

ATYPICAL STERNAL PAIN IN A BREAST CANCER PATIENT MIMICKING ACUTE MYOCARDIAL INFARCTION

Dor esternal atípica no câncer de mama mimetizando infarto agudo do miocárdio

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ABSTRACT

Radiation therapy on the left side of the chest, some chemotherapy drugs, and trastuzumab raise the risk of cardiac events. Acute chest pain associated with breast cancer is not common, but it is possible. Electrocardiogram, which can result normal in up to 80% of cases of infarction, and serial dosing of myocardial necrosis markers are fundamental for differential diagnosis. Total creatine kinase (CK), creatine kinase-MB fraction (CK-MB), and troponins are frequently used. We present the case of a patient with atypical chest pain associated with elevation of CK and CK-MB, whose evolution and complementary exams showed to be a thoracic tumor recurrence. We discuss the use of these markers for acute chest pain; possible differential diagnoses, the use of CK-MB relative index and, particularly, the presence of macro CK in some breast cancer patients — which in the case herein presented was a marker of tumor progression.

KEYWORDS: Breast neoplasms; recurrence; myocardial infarction; differential diagnosis; non-st elevated myocardial infarction.

RESUMO

A radioterapia do lado esquerdo do tórax, alguns quimioterápicos e o trastuzumabe elevam o risco de eventos cardíacos. A dor torácica aguda associada ao câncer de mama não é um evento frequente, mas é possível. No diagnóstico diferencial, faz-se necessário o eletrocardiograma, que pode ser normal em até 80% dos infartos, e a dosagem seriada de marcadores de necrose miocárdica, sendo frequentemente utilizados a creatinoquinase (CK) total, a creatinoquinase fração MB (CK-MB) e as troponinas. Apresentamos o caso de uma paciente com dor torácica atípica associada à elevação sérica da CK e da CK-MB, sendo que a evolução e os exames complementares mostraram tratar-se de uma recorrência tumoral torácica. Discutem-se a utilização desses marcadores na dor torácica aguda, os diagnósticos diferenciais possíveis, a utilização do índice relativo CK-MB e, em especial, as macro CK presentes em algumas portadoras de câncer de mama, o que, nessa paciente, foi um marcador de progressão tumoral.

PALAVRAS-CHAVE: Neoplasias da mama; recidiva; infarto do miocárdio; diagnóstico diferencial; infarto do miocárdio sem supradesnível do segmento ST.

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INTRODUCTION

Breast cancer treatment is a multidisciplinary effort based on association of radiotherapy, cytotoxic chemotherapy, hormone therapy, and target therapy. In addition to age, some types of cancer treatment may lead to increased risk of cardiovascular disease. Reports are contradictory regarding the relation between radiotherapy and risk of acute myocardial infarction (AMI).^{1,2} A study carried out with patients submitted to lumpectomy and radiotherapy showed different risk ratios depending on the side irradiated. Patients with left-side breast cancer who have been submitted to radiotherapy presented with a significant 1% increase in AMI incidence.³ On the other hand, tamoxifen² and raloxifene⁴ were not related to increased risk of AMI. When it comes to chemotherapy and target therapies, doxorubicin is associated with cardiac complications in 4-36% of cases; paclitaxel causes bradycardia, bundle branch block or arrhythmia in 0.5% of patients; and trastuzumab causes cardiac events in 1.7-5.0% of patients. When the development of myocardial ischemia was assessed, 5-Fluorouracil was found to be associated with it in 1-68% of cases (more common in cases of continuous infusion), docetaxel in 1,7% of cases, and paclitaxel in 1-5% of cases.⁵

Acute chest pain is not a common event among patients with breast cancer, as there is a limited number of studies addressing this subject. Previous studies analyzed possible association of AMI occurrence with the use of doxorubicin⁶ and tamoxifen,⁷ and described cases of left bundle branch block during treatment with trastuzumab.⁸

Although electrocardiogram is mandatory when AMI is suspected, up to 80% of infarctions occur without any alteration shown in examinations. In these terms, markers of myocardial necrosis revolutionized AMI diagnosis. In Brazil, until recently, only creatine kinase (CK) and creatine kinase-MB (CK-MB) were recommended as markers. When available, troponin alone is currently recommended for being more specific to the myocardium. However, we are in a transitional phase since troponin is not available in all services.

Because of its frequency in the general population, AMI should always be considered in differential diagnosis of severe and short-term chest pain. In this paper, we describe the case of a patient with breast cancer presenting with severe chest pain of recent onset. Electrocardiogram showed absence of ST segment elevation. CK and CK-MB levels were elevated. Complementary tests and evolution of the picture showed a false positive result.

CASE REPORT

We report the case of a female diabetic patient, aged 47 years, with left-sided breast cancer, T3N1M0, stage IIIA, Luminal B, HER2/neu-positive. She was submitted to neoadjuvant

chemotherapy – paclitaxel 80 mg/m²/week for 12 weeks associated with trastuzumab in a loading dose of 8 mg/kg followed by 6 mg/kg every 21 days; 4 cycles of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² every 21 days – with partial clinical response. After neoadjuvant chemotherapy, the patient underwent skin-sparing mastectomy associated with contralateral mastopexy and axillary lymphadenectomy levels I, II and III. Anatomopathological examination found pathological partial response (yT1micYpN0). She was submitted to 17 cycles of adjuvant trastuzumab supplementation (1-year treatment) followed by radiotherapy of chest wall (5000 cGy). She was in adjuvant hormone therapy taking anastrozole 1 mg/daily and goserelin for ovarian suppression. Thirty-two months after mastectomy, the patient returned with a complaint of precordial and retrosternal pain radiating to the back for one week and partial improvement with the use of anti-inflammatory drugs. She also reported asthenia and inappetence. Plain chest x-ray and electrocardiogram were normal (Figure 1A). Biochemical analysis showed glutamic oxaloacetic transaminase (GOT) 238 U/L, glutamic-pyruvic transaminase (GPT) 128 U/L, CK 1144 U/L, CK-MB 2340 IU/L and troponin <0.1 ng/mL. Follow-up examinations 6 and 12 hours later showed similar results. Therefore, the initial hypothesis of AMI was discarded.

Echocardiogram showed ejection fraction of 72% and absence of changes in segmental contractility. Computed tomography (CT)

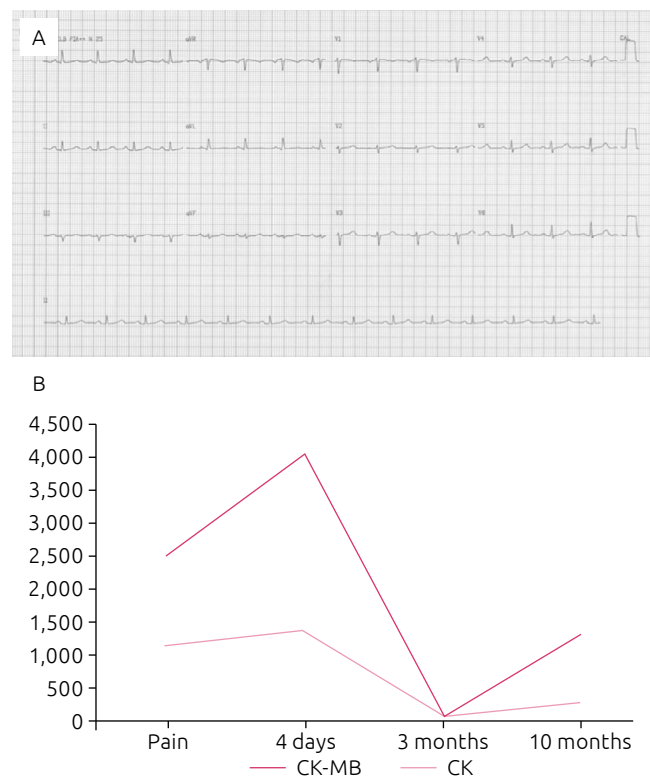


Figure 1. (A) ECG in clinical picture of pain; (B) Enzymatic curve for CK and CK-MB enzymes in response to treatment and recurrence.

scan of the chest and whole abdomen revealed a solid mass in left retrosternal and parasternal regions (8.5 x 4.6 cm) involving internal mammary artery, associated with a lytic osseous lesion in the sternal manubrium, suspicious pulmonary nodules and multiple liver metastases (Figure 2).

First-line palliative chemotherapy was started with weekly paclitaxel associated with trastuzumab. A 3-month follow-up CT examination showed disappearance of the mediastinal mass, pulmonary nodules and lytic sternal area, with decrease of the hepatic lesion (Figures 3A, 3B and 3C). Normalization of cardiac enzymes (Figure 1B) and liver transaminases were then seen. The patient completed 12 cycles of paclitaxel associated with trastuzumab. Post-treatment skeletal scintigraphy was normal. Chest CT showed reduction of the pulmonary disease and disappearance of the sternal lesion with stable liver disease. Due to

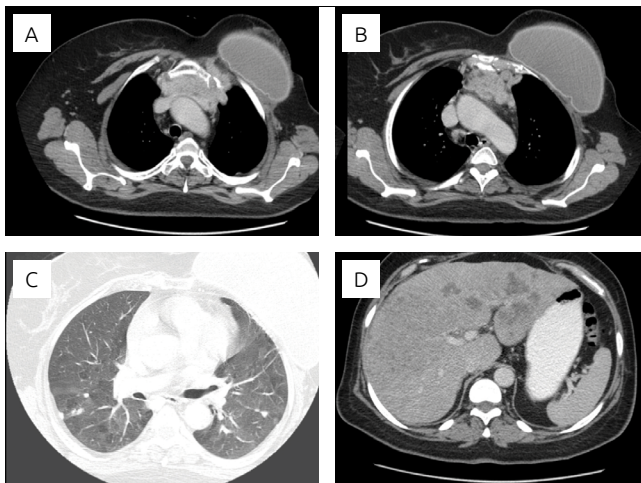


Figure 2. Tomography in clinical picture of pain: (A) thoracic mass with sternal invasion; (B) associated lymphadenomegaly; (C) lung metastasis; (D) liver metastasis.

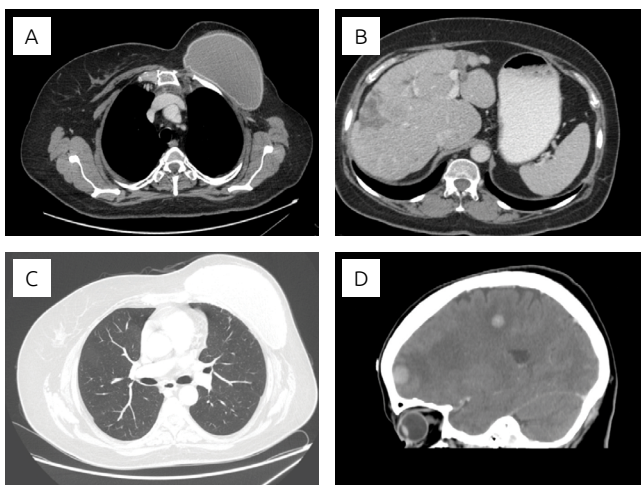


Figure 3. Response to chemotherapy: (A, B, and C) Tomography at three months showing regression; (D) Tomography at ten months showing brain recurrence.

clinical and radiological improvements, the patient was started on exemestane with trastuzumab maintenance therapy. Ten months after the beginning of palliative care, the patient sought medical attention with complaints of headache and dizziness. Cranial CT scan revealed bilateral multiple brain metastases (Figure 3D), CK 291 U/L and CK-MB 1,073 IU/L. The patient was submitted to palliative radiosurgery, with progression of disease and orbit two months after the onset of brain recurrence (15 months after the first recurrence). The enzymatic curve is shown in Figure 1B.

DISCUSSION

Pain in the area under treatment is a frequent complaint among breast cancer patients. However, this discomfort is mild and often associated with local denervation and radiation therapy side effects. Other common symptoms include neuropathic pain, pain related to local recurrence, metastatic bone disease or lung/pleural disease, and degenerative changes of the shoulders. Although complementary exams have limited sensitivity/specificity in cases of severe recurrent pain, they are reliable for a correct etiological diagnosis. The literature reports a patient with suspected angina submitted to myocardial perfusion imaging with positron emission computed tomography (PET-CT), which revealed thoracic osseous recurrence.⁹

AMI is a potentially fatal entity, and differential diagnosis should be considered when facing severe and acute chest pain. Atypical chest pain, diabetes mellitus, and old age makes AMI diagnosis difficult. Normal electrocardiogram results are another worth mentioning element, since up to 80% of AMI cases lack the classical ST-segment elevation. Enzymes previously used in clinical practice, such as CK and CK-MB, are currently less used and replaced by more specific markers such as troponins. Nevertheless, the literature describes the case of a patient with chest pain, ST segment alteration, T-wave inversion and elevated troponin, but no changes in coronary arteries. In that specific case, chest pain was being caused by heart metastasis.¹⁰

Laboratory diagnosis of AMI has evolved a lot in recent decades. Initial markers include LDH (lactic dehydrogenase), AST, and CK. Advances in electrophoresis allowed identifying specific enzymes such as CK-MB.¹¹ CK-MB sensitivity depends on time, varying from 40-76% in the first four hours and to 60-100% in up to 12 hours, with 85-100% specificity.¹² Currently, the evaluation of serum troponin is associated with high sensitivity and specificity in cases of myocardial necrosis, the protein being able to detect small myocardial lesions.¹³ Laboratory test is chosen when AMI is suspected. However, CK and CK-MB are still to be investigated whenever laboratory conditions for troponin analysis are poor.¹³

CK is a molecule found in large quantities in skeletal and cardiac muscles, also found in the brain and kidneys. CK enzymes consist of two types of subunits: the B type (predominant in the

brain) and M type (predominant in skeletal muscle). These enzymes are able to combine to create three isoenzymes — CK-BB, CK-MB, and CK-MM —, running with the approximate size of 80-kDa dimer during electrophoresis. Elevations of CK-MB are associated with trauma, muscular dystrophy, myositis, and vigorous exercise. False-positives can occur in conditions associated with elevated CK.¹² Two atypical types have higher molecular weights (greater than 200kDa) and are classified as macro CK. Macro CK types 1 and 2 are found in 0.43% and 1.2% of the population, respectively. Macro CK type 1 generally occurs in subjects with rhabdomyolysis, and may also be present in cancer patients. Macro CK type 2, in turn, usually occurs in patients with malignant neoplasias including prostate and breast cancers.^{14,15} The order of migration of CK isoenzymes with electrophoresis is CK-BB, followed by CK-MB, then CK-MM. Macro CK type 1 can migrate to or between CK-MB and CK-MM regions; macro CK type 2 migrates after CK-MM fraction,¹⁶ which may be a confounding factor for AMI diagnosis depending on the methodology used. Thus, CK-MB mass dosage may be overestimated in situations where the serum concentrations of macro CK-BB are excessive.¹⁷

Therefore, the serum level of macro-CK-BB should be measured to confirm a false-positive result. From then on, the use of other methods for CK-MB in AMI evaluation should be considered (such as the relative CK-MB index [IR CK-MB = 100 (CK-MB/CK total)], in which values between 5% and 25% are associated with heart-related changes, and values above 25% indicate possible interference by CK-BB or macro CK).¹⁷

In our case described, sternal metastasis was the reason of local pain. The titers of CK and CK-MB enzymes made us suspect of AMI, which was discarded by the relation between results and normal serial troponin values. Etiological diagnosis was only confirmed after tomography and by exclusion. Metastatic disease was then confirmed, with decrease in CK and CK-MB levels as a therapeutic response and elevation of these markers after further disease progression (Figure 1C). Thus, CK and CK-MB enzymes were to be considered tumor markers in the case we depicted, and this is not a common fact in clinical practice. The present report is justified by the discussion about the limitation of CK and CK-MB in AMI investigation, especially when there is association with breast cancer, in which macro CK-BB is proven present.

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