Management of Epicardial Metastasis in Breast Cancer

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Rezumat

Managementul terapeutic al metastazelor epicardice în cancerul de sân

Context: Metastazele cardiace pot fi întâlnite mai frecvent decât tumorile cardiace primare. Sunt descoperite la autopsii cu o incidență cuprinsă între 1,5 - 20%. Tumorile primare care generează metastaze cardiace sunt melanoamele, limfomul, tumorile pulmonare, esofagiene și de sân. Cel mai afectat organ este pericardul (62-81%). În 90% din cazuri din punct de vedere clinic, acestea sunt în general silențioase. În cazul pacientelor diagnosticate cu neoplasm de sân și care au fost supuse radioterapiei, diagnosticul diferențial cu fibroză după radioterapie interferează. Tratamentul este paliativ și trebuie administrat în funcție de localizarea primară a tumorii și de statusul de performanță al pacientei

Prezentare de caz: În lucrarea de față vă prezentăm cazul unei paciente în vârstă de 73 de ani diagnosticată și tratată pentru un neoplasm de sân în 2006. După o perioadă de timp, 9 ani, în 2015 pacienta este diagnosticată cu determinarea secundară osoasă sternală pentru care a efectuat ședințe de radioterapie și pentru care se inițiază tratament hormonal. În 2018, pacienta a efectuat evaluare imagistică de etapă care a relevat continuarea de evoluție a bolii prin metastaze pulmonare. La momentul perioadei de urmărire a bolii, efectuată în 2020, este observată din nou o continuare a evoluției bolii, de această dată prin determinări secundare epicardice.

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Concluzie: Metastazele cardiace sunt rare și, în majoritatea cazurilor, sunt silențioase. Incidența s-a modificat datorită opțiunilor de tratament și a investigațiilor imagistice performante. Radioterapia stereotactică poate fi considerată o opțiune terapeutică în cazurile cu status de performanță bun și pentru pacienții diagnosticați cu boală oligometastatică.

Cuvinte cheie: neoplasm sân, metastaze epicardice, radioterapie, chirurgie, chimioterapie

Abstract

Background: Cardiac metastasis may be encountered more frequently than primary cardiac tumors. They are discovered at autopsies with an incidence between 1.5 – 20%. The primary tumors that generate cardiac metastasis are malignant melanomas, lymphoma, the lungs, the breast, the esophagus. The organ most affected is the pericardium (62-81%). In 90% of cases from a clinical point of view, they are generally silent. In the case of patients diagnosed with breast cancer and who have undergone radiotherapy, differential diagnosis with fibrosis post radiotherapy interferes. The treatment is palliative and should be administered according to the primary location of the tumor and the patient's performance status.

Case presentation: We are presenting the case of a 73-year-old diagnosed and treated for a breast neoplasm in the left breast in 2006. After a period of time of 9 years, the patient presents secondary sternal bone determination, radio-treated and for which she once again goes under hormonal therapy. In 2018, patient performed an imaging evaluation that revealed lung metastases. At the moment of stage review, performed in 2020, secondary epicardial determinations are noted. We present the case, the therapeutic management, diagnostic procedures and treatment and also, we discuss the data from literature.

Conclusion: Cardiac metastases are rare and in most cases are silent. The incidence has changed due to treatment options and imaging investigations. Stereotactic body radiation therapy can be considered a therapeutic option in the cases with good performance status and with oligometastatic disease.

Key words: breast tumor, epicardial metastases, radiotherapy, surgery, chemotherapy

Introduction

Cardiac metastasis are more frequent than primary cardiac tumors. They are discovered at autopsies in a percentage between 1.5 – 20%. The primary tumors that metastasize in heart area are malignant melanomas, lymphoma, the lungs, the breast, the esophagus (1). The most affected organ is the pericardium (62-81%). From a clinical point of view, in almost 90% of cases, they are generally silent (2).

In the case of breast cancer, differential diagnosis is difficult and might be confused with fibrosis post radiotherapy. The treatment is palliative and should be administered

according to the primary location of the tumor and the patient's performance status. Primary or metastatic cardiac tumors are rare, but when malignant, they have poor prognosis (3).

The incidence of heart metastases is increasing, reaching just over 10%. Neoplasms that metastasize to the heart can be divided into three categories of incidence: (1) primary tumors that have a high rate of metastasis to the heart including malignant melanoma, germ cell malignancy, malignant thymoma, (2) malignant tumors with an intermediate rate of cardiac metastasis, and represents the highest number of cardiac metastases (carcinoma of the stomach, liver, ovary, colon and rectum), (3) tumors that rarely metastasize to the

heart. There are four ways in which non-cardiac tumors can invade the heart: direct mediastinal infiltration of heart tissue in lung cancer, breast cancer or mediastinal lymphoma, hematogenous spread through systemic tumors, such as malignant melanoma, lymphoma, leukemia, or sarcoma, venous spread from the inferior vena cava in the case of renal or liver tumors and from the pulmonary vein in the case of lung cancer; and the last mode of invasion represented by lymphatic spread (4,5).

Case Presentation

We present a case of breast cancer in a female patient, 73 years old, with heart metastases developed after 14 years from diagnosis and treatment of the primary tumor. The patient's past medical history was significant for a left-sided total mastectomy with axillary dissection for carcinoma in 2006, in the Institute of Oncology Bucharest; histological diagnosis was well-differentiated ductal invasive carcinoma of the breast.

The patient was staged as ypT1aN2M0, 8 lymph nodes were positive; Immunohistochemistry (IHC) revealed: positive estrogen receptors (ER+) 40%, positive progesterone receptors (PR+) 5%, human epidermal growth factor receptor 2 (HER-2/neu) was negative and proliferation index Ki 67 was 15%.

At that time, she underwent chemotherapy (3 cycles, protocol AC: doxorubicin/ciclofosfamide) and adjuvant radiation therapy (RT), total dose (TD)= 50Gy/ 25 fractions on target volumes: chest wall, axillary lymph nodes (level I, II, III), and supraclavicular lymph nodes, at Sf. Apostol Andrei Emergency Clinical Hospital of Galați, Department of Radiotherapy; also, she received hormonal therapy with aromatase inhibitors, letrozole during 2005-2013.

Disease free survival was 9 years. In May 2015, the patient was diagnosed by bone scintigraphy with unique sternal bone metastases which were treated by radiotherapy TD=37.5 Gy/15 fractions, 2.5Gy/ fraction with good clinical outcome.

Subsequently, she was treated with another hormone treatment regimen, tamoxifen for three years. Between 2015 and 2017, periodic evaluations revealed tumor regression without new metastases. In 2017, on a regular oncological follow-up with computed tomography scan (CT) the patient was diagnosed with pulmonary nodes in the left lung lobe (LSS) 6/15mm, and tumors marker carbohydrate antigen 15-3(CA 15 - 3)=30.51U/ml. In December 2017, after performing the PET-CT that identified two subpleural nodules (8-10 mm) located in the left cardio-phrenic angle with FDG uptake (SUV max 4.1) for which the atypical resection was performed in January 2018 at Marius Nasta Institute of Pneumology. The histopathological report was carcinomatous tumor proliferation, without infiltration of the visceral pleura (PL0), lymphatic invasion present (L1), vascular invasion present (V1), and IHC test revealed ER 30%, HER2 overexpression, KI 67 20%, chromogenic in situ hybridization (CISH) negative.

In February 2018, a CT scan showed disease progression by two solid iodophilic nodes in epicardial adipose tissue with a diameter of 6/9 mm) and high values of tumor marker CA 15-3= 41.38U/ml suggested clinical relapse, and she started second line hormonal therapy with fulvestrant and letrozole; also, in December 2018, capecitabine was initiated.

In June 2020, after 27 months of hormone treatment and 18 months of capecitabine, a complete CT imagistic re-evaluation (*Fig. 1*) describe two solid iodophilic nodes in epicardial adipose tissue with a diameter of 11/9 mm and 12.5/9 mm, respectively, one of these being in dimensional progressive respect of previous scan. This was confirmed by positron emission tomography (PET-CT) scan from July 2020 (*Fig. 2*).

PET-CT (July 2020) highlighted 2 small lesions with metabolic activity SUV=3.73 in left anterior cardiophrenic region (*Fig. 2*). Clinically, the patient was asymptomatic, with good performance status, IP=0, Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS).

Cardiovascular examination revealed no

Figure 1. CT scan from June 2020

pathological electrocardiographic changes, blood pressure of 140/70 mmHg; echocardiography revealed no dilated left ventricle with global systolic function in normal limits, left ventricle ejection fraction 65%, diastolic dysfunction type late relaxation, minor mitral regurgitation without hemodynamic significance, without ultrasound sings of intra-pulmonary hypertension.

She was candidate for palliative radiation therapy, SBRT, which was delayed until the

Figure 2. PET-CT July 2020

moment of writing this article. Two previous irradiations (chest wall, in 2D technique and sternal bone, in 3D conformal therapy) and anthracycline toxicity should be considered in order to perform the SBRT treatment plan.

Discussion

Although primary cardiac tumors are rare, secondary are not, and the exact incidence of cardiac metastasis is unknown (5-7). About 2/3 of all heart metastases are in the pericardium and only 1/3 are in the epicardium or myocardium (8). The main sites of breast cancer metastasis are the bones, lungs, regional lymph nodes, liver, and brain.

The diagnosis of cardiac metastases in patients with advanced neoplasms has become easier to identify due to modern imaging techniques, which has also led to an increase in survival (9).

There is no strong correlation between the extent of cardiac metastases and clinical symptomatology. The symptomatology and clinical presentation may vary depending on location or the tnumber of metastases and can be classified as extra cardiac (constitutional and mechanical), cardiac (pericardial, myocardial and intracavitary), or combined (10).

It is difficult to make a differential diagnosis between cardiac metastases and other heart diseases due to the fact that it manifests itself in the same way by including dyspnea, palpitations, atrial flutter or fibrillation, lower-extremity edema, and chest pain. Cardiac metastasis may also present with dramatic and life-threatening manifestations like cardiac tamponade from pericardial involvement, which is a medical emergency.

Echocardiography represents the initial method to detect pericardial effusions and to assess the presence and clinical consequences of any cardiac metastasis. Cardiac magnetic resonance imaging (CMR), computed tomography, and positron emission tomography can provide additional information of cardiac masses. Even if the imaging is suspicious of cardiac metastases, the definite diagnosis is made on the basis of histopathological exami-

nation, which differentiates metastatic from non-metastatic lesions.

Although exploratory thoracotomy and open biopsy is sometimes necessary to identify cardiac metastases, various techniques for obtaining tumor cells do not require thoracic surgery. Malignant cells can be identified in the majority of malignant pericardial effusions drained by pericardiocentesis, and the cytology of malignant cells has an extraordinarily high correlation with the histological diagnosis. The most important goals of intervention should include palliation of symptoms and prevention or delay of symptom recurrence (11).

Management of malignant cardiac tumors has always been a challenge for cardiac surgeons due to invasive growth and limitations of resection inside the heart (12).

Despite significant advances in the treatment of cancer, no standard-of-care exists for treating patients with cardiac metastases. These patients have a poor prognosis, the decision of whether and how they can be treated is difficult (13).

Surgical resection in rare cases is generally reserved for cases in which prognosis is otherwise good, for patients in whom complete resection is technically feasible, or for specific cases of intracardiac obstruction. Decision of heart surgery may be difficult and must take into consideration the post-surgery complications.

Intracardiac obstruction by cardiac metastases may require surgery, although outcomes may be poor if ventricular function has been irreversibly compromised (14). The resection of cardiac metastasis can offer, theoretically, maximum local control (15).

Radiotherapy and chemotherapy can also be useful for the treatment of cardiac metastases. Data about palliative radiotherapy from the literature are limited. It is therefore important to involve a multidisciplinary team in the evaluation and management of the patient with cardiac metastasis. The use of palliative radiotherapy in the management of these patients has been limited presumably due to technical difficulties limiting the ability to

safely deliver a clinically useful radiation dose to the heart and/ or the concern about radiation-induced toxicity. The risk is associated with the radiation dose, treatment duration, and radiation volume (16).

Re-irradiation for cardiac metastases is difficult in this case due to the late cardio-toxicity after treatment with anthracycline, used as the first line of treatment, after 2D radiotherapy and after 3D conformal radiotherapy for sternal bone metastases. Considering the long-term hematological and cardiac toxicity induced by anthracyclines, the importance of regimen and dose density chosen in breast cancer patients and their necessity in the adjuvant setting might be indicated by several tissue biomarkers assessable through immunohistochemistry (IHC) techniques, allowing for the choice of personalization of treatment (17-19).

Cardiac radiotherapy for radiation-sensitive cardiac tumor seems a reasonable treatment, but is rarely used in clinical practice, probably because of the rarity of clinical evident cardiac tumors and for concerns of cardiac toxicity from radiation. Few case reports and small case series have described various cardiac tumors and most of which showed symptomatic or image resolution after cardiac radiotherapy (20).

Despite its inability to cure metastatic cancer, cardiac radiotherapy has beneficial effects on transient local tumor control, symptomatic relief, and may improve life quality.

There are few studies in specialty literature regarding radiotherapy delivered to the heart. One of these is the study by Ghiam et al. which analyzed patients who received RT to the heart, in Princess Margaret Cancer Centre, Canada; ten patients with mural-based metastatic deposits in the heart from various histologies were identified between 2003 and 2014, three of them received radiotherapy alone with palliative intent, in 3DCRT, IMRT, VMAT techniques. It appears that the total radiation dose of 30–45 Gy in 1.8–2 Gy per fraction is safe, effective, and desirable to provide symptom control in patients with cardiac metastases. Radio-

therapy was very well-tolerated in all cases, with few acute side effects with complete or partial resolution of symptoms. Using simple techniques, palliative radiotherapy was effective to relieve distressing symptoms of dyspnea, palpitation, and chest pain in these cases. The documented duration of response was between 3 and 11 months in these patients, and treatment was associated with low toxicity. The irradiation of cardiac metastases should be considered in the management of these patients, especially when we have no other therapeutic options (21).

Katalinic et al. (3) published a case in 2013 of a 64-year-old woman with a history of breast cancer diagnosed and treated who developed cardiac metastases after 27 years from primary tumor treatment. The patient presented at the hospital with dyspnea and orthopnea, with IP=4 (ECOGPS) and she was diagnosed with cardiac metastases. The patient received symptomatic treatment and palliative RT was also initiated, but because of the patient's severe general condition, a total dose of only 6 Gy/day was delivered as palliative thoracic radiotherapy, but without an improvement in her general condition (22).

Another study published by Bonomo, based on the experience of the University of Florence, concluded that the use of SBRT for the treatment of cardiac and paracardiac metastases is a safe and effective option (23).

Ernst et al. (24) published a very important article in 2019 analyzing 17 patients (4 with relapsed cardiac sarcoma, 13 with cardiac or paracardiac metastases) and bringing an important contribution to management of cardiac and paracardiac tumor, taking into consideration paucity of literature data. These patients were treated with stereotactic body radiotherapy (SBRT) which was effective and well-tolerated.

Due to the experience gained on the benefits of adjuvant RT for soft tissue sarcoma in terms of local control in primary tumors, it was concluded that certain cases with cardiac metastases may benefit from adjuvant RT for good local tumor control and may improve palliative control (25).

Radiation therapy can cause thrombosis of the tumor by obstructing blood flow to the tumor. If high doses are used, an arterial embolism or rupture of the vessel wall may occur (26). Arrhythmias or other heart conditions present in these patients could further complicate treatment (27).

Another issue that can be debated is the relationship between the patient and the physician who a supportive role, a relationship which must be based on trust and reciprocity, when communication is open, sincere and fully honest. Supportive psychotherapy must focus on solutions, and in all medical cases, supportive groups may be efficient by sharing individual experiences, such as patient groups with the same diagnosis or patient groups with the same therapeutical sequence (28).

Conclusion

Epicardial metastases are rare and frequently silent. The treatment is palliative and must be individualized according to the location of the primary tumor and the status of performance of the patient. Patients should be monitored for the appearance of a second neoplastic location.

Clinicians must take into consideration cardiac metastases even in the absence of clinical symptomatology, and, also, must consider cardiac metastases for differential diagnosis in patients with neoplastic history.

No standard-of-care therapy exists for the management of patients with cardiac metastases. It is recommended that irradiation of cardiac metastases should be considered early in the management of treatment of these patients, particularly when other treatment options are not feasible or do not seem promising. SBRT represents a safe and effective treatment option for patients with cardiac and paracardiac metastases. The optimal radiotherapy dose and fractionation should be individualized based on: patient's characteristics, tumor characteristics, and treatment-related factors, such as history of previous thoracic radiotherapy and the use of anthracyclines.

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