixed histology on H&E-staining with negative immunostaining for estrogen and progesterone receptors and an identical *KRAS*-mutation (c.35G>A p.G12D). Two matched cases in the report of da Silva et al. [12] harbored a clonal *KRAS*-alteration in the primary endometrial ML-AC, its abdominal wall metastasis (p.G12V) and a pulmonary lesion (p.G12D). In the present case, identical *KRAS*-mutations were seen within the endometrial primary, a peritoneal implant as well as a lymph node metastasis (Figure 6a-c). Compared to the endometrial primary, no additional mutational alterations were found in the peritoneal and lymph node disease as well as within the hepatic recurrence (Figure 6d).

A molecular classification had been recommended for endometrial cancer to improve prognostication, to identify patients who may be affected by Lynch syndrome and to guide appropriate treatment decisions [27, 28]. The examined cases of ML-AC presented p53 wildtype immunostaining [1, 3, 4, 6-8, 14] and a retained mismatch-repair protein expression (p-MMR) [1, 4, 9, 14] without a *POLE*-mutation [3, 14]. Therefore, they fall into the molecular group of no special molecular profile (NSMP) endometrial cancers [4, 13, 14, 25]. 12 of 472 NSMP-endometrial carcinomas (2.5%) were found to be ML-AC in the study of Momeni-Boroujeni et al. [13].

There is an increasing evidence that endometrial ML-AC show aggressive clinical behavior with poor prognostic outcome and that 60 to 80% of the patients will recur and/or die of the disease [1, 5, 6, 8, 10].

Euscher et al. [10] reported the median progression-free survival for low-grade endometrioid endometrial carcinoma to be 183 months, for serous cancers 67.1 months and for ML-AC 18.2 months ($p<0.0001$). The median overall survival for patients with ML-AC was significantly shorter compared to serous carcinomas (70.6 versus 139.1 months; $p<0.0001$). Park et al. [26] described a median disease-free survival of 7.7 months in 35 ML-AC. Pors et al. [5] reported an advanced stage of the disease (FIGO stage II to IV) in 58% (25/43) and lymph node involvement of 32% of the ML-AC (11/34). The reported recurrence rate in that study was 59% (24/41), with a 5-year progression-free survival of 27.5% and a 5-year overall survival of 72%.

It has been reported that endometrial ML-AC show a higher frequency of pulmonary spread [2, 5, 10], compared to other

subtypes of endometrial cancer [26, 29, 30]. Mao et al. [30] reported pulmonary metastases in 1.5% of endometrioid endometrial cancer patients. In contrast, lung metastases detected either at the time of initial diagnosis or during follow-up were seen in 56% (14/25) [7] to 60% (21/35) [26] of patients with ML-AC. Da Silva et al. [12] reported pulmonary involvement in 58.3% of ML-AC patients (7/12 of informative cases) at time of recurrent disease, Pors et al. [5] in 64% of patients (14/22 cases presented with distant recurrence). Euscher et al. [10] described the diagnosis of recurrent disease within the lung during follow-up in 30.4% (9/12; mean follow-up time of 24.5 months; range 5-84 months).

Metastatic involvement of the liver is rare in patients with endometrial cancer. It has been reported in 0.5% of patients with endometrioid and in 2.5% of women with serous histology [30]. Although pulmonary disease is the most common site of distant disease in ML-AC, hepatic spread has been reported in 12.5% (/24) by Pors et al. [5] and in 8.7% (2/23) by Euscher et al. [10]. Hepatic recurrence was described in the case presented by Deolet at al. [4] nine months after initial diagnosis. In the present case, there was hepatic recurrence after 11 months of follow-up (Figure 7a).

A substantial number of patients with endometrial ML-AC is associated with an increased frequency of adverse clinico-pathological factors including large tumor size, deep myometrial invasion, cervical stromal involvement as well as lymphatic and/ or blood vessel invasion [6, 9, 10, 14, 26].

Regardless of the reported increased frequency of poor prognostic factors in patients with endometrial ML-AC [6, 10, 14], the presence of a mesonephric-like histology itself may represent an independent factor for adverse prognostic outcome of the affected patients [4, 7, 9, 10]. Pors et al. [5] reported that uterine carcinosarcomas had the worst progression-free survival, followed by ML-AC. All other histopathologic subtypes including serous endometrial cancers were associated with higher progression-free survival rates. Kim et al. [6] reported that endometrial ML-AC had the lowest progression-free survival rates of all histologic subtypes.

Therefore, the FIGO-grading system as used for endometrioid endometrial cancers does not apply for endometrial ML-AC [5, 10] and the tumor type should be incorporated in the group of non-endometrioid high-grade tumors [5, 9, 10, 14]. The fact that mesonephric-like histopathology per se will represent an adverse prognostic factor is supported by the following results. *Non*-mesonephric-like endometrial carcinomas are associated with a *KRAS*-mutation in about 17% and have a better prognosis than *KRAS*-wild type tumors [1]. It may therefore be expected that endometrial ML-AC, a group of tumors with frequent *KRAS*-mutations [1, 7, 8, 14], will have a similar favorable prognostic outcome compared to other *KRAS*-mutated endometrial cancers [10]. Interestingly, this is not the case.

ML-EC are associated with a poor prognosis [5, 10] and show an increased frequency of pulmonary metastases [1, 5] and metastases at other uncommon sites [e.g. ocular [9], liver, brain, spleen and vertebrae [4, 5]. Additionally, they may present with unusual tumor spread mimicking advanced ovarian cancer as in the present case. The data suggest that ML-AC represent a separate morphomolecularly-defined entity within the subgroup of NSMP-ECX, characterized by a worse prognostic outcome compared to NSMP with endometrioid morphology [31].

In order to recognize those features it is important to understand ML-AC of the endometrium as a distinct tumor entity.

Because of the reported aggressive behavior of the majority of endometrial ML-AC, the correct diagnosis of this tumor subtype is important in the clinical setting. Until now, there are no clinical guidelines to manage affected patients [4, 6, 10]. Abstracting the data from the reported cases [4-6, 10, 11], close oncologic follow-up is necessary. Mills et al. [11] suggested that chest imaging should be incorporated in the staging procedure after establishing the histopathological diagnosis of endometrial ML-AC.

Because of the high frequency of *KRAS*-mutations in endometrial ML-AC [see above], therapy targeting the *RAS/MAP*-kinase pathway may offer a therapeutic option in cases with underlying targetable *KRAS*-p.G12C-mutation, as reported for lung [32] and colorectal cancers [33]. Interestingly, one case in the study of da Silva et al. [12] showed a clonal mutation of *KRAS* (p.G12V) in the primary endometrial tumor and matched abdominal wall metastasis, but depicted two additional mutational alterations of the *RAS/MAPK* pathway, which were only seen in the metastatic lesions (*MAP3K13*; p.G100R and *MAPK3*; p.E358V). As mentioned above, an identical clonal *KRAS*-mutation was detected when the endometrial primary was compared to distant tumor sites in the case of Al Nabhani et al. [9] as well as in the present case (Figure 6a-d).

4. Conclusion

ML-AC of the endometrium is a rare, aggressive variant of endometrial adenocarcinoma that imitates clinical signs of ovarian cancer due to its unusual metastatic spread and has an aggressive clinical behavior with poor prognostic outcome. Histologically the tumor shows various architectural patterns and a typical immunophenotype with positivity for TTF-1, GATA-3 and CD 10. The majority of endometrial ML-AC harbor *KRAS*-mutations. Abstracting from the data available, endometrial ML-AC represents a separate endometrial tumor type with characteristic morphomolecular features. In contrast to other subtypes of endometrial carcinomas, a *KRAS*-mutation may not be accompanied by a better prognostic outcome but may represent a targetable alteration within a specialized therapeutic approach. That suggests that the presentation of mesonephric-like histopathology itself is of prognostic impact. Therefore, ML-AC should be included in the group of non-endometrioid high grade tumors.

Declaration of Interest Statement

The authors declare that there are no declarations of interest. All authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

CRediT Author Statement

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