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CASE REPORT

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The clinical course and management of cervical cancer with splenic metastasis: Case report and review of the literature

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Abstract

Adenovirus-mediated herpes simplex virus thymidine kinase gene therapy (ADV-TK) in combination with interventional treatment could relieve the symptoms in patients with widespread splenic metastasis.

KEYWORDS

ADV-TK, cervical cancer, chemotherapy, interventional therapy, splenectomy, splenic metastasis

1 | INTRODUCTION

We report a rare case of metastasis squamous cell cervical cancer to the spleen and outcomes of adenovirus-mediated herpes simplex virus thymidine kinase gene therapy (ADV-TK) intervention. ADV-TK, in combination with interventional treatment, could relieve the symptoms in patients with widespread metastasis.

Globally, cervical cancer represents one of the most common malignancies and is the third most common cause of cancer death among women.[1] Hematogenous spread is a rare pathway of dissemination and commonly involves the lungs, bones, or liver. Solitary splenic metastasis of solid tumors is rare. Splenic metastases from nonhematological malignancies are unusual, with an incidence of 0.6%-1.1% in carcinoma populations.[2] Metastasis from the cervix to the spleen is also very uncommon, with most cases found at autopsy. Spleen metastasis at autopsy is reported to be 1.6% to 30%.[3] We present a case report of splenic metastases in a patient with cervical squamous cell cancer. A literature review to describe the phenomena was also conducted to appropriately assess clinical features, treatment, and prognosis of splenic metastases.

Qing Liu and Ming Wang contributed equally to work.

2 | CASE PRESENTATION

A 49-year-old woman was diagnosed with squamous cell cervical cancer in 2009. At that time, she presented to another hospital with vaginal bleeding. Cervical biopsy revealed the presence of moderately to poorly differentiated squamous cell metaplasia, and lymphovascular space invasion (LVSI) was positive. Bimanual pelvic examination revealed a stage IIB cervical tumor according to the International Federation of Gynecology and Obstetrics (FIGO) criteria, as the cervical lesion extended to the left parametria. Treatment was initiated with radical radiotherapy with concurrent weekly chemotherapy. Subsequently, she received pelvic radiation included external beam radiation with 50 Gy and high dose rate intracavitary brachytherapy with 46 Gy. The patient suffered from radiation enteritis during her first month of therapy, which self-resolved. Upon completion of radiation therapy, MRI revealed near-complete remission, and cervical biopsy revealed cervical intraepithelial neoplasia I (CIN I). She was followed up regularly and remained in a stable condition for 5 years.

In 2014, sixty months after the diagnosis of cervical cancer, the patient presented to our hospital with left upper abdominal distension and anorexia. Pelvic examination revealed the upper part of the vagina has adhesions, and the cervix was invisible. No mass was palpated in the uterus or bilateral adnexa. Computed tomography (CT) scan showed a large splenic isolated wrapped hypodense lesion sized 5.0 × 6.5 cm. The levels of carcinoembryonic antigen (CEA), CA125, and CA199 were elevated to 70.3 ng/mL, 190.60 U/mL, and 37.99 U/mL, respectively. The squamous cell carcinoma antigen (SCCA) level of the patients was 0.3 ng/mL. An exploratory laparotomy was performed, and the spleen was removed (Figure 1A). Postoperatively, she underwent six adjuvant chemotherapy courses consisting of paclitaxel (145 mg/m^2/3 weeks, 230 mg) and cisplatin (75 mg/m^2/3 weeks, 120 mg). The tumor maker decreased to the normal range, and follow-up visits were conducted routinely. Follow-up at 34 months revealed no evidence of recurrence. Pathology results from the splenectomy were consistent with metastasis from cervical cancer (Figure 1B,C). Immunohistochemistry showed neoplastic cells diffusely expressing CK 5/6 and p16, suggesting squamous cell carcinoma associated with high-risk human papillomavirus.

In 2017, thirty-four months after remission, the levels of CEA, CA125, and CA199 were elevated to 55.31 μg/L, 50.87 μ/mL, and 105.20 μ/mL, respectively. PET/CT showed multiple metastases in the bilateral adnexa and inguinal region. She was retreated with six cycles of cisplatin and paclitaxel. After the chemotherapy, the tumor makers decreased the normal level (Figure 2). In 2018, seven months after the chemotherapy, she complained of anorexia, and CT/MRI

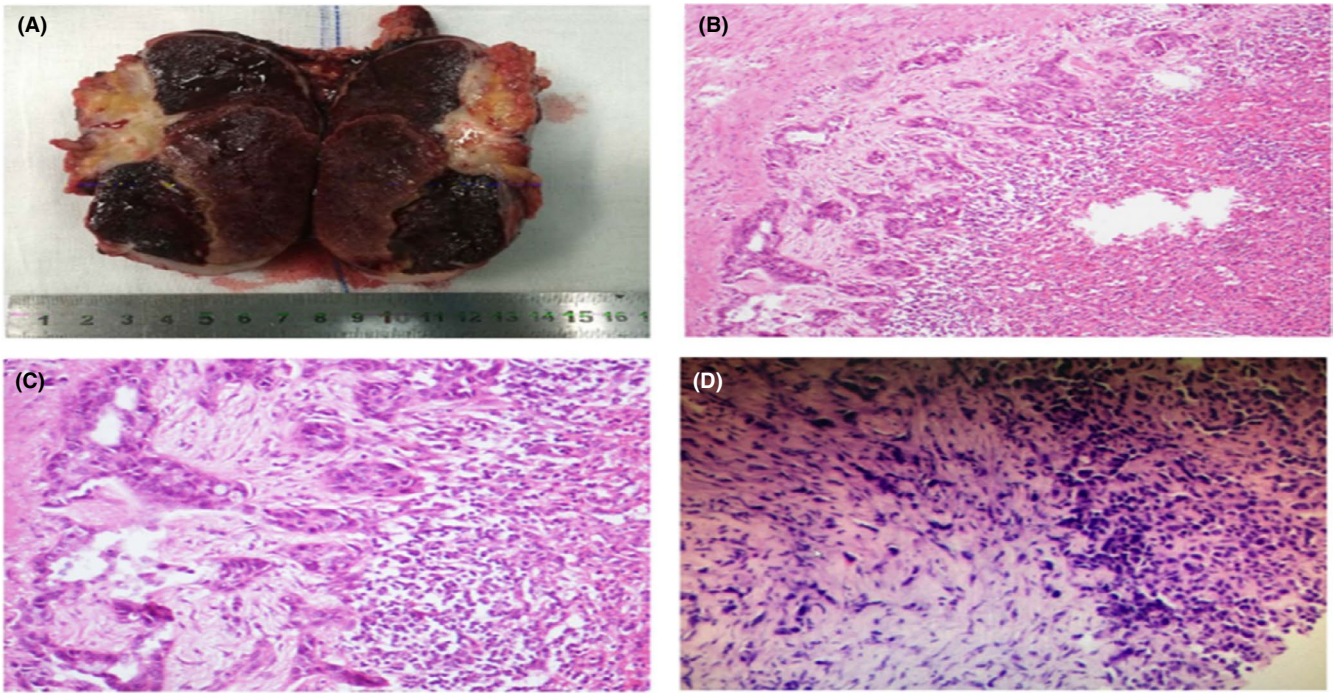

FIGURE 1 Gross pathology of the spleen, microscopic examination of the spleen and liver. A, The specimen of splenectomy is transected: apparition of a large tumor lesion at the upper pole of the spleen. B, Microphotography showing neoplastic cell proliferation organized in nests of tumor cells, within the Spleen tissue in hematoxylin-eosin staining (4 × 10). C, Microphotography showing neoplastic cell proliferation organized in nests of tumor cells, within the spleen tissue in hematoxylin-eosin staining (20 × 10). D, Liver biopsy showing squamous cell in hematoxylin-eosin staining (20 × 10)

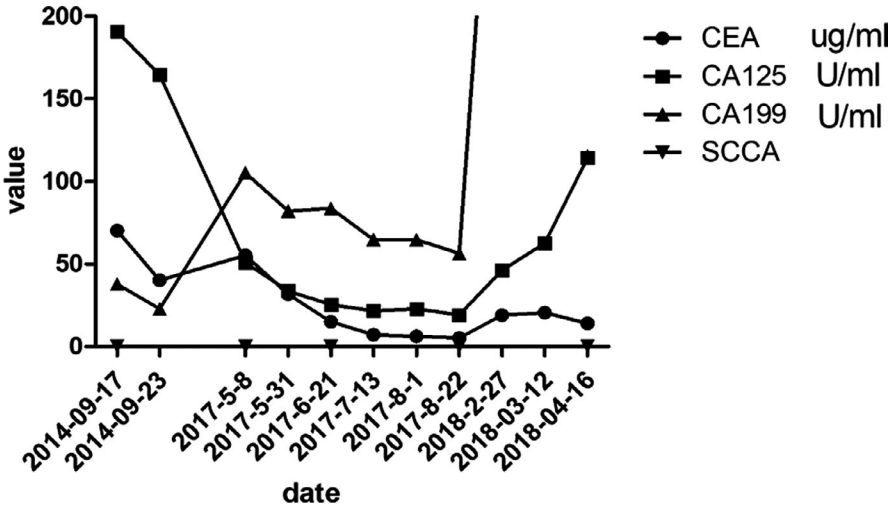

FIGURE 2 The changes in tumor marker levels during the course of treatment

revealed multiple metastases in the left lobe of the liver, the hilar bile duct, and the right septum. Liver biopsy confirmed liver metastasis (Figure 1D).

She received adenovirus-mediated herpes simplex virus thymidine kinase gene therapy ADV-TK (Tian Dakang Co.) treatment for liver metastasis; a total of 1×10^{12} viral particles of ADV-TK were administered. Systemic ganciclovir therapy was delivered at a dose of 5 mg/kg, every 12 hours at 36 hours after ADV-TK therapy for 10 days. Subcutaneous, transcutaneous biliary drainage (PTCD) and transcatheter arterial chemoembolization under the surveillance of DSA (digital subtraction angiography) were concurrently conducted on account of biliary tract obstruction. The patient's clinical symptoms improved, and the jaundice was alleviated.

In 2018, one hundred and six months after the diagnosis of cervical cancer and 46 months after the diagnosis of splenic metastasis, unfortunately, she developed a fever that persisted for 1 month, and the venous culture access port revealed Candida Albicans infection. A biliary stent was placed for biliary infection. Due to multiple organ dysfunction syndrome causing by cachexia and infection, she expired 46 months after the diagnosis of splenic metastasis.

3 | DISCUSSION

As a part of the reticuloendothelial system, the spleen is a common organ involved in hematogenous spreading cancer metastases but should be rare for a nonhematogenous spreading cancer such as cervical cancer. As reported in the literature, the incidence of splenic metastases from cervical cancer ranged from 1/92 to 8/108 in autopsy cases.[4] To the best of our knowledge, only 17 cases of splenic metastasis resulting from cervical cancer have been reported in the literature (Supplementary Table S1), including ours.[5-15] The stages of the 17-splenic metastasis retrieved from the literature were as follows: 11.76% (2/17) in stage IB, 23.53% (4/17) in stage IIA, 47.06% (8/17) in stage IIB, 5.88% (1/17) in stage IIIB, and 5.88%(1/17) in stage IVA. Based on this, splenic metastasis in cervical cancer was more likely to occur in stage IIA or IIB. This may be explained by early-stage disease (stage I) being more curable with effective treatment and stage III to IV dying of more common relapses or metastasis. Nine of 17 patients presented with chief complaints of fullness or pain in the left hypochondriac region. Two cases have the elevation of the level of the SCC antigen before the diagnosis of splenic metastasis. Three cases were discovered through routine imaging (CT, MRI, and PET-CT). Before the hospitalization for splenic metastases, our patient had abdominal pain and fullness for 6 months, and the SCC antigen ranged from 0.3 to 0.6 ng/mL after the diagnosis of splenic metastasis. SCC elevation can predict the clinical diagnosis of cervical cancer relapse in 46%-92% of cases, with a mean lead time ranging from 2 to 7.8 months.[16] Therefore, routine surveillance of the SCC antigen and imaging modalities such as CT, MRI, and PET-CT may aid in the early diagnosis.

Splenic metastases from cervical carcinoma are divided equally between metastases as a part of the disseminated disease and solitary metastases.[17] Among the 17 patients, eight patients were isolated splenic metastasis, and nine splenic metastases from cervical cancer were multiple metastases. In the multiple metastases patients, four cases have other distant metastases: left supraclavicular node, femoral region, vertebrae, and right humerus, and breast, and advanced cervical. The common sites of multiple metastases were the pancreas (4 cases), followed by liver (2 cases), stomach (2 cases), and adrenal (2 cases). In the multiple metastases patients, four cases expired in 12 months after receiving chemotherapy without any surgery. Splenectomy is an appropriate treatment for local disease control and can help with the diagnosis using histopathology. Splenectomy can also prevent the splenic metastasis from being a source of further metastasis disease, particularly in patients with a solitary lesion or multiple lesions without the widespread

disease.[18] Cisplatin/Paclitaxel combination is one of the treatments of recurrent or metastatic cervical cancer.[19] Among the 17 patients, 11 patients received chemotherapy platinum-based. In our case, a combination regimen of cisplatin and paclitaxel was able to control but not stop the recurrence based on tumor marker changes. The diagnosis of liver metastasis changed the required therapy to an interventional treatment in combination with ADV-TK therapy. The patient's quality of life was improved, and the jaundice was relieved. In a trial by Li et al, ADV-TK treatment showed an increased survival rate in nonvascular hepatocellular cancer patients who received liver transplantation and ADV-TK/ganciclovir adjuvant gene therapy. The 3-year overall survival (OS) rate was 100%, and the recurrence-free survival (RFS) rate was 83.3%.[20] The use of both interventional treatment and ADV-TK treatment showed a 3-month improvement in liver function and quality of life in our patient, but eventually, the patient died of infection and cachexia.

The median survival time from diagnosis of splenic metastases to the literature published varied from 5 to 30 months (15.86 ± 7.95 months) in solitary metastasis patients. In widespread cases, the median survival time varied from 3 to 12 months (7.50 ± 5.20 months). Of these, 12 have been due to squamous cell carcinoma, two from adenocarcinoma, and one from an adenosquamous carcinoma. The patients with solitary metastasis seemed to be younger than multiple metastases 43.22 ± 9.52 vs 46.75 ± 7.96. The disease-free interval was 40.25 ± 22.18 months in the former group and 27.44 ± 15.09 months in the latter. During the primary treatment before solitary splenic metastasis, 37.5% (3/8) had surgery only, 37.5% (3/8) had surgery and radiation, and 25% (2/8) had radiation alone. In the multiple metastases, 22.2% (2/9) had surgery only, 33.3% (3/9) had surgery and radiation, and 44.4% (4/9) had radiation alone; the meantime of follow-up was 6.33 ± 4.41 months, which was shorter than in solitary metastases (17.00 ± 13.68 months). More cases seemed to receive surgery rather than radiotherapy in the solitary splenic metastasis group. The relatively long disease-free interval and the isolated nature of recurrence might suggest those patients' less aggressive nature. Because our case underwent the surgical excision followed by chemotherapy of metastatic splenic lesions, the patient lived more than 36 months. Further investigation is necessary to establish the biological and chemical differences between the two group patients.

In conclusion, cervical cancer rarely culminates in splenic metastases. Although rare, the metastasis of this case followed a classic sequence from the primary site cervix to bilateral adnexa through invasion, to inguinal node through the lymphatic duct, to splenic and liver parenchyma through hematogenous spread. The majority of splenic metastasis was seen in stages from IB to IIB. Solitary metastasis might have some different characteristics from multiple metastases, which may necessitate adequate treatment. In solitary tumors, radical treatment could achieve a more prolonged remission. ADV-TK, in combination with interventional treatment, could relieve the symptoms in patients with widespread metastasis. Our patient had a long response time, which indicates the inadequate capacity of proliferation and immune escape of tumor cells. Further research is warranted to prevent the anaplasia of tumors with the ability of rapid proliferation, invasion, and metastasis. The use of bevacizumab or PD-1/PDL-1 inhibitors 21 might contribute to more prolonged remission or improvement.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

QL: proposed the concept and collected the data. QL and MW: performed the literature research. MW, QL, and CQP: analyzed and interpreted the data. QL and MW: wrote the first draft with guidance from CQP. CQP and VG: revised the manuscript. All authors reviewed and approved the final version of the manuscript. CQP: communicated with the journal and addressed the reviewers' comments.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Our Institutional IRB approved the current study.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report. Consent was also obtained from the patient's legal representative (Husband) after her death for the publication of the case report. The copies of the aforementioned two written consent forms are available for review by the journal editors if requested.

DATA AVAILABILITY STATEMENT

The source documents are available in our division for verifying all data presented in the current report.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA: A cancer Journal for Clinicians*. 2015;65(1):5-29.
2. Lam K, Tang V. Metastatic tumors to the spleen: a 25-year clinicopathologic study. *Arch Pathol Lab Med*. 2000;124(4):526-530.
3. Rappaport H. Tumors of the hematopoietic system. Atlas of tumor pathology, 1966.
4. Lam KY, Tang V. Metastatic Tumors to the Spleen. *Arch Pathol Lab Med*. 2000;124(4):526-530.
5. Brufman G. Solitary metastatic involvement of the spleen in squamous cell carcinoma of the cervix. *Harefuah*. 1977;92:349-350.
6. Carvalho L, Azevedo I, Salgado L, et al. Squamous cell carcinoma of the cervix metastatic to the spleen—case report. *Gynecol Oncol*. 1997;67(1):107-110.
7. Goktolga U, Dede M, Deveci G, et al. Solitary splenic metastasis of squamous cell carcinoma of the uterine cervix: a case report and review of the literature. *Eur J Gynaecol Oncol*. 2004;25(6):742-744.
8. Pang LC. Solitary recurrent metastasis of squamous cell carcinoma of the uterine cervix in the spleen: case report. *South Med J*. 2004;97(3):301-304.
9. Gupta T, Nair N, Fuke P, Bedre G, Basu S, Shrivastava SK. Splenic metastases from cervical carcinoma: a case report. *Int J Gynecol Cancer*. 2006;16(2):911-914.
10. Di Donato V, Palaia I, Perniola G, et al. Splenic metastasis from cervical cancer: case report and review of the literature. *J Obstet Gynaecol Res*. 2010;36(4):887-890.
11. Zamurovic M, Pesic-Stevanovic I, Perisic Z. Rare metastases of carcinoma of uterine cervix. *Eur J Gynaecol Oncol*. 2011;32(5):594-596.
12. Taga S, Sawada M, Nagai A, Yamamoto D, Hayase R. Splenic metastasis of squamous cell carcinoma of the uterine cervix: a case report and review of the literature. *Case Rep Obstet Gynecol*. 2014;2014:1-4.
13. Aitelhaj M, Khoyaali SL, Boukir A, et al. Breast and splenic metastases of squamous cell carcinoma from the uterine cervix: a case report. *J Med Case Rep*. 2014;8(1):359.
14. Dixit J, Mohammed N, Shetty P. Splenic metastasis from cancer of uterine cervix—A rare case. *Indian J Surg Oncol*. 2016;7(4):479-483.
15. Bacalbasa N, Balescu I, Marcu M, Oprescu DN, Anca AF. Solitary splenic metastasis after surgically-treated cervical cancer–a case report and literature review. *Anticancer Res*. 2017;37(5):2615-2618.
16. Gadducci A, Tana R, Fanucchi A, Genazzani AR. Biochemical prognostic factors and risk of relapses in patients with cervical cancer. *Gynecol Oncol*. 2007;107(1):S23-S26.
17. Piura E, Piura B. Splenic metastases from female genital tract malignancies. *Harefuah*. 2010;149(5):315-320, 335, 334.
18. Piura B, Rabinovich A, Apel-Sarid L, Shaco-Levy R. Splenic metastasis from endometrial carcinoma: report of a case and review of literature. *Arch Gynecol Obstet*. 2009;280(6):1001-1006.
19. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2009;27(28):4649.
20. Li N, Zhou J, Weng D, et al. Adjuvant adenovirus-mediated delivery of herpes simplex virus thymidine kinase administration improves outcome of liver transplantation in patients with advanced hepatocellular carcinoma. *Clin Cancer Res*. 2007;13(19):5847-5854.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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