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The Cost of Delay: A Case Report of Doxorubicin Extravasation

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1. Abstract

1.1. Introduction

Extravasation is a dangerous complication of doxorubicin administration, leading to extreme pain, vascular damage, infection, and tissue necrosis. These adverse effects can be minimized with administration of the antidote (dexrazoxane) within six hours.

1.2. Case Presentation

The patient is a 40-year-old woman with invasive breast cancer, status post bilateral mastectomy and chest port failure who presents with doxorubicin extravasation in the left arm. Doxorubicin was administered through a peripheral IV and the patient noted a burning sensation, warmth, and tightness. Dexrazoxane was administered 5.5 hours later, as the extravasation was not immediately recognized, and the infusion center did not have dexrazoxane on site. Over the subsequent 1.5 months, the patient developed a persistent ulcer and superficial thrombophlebitis at the administration site. On eventual hospitalization, ultrasound revealed a small fluid collection and sensory loss in the medial three fingers of her left hand, prompting explorative surgery and tissue debridement. Post-operatively, she reported significant improvement of her pain and no lingering sensory abnormalities.

1.3. Discussion

This case depicts multiple individual and system-level errors in recognizing and treating doxorubicin extravasation, exemplifying the Swiss cheese model. From the first issue, where there was a misunderstanding of risks and benefits of peripheral administration of doxorubicin, to failure to recognize the extravasation when classic signs and symptoms were displayed, to a near-miss of timely antidote administration due to unavailability of the antidote onsite. This case highlights the need for further education on the diagnosis and treatment of doxorubicin extravasation.

2. Introduction

Doxorubicin is an anthracycline used in the treatment of a variety of malignancies. Despite its effectiveness as a chemotherapeutic agent, doxorubicin is associated with cardiotoxicity and hematological toxicity [1]. In addition to the systemic toxicities inflicted with doxorubicin use, it may also cause significant morbidity due to extravasation. Extravasation occurs when intravenously administered drugs leak out of blood vessels and into the surrounding tissues [2]. Specific chemotherapeutic agents given through a peripheral IV can have the potential of extravasation [3], which can lead to rapid tissue damage, extensive pain, intense inflammation, swelling, and tissue necrosis. When administered intravenously, chemotherapy extravasation can occur in as many as 6% of cases [4], making the dangerous effects of extravasation an important consideration for peripheral chemotherapy administration. Fortunately, dexrazoxane can be administered as an antidote to mitigate both the cardiotoxicity and extravasation complications of doxorubicin. In the event of doxorubicin extravasation, dexrazoxane should be administered as soon as possible, but no later than 6 hours [5]. A previous study examining the efficacy of dexrazoxane as a specific antidote for anthracycline (doxorubicin and epirubicin) extravasation found that treatment within 6 hours prevented extensive necrosis that would have otherwise required surgical intervention in 53 out of 54 patients (98.1%); 38 patients (70.4%) were also able to continue chemotherapeutic treatment [6]. Similarly, another report showed that administration of dexrazoxane within 6 hours alleviated the need for surgical debridement due to anthracycline extravasation in 26 out of 28 patients (92.9%). In both cases, harmful side effects such as tissue necrosis requiring a surgical intervention, were alleviated after dexrazoxane administration - highlighting the necessity of early recognition of anthracycline extravasation and administering dexrazoxane within the recommended 6 hours. Due to the dangerous complications of chemotherapy extravasation, medical professionals must be aware of the harmful effects of chemotherapy extravasation and be fully prepared to prevent and treat such events. As a result, medical staff must be able to recognize when chemotherapy extravasation has occurred and address this promptly. The dangers of delaying antidotal medications in the face of extravasation are exemplified in the case reported here - where a 40-year-old woman with breast cancer was treated with doxorubicin through a peripheral vein, that ultimately extravasated.

3. Case Presentation

A 40-year-old woman with invasive ductal carcinoma of the left breast presented to the emergency department with doxorubicin extravasation three months after bilateral mastectomy. Prior to doxorubicin administration, this patient was diagnosed with ER+, PR+, HER2- breast cancer and underwent a bilateral mastectomy. Six weeks later, a chest port was placed. However, it was subsequently removed after it migrated into the mastectomy cavity. Due to the chest port failure, the patient was offered placement of a peripherally inserted central catheter (PICC) line or peripheral intravenous (IV) administration. During the discussion with her oncologist, the limitations on her life imposed by a PICC line were discussed; however, the potential risks of having doxorubicin administered through peripheral IV were not. Believing the risk profile to be the same, the patient opted to receive doxorubicin peripherally so she could participate in summertime activities with her children such as swimming. No complications were noted on the first three rounds of doxorubicin administration. However, on the fourth round of administration, the patient noted burning and tightness. On inspection, no abnormalities were noted, and aspiration of the line showed blood, indicating proper placement so the infusion was continued. Fifteen minutes later, the patient continued to complain of burning and tightness in the area. At this time, the nurse noted the area to be warm and hard. The IV was removed, ice was placed on the site, and a subsequent IV was placed in her right arm to finish the infusion of doxorubicin and cytoxan. The pain and redness in the left arm continued to progress which prompted the nurse to

suspect doxorubicin extravasation. The physician was notified and confirmed the likely extravasation. Topical DMSO was attempted to be administered, however it was not available at the pharmacy on site. As a result, dexrazoxane was administered. However, due to the delay in recognizing the extravasation, as well as the infusion center not having this antidote on site, dexrazoxane was not administered until 5.5 hours after extravasation. Dexrazoxane was administered per the typical 3-day schedule-once on the day of the extravasation and once daily over the next two days after the event. Upon her return, the extravasation site displayed increased in soreness, warmth, and appeared dark red and yellow in color (Figure 1). On day three post extravasation, the patient was started on a 10-day course of empiric doxycycline and a seven-day course of topical DMSO. On the following week, the patient's symptoms persisted and she reported continued discoloration with increased induration but no associated pain or soreness. Ten days after the initial extravasation, the patient reported that the wound still had not closed and had a slightly yellow fluid coming out of it. On day 12, the patient reported return of arm pain with increasing severity stating it was: "pretty bad." (Figure 2).On day 16, the patient reported continued worsening pain leading to difficulty straightening her arm. The patient subsequently went to the emergency room where she underwent an ultrasound which revealed superficial thrombophlebitis of the cephalic and basilic veins. She was started on cephalexin due to ongoing symptoms and given a prescription of rivaroxaban to prevent blood clots. Over the next few weeks, the patient visited the emergency room and various clinics numerous times regarding pain, swelling, redness and numbness in her left arm with no definitive resolution (Figure 3). In an emergency room visit about a month after the initial extravasation, an MRI of her elbow showed cellulitis in her left arm with skin thickening and edema in the soft tissues of her elbow with no abscess or bone involvement. In the following days, she was seen in the emergency room again, and had a follow-up ultrasound that showed an increase in the size of the superficial blood clot but no deep vein thrombosis. The patient's symptoms continued to progress prompting her to revisit the emergency room again with subsequent admission to the hospital where she began treatment with cefepime and clindamycin due to concerns of necrotizing fasciitis, as well as hydromorphone for pain management. Despite this, the redness continued to spread. Surgery was consulted and determined that the risk of necrotizing fasciitis was relatively low which prompted a change in antibiotics to cefepime and vancomycin, then cefepime and piperacillin-tazobactam. Despite the use of broad-spectrum antibiotics, her cellulitis continued to progress and spread towards her left shoulder (Figure 4). Initially, it was recommended that she continue the supportive care with IV antibiotics. A follow up ultrasound showed multiple areas of small collections but no discrete wall or abscess. The patient also began to experience numbness and tingling in her left hand consistent with ulnar nerve compromise - which prompted left arm incision and drainage, as well as exploratory surgery. Explorative surgery revealed a three-centimeter subcutaneous pocket of pus that was removed along with all of the necrotic and infected tissue. After surgery (Figure 5), the patient felt remarkably better, and her left arm pain had improved. Since the surgery, she no longer required IV pain medications. The patient and her medical team wish to continue her chemotherapy treatment, but given the situation at hand, she cannot receive chemotherapy through her left arm. Additionally, chemotherapy through her right arm is not recommended, as any damage here can severely impact her ability to receive future intravenous treatments including those outside of chemotherapy. As a result, she is discussing with her team on alternate sites for port placement.

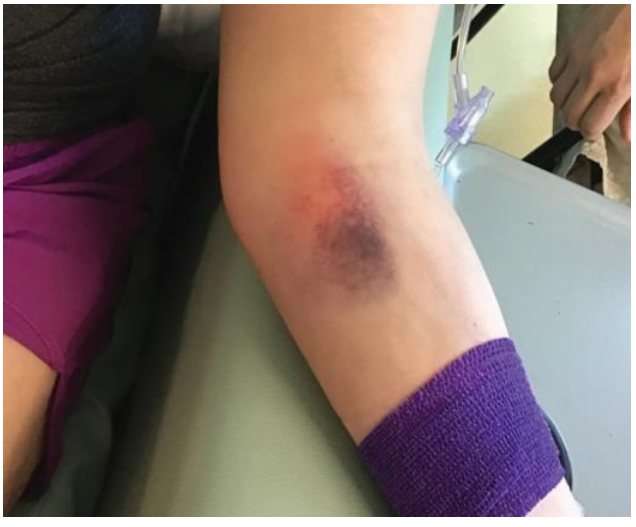

Figure1: Extravasation site the following day after initial doxorubicin extravasation was observed

4. Discussion

The case presented here demonstrates the significant morbidity that may be associated with doxorubicin extravasation. To our knowledge, this is the first case report describing the severe consequences occurring after untimely antidote administration to doxorubicin extravasation, including complications such as superficial

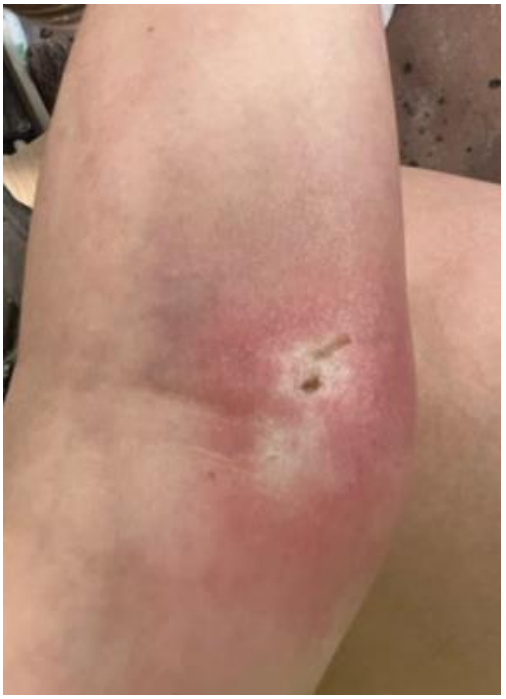

Figure2: Extravasation site almost 2 weeks after the initial doxorubicin extravasation,where the wound had still not closed.

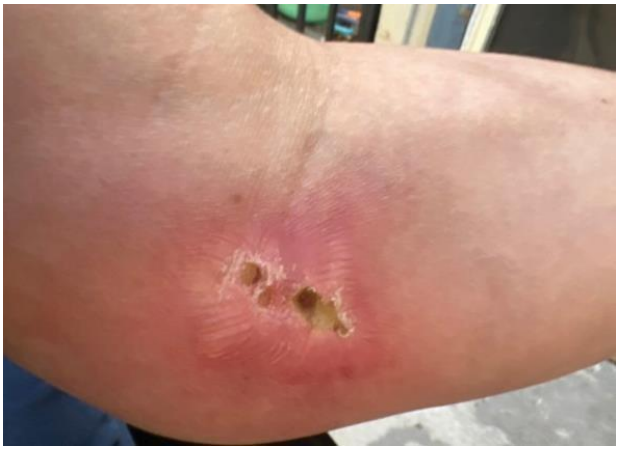

Figure3: Extravasation site three and a half weeks after initial extravasation.

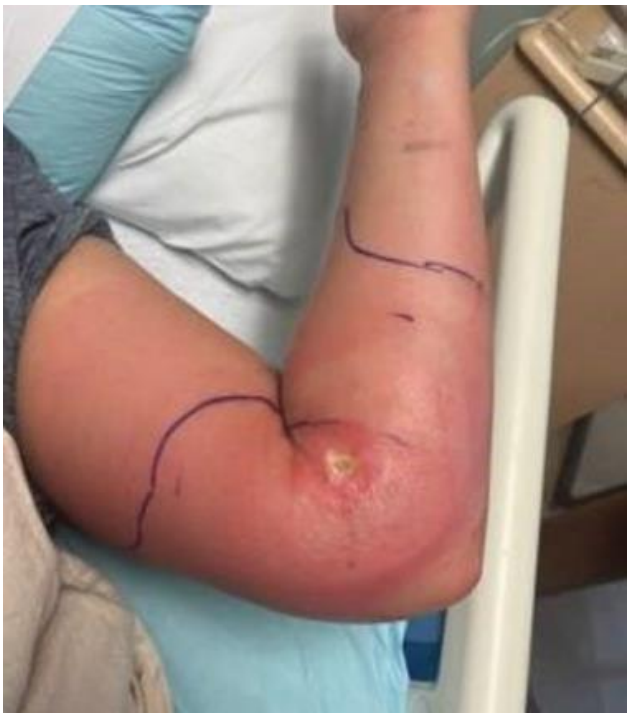

Figure4: Extravasation site almost five weeks after initial extravasation, with cellulitis spreading outside of the original demarcation and up to the patient's shoulder.

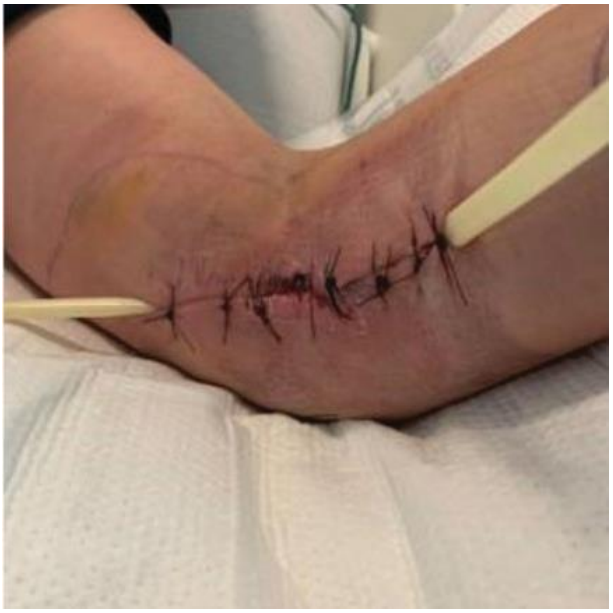

Figure5: Extravasation site post exploratory surgery and left arm incision and drainage.

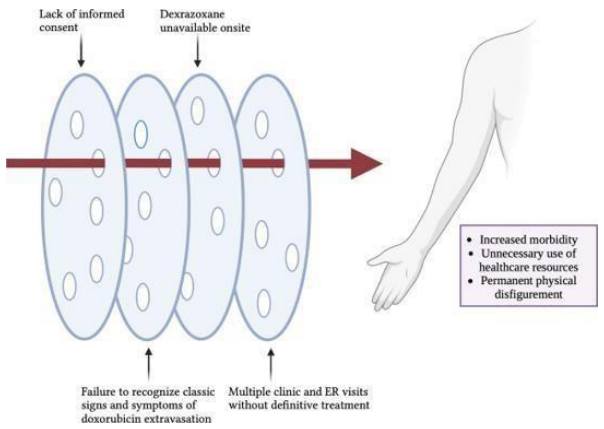

Figure6: Swiss cheese model of medical errors implicated in this case.

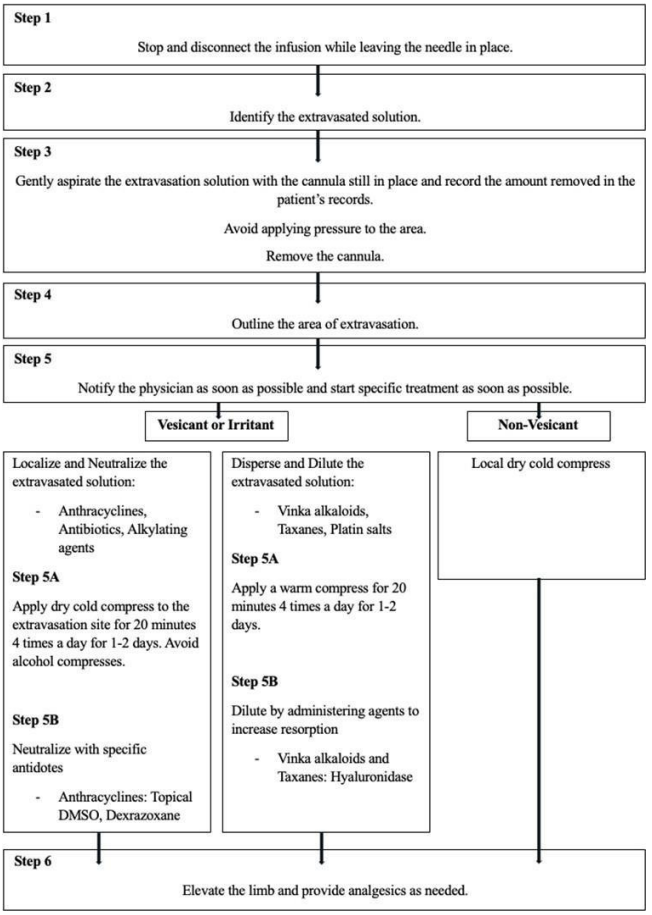

Figure7: Management of chemotherapy extravasation from peripheral IVs adapted from Annals of Oncology 2012, ESMO-EONS Clinical Practice Guidelines.

thrombophlebitis and ulnar nerve palsy. Moreover, it highlights specific instances over the course of the patient's treatment where medical errors built up and led to devastating consequences, which is exemplified by the Swiss cheese model illustrated in Figure 6 [7].The initial deficit in the medical system began before the chemotherapeutic agent was administered when there was insufficient discussion on the risk and benefits associated with administration of doxorubicin through a peripheral vein. In the present case, the patient reported that she was not given information regarding why a PICC line was the preferred method for doxorubicin administration. Furthermore, she stated that she opted for the IV so that she would still be able to participate in aquatic activities with her family that summer. Shared decision making with the patient would have been a valuable tool to ensure that she had the appropriate information about the risks and benefits of both the PICC line and the IV for chemotherapy infusion so that she could make an informed decision about her own healthcare and her goals of care [8].This case report highlights the necessity of administering chemotherapeutic agents through a central venous chest port or through a PICC line, rather than through a peripheral IV as the rates of extravasation are lower amongst central venous access devices (0.26% to 4.7% vs 0.1% to 6%) [4]. Moreover, it has been well established that chemotherapeutic drugs can damage peripheral veins, leading to extravasation and tissue damage [9]. Thus, it is crucial that medical professionals properly inform patients of the risks and benefits of receiving chemotherapy peripherally vs through central vasculature [10].

Table1: Common Terminology Criteria for Adverse Events (CTCAE) Extravasation Grade.

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion site extravasation	Painless edema	Erythema with associated symptoms (eg, edema, pain, induration, phlebitis)	Ulceration or necrosis, severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

The next deficit in this case was the failure to initially recognize the extravasation.

Common signs and symptoms of doxorubicin extravasation include swelling, erythema, burning sensation, and pain [4]. Onset of these symptoms should prompt the healthcare provider to immediately stop the chemotherapeutic infusion and provide appropriate interventions [4]. In this case, the patient complained several times of burning pain and tightness before the infusion was halted highlighting a need for further education for health care professionals on the warning signs of extravasation. Fortunately, this patient received dexrazoxane within 6 hours of the initial extravasation. However, the failure of the infusion clinic to possess the antidote onsite creates a potential for delayed administration in future extravasation events. Had the antidote been acquired even 45 minutes later, it would have been administered outside the time period recommended by the Food and Drug Administration (FDA) [5]. This near-miss event highlights the importance of possessing the antidote of any administered chemotherapeutic onsite and requires system level evaluation and education in the management of chemotherapy extravasation from peripheral IVs as shown in Figure 7 to prevent similar occurrences in the future [11].Another factor complicating this case is the fact that the patient did not receive definitive treatment until weeks after initial extravasation occurred. According to the Common Terminology Criteria for Adverse Events (CTCAE), published by the United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute, extravasation can be classified into 5 grades as shown in Table 1.Based on these grades, this patient met criteria for operative intervention when she developed ulceration at the extravasation site. The ulceration developed within a week after the initial extravasation. However, she did not receive operative intervention until over 1.5 months after the extravasation. This not only prolonged the patient's agony, but also resulted in numerous clinic visits, ER visits, and five-day hospital stay, placing an enormous financial burden on the patient and her family.This case highlights the need for greater education on recognition of complications of doxorubicin extravasation, and its definitive treatment options. Previous case reports have detailed similar disastrous effects of intravascular doxorubicin extravasation when treatment is delayed. For example, in a 52-year-old patient where doxorubicin was administered intravenously through a peripheral vein in the hand, extensive tissue necrosis and erythema occurred because of delayed recognition and treatment of extravasation [12]. Due to the rarity of doxorubicin extravasation, raising awareness of its presentation through case reports allows for improved care for patients with similar complications in the future. Cellulitis and necrotizing fasciitis were also considered as complications of doxorubicin extravasation as both can present with similar symptoms to an abscess. Cellulitis can present with edema, inflammation, redness, warmth, and swelling [13]. These symptoms mirror what this patient was experiencing, thus explaining why cellulitis was a consideration in this patient's diagnosis and treatment. Necrotizing fasciitis can be diagnosed with an ultrasound and/or MRI, along with symptoms of bruising, blistering, and necrosis [14]. Coupled with lack of abscess on presenting ultrasound along with nonspecific symptoms, the initial diagnosis of abscess was not clear but the patient was later found to have a cellulitis, necrotizing fasciitis complicated by an abscess. This again highlights that medical professionals must be aware of the complications of doxorubicin extravasation and be well equipped to recognize and treat such outcomes. Due to the present tissue damage, the direction of the patient's future chemotherapeutic treatment is unclear making an overall resolution more difficult. Thus, precautions should be taken to ensure that doxorubicin and other chemotherapeutic agents are administered through central veins whenever possible to avoid peripheral extravasation and limit tissue damage.In terms of extravasation, medical staff should be well equipped to recognize and make this diagnosis. Previous case reports detailing extensive tissue necrosis after delayed dexrazoxane administration after doxorubicin extravasation [12] underscore the necessity of recognizing and treating extravasation in a timely manner. After diagnosing extravasation, the appropriate steps (including aspirating the extravasated solution and administering the drug specific antidote) should be taken as soon as possible [15]. Consistent follow-up and early definitive treatment can significantly reduce morbidity by preventing progression of symptoms, minimizing long term complications, and avoiding emergent interventions such as surgical debridement.

5. Conclusion

Doxorubicin, while an effective chemotherapeutic agent in the fight against cancer, carries the risk of extravasation - a rare but potentially devastating complication. In this case four critical moments stand as missed opportunities to prevent significant harm. Omitting informed consent for the peripheral IV versus PICC line denied the patient agency and knowledge; inability to identify the early signs and symptoms of extravasation - burning, erythema, and swelling - allowed the damage to progress; the absence of on-site dexrazoxane prolonged the time before the patient got the antidote; and a fragmented care journey underscored the need for greater awareness generally for doxorubicin extravasation and its subsequent complications. This case serves as a wake-up call for improved educational initiatives on doxorubicin extravasation and systemic healthcare level changes to prevent inaccessibility to reversal agents, empowering healthcare professionals to recognize early signs, understand long-term risks, and administer efficient treatment will ultimately prevent invasive procedures and minimize long-term suffering for patients.

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