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Clinical Results After Doxorubicin Extravasation Treated With Excision Guided by Fluorescence Microscopy

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Doxorubicin (DR) and epirubicin (ER) produce progressive tissue necrosis when extravasation occurs. Early detection and excision of all affected tissue is important. The clinical experience with fluorescence microscopic guided detection and excision in 24 patients is evaluated. 9 patients with fluorescence negative specimens were kept under observation without excision. None developed necrosis. Wide excision was performed on 15 patients with fluorescence positive specimens. Sequelae, defined as impaired function of the affected limb at the last control examination in the out-patient clinic, were observed in 8 patients. 4 of 5 patients with extravasation in the hand and 2 of 3 with extravasation in the cubital fossa were among these. Delay, defined as time from injury to surgery, was a median of 7 h, range from 3 h to 69 days. Patients developing sequelae had a median delay of roughly 4-fold that of patients without these complications. Patients with extravasation in the cubital fossa were hospitalised for the longest period: 30 days, range 24–45 days, vs. 12 days, range 7–80 days, for those with extravasation at other sites ($P < 0.03$). Our conclusions are: (1) fluorescence microscopic analysis is a reliable method for the detection and delineation of extravasation of DR or ER. (2) Do not use the cubital fossa or hand for the infusion of these cytostatics. (3) Act promptly if extravasation is suspected—delay leads to sequelae.
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INTRODUCTION

CYTOSTATICS as an infusion are frequently used in the treatment of certain types of cancer. Extravasation occurs in about 2–5% of patients treated in this manner [1]. One particular group of cytostatics is extremely dangerous in this respect: the anthracycline antibiotics doxorubicin (DR) and epirubicin (ER). In addition to causing early injury to the surrounding tissue, these drugs become bound to the nucleic acids within the cell [2]. The drug is still active even after being released from necrotic cells, and is able to damage adjacent cells, after which progressive necrosis may take place [3]. Therefore, early detection of extravasation as well as excision of all affected tissue is crucial [2, 4]. Such excision was earlier guided by clinical signs alone, and as a consequence delay frequently occurred and led in a number of cases to reoperation and even amputation in these otherwise fragile patients. It is possible, using fluorescence microscopic analysis, to confirm the diagnosis and delineate the affected tissue [5].

We report here our experience with this method in 24 patients referred to our department with suspected extravasation.

PATIENTS AND METHODS

24 patients were admitted to our department due to suspected extravasation of DR or ER during the period 1987 to mid-1991. There were 6 males and 18 females with a median age on admission of 56 years, range 10–78 years. The cytostatics had been administered systemically because of disseminated breast cancer ($n = 12$), metastases from lung cancer ($n = 4$), malignant lymphoma ($n = 4$) and other malignancies ($n = 4$).

The skin area of the suspected extravasation was outlined and representative specimens of the skin and subcutaneous tissue around the site of injection were taken. Fluorescence microscopic analysis was immediately carried out on frozen sections of these specimens [4]. If the specimens were negative, the patients were merely kept under observation. If the specimens were positive, excision of the affected skin and subcutaneous tissue was performed immediately with a margin of 1 cm all the way round and to a depth of at least the muscle fascia. New specimens were then taken from the borders of the wound. If still positive, the excision was continued until a free margin was obtained. The wounds were covered with a dressing and the patients kept under observation for the following 2 or 3 days, paying special attention to the possible development of tissue necrosis. The defects were then covered with split skin grafts, providing no signs of necrosis were present.

The Mann–Whitney two-sample rank-sum test was used for statistical analysis. Differences between observed groups with P values of < 0.05 were considered significant.

RESULTS

All of the patients presented with clinical signs of extravasation: pain, swelling, erythema and in some, necrotic skin (Fig. 1).

Fluorescence microscopic analysis was negative in 9 cases. These patients were kept under observation and no signs of necrosis or sequelae were seen. 15 patients had fluorescence positive specimens and excision of the affected area was carried out on all 15 (Fig. 2).

Of these 15, 5 suffered extravasation in the hand, 6 in the forearm, 3 in the cubital fossa and 1 in the chest wall (Table 1). The defects after surgery were most extensive in the cubital

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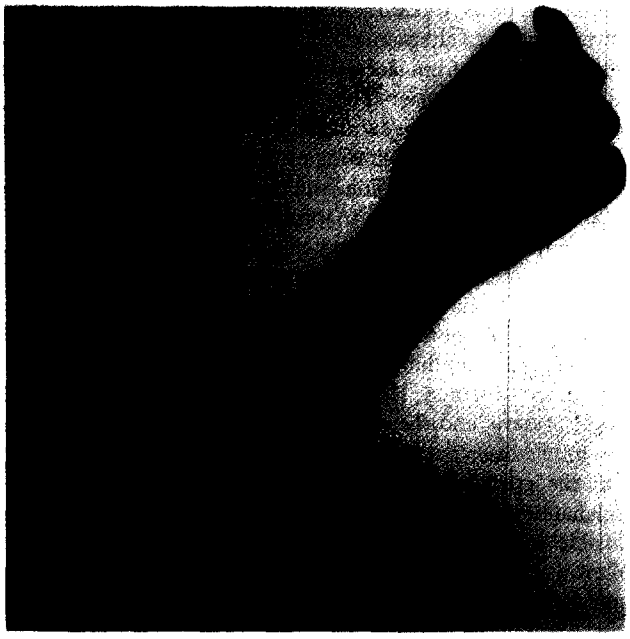

Fig. 1. Erythema of the skin following extravasation. Cannula was placed on the distant part of the antebrachium. Notice the small area with erythema marked near the cubital fossa.

fossa; median 25 cm, range 24–30 cm as against 8 cm, range 6–20 cm at the other sites.

4 of these 15 patients had to be subjected to re-operation because of subsequent necrosis. There had been traces of DR or ER at the end of the operation; the whole affected area could not be removed for technical reasons. 2 of the 3 patients with extravasation in the cubital fossa were among those where re-operation was necessary.

Sequelae, defined as impaired function of the affected limb at the last control in the out-patient clinic, were reported in 8 of the 15 patients (Table 2). 4 of the 5 patients with extravasation in the hand suffered sequelae, as did 2 of the 3 with extravasation in the cubital fossa.

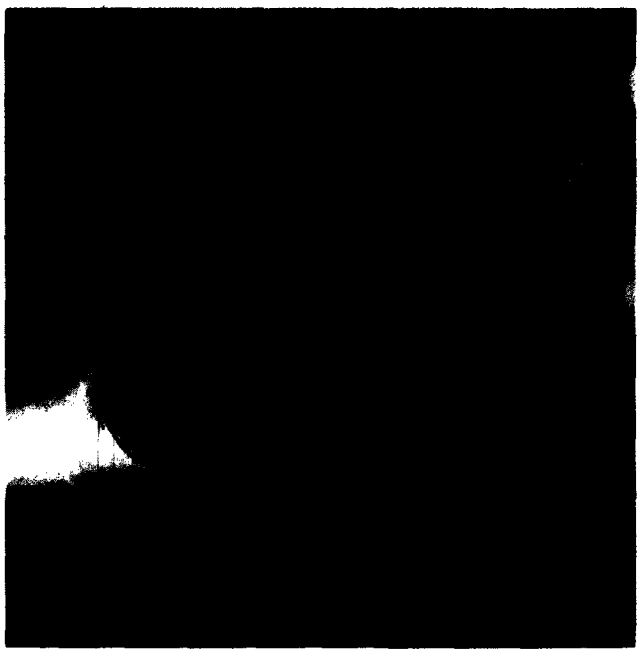

Fig. 2. All of the affected skin and subcutaneous tissue was excised down to muscle fascia.

Table 1. Size of defects and number of re-operations in 15 patients with doxorubicin or epirubicin extravasation. Excision guided by fluorescence microscopic analysis

Region	Number	Defect (median) range	Re-operation number
Hand	5	8 (6–12) cm	1
Forearm	6	8 (6–20) cm	1
Cubital fossa	3	25 (24–30) cm	2
Chest	1	—	0

Delay, defined as the time from injury to surgery, was 7 h (median), range 3 h to 69 days. Those patients who developed sequelae had a median delay of roughly 4-fold that of those without later impaired function, 32.5 h, range 3 h to 69 days as compared with 7 h, range 3 h to 60 days. The difference in delay, however, was not significant ($P = 0.79$).

Patients with extravasation in the cubital fossa were hospitalised for a considerably longer period than those with extravasation at other sites; 30 days, range 24–45 days vs. 12 days, range 7–80 days, respectively ($P < 0.03$) (Table 2).

DISCUSSION

Fluorescence microscopic analysis appears to be an excellent tool in the important task of identifying and delineating DR and ER extravasation. Dahlstrøm *et al.* [5] demonstrated, in a rat model, that even very low concentrations of these drugs can lead to necrosis, depending on the volume. The concentration leading to necrosis correlated with the quantity of cytostatic that it was possible to detect by means of fluorescence microscopic analysis. None of the patients in the present study having fluorescence negative specimens developed necrosis. In contrast, patients with fluorescence positive specimens who, of necessity, had to be subjected to re-operation due to subsequent necrosis, all had traces of DR or ER in the wound at the end of the primary excision. More extensive excision had not been carried out in an attempt at saving important anatomic structures, i.e. blood vessels and nerves.

Clinically it is often impossible to be sure whether extravasation has occurred or not. Nevertheless, it is of paramount importance to detect extravasation as soon as possible because of the risk of subsequent necrosis. Furthermore, many of these patients are cytopenic and as a consequence, necrosis may lead

Table 2. Length of hospitalisation and number of patients with sequelae after extravasation of doxorubicin or epirubicin. Excision guided by fluorescence microscopic analysis

Region	Number	Stay at hospital median (range)	Sequelae number*
Hand	5	11 (10–47) days	4
Forearm	6	13 (7–80) days	2
Cubital fossa	3	30 (24–45) days	2
Chest	1	—	0

* Number of patients with sequelae.

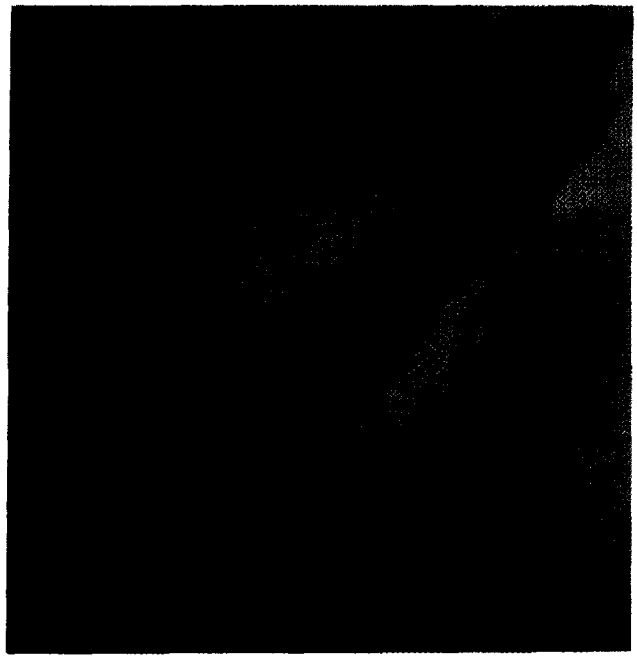

Fig. 3. End result after dressing with split skin grafts. Function was restored, there was no oedema but, of course, some cosmetic sequelae.

to fatal infections [6]. It has been suggested in some studies that such extravasations should be kept under observation, as in many cases no serious effects can be seen [7, 8]. However, these studies were unable to prove that extravasation had actually taken place, because the diagnosis was based on clinical signs and symptoms only, and these are similar to those brought about by phlebitis and/or infection [6].

The prognosis, based on late sequelae, was related to two factors: the anatomical region chosen for the infusion, and the time from accident to surgery; this appears to lend support to the results of Linder *et al.* [6]. With regard to the choice of anatomical region, the cubital fossa and the hand should be avoided as far as possible, due to the serious complications should extravasation occur [9]. The cubital fossa is difficult to handle because of the important anatomical structures in the area and should extravasation take place then it occurs deep in subcutaneous tissue or even under the muscle fascia. In cases in our study with extravasation in this area, it was necessary to limit the excision when only slight fluorescence remained in the marginal sites in an attempt to preserve the brachial artery and the median nerve. Unfortunately, this may lead to further necrosis. Impaired function of the hand was seen because of involvement of the extensor tendons in this region. Some of the patients suffered immobility of the hand or arm as well as loss of sensibility. All of our patients had some cosmetic sequelae, although to a varying degree (Fig. 3).

In order to avoid such deplorable accidents, the forearm is the preferable site for infusion of such potent cytostatics. If cannulation of the forearm cannot be employed, then the use of central veins is an alternative.

Shorter delay from accident to surgery resulted in fewer patients with sequelae. Therefore, action should be taken promptly in cases where extravasation is suspected. Our department recommends the following procedure [5, 9]. The first step is to discontinue the infusion, and do not use the cannula again as no antidote is available. Aspirate through the cannula and then remove it. Mark the area of pain, erythema or swelling. Take specimens from representative areas for fluorescence microscopy. If these are negative, then keep the patient under observation for a number of days. If they are positive, carry out excision guided by fluorescence microscopic analysis until free margins are obtained. Keep the defect under observation for a couple of days, and then cover with a skin graft. Mobilise the extremity as soon as possible.

In the great majority of these cases there is no obvious explanation as to how they have occurred. It would have been possible to avoid some of these events as illustrated by the following examples: 1 patient had more than one puncture of the same vein, this resulted in extravasation from the extra holes. In another case, a very small cannula (butterfly) was inserted in a cubital vein, this resulted in extravasation due to displacement of the cannula following flexion of the elbow. In a third case the patient was obese and the injection port was placed deep in the subcutaneous tissue of the trunk. This lead to uncertainty as to the placement of the needle at infusion. The result was extravasation. These and other causative factors are well-known [6].

Our conclusions are: (1) fluorescence microscopic analysis is a reliable method for both the detection and delineation of such extravasation. (2) Do not use veins in the cubital fossa or hand for infusion of potent cytostatics. Use the forearm or a central vein for cannulation. (3) Act promptly if extravasation is suspected. Delay leads to sequelae.

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