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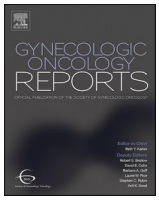

Case report

A rare case of cardiac metastasis of squamous cell carcinoma of the cervix with a review of existing case reports and treatment modalities

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1. Introduction

We present the case of squamous cell carcinoma (SCC) of the uterine cervix metastasizing to the heart, which is an incredibly rarer occurrence. In one systemic review, there were only 12 published cases of SCC of the cervix metastasizing to the heart between 2004 and 2014 (Takeda et al., 2014). Prognosis associated with such a tumor is very poor, with case reviews showing a median survival of 3.5–6.0 months after diagnosis of cardiac metastasis, and over 90 % of patients reportedly have died within 1 year of diagnosis (Takeda et al., 2014; Tsuchida et al., 2016; Kapoor et al., 2016). Because of the rarity of the tumor and the clinical complexity of each case, there is no standardized approach to treatment of patients with cardiac metastasis of cervical SCC, and it is controversial if aggressive treatment improves survival (Meng et al., 2022; Kasai et al., 2020; Lemus et al., 1998). In addition to presenting this rare clinical case, we also review treatment modalities utilized in previously published cases and discuss new treatment modalities as potentially prolonging survival.

2. Case

We present the case of a 49-year-old patient with Stage IIIC2(r) HPV-associated squamous cell carcinoma (SCC) of the cervix with recurrence presenting as a distant cardiac metastasis noted on surveillance imaging.

The patient initially presented to care at 47 years of age with multiple years of post-coital spotting. She had not seen a provider in 16 years, and her history was notable for a 10 pack-year smoking history. Physical exam at the time of presentation revealed a 3 cm fungating mass on the anterior lip of cervix with no evidence of parametrial or rectovaginal septum involvement on bimanual exam. Workup revealed invasive squamous cell carcinoma with positron emission tomography–computed tomography (PET-CT) demonstrating metastatic periaortic lymph nodes, consistent with FIGO Stage IIIC2(r) disease. She underwent treatment with curative intent with cisplatin and radiation. The addition of Pembrolizumab as a first-line therapy (as supported by Keynote-826 which had been published approximately a month prior to her diagnosis) was not recommended in this patient as she was undergoing curative-intent radiation therapy with extended field pelvic brachytherapy with tandem, ovoids and interstitial therapy, which was an exclusion criterion for Keynote (Colombo et al., 2021).

Approximately 9 months after completing definitive treatment, surveillance imaging showed new mediastinal lymphadenopathy with 18F-fluorodeoxyglucose (FDG) avidity of the right atrium as well, concerning for cardiac metastasis. She had no cough, chest pain, or shortness of breath, but did note increased “chest pressure” that she had attributed to anxiety. Biopsy of this mediastinal lesion confirmed metastatic disease, and cardiac MRI confirmed a right atrial mass, measuring 4.1 x 3.0 x 5.5 cm that invaded into the right ventricle and encapsulated the right coronary artery.

Her case was extensively discussed with gynecologic oncology, radiation oncology, cardiac oncology, and cardiothoracic surgery, and given her poor prognosis overall and morbidity of surgery, the decision was made to offer palliative chemoradiation rather than surgical excision of the tumor.

While receiving radiation treatment, she presented to the Emergency Department with palpitations and near-syncope. Echocardiogram revealed a large pericardial effusion with tamponade physiology, which was treated with pericardiocentesis. Cytology of pericardial fluid showed metastatic squamous cells consistent with SCC of the cervix. After stabilization, she completed radiation therapy to the heart, receiving a total dose of 3,000 cGY divided into 10 fractions. Her pericardial effusion reaccumulated, and she required a subxiphoid pericardial window to prevent re-accumulation.

After radiation, she received treatment with carboplatin, paclitaxel, and bevacizumab, a standard second-line therapy supported by the GOG-240 protocol which uses a similar platinum-based regimen (Tewari et al., 2014). She did not receive bevacizumab for the first 3 cycles of chemotherapy to promote wound healing given her recent subxiphoid

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pericardial window. Additionally, due to chemotherapy-induced thrombocytopenia, she received delayed carboplatin and paclitaxel for several cycles. After 6 cycles, unfortunately a PET-CT showed an increase in size of mediastinal lymphadenopathy as well as increased FDG avidity within the right atrium.

Molecular testing of the patient's tumor showed Programmed Death-Ligand 1 (PD-L1) positivity with a Combined Positivity Score of 3. After consultation with cardio-oncology, the recommendation was made to proceed with pembrolizumab. She received 3 cycles every 21 days of pembrolizumab. Following pembrolizumab, 9 months after diagnosis of the cardiac metastasis, the patient began to have a new symptom of chest wall and rib tenderness, and imaging again showed progression of disease with new metastasis to the lungs and soft tissues of the chest wall. Given the progression, the patient was recommended tisotumab vedotin as the next treatment option. She completed 3 cycles of tisotumab vedotin every 21 days and follow up imaging again showed progression of disease with new hepatic metastasis.

At the time of this writing, more than 16 months after diagnosis of her cardiac metastasis, the patient has opted to trial a second treatment with carboplatin, paclitaxel, and bevacizumab, and she is being considered for clinical trials. From a cardiac standpoint, her pericardial effusion has not re-accumulated following her pericardial window, and despite the tumor encasing the right coronary artery, she has never developed anginal symptoms. However, Cardiac MRI has revealed the development of heart failure with the patient's ejection fraction decreasing from 59 % to 47 %. Subjectively, while the patient's rib pain has continued to worsen, she has continued to maintain a high quality of life.

3. Discussion

This is a case of a 49-year-old female with recurrent Stage IIIC2(r) squamous cell carcinoma with metastasis to the heart who continues to maintain a high quality of life 16 months after diagnosis of cardiac metastasis. To our knowledge, this represents the longest documented survival of any patient following diagnosis of cardiac involvement of SCC of the cervix.

In general, the heart is a relatively uncommon site of metastasis for cancers, with post-mortem examinations showing that approximately 7–9 % of all patients with a known cancer diagnosis have a cardiac metastasis (Bussani et al., 2007; Lichtenberger et al., 2016). Lung cancers, breast cancer, melanoma, and leukemia/lymphomas are among the most common cancers to metastasize to the heart (Bussani et al., 2007; Lichtenberger et al., 2016; Al-Mamgani et al., 2008). However, as cancer treatments prolong life expectancy and surveillance modalities become more robust, the incidence of cardiac metastasis is increasing (Bussani et al., 2007; Al-Mamgani et al., 2008). Among patients with metastatic melanoma for example, 28–64 % of post-mortem examinations display cardiac involvement of the disease (Balinski et al., 2023).

Multiple other publications have included reviews of available cases on cardiac metastasis of cervical cancer and have summarized findings such as the most common presenting symptom, imaging modalities, and mortality (Takeda et al., 2014; Tsuchida et al., 2016; Lichtenberger et al., 2016; Okamoto et al., 2015; Senzaki et al., 1999). Here we will review the treatment modalities utilized for cardiac metastasis of cervical cancer and the survival time from diagnosis of cardiac metastasis. As denoted in Table 1, cytotoxic chemotherapy is the most common method of treatment used, with 14/24 (58.3 %) of documented receiving some form of cytotoxic chemotherapy. 9/24 (37.5 %) of patient cases used each radiation therapy or surgical excision. 12/24 (50 %) of cases used a multimodal approach to treatment, employing a combination of chemotherapy, radiation, or surgery. 2/24 (8.3 %) of patients declined any therapy, and 3/24 (12.5 %) of patients demised before treatment could be initiated.

On review of available case reports, surgery was most often used in patients who either presented with acute cardiac complaint

Table 1
Published cases of cardiac metastasis of SCC of the cervix with review of treatment modalities and months to mortality.

Reference	Year	Age	Stage*	Treatment	Time to Death**
Al-Ebrahim (Al-Ebrahim, 2013)	2013	22	IVB	-Surgical excision -Chemotherapy, unspecified -Radiation	>6
Borsaru (Borsaru et al., 2007)	2007	42	IVB	-Surgical excision	Unknown
Byun (Byun et al., 2013)	2013	32	IIA2	Surgical excision -Chemotherapy: carboplatin, paclitaxel	13
Ferraz (Ferraz et al., 2006)	2006	63	Unknown	-Surgical excision	~5
Feys (Feys et al., 2005)	2005	37	IIIb	-Radiation -Chemotherapy: cisplatin, ifosfamide, 5-Fluoruracil	>8
Han (Han et al., 2017)	2017	44	IVB	-Surgical resection -Chemotherapy: paclitaxel and cisplatin	15
Helm (current case)	2023	49	IIIC2	-Radiation -Chemotherapy: carboplatin, paclitaxel -Biologic: bevacizumab, pembrolizumab, tisotumab vedotin	>16
Iwaki (Iwaki et al., 2001)	2001	49	IVB	Unspecified	Unknown
Kalvakuri (Kalvakuri et al., 2016)	2016	49	IVB	None	<1
Kapoor (Kapoor et al., 2016)	2016	35	IIB	-Chemotherapy, unspecified	>3
Kasai (Kasai et al., 2020)	2020	52	IVB	-Surgical resection -Chemotherapy: cisplatin -Radiation	>12
Lemus (Lemus et al., 1998)	1998	53	IB	-Chemotherapy: cisplatin -Radiation	1
Lemus (Lemus et al., 1998)	1998	49	IIIB	-Chemotherapy: cisplatin, 5-FU -Radiation	13
Meng (Meng et al., 2022)	2022	35	IIIC1	-Chemotherapy, unspecified	Unknown
Nakao (Nakao et al., 2006)	2006	57	IIIB	-Surgical resection -Patient declined further therapy	2
Nesser (Nesser et al., 2006)	2006	81	Unknown	None	<1
Okamoto (Okamoto et al., 2015)	2015	27	Ib1	-Patient declined therapy	<1
Saitoh (Saitoh et al., 2005)	2005	68	IIIB	-Surgical resection -Chemotherapy, regimen unspecified	5
Sasidharan (Sasidharan et al., 2016)	2016	47	IIIB	-Patient declined therapy	11
Schawkat (Schawkat et al., 2014)	2014	33	IIB	-Chemotherapy, unspecified	Unknown
Senzaki (Senzaki et al., 1999)	1999	28	IB	-Chemotherapy, unspecified -Radiation	6

(*continued on next page*)

Table 1 (*continued*)

Reference	Year	Age	Stage*	Treatment	Time to Death**
Takeda (Takeda et al., 2014)	2014	48	IIA2	-Surgical resection -Chemotherapy: carboplatin, paclitaxel -Radiation	>5.5
Togo (Togo et al., 2013)	2013	39	IIA	-Radiation	12
Tsuchida (Tsuchida et al., 2016)	2016	78	IIIB	None	1

*Stage – Stage is reported as-written in publication, and not updated to reflect 2018 Updated FIGO Staging.
**Time to Death – measured in months. If time to death is indicated with a ">", this indicates the case report was published prior to demise.

necessitating life-saving surgery, or as a means of palliation. This differs from the treatment of cardiac metastasis from other tumors such as melanoma, where surgery is employed for more than half of patients because remission has been achieved among patients with cardiac involvement of melanoma following aggressive multimodal treatment (Balinski et al., 2023). For patients with cervical cancer, however, remission following cardiac metastasis has never been documented. While data is too sparse and the clinical cases too varied to draw any confident conclusions on effectiveness of different treatment modalities among cervical cancers, interestingly, no other publications have reported utilizing biologic therapies for treatment of cardiac metastasis of SCC of the cervix.

There are multiple biologic immunotherapies approved for cervical cancer. Bevacizumab is a VEG-F inhibitor that was approved by the Food and Druga Administration in 2014 for use in recurrent cervical cancer (Tewari et al., 2014), and Pembrolizumab is approved for use in advanced cervical cancer among patients with programmed death ligand-1 (PD-L1) positive tumors (Colombo et al., 2021). More recently, in 2021 tisotumab vedotin was approved for cervical cancers as a combination of a monoclonal antibody against tissue factors and a drug that inhibits cell division (Coleman et al., 2021). In the present case, all available biologic agents approved for cervical cancer were utilized, and the patient has maintained a remarkable quality of life despite her advanced disease. Multiple factors likely contribute to this, including the early recognition of her cardiac disease during surveillance imaging and her desire for aggressive treatment where other patients may have declined further therapy, however it is quite possible the use of biologic has improved her outcomes, and should be considered in other patients with a similar presentation.

All authors declare that they have no conflicts of interest.

Written informed consent was obtained from the patient prior to publication of this report.

CRediT authorship contribution statement

Eric D. Helm: Writing – original draft, Investigation, Data curation. **Saketh R. Guntupalli:** Writing – review & editing, Conceptualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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