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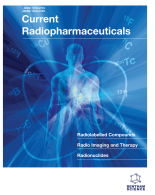
CASE REPORT

Analysis of Unusual Adverse Effects After Radium-223 Dichloride Administration



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Abstract: ***Background:*** To our knowledge, no previous study or literature review has been performed about the effects of the extravasation of therapeutic radiopharmaceutical agents and its potential consequences, especially regarding alpha-particle emitting radiopharmaceuticals.

Methods: Even if Radium-223 dichloride is known to be a relatively safe drug to manage, despite the correctness of the procedures applied , unexpected delayed adverse effects can occur.

In our vast experience, we rarely observed lymphedema, even after some time, at the site of administration.

Results: Management of lymphedema caused by radiopharmaceuticals administration has been addressed through clinical examples. The sudden intervention allowed a fast remission of the signs and symptoms complained by patients treated with Radium-223 dichloride.

Conclusion: The management of adverse effects after radiopharmaceuticals administration as in case of lymphedema onset, is extremely simple. These data confirm the safety of Radium-223 treatment.

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1. INTRODUCTION

The growth and expansion of nuclear medicine procedures and the corresponding use of radiopharmaceuticals lead to an increase in the frequency of adverse reactions. The frequency of reported adverse effects is generally considered to be 0.1% compared to that relative to other drugs [1], so the radiopharmaceuticals are regarded as safe medicines. Nevertheless, even if quite rare, the possibility of adverse reaction to an administered radiopharmaceutical does exist. By analogy, this trending issue is involving the novel radiopharmaceutical Radium-223 and its administration. Radium-223 dichloride is an FDA-approved alpha-particle emitting therapeutic radiopharmaceutical agent indicated for the treatment of patients with castration-resistant prostate cancer (mCRPC) [2, 3], symptomatic bone metastases and no visceral metastatic disease [4]. Radium-223 is an alpha emitter with a physical half-life of 11.4 days and a whole body effective half-lives were highly dependent upon fecal compartment transfer, ranging from 2.5-11.4 d. Radium-223 decays in six steps via a chain of alpha and beta emissions into a stable isotope of lead, 207Pb. The total amount of emitted energy per the 223Ra decay series is 28.2 MeV. Alpha particles have a short path length in tissue (50-100 μm) compared with beta particles (1000-10,000 μm). The short range of alpha particle radiation allows to minimize cytotoxic damage in non-targeted cells, enabling specific cancer cell targeting with reduced toxicity to normal cells. Although Radium-223 is primarily an alpha-emitting radionuclide (> 95% of the total energy), 3.7% of the energy is emitted as beta particles and 1.1% of the energy is emitted as gamma photons. The short-range high-LEt alpha particles are responsible for the majority of the therapeutic value. A phase III study of Radium-223 dichloride in 921 patients with mCRPC and symptomatic bone metastases showed that Radium-223, compared with placebo, significantly improved median overall survival by 3.6 months, delayed the time to first symptomatic skeletal event and improves pain control and quality of life dramatically [5]. Moreover, Radium-223 had a highly favorable safety profile with a low incidence of myelosuppression [6-8]. In a phase IIa clinical trial [9] the effects of Radium-223 on bone markers, brief pain inventory (BPI) score and tumor metabolism assessed by 18F-

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fluorodeoxyglucose PET imaging provided to highlight the effectiveness of Radium-223 dichloride in treating bone metastases, even in patients with breast cancer and bone-dominant disease, combined with a minimal myelotoxicity, less than typically seen with the conventional beta-emitting radioisotopes (Samarium-153 and Strontium-89). Additional studies in patients with breast cancer are still ongoing to further investigate the efficiency and safety of Radium-223. In our center, nowadays more than 180 patients have been treated with Radium-223. We present cases of patients with prostate and breast cancer who have had unusual adverse events. This cases report was approved by the Institutional Review Board and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients signed a written Informed Consent.

2. CLINICAL CASE 1

A 71 aged female with IV stage breast cancer, treated with right mastectomy and subsequent chemo-radiotherapy, currently in hormonal therapy (i.e. aromatase inhibitor), underwent Radium-223 dichloride administration for secondary bone involvement in our Nuclear Medicine Unit. During the administration of Radium-223 dichloride (about 5 MBq at the reference date, 55 kBq/kg body weight), via IV access line in the cubital region of the left upper limb, flushed prior to and after with 5ml of sodium chloride isotonic solution. Attention was paid to avoiding the IV access line on the right arm because of the relatively radical surgery sustained by patient on this side. About seven days after, the patient's left upper limb showed an evident swelling and fullness. The patient did not complain any pain in the region of injection nor in the whole left upper limb, no fever was observed, but she felt stiffness, heaviness and a reduced flexibility of the left elbow, as observed in lymphedema syndromes clinical presentation (Fig. **1**). No ulceration of the skin or subcutaneous tissue alterations were detected at physical examination, but just a slight erythema around injection site. Conventional radiological imaging [*i.e.* ultrasound and computed tomography] was carried out and there were no significant alterations of the affected arm and homolateral axillary structures (Fig. **2**). We decided to perform the long-established conservative treatment, consisting in elevation, compression bandaging and therapeutic muscular exercise to enhance lymphatic drainage. In a time frame of three weeks, the lymphedema condition and the heaviness complained by the patient gradually reverted and, at present, they did not recur. The patient is still in clinical follow up.

3. CLINICAL CASE 2

An 81 years old male, enrolled in our Nuclear Medicine Unit for radium-223 treatment for castration-resistant prostate cancer and bone secondary lesions, came to our attention about 4 weeks after the last Radium-223 dichloride administration with a moderate swelling, increase of volume of the right forearm, more pronounced in the hand and an evident pitting edema (Fig. **3**). No skin or subcutaneous tissue have been detected and the patient complained just a slight sense of heaviness. Furthermore, there were no relevant nursing or clinical issues before, apparently no extravasation occurred during or after the mentioned Radium-223 dichloride administration (about 5 MBq at the reference date, 55 kBq/kg body weight), via IV access line in the cubital region of the right upper limb, flushed prior to and after, with 5ml of sodium chloride (0,9%) isotonic solution. Moreover, the patient's clinical conditions did not show any pathologies that could be indicated as the cause of lymphedema As in the previous case, we recommended a conservative lymphatic decongestive treatment, consisting in elevation, compression bandaging and muscular exercise to enhance lymphatic drainage. The patient is currently under clinical follow-up.

4. DISCUSSION

Various national reports have been published in recent years about the occurrence of adverse effects in nuclear medicine departments after radiopharmaceutical administration [10]. The frequency of reported adverse effects is generally considered to be 0.1% compared to that relative to other drugs [1], so the radiopharmaceuticals are regarded as safe medicines. Salvatori *et al*. [11] published a meta-analysis on the occurrence of radiopharmaceuticals adverse reactions, resulting in a global incidence of $1.9 \times 10{-}5$ administrations. In a recent meta-analysis conducted by Laroche *et al*. [1], it has been showed that for all reports involving radiopharmaceuticals used with therapeutic purpose were collected 97 of

Fig. (1). Marked asymmetry between the upper limbs for significant enlargement and swelling of the left arm on clinical examination. Evident swelling of the left arm in addition to a sense of fullness and heaviness complained by patient.

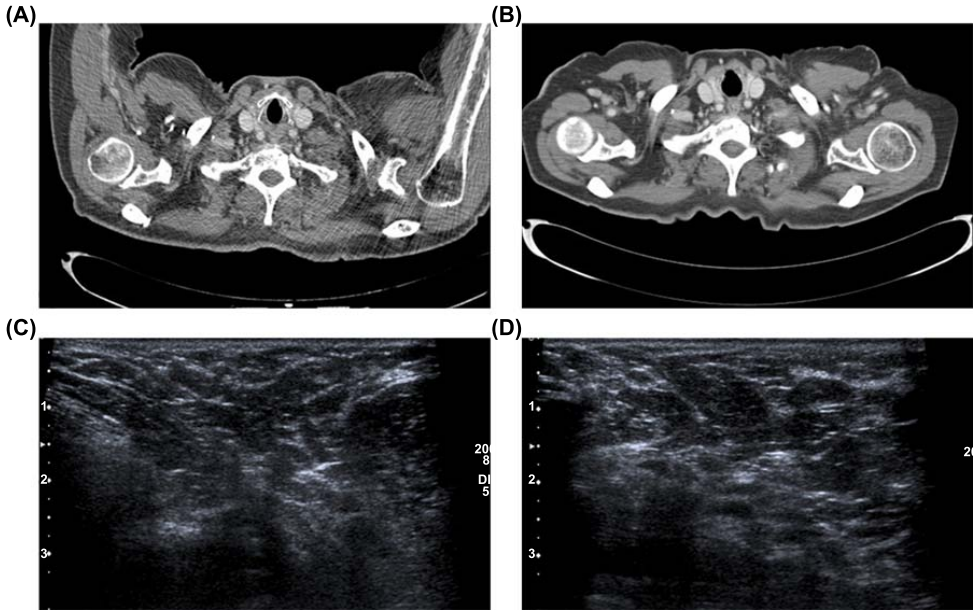

Fig. (2). Patient#1. CT scan (**A**, **B**) and US exam (**C**, **D**) images of the axillary region showing no significant morpho-structural alterations.

Fig. (3). Moderate swelling and increased volume of right forearm, more evident on the hand. Remarkable sign of pitting edema on the ventral side of right forearm.

adverse reactions (17.7%); pulmonary disorders were the most frequent effects reported (44.3%), usually occurred after administration of 131I-lipiodol. 153Sm-lexidronam, 90Y-ibritumomab-tiuxetan and 89Sr-chloride are accounted with a relatively much smaller prevalence.

It is widely admitted that diagnostic imaging radiopharmaceuticals are more often involved in allergic reactions, due to the carrier biochemical features, whereas radiopharmaceuticals used with a therapeutic purpose could induce rather serious adverse effects, caused by the physical properties of compound and its radiobiologic effects, therefore it should be emphasized that only to trained personnel could place iv lines before therapy. Despite the relatively wide number of studies regarding the overall radiopharmaceutical adverse effects above mentioned, we noticed a significant underreporting of the incidence and potential complications of the radiopharmaceutical extravasation or infiltration in current literature. In nuclear medicine practice, the extravasation of radionuclides results in a localized tissue retention of the radiopharmaceutical and subsequently in an unintended local radiation exposure to the regional tissues. As extravasations, particularly small ones, are frequently asymptomatic, we can postulate that their occurrence is probably underestimated. Considering the relatively high prevalence of extravasation in standard diagnostic procedures, the same might take place for therapeutic radiopharmaceuticals administration. Despite some cases of mild tissue damage following extravasation of diagnostic radiopharmaceuticals have been reported (37 publications reported 3016 cases of which 3 cases reported symptoms), extravasation of therapeutic radio compounds has the highest tendency to result in tissue damage (8 publications reported 10 cases), because of the physical characteristics of the radioisotopes used [12, 13]. In the last few years, Radium-223 dichloride has obtained marketing authorization in Europe and USA for radiometabolic treatment of patients with mCRPC and symptomatic bone metastases, as the first and, to date, only alpha emitter radionuclide. Because of that, at present, very little is known about incidence, clinical conse-

quences and eventual possible interventions after alpha emitter agents extravasation. To our knowledge, we observed thirty-four different intervention and prevention strategies performed or proposed, therefore it's self-evident a notable confusion regarding this argument. No previous study or literature review has been performed about the effects of the extravasation of commonly applied diagnostic or therapeutic radiopharmaceuticals, especially with regard of alpha emitter radiopharmaceuticals. The EANM procedure guideline for 90Y-ibritumomab tiuxetan (Zevalin®) [14] is the only guideline giving some practical advice in case of extravasation, advising local hyperthermia, elevation and massage. Other EANM and SNMMI guidelines focused on radionuclide therapy do not promote any particular practical advice in case of extravasation, regardless of the potential complications. The options of lymphedema conventional treatment include elevation, compression garments, pneumatic pumping, lymphatic massage, diuretics, surgical debulking and microsurgical reconstruction. Complete decongestive therapy (CDT) is commonly used worldwide and recommended as the clinical best practice for lymphedema medical treatment as reported in a recent systematic review [15]. Weight management, full-body exercise, information disposal, prevention and early intervention protocols are also likely to be effective [16]. Even though we experienced more than 180 patients with mCRPC and breast cancer in treatment with Radium-223 dichloride in our Nuclear Medicine Unit, and despite the correctness of the procedures applied, the clinical pictures described above were unexpected and unique events, at present unrecognized in literature and it would be worth of further consideration and investigation in the field of radiopharmaceutical extravasation. It seems appropriate to underline on the basis of these considerations, that the patient must be informed at time of therapy to watch out for possible side effects and refer to the hospital in case they appear, even in the days following administration.

On the other hand, in our experience, in which for dosimetry reasons, we obtain images of the biodistribution of 223-Ra in the days following administration, we have never observed areas of skin contamination in the area of injection.

We suggest a longstanding conservative treatment involving elevation, compression bandaging and garments and muscular exercise, in case of fever and relevant local pain occurrence, an approach with antibiotic coverage and antithrombotic heparin therapy should be preferred. These rare occasional events have confirmed the safety and simplicity of Radium-223 procedures, even in the case of unexpected events. Our experience however, underline the need for a greater and stronger knowledge regarding incidence, presentation and severity of these adverse effects with the aim of an adequate clinical response in case of extravasation, as well as for the development of more accurate guidelines covering radiopharmaceutical extravasation.

LIST OF ABBREVIATIONS

mCRPC = Metastatic Castration-resistant Prostate Cancer

MeV = Megaelettronvolt

LET = Linear Energy Transfer

BPI = Brief Pain Inventory

EANM = European Association of Nuclear Medicine

SNMMI = Society of Nuclear Medicine and Molecular Imaging

CDT = Complete Decongestive Therapy

STANDARD OF REPORTING

CARE guidelines and methodologies have been followed.

CONSENT FOR PUBLICATION

Informed consent was obtained from all individual participants included in the study and any accompanying images.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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