CASE REPORTS

CHEMOTHERAPY HAZARDS: ANTHRACYCLINE EXTRAVASATION INTO PLEURAL SPACE

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Abstract

The extravasation of doxorubicin, a cytostatic from the anthracycline group, is a rare and feared complication of intravenous chemotherapy due to tissue toxicity of these drugs. We describe a case of a 64-year-old woman with breast cancer undergoing adjuvant chemotherapy with doxorubicin and cyclophosphamide using a tunneled central catheter. After a chemotherapy cycle, the patient developed cough, dyspnoea and chest pain, due to a pleural effusion secondary to cytostatic leakage. A pleural drainage was placed and dexrazoxone was administred with resolution of the condition. The authors wish to highlight that the use of dexrazoxone should be considered after intra-pleural extravasation of anthracyclines given its effectiveness in preventing tissue damage and long-term sequelae in peripheral extravasation.

Keywords: *Doxorubicin; Central Venous Catheters; Adjuvant Chemotherapy; dexrazoxane; pleural effusion*

INTRODUCTION

The extravasation of cytotoxic agents, in particular, DNA-binding vesicant drugs, such as anthracyclines, can lead to extensive damage[1,2].

The reported incidence of such extravasation varies from 0.01% to 7%[3]. However the intrathoracic extravasation of the cytotoxic agents administered by a central venous access device (CVAD) is a rare complication that occurs in 0,24%[4]. In a recent review of the literature, only eight cases of intra-pleural and mediastinal anthracycline extravasation were identified.[5]

The most frequent symptom of CVAD extravasation is acute thoracic pain, with clinical suspicion confirmed with imaging techniques, namely thoracic CT scan.

While management of extravasation into soft tissues has been established, scarce data exist on treatment of intrathoracic extravasation and are based on case reports.

We describe a case of intra-pleural extravasation of doxorubicin from a CVAD.

CASE REPORT

A 64-year-old healthy woman was diagnosed with a left breast cancer at stage IIA (T1cN1M0). She underwent a left mastectomy with axillary lymphadenectomy. Thereafter, adjuvant chemotherapy, radiotherapy and hormone therapy were initiated.

For chemotherapy, a CVAD was placed in the right

subclavian vein without complications. Proper position of the catheter tip was verified by chest X-ray.

At the 1st cycle of chemotherapy with doxorubicin and cyclophosphamide, the patient had cough. Three weeks later, at the end of the 2nd cycle, she complained of right chest pain with dry cough and dyspnea. For etiological investigation, a chest X-ray was performed and a right pleural effusion was discovered. Then, a thoracic CT scan was performed which revealed the catheter tip outside the superior vena cava in a sub-pleural location. (Figure 1)

Once cytostatic extravasation into the pleural space was proven, a pleural drainage (32 Fr) was placed with outflow of serohematic pleural fluid classified as exudate. Dexrazoxane was administered i.v. in a 3-day schedule (1000, 1000 and 500 mg/m2), 18 hours after the extravasation.

For closer monitoring, she was initially admitted to the respiratory intensive care unit and then transferred to the Pulmonology ward. The fluid drained reduced significantly, with drainage removal on the 7th day of hospitalization. On the reassessment CT, one month after the extravasation, a small pleural effusion persisted in a postero-inferior location. For complete pulmonary reexpansion and to avoid organization, echo-guided thoracentesis was performed. Resolution of the pleural effusion was confirmed on X-ray at discharge date. At the end, she removed the CVAD, under local anesthesia, without complication.

In a reassessment consultation at 6 and 12 months, the patient was asymptomatic and without residual pleural sequelae in imaging tests. (Figure 2)

Regarding breast cancer, the patient continued the chemotherapy via peripheral access without complications. She also performed radiotherapy and started hormone therapy, with no signs of recurrence to date.

DISCUSSION

The anthracyclines are considered the most vesicant agents when extravasated, potentially resulting in ulcers and tissue necrosis[2].

Regarding the mechanism of anthracycline damage, the drug binds to the topoisomerase II-DNA complex, resulting in DNA break that is lethal to the cell. Then, anthracycline is released, incorporated to adjacent cells, leading to a vicious cycle of damage[2].

Currently, anthracyclines are typically administered i.v. through a CVAD[6]. Extravasation, with cytostatic leakage to mediastinum or pleura, is rare but possible with these implantable venous access[3]. The main mechanisms that explain the extravasation are: thrombus or fibrin sheath formation at the catheter tip, perforation of the vein wall, catheter fracture[7,8].

Whenever the patients develops acute chest pain at the time of chemotherapy infusion, this should raise the suspicion for intrathoracic extravasation. The diagnosis must be confirmed by a thoracic CT scan[3].

The greatest amount of evidence on this complication is related to peripheral extravasation. According to current guidelines, anthracycline extravasations' treatment includes the use of dimethyl sulfoxide combined with cooling or dexrazoxane. In the cases of unresolved necrosis or pain lasting more than 10 days, surgical de-

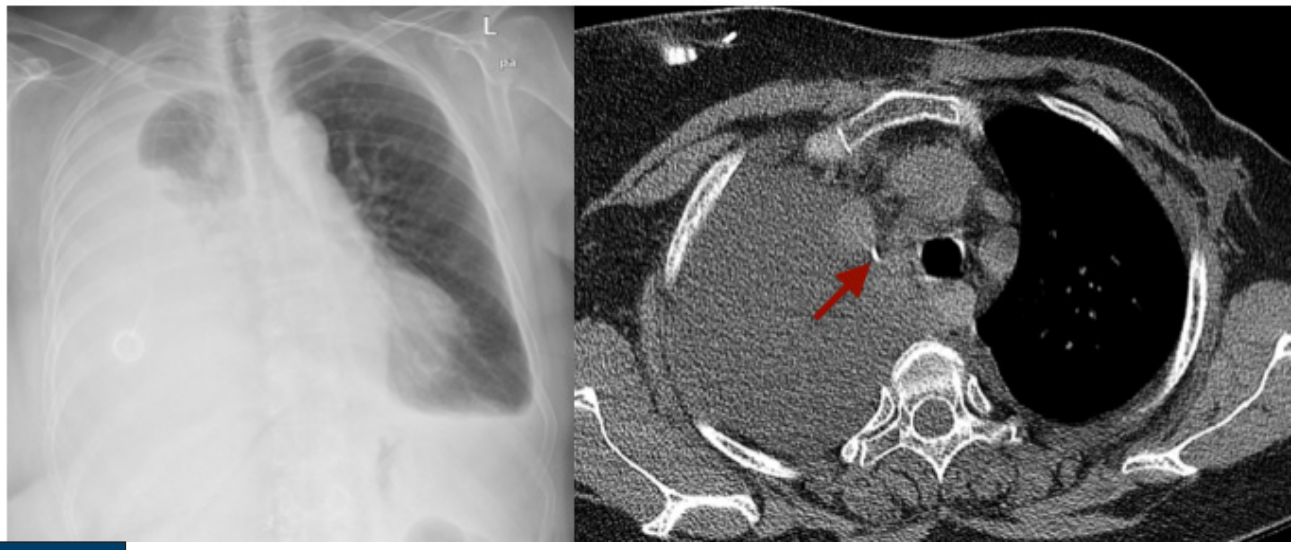

Figure 1 *Cytostatic extravasation into the pleural space. A) Right pleural effusion in X-ray; B) Thoracic CT with right pleural effusion and catheter tip outside the superior vena cava in a sub-pleural location (red arrow)*

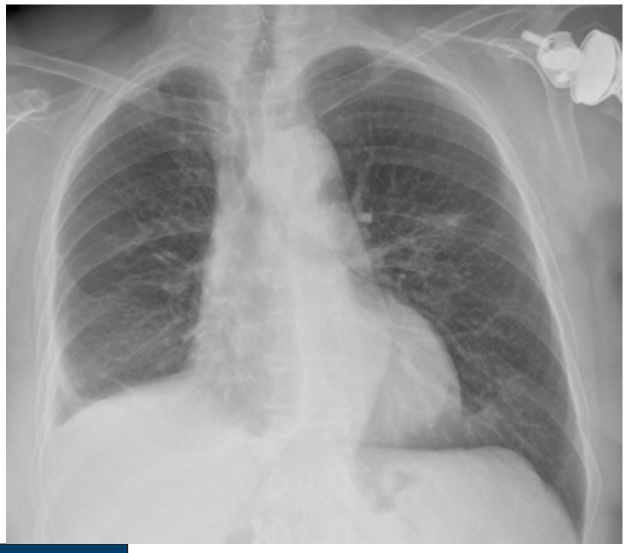

Figure 2 *6-month X-ray reassessment without major sequelae*

bridement is indicated[3].

The dexrazoxane was approved by EMEA and by FDA for the treatment of peripheral extravasation of anthracycline chemotherapy[6]. Dexrazoxane decreases tissue damage of anthracycline by catalytic inhibition of DNA topoisomerase II, preventing double-strand DNA break.[2,9]. It is well tolerated and its most frequent side effects are hematologic toxicity, hypertransaminasemia, nausea and local pain at the site of the infusion. It should be given intravenously in a 3-day treatment (1000mg/m2 on days 1 and 2 and 500mg/m2 on day 3), within 6 h after the event3.

Data about the management of CVAD extravasation is lacking in the medical literature and is primarily from case reports.

In the review of intrathoracic extravasation of anthracycline from CVAD by Kazakova et al[3], only eight cases has been reported. Half of the patients developed pleural effusion and the other half had extravasation into the mediastinum. In all cases, as soon as extravasation is suspected, the infusion was promptly stopped. Systemic administration of corticosteroids was used in five out of eight cases. However, according to current guidelines for management of chemotherapy extravasation, glucocorticoids are no longer recommended. Since the approval of dexrazoxane, it was administered in four cases of intra-pleural and mediastinal anthracycline extravasation. In three cases VATS was performed and in other four patients pleural drainage was preferred. In the described cases all patients survived and developed minimal long-term sequelae.

Taking into account the evidence available in the literature and the various strategies used, we decided to place a percutaneous drainage and start dexrazoxane in a 3-day treatment, with significant clinical improvement.

In conclusion, the authors highlight the following key points:

1) If the patient begins with chest pain during or at the end of the chemotherapy session, intrathoracic extravasation should be considered as a differential diagnose. This has to be further confirmed by thoracic CT scan;

2) Management consists of stoping the infusion and considering the removal of the leaking agent with percutaneous drainage and/or VATS procedure with normal saline irrigation.

3) If the extravasated agent is an anthracycline, dexrazoxane should be considered as an antidote.

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