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# **Unusual Case of Splenic Metastasis** in Adenosquamous Carcinoma of the Cervix Uteri: **Diagnosis and Treatment Considerations**

Authors' Contribution: Study Design A Data Collection B Statistical Analysis C Data Interpretation D Manuscript Preparation E Literature Search F

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None declared None declared

Patient:

Female, 37-year-old

**Final Diagnosis: Symptoms:**  Adenosquamous carcinoma of the cervix uteri • splenic metastasis

Intermittent left-sided abdominal pain • vaginal bleeding

**Clinical Procedure:** 

Specialty:

Obstetrics and Gynecology • Pathology • Radiology

Objective:

Unusual clinical course

**Background:** 

**Case Report:** 

destined organ of frequent metastatic colonization in the case of primary solid carcinoma. Hence, the mode of diagnosis and the preferred treatment of a lesion highly suspicious of splenic metastasis must be decided on a case-by-case basis, considering not only the biological tumor entity but also the stage of the primary disease. In the present case, we demonstrate the clinical course of a 37-year-old female patient who initially presented to our clinic with irregular vaginal bleeding. A consecutive gynecological examination revealed a 3×3-cm large mass of the cervix uteri, and the subsequent histomorphological workup led to the diagnosis of an adenosquamous carcinoma of the cervix uteri. Therapeutically, the patient received multimodal treatment, namely radical hysterectomy with adjuvant radio-chemotherapy. After 1.5 years, the patient presented to our Emergency Department with intermittent left-sided abdominal pain. Subsequent abdominal imaging (computed tomography scan, magnetic resonance imaging, positron emission tomography) determined a metabolically active splenic lesion with a central necrosis - signs of malignancy in line with a splenic metastasis. Presentation and discussion of the case within our interdisciplinary tumor board led to the decision of splenectomy followed by

Due to several factors such as its specific cellular and biochemical microenvironment, the spleen is not a pre-

Conclusions:

The collection and reporting of atypical clinical courses remains a key factor in precision medicine to enable

chemotherapy, a procedure that could be considered as therapeutic treatment in such exceptional cases.

the most evidence-based decision making in such cases.

**Keywords:** 

**Uterine Cervical Neoplasms • Spleen • Neoplasm Metastasis** 

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# **Background**

Clinical observations and reports of cervical carcinoma have a long historical tradition, ranging from the descriptions of Hippocrates and Aretaeus to Rigoni-Stern's studies of its prevalence in Italian nuns [1,2]. The collection of exceptional cases and clinical data of this neoplasm and its rare clinical presentations is therefore not only part of a historical-scientific continuity, but rather aims for potential evidence-based therapeutic and diagnostic decision making also in individual situations. Even though single cases in the literature report on the rare phenomenon of splenic metastasis from squamous epithelial tumors of the cervix uteri [3-6], a literature review (Medline, Scopus, Embase) resulted in solely 5 published cases of splenic metastasis of cervical adenocarcinoma [7-11]; for a comprehensive overview of published cases known to date see **Table 1** [12-26]. In the following case report, we present the clinical course of a 37-year-old female patient who was diagnosed with an adenosquamous carcinoma of the uterine cervix and a subsequent solitary splenic metastasis. To the best of our knowledge, this is the first description of a splenic metastasis of this distinct pathological entity. All details presented are in best alignment with the CARE writing guidelines [27,28].

### **Case Report**

We report on a 37-year-old female patient who presented to our clinic with repetitive intermediate vaginal bleeding as well as irregular contact bleeding during intercourse. An initial clinical examination confirmed a 3×3-cm large mass of the cervix uteri, and subsequent collection of biopsies determined the presence of a malignant cervical neoplasm. Further staging examinations resulted in the clinical suspicion of a FIGO IIA tumor; therefore, the indication for surgical staging and sentinel lymphonodectomy with consecutive histopathological examination of frozen sections was given. Due to a negative lymph node status, laparotomy with radical hysterectomy (Piver II-III) and bilateral salpingectomy was performed [29,30]. An acute diffuse intraoperative hemorrhage and an emerging hemorrhagic shock caused by a cefuroxime/gelafundin allergy required transfusion of packed red blood cells and fresh frozen plasma as well as abdominal packing with 3 lab sponges to control the hemorrhage; a 2-stage procedure with re-laparotomy allowed for removal of the intraabdominal lab sponges and concurrent oophoropexy prior to adjuvant radio-chemotherapy with cisplatin 40 mg/m<sup>2</sup>. The gross examination of the surgical specimen showed a beige-reddish, firm mass of the cervix uteri with a diameter of 4.2×3×4.2 cm, extending toward the isthmus uteri and affecting the right parametrium. The histopathological assessment of the specimen revealed an infiltrating epithelial neoplasm of the cervix uteri, forming both atypical glands as well as a solid growth pattern,

with densely packed eosinophilic cells showing keratinization (Figure 1). The moderately differentiated tumor cells displayed an increased nuclear-cytoplasmatic ratio, distinct nuclear atypia, and high rate of (partly atypical) mitosis. Further immunohistochemical analysis alternately stained the glandular (CK7, CEA, and PAX8 reactivity) and squamous (p40 reactivity) tumor aspects; only p16 showed cytoplasmatic reactivity in both morphological tumor components. In situ hybridization (INFORM HPV (human papillomavirus) III Family 16 Probe (B), Ventana Medical Systems, AZ, USA) of tumorous tissue fragments did not determine an oncogenic HPV type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, or 66 association. No veins, lymphatic vessels, nor adjunct nerves were affected, and all included lymph nodes (sentinel and non-sentinel) as well as resection margins were tumor free. Based on the WHO classification of female genital tumors (5th edition), the neoplasm was classified as an adenosquamous carcinoma of the uterine cervix, HPV negative [31,32]. In accordance with the TNM (tumor, node, metastasis) Classification of Malignant Tumors (8th edition), the tumor stage was: pT2b, pN0 (0/5; sn-), L0, V0, Pn0, R0, G3. Post-therapeutically, no local or distant tumor progression was determined in the subsequent standard follow-up-screenings but due to intra-abdominal adhesions and a resulting mechanical ileus, the patient underwent re-surgery with adhesiolysis and small bowel resection with sideto-side anastomosis.

After a progression-free survival of 1.5 years, the patient presented to the Emergency Department with intermittent left-sided abdominal pain. Consecutive abdominal computed tomography (CT) scans revealed a lesion with a central hypodense (necrotic) area within the mediodorsal area of the spleen (Figure 2A). Primary splenic tumors such as benign hamartoma or splenic angiosarcoma could already be ruled out after CT because of the extensive, but somehow well-circumscribed, necrotic area. For more precise diagnosis, magnetic resonance imaging (MRI) and positron emission tomography (PET) scans were performed and showed a capsulated lesion with an intense glucose metabolism at tumor margins and a central necrosis, aspects highly suspicious of splenic metastasis (Figures 2B, 2C and 3). On calculated ADC maps, the solid rim showed somewhat lower signal intensities correlating to a diffusion restriction, whereas the necrotic center displayed high signal intensities consistent with a T2 shine through. Since the rim comprised only a very narrow zone, measurement of ADC values was dispensed with and a visual evaluation was conducted instead. Subsequent discussion of the case in our interdisciplinary tumor board led to the decision of surgical metastasis removal, not only enabling further diagnostics and histopathological determination of the tumor origin, but also representing a potential therapeutic option in such a case. Accordingly, splenectomy was performed (Figure 4), and thorough pathological examination of all macroscopically

Table 1. Synopsis of published clinical cases of solitary splenic metastasis in patients with diagnosed primary carcinoma of the cervix

Author/Year of publication [ref]	Primary tumor entity/FIGO	Patient age	Metastatic symptoms	Diagnostics	Primary treatment	Secondary treatment of metastasis
Kumar et al [12] (2022)	SCC/ns	46	ns	PET scan, CT scan	Surgery, radiotherapy, chemotherapy	Surgery (splenectomy), adj. chemotherapy
AlQattan et al [7] (2021)	Adenocarcinoma/ IIIB	54	ns	MRI	Radiotherapy, chemotherapy	Surgery (splenectomy), adj. chemotherapy
Liu et al [13] (2021)	SCC/IIB	49	Anorexia, abdominal distension	CT scan; carcinoembryonic antigen, CA125, CA199 antigen levels	Radiotherapy, chemotherapy	Surgery (splenectomy), adj. chemotherapy
Shankar et al [14] (2020)	SCC/IVA	55	ns	PET scan, CT- guided biopsy	Radiotherapy, chemotherapy	Surgery (splenectomy)
Filipescu et al [15] (2018)	SCC/ns	30	ns	ns	Neoadjuvant radiochemotherapy, surgery	Surgery (splenectomy)
Bacalbasa et al [16] (2017)	SCC/IIB	31	ns	Diagnostic surgery	Neoadjuvant chemotherapy & radiotherapy, surgery	Surgery (splenectomy), adj. chemotherapy
Applebaum et al [17] (2017)	SCC/ns	46	ns	PET scan, CT scan	Surgery, radiotherapy,	Surgery (splenectomy)
Dixit et al [5] (2016)	SCC/IIA	46	Fever and anorexia	PET scan, CT scan	Surgery, radiotherapy, chemotherapy	Surgery (splenectomy, segmental resection of ileum, omentectomy and partial peritonectomy), adj. chemotherapy
Villalón-López et al [8] (2014)*	Adenocarcinoma/ IB	76	Abdominal pain	CT scan, CA-125 antigen levels	Surgery, radiotherapy	Surgery (splenectomy), adj. chemotherapy
Taga et al [4] (2014)	Undifferentiated carcinoma/IIB	49	ns	CT scan, explorative laparotomy	Radiotherapy, chemotherapy	Surgery (splenectomy), adj. chemotherapy
Zamurovic et al [18] (2011)	Planocellular carcinoma/IB	40	Abdominal pain, rice water stools	Ultrasonography, CT scan	Surgery, radiotherapy	Surgery (splenectomy)
Di Donato et al [19] (2010)	SCC/IVA	30	Abdominal pain	CT scan, PET scan, SCC antigen levels	Neoadjuvant chemotherapy, surgery	Surgery (splenectomy, distal pancreatectomy, and partial gastric resection), adj. chemotherapy
Kim et al [9] (2008)	SCC/IIB	54	No abdominal discomfort/mass	SCC antigen levels, CT scan, PET scan	Radiotherapy, chemotherapy	Surgery (splenectomy), adj. chemotherapy
Kim et al [9] (2008)	Adenocarcinoma/ IIB	46	No abdominal discomfort/mass	MRI	Radiotherapy, chemotherapy	Surgery (splenectomy), adj. chemotherapy

**Table 1 continued.** Synopsis of published clinical cases of solitary splenic metastasis in patients with diagnosed primary carcinoma of the cervix uteri.

Author/Year of publication [ref]	Primary tumor entity/FIGO	Patient age	Metastatic symptoms	Diagnostics	Primary treatment	Secondary treatment of metastasis
Bhardwaj et al [20] (2008)	SCC/IIB	50	Painful abdominal mass, intermittent fever	Ultrasonography, explorative laparotomy	Radiotherapy	Surgery (splenectomy)
Komatsu et al [21] (2004)**	SCC/ns	52	ns	CT scan	Surgery	Surgery (splenectomy)
Goktolga et al [22] (2004)	SCC/IIA	45	Abdominal fullness and pain	CT scan and fine needle aspiration	Surgery and adjuvant radiotherapy	Explorative laparotomy; chemotherapy due to multifocal tumor invasion
Pang LC [23] (2004)	SCC/IIA	50	ns	SCC antigen levels, CT scan, MRI, PET scan	Surgery and adjuvant radiotherapy	Surgery (splenectomy), adj. chemotherapy
Carvalho et al [24] (1997)	SCC/IIB	47	Pain of regio hypochondriaca; weight loss	Explorative laparotomy	Radiotherapy	Chemotherapy
Valls et al [7,10] (1992)	Adenocarcinoma/ ns	55	Abdominal pain	CT scan	Surgery, radiotherapy	Surgery (splenectomy)
Campagnutta et al [11] (1992)***	Adenocarcinoma/ ns	47	Abdominal pain	CT scan, scintigraphy	Surgery, radiotherapy	Surgery (splenectomy, adj. chemotherapy
Klein et al [3,25] (1987)	SCC/IIB	28	Abdominal pain	CT scan	Radiotherapy	Surgery, chemotherapy
Brufman et al [3,26] (1977) #	SCC/IB	43	ns	ns	Surgery	Chemotherapy

CT – computerized tomography; MRI – magnetic resonance imaging; ns – not specified; PET – positron emission tomography; SCC – squamous cell carcinoma. Additive splenic metastases as part of a disseminated disease were not considered. For an indepth analysis of splenic metastasis in case if squamous cell carcinoma of the cervix uteri, see also the comprehensive overview of Marcu et al [3] \* Spanish article with English abstract available. \*\* Japanese article with English abstract available. \*\*\* Italian article with English abstract available. # Article in Hebrew.

suspicious foci revealed the presence of a poorly differentiated carcinoma composed of solid nests of eosinophilic tumor cells with pleomorphic nuclei, distinct nucleoli, a high rate of atypical mitosis, and partly necrotic areas (Figure 5). The lesion was morphologically and immunohistochemically (strong nuclear immunoreactivity for p40 in all tumor cells) without glandular tumor components. Given the absence of glandular components, the history of a known adenosquamous carcinoma of the cervix uteri and no other site of squamous cell carcinoma in the extension workup, the diagnosis of a metastasis of an adenosquamous carcinoma in the form of a poorly differentiated squamous cell carcinoma well in line with the squamous component of the previously diagnosed epithelial tumor was made. Additional analysis of the metastatic tumor tissue showed a positive membranous PD-L1 expression in over 90% percent of the tumor cells (Tumor Proportion Score PD-L1: 90%, Cologne Score: 5). Re-evaluation within the tumor board review resulted in the recommendation of adjuvant chemotherapy (6 cycles of carboplatin AUC5, paclitaxel 175 mg/m², pembrolizumab 200 mg, and bevacizumab 15 mg/kg/KG intravenously every 3 weeks, followed by maintenance pembrolizumab 200 mg and bevacizumab 15 mg/kg/KG); at the time of publication the patient is under treatment and with no further evidence of local or distant metastasis for 10 months.

#### **Discussion**

Splenic metastases are rare per se [33] and a condition to which many different potential causes, such as mechanical aspects of the splenic anatomy (capsule), but also physiological aspects, namely a high concentration of resident phagocytes

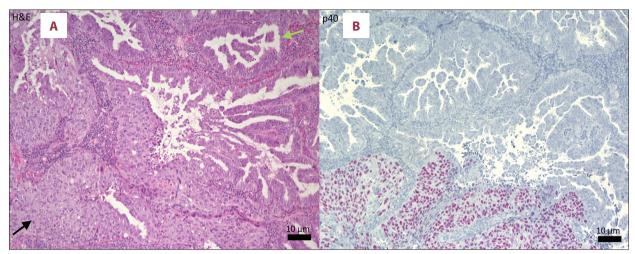


Figure 1. (A) Histological assessment of the cervical lesion showed an epithelial tumor consisting of both atypical glands (green arrow) and a solid growth pattern (black arrow). (B) Only the squamous tumor component showed immunohistochemical p40 reactivity.



Figure 2. (A) The portalvenous phase computed tomography scan showed a splenic lesion with a central hypodense area and a thick enhancing rim, while the adjacent adipose tissue is unremarkable. (B) The venous phase T1 fs magnetic resonance imaging (MRI) displayed a solid, strong enhancing rim of the splenic lesion with no hyperperfusion of the adjacent splenic tissue.

(C) Correspondingly, the T2w MRI (HASTE) showed a high signal center, indicating the necrotic area. The splenic lesion is marked by a blue arrow bar.

and a pro-apoptotic microenvironment, can contribute. So far, they appear either as a solitary metastasis or as part of a disseminated disease [34,35]. A hematogenous spread and subsequent extravasation/colonization of squamous cervical cancer cells in the splenic parenchyma have been rarely described in the literature [3,7], although the present case is, to the best of our knowledge, the first description of splenic metastasis of an uncommon cervical tumor entity, namely an adenosquamous carcinoma of the cervix uteri. Our patient's age was below the mean age of 46 years for patients with adenosquamous carcinoma of the cervix uteri [31]. In comparison to recent reports of splenic metastasis of squamous carcinomas of the cervix uteri, with more than 75% of patients older than 40 years [3], our patient was again somewhat younger, at 38 years old, when her abdominal metastasis was detected via abdominal imaging. Since imaging techniques are in general sensitive to detect malignant splenic lesions, adding 18F-fluorodeoxyglucose PET/CT may even improve the detection rate, as it proved diagnostically helpful also in our case; biopsy for diagnostic purposes should be reserved for lesions with unclear malignancy to rule out possible differential diagnoses, such as infectious causes or granulomatous diseases [12].

It is notable that solely the dedifferentiated squamous component of our reported adenosquamous neoplasm formed metastatic lesions, which is in line with single cases in the literature that described a change or a worse histological appearance of splenic metastasis tumors than that of the primary side tumors [5,16,19,20]. Nevertheless, initial diagnosis of adenosquamous carcinoma of the cervix uteri within the primary site required both malignant squamous and glandular components in routine hematoxylin and eosin sections as

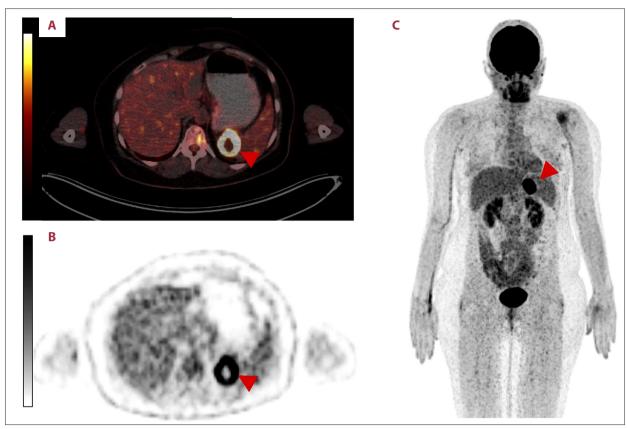


Figure 3. An intense circular uptake at the mediodorsal splenic pole (red arrowheads) can be seen in positron emission tomography/computed tomography (PET/CT) scan with [18F] FDG (179 MBq). (A) Exemplary transversal image of PET/CT fusion and (B) PET; (C) maximum intensity projection.

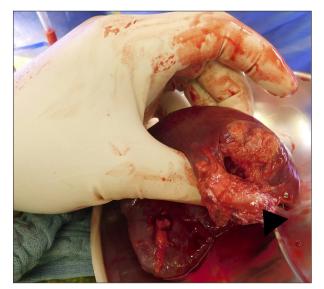


Figure 4. Intraoperative view of the mediodorsal area of the spleen. The gross pathological finding of a solid, irregularly shaped lesion with an inhomogeneous whitish-brownish appearance and a centrally softened consistency on the cut surfaces is highly suspicious for splenic metastasis (arrow-mark).

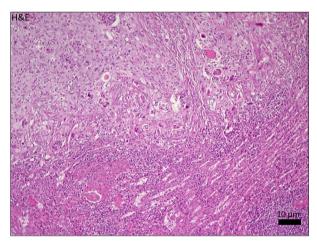


Figure 5. The histopathological examination after splenectomy revealed an epithelial lesion with pleomorphic nuclei and a high rate of mitosis diffusely infiltrating the local splenic parenchyma.

essential diagnostic criteria. The use of specific immunochemical methods could be helpful but is not mandatory for a definitive diagnosis. The preferably unimodal, therapeutic options of the primary tumor depend on the initial tumor stage and associated risk factors and provide a broad spectrum of possible treatment modalities (surgery/radio-chemotherapy) [29]; despite the existing potential therapeutic options for solitary splenic metastases [15], there is to date no evidencebased first-line therapy. In a recent literature review, Marcu et al highlighted the biological impact of splenectomy (diagnostic tissue assessment, prevention of local complications, such as rupture and thrombosis) and adjuvant chemotherapy (distant metastasis [5]) in solitary splenic squamous metastases, although the effect of surgery has been questioned in cases of disseminated disease [3,4]. In our review of cases of splenic metastasis of squamous cell carcinoma and adenocarcinoma of the cervix uteri, determination of explicit prognosis (5 to 30 months of median survival [7]) did not prove to be feasible, nor could correlation of clinical parameters and patient outcomes be made [3]. Since known survival data is based on tumor entities different from that in our presented case, explicit deduction remains questionable, especially since a prognostic evaluation of the primary tumor itself is largely unclear in case of adenosquamous carcinoma of the cervix uteri [31].

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#### **Conclusions**

We presented a splenic metastasis of an adenosquamous carcinoma of the cervix uteri, indeed a rare course of one of the most frequent malignancies in women. Especially in such rare clinical cases, further data collection and reporting remain key to gain experience, enabling evidence-based decision making in those rare cases as well.

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# **Declaration of Figures' Authenticity**

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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