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Ultrasonographic assessment of an induration caused by extravasation of a nonvesicant anticancer drug

A case report

Mari Abe-Doi, RN, MHS[a], Ryoko Murayama, RN, RNM, PhD[a,b], Koichi Yabunaka, PhD[b,c], Hidenori Tanabe, MS[a,d], Chieko Komiyama, RN, MNS[e], Hiromi Sanada, RN, WOCN, PhD[b,f,*]

Abstract

Rationale: Induration may occur after an anticancer drug extravasation in patients who recurrently receive chemotherapy because of reduced choice of an appropriate vein for inserting a peripheral intravenous catheter, resulting in catheter placement difficulty. Although induration affects treatment, its size, shape, or hardness remains unclear in the conventional observation method using palpation and inspection. Here, we report our observation results in using ultrasonography to assess the induration that occurred after an anticancer drug extravasation as a new assessment method.

Patient concerns: A 58-year-old woman with cervical cancer who complained of pain during the administration of a nonvesicant anticancer drug via a peripheral intravenous catheter. The medical staff's examination showed a swollen site; therefore, the catheter was replaced.

Diagnosis: Induration occurred on the site after an extravasation. Over 6 months later, pigmentation and induration, which can easily be confirmed through palpation, persisted.

Interventions: The subcutaneous tissue in the induration site was observed using ultrasonography (B-mode and elastography).

Outcomes: The subcutaneous tissue might have degenerated the tissues surrounding the vein, making it thinner. Moreover, the hardness of the subcutaneous tissue was approximately 7 times than that of the surrounding tissues.

Lessons: Induration that affects the vein form and its surrounding tissues should be prevented, and ultrasonography is an effective method to objectively observe the site where extravasation occurred.

Abbreviations: Bev = bevacizumab, CPT-11 = irinotecan, ROI = region of interest, SR = strain ratio, TP = paclitaxel + cisplatin.

Keywords: bevacizumab ultrasonography, elastography, extravasation, induration, nonvesicant drugs

1. Introduction

Anticancer drug therapy warrants recurrent administration through an intravenous catheter, posing a risk of extravasation. Possible signs and symptoms of extravasation include swelling, pain at the infusion site, erythema, and blistering and/or blanching of the overlying skin.[1] In cancer therapy, extravasation is defined as the process by which any liquid (fluid or drug) accidentally leaks into the surrounding tissues.[2] Anticancer drug extravasation can cause blisters, ulcers, and induration.[2–4] Anticancer drugs can be grouped into the following 3 broad categories depending on their potential to cause tissue damage upon extravasation: nonvesicants, irritants, and vesicants.[2,3] Irritant drugs pose a risk of inflammation, whereas vesicant drugs pose a risk of ulceration or necrosis if leaked even in small amounts. In contrast, nonvesicants do not impair or destroy the surrounding tissues. In addition, most nonvesicant drugs can be administered intramuscularly or subcutaneously besides intravenously. However, regarding the vesicant and irritant drugs, nonvesicant drug extravasation could result in induration. Induration does not require surgical treatment as ulcer or necrosis; however, its occurrence is a prominent clinical challenge because a catheter cannot be inserted into the site. Further, medical staff members avoid the site for catheter placement, thereby decreasing the options of veins for catheter placement,

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[a] Department of Advanced Nursing Technology, [b] Global Nursing Research Center, [c] Department of Imaging Nursing Science, Graduate School of Medicine, The University of Tokyo, Tokyo, [d] Terumo R&D CENTER, Kanagawa, [e] Department of Nursing, The University of Tokyo Hospital, [f] Department of Gerontological Nursing/Wound Care Management, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

[*] Correspondence: Hiromi Sanada, Department of Gerontological Nursing/Wound Care Management, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan (e-mail: hsanada-tky@umin.ac.jp).

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thereby decreasing its success rate. Thus, ensuring the actual induration condition occurring due to anticancer drug extravasation is imperative to prevent its development.

In the current clinical settings, induration is evaluated by performing inspection and palpation; however, this conventional method cannot assess the actual induration conditions sufficiently (e.g., size, hardness, effects on the vein, and site of occurrence). In addition, other assessment methods are warranted to investigate causal factors, elucidate the severity, and monitor the follow-up results. This study focused on using ultrasonography to assess the actual induration conditions, showing that it is an appropriate method to examine induration because B-mode is already an established method used to assess the degree of edema in the tissues surrounding the blood vessels, blood vessel walls, and thrombus[5,6] and elastography could provide information regarding the hardness in the subcutaneous tissue.[7]

Herein, we present a case of induration assessed using ultrasonography (B-mode and elastography), which occurred after the extravasation of a nonvesicant anticancer drug. We believe that this is the 1st observational report on induration caused by extravasation using ultrasonography.

2. Case report

A 58-year-old woman with cervical cancer was hospitalized and received paclitaxel + cisplatin (TP) + bevacizumab (Bev) through an infusion pump on the 4th course. Before the TP + Bev treatment, the patient had never received chemotherapy.

On treatment day 1, chemotherapy was started at 11 AM. First, a steroid (dexamethasone 19.8 mg + ranitidine hydrochloride 1500 mg, administered at 200 mL/h for 30 minutes) and antiemetic drug (palonosetron hydrochloride 0.75 mg administered at 100 mL/h for 30 minutes), followed by an anticancer drug (paclitaxel 196 mg administered at 45 mL/h for 24 hours), were administered through a peripheral intravenous catheter on her right wrist. Although no problem was reported during the dripping drug infusion, a doctor replaced the peripheral catheter on her left forearm; the catheter was placed 5 cm away from her elbow joint, because of pain and slight erythema at the cannulation site complained at 11 PM, 10 hours after starting the administration of a vesicant drug (paclitaxel). The treatment was continued without complications until the next afternoon, and an irritant drug (cisplatin 53 mg administered at 220 mL/h for 120 minutes) was successfully administered. However, at 3:20 PM, she complained of pain around the site of the indwelling catheter to the medical staff members, which was 15 minutes after starting a nonvesicant drug (bevacizumab 767 mg administered at 260 mL/h for 30 minutes). In addition, a medical staff member confirmed swelling. However, induration was not yet confirmed during this time. Medical staff members suspected the occurrence of extravasation based on these symptoms, removed the catheter, and medically treated the affected site with steroid-containing ointment (betamethasone valerate). Figure 1 shows details intravenously administering drugs, including nonanticancer ones.

On the next treatment day, 4 weeks after the extravasation event, internal bleeding, and slight swelling were observed at the extravasation site; however, no pain and signs of inflammation were noted. She had stopped using the ointment during this time and did not use any medication. The patient had received the TP + Bev treatment recurrently until the 6th course; then, the chemotherapeutic regimen was changed to irinotecan (CPT-11) because of the occurrence of hydronephrosis. CPT-11 should be infused weekly, which was regularly administered at an outpatient service. At 6 months after the extravasation event, the site was never used for catheterization (Fig. 2).

Besides conventional methods (inspection and palpation), induration was diagnosed via ultrasonography at the outpatient service 5 and 6 months after the extravasation event. The patient had a clear pigmentation and induration, which was easily confirmed on that site (Fig. 3). The induration develops in the forearm, approximately 5 cm from the cubital fossa.

A clinical nurse who had over 10 years of clinical experience assessed that this was not an appropriate puncture site. In addition, the nurse's palpation findings were as follows: induration was present in the subcutaneous tissue or vein, with an oval shape, moderate hardness, and clear boundary. Repeat ultrasonography was performed at 5 and 6 months after the extravasation; however, no changes were noted. In this report, image data obtained 6 months after the extravasation were used.

A probe was placed immediately above the center of the induration site, and several images were captured in the short and long axes. Noblus (Hitachi Ltd, Medical, Taito, Tokyo, Japan) was used with a linear-array (5–18 MHz) 2-dimensional probe. In addition, elastographic imaging was performed using an acoustic coupler as a hardness reference material. While the region of interest (ROI) was placed on the target induration on B-mode images, another ROI was placed on an acoustic coupler, placed just above the induration area, to evaluate the strain ratio (SR). The SR was evaluated by comparing the strain reference value with that of the targeted induration.

The B-mode and elastography images on the induration site showed hyperechoic and hardened areas. Images of the mass with hyperechoic area was obtained and suspected to be consistent with the induration site upon palpation. In the short-axis image, the shape of the mass was circular, with a heterogeneous echoic image inside. Although tiny echo-free areas resembling veins were detected at the edge of the mass, they could hardly be observed at its center (Fig. 4A,B). The size of the circular hyperechoic area was 4.5 mm × 6.8 mm. In the long-axis image, the hyperechoic oval area was detected with an unclear outline, and the inside had an echo-free area that seemed like a vein. Remarkably, the shape of the echo-free area was linear (Fig. 4C).

Hardness was measured as the SR by obtaining 3 elastographic images at the site for stable images (Fig. 5A,B) and assessed for SR induration and the surrounding tissue from each image (Fig. 6A, B). Then, the 3 values were averaged. When the acoustic coupler was set to 1, the SR in the induration site and the surrounding tissues were 1.60 and 10.22 in the short-axis images and 2.39 and 18.11 in the long-axis images, respectively.

2.1. Ethical considerations

This study was approved by the ethical committee of The University of Tokyo, which conformed to the guidelines in the Declaration of Helsinki: No. 11599-(1). Informed written consent was obtained from the patient for publication of this case report and accompanying images.

3. Discussion

To the best of our knowledge, this is the 1st report to objectively assess subcutaneous tissue induration, which occurred because of a nonvesicant anticancer drug extravasation using ultrasonography. Besides providing information obtained by the conventional method, ultrasonography could create visualization, quantify the size, and determine the hardness of induration.

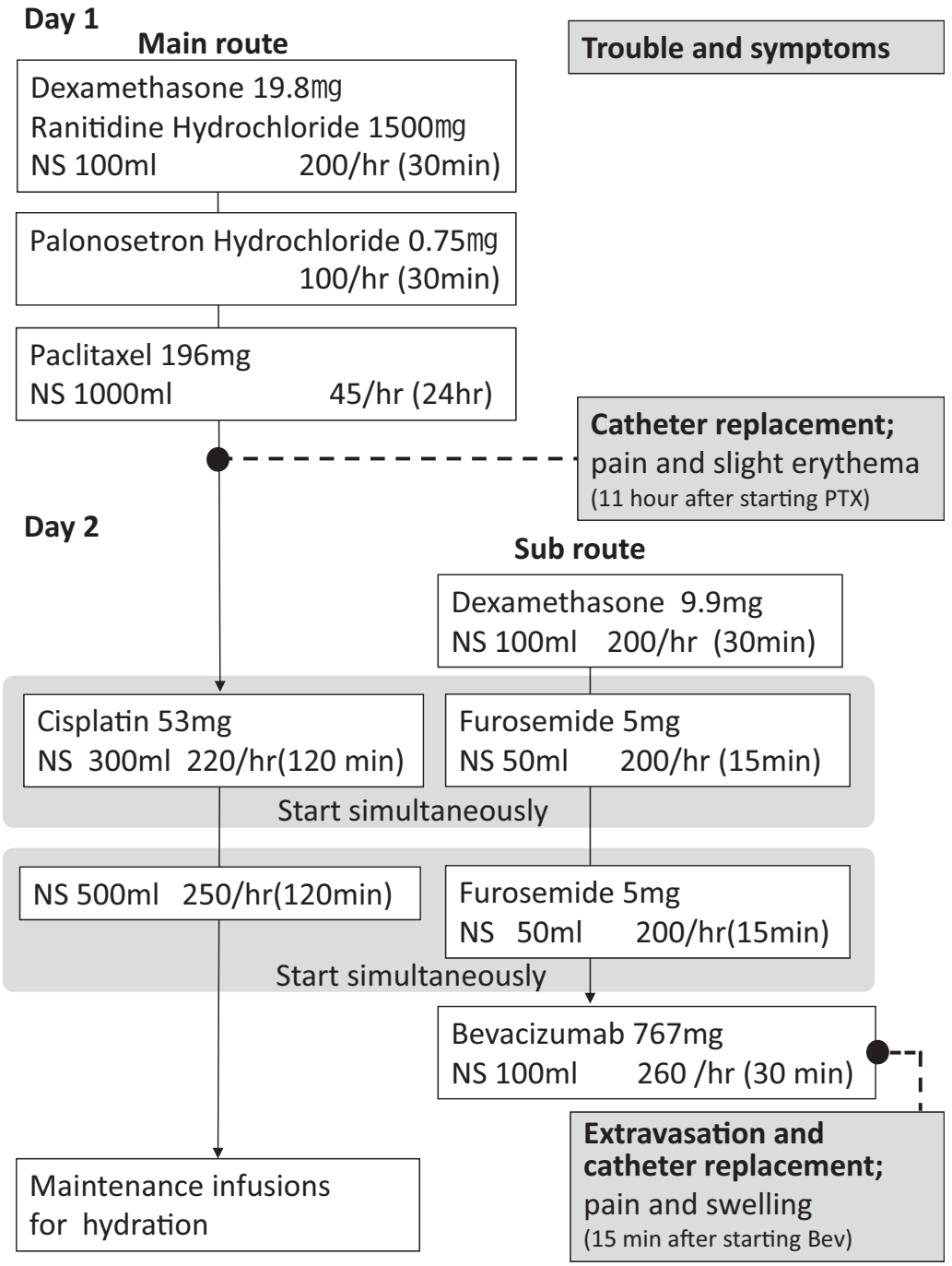


Figure 1. Details of drug administration. NS = normal saline.

The patient in this case report had site pigmentation, and the hyperechoic area at the induration site was noted in B-mode images. In addition, the area was harder than the surrounding tissue (short-axis: 6.39 times; long-axis: 7.58 times). These results could be attributed to the occurrence of fibrosis in the surrounding tissue of the vein due to postextravasation inflammation. Furthermore, fibrosis could possibly make the vein thin.

Residual pigmentation was noted even 5 months after the occurrence of nonvesicant drug extravasation. Apparently, pigmentation is a big cosmetic issue. Moreover, vein stenosis caused by fibrosis in the perivascular tissue is a clinical challenge in patients who required recurrent administration of anticancer drugs through a peripheral vein catheter because of catheter placement difficulty. Typically, nonvesicant drugs are known not to impair or destroy the surrounding tissues[8,9]; measurement of nonvesicant drug extravasation might not be included in the current extravasation management practice. These events are not managed like that of vesicant or irritant drug extravasation. In most guidelines, anticancer drug extravasation measures focused on vesicant drugs, as these pose risks of severe tissue damage requiring surgical treatment.[2,9,10] However, nonvesicant drug

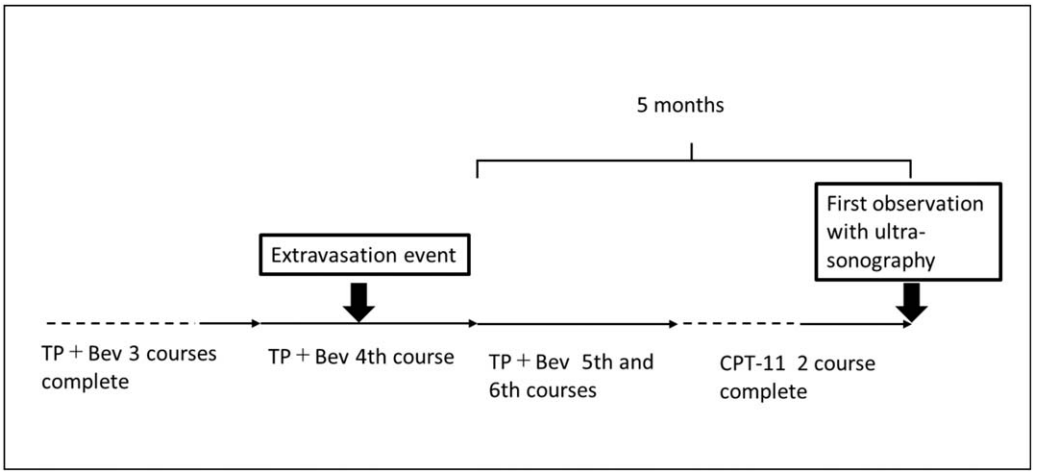


Figure 2. Treatments and event and observation points. Bev = bevacizumab, CPT-11 = irinotecan, TP = paclitaxel + cisplatin.

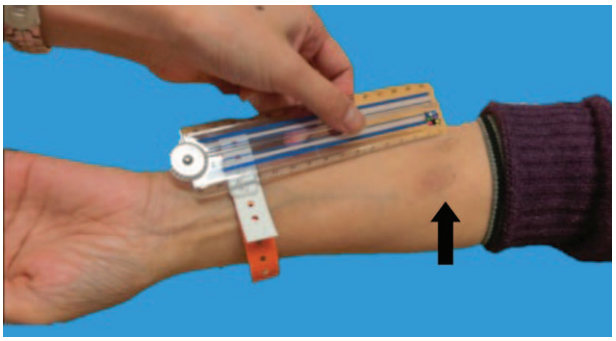


Figure 3. Pigmentation. Black arrow indicates pigmentation on the left arm.

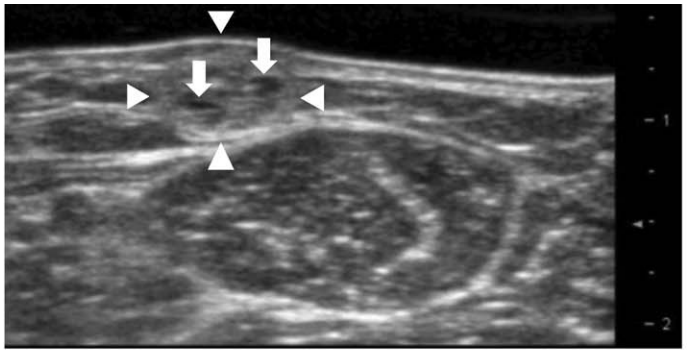
extravasation might lead to severe induration, as in this case, and could affect the catheterization, which is essential for chemotherapy. Hence, nonvesicant drug extravasation should also be prevented as that in vesicant or irritant drugs, and medical staff members should recognize this risk and take adequate measures, especially against extravasation in highly at-risk patients, such as those with obesity, advanced diabetes, and peripheral vascular disease.[2]

This patient had no disease that would lead to extravasation, such as diabetes or vascular disease. Dorsal hand or wrist are not appropriate site as a catheterization from preventing extravasation[3]; however, the catheter had been placed at the median antebrachial vein, meaning it was placed at the low-risk site. However, she had other risk factors for extravasation. First, she received infusion with high flow.[2] Second, she had received prolonged infusion therapy.[2] Although the catheter was replaced once, it was used for over 16 hours. Reportedly, the catheter used for long time tended to result in catheter-related inflammation,[11] and this patient was administered with paclitaxel (vesicants) for a long time period, which may lead to extravasation risk in the vessel walls exposed to chemical stimulation. Third, she had received cisplatin (irritant drug). Since extravasation occurred after administering cisplatin, which is a risk factor for chemical phlebitis,[2] continuous infusion with high flow pressure against fragile vessel wall caused by inflammation due to cisplatin administration might have been led to extravasation. For these reasons, even if the patient had no diseases as risk factors or the catheter was placed in the appropriate site for infusion, the medical staff should perform careful assessment while considering the administration method or pharmacologic risk.

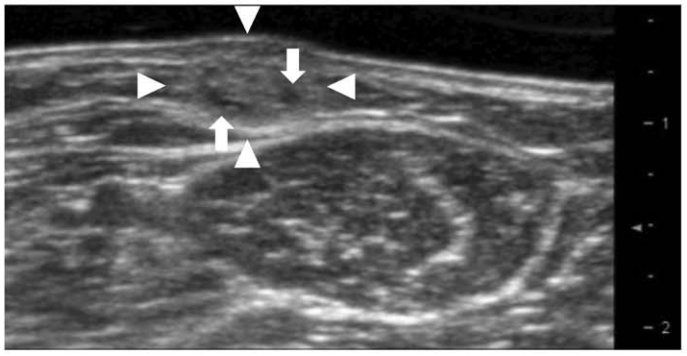
Reportedly, extravasation occurrence was not correlated with the use of an infusion pump[12]; however, an infusion pump should not be used during an anticancer drug administration, especially for vesicant or irritant drugs, to prevent worsening of the extravasation.[13] Therefore, it should be used cautiously even in administering nonvesicant drugs, such as increasing the sensor sensitivity to detect an increase in the inner tube pressure, especially at high infusion rate.

Apparently, nonvesicant drugs are known to exert little tissue damage; however, the patient developed severe induration in this case. A significant amount of drug extravasation could be one of the reasons for this occurrence. The patient was administered with drugs at high infusion rate (260 mL/h) using an infusion pump, which resulted in an extravasation event. Besides, a nurse noted swelling on the site macroscopically. Therefore, the patient may be highly exposed to a large amount of nonvesicant drugs. Reportedly, the extravasated amount is associated with tissue damage, which is similar to the type of medicine[9]; thus, the amount of extravasated drugs to the tissue should be estimated to assess the damage.[14]

In this case report, how and when the soft tissues start degenerating and changed to induration remain unclear, because the site had not been observed using ultrasonography for 5 months since the extravasation event. Evidently, vein and surrounding tissue conditions can be confirmed by ultrasonography.[5,6] Thus, if more cases of extravasation can be longitudinally assessed using ultrasonography immediately after the extravasation occurrence, the subcutaneous tissue characteristics that changed into induration can be determined. Furthermore, longitudinal observation using ultrasonography should be performed to detect early tissue damage caused by extravasation because it may be late onset. The onset of induration can possibly be prevented if subcutaneous tissue or vessels are appropriately monitored, even if extravasation occurs.



A



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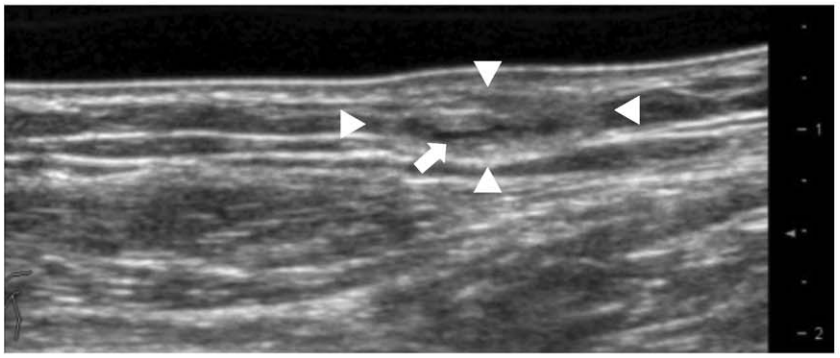

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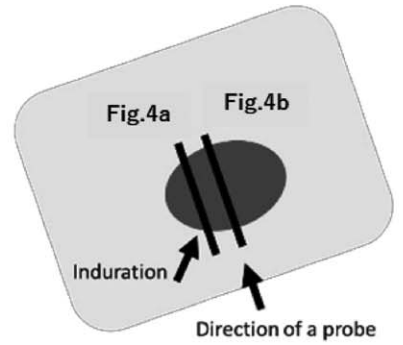


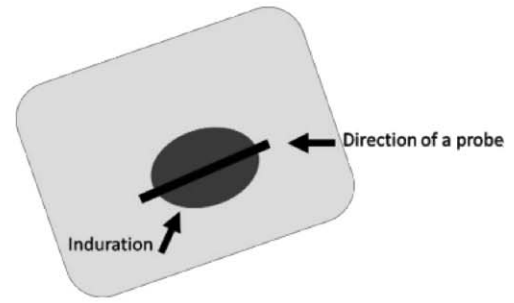
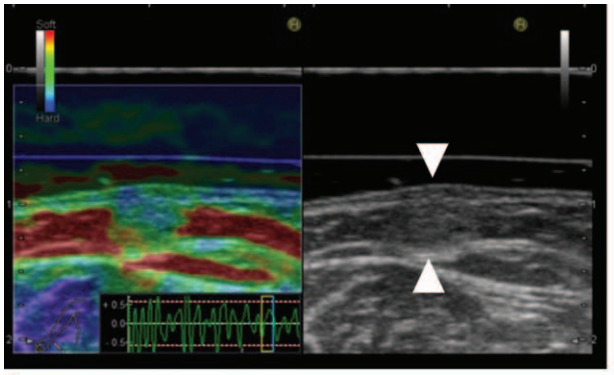


Figure 4. Areas of induration in the B-mode image. Short-axis image: (A) An image at the edge of the mass. The hyperechoic mass shows a circular heterogeneous appearance (arrowheads) with a tiny echo-free area (arrow), which looks like a vein. (B) An image at the center of the mass, demonstrating the echo-free area is getting smaller. The illustration on the right shows the direction of the probe. (C) Long-axis image: the unclear hyperechoic mass shows a heterogeneous oval appearance (arrowheads) with a linear echo-free area (arrow), which looks like a vein. The illustration on the right shows the direction of the probe.



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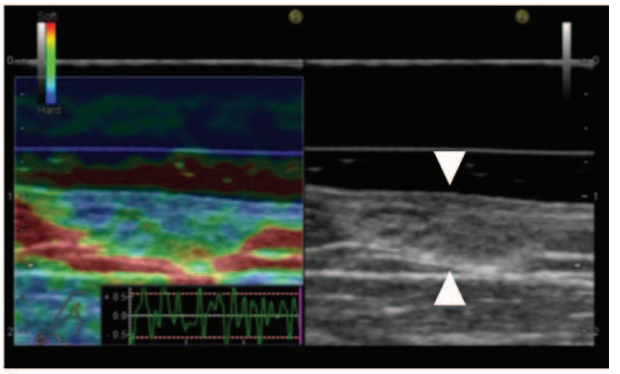

B

Figure 5. Elastographic and B-mode images of the same site. Left side image, the elastography image. Blue color, harder than red; white arrowheads, the center of induration. (A) The short-axis image. The circular induration site is blue or green, and the surrounding tissue is red. (B) The long-axis image. The induration site is blue or green, and the surrounding tissue is red, which is similar with the short axis.

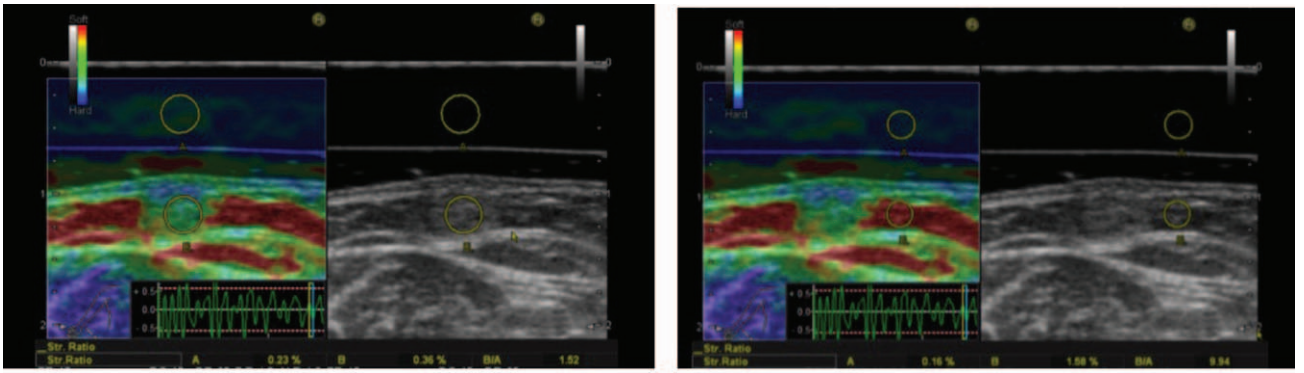

Figure 6. One case of hardness (strain ratio, SR) at the measurement site. (A) Upper circle, the ROI of the acoustic coupler; lower circle, the ROI of the induration site in the short-axis image. The SR is 1.52. (B) Upper circle, the ROI of the acoustic coupler; lower circle, the ROI of the surrounding tissue of the induration site in the short-axis image. The SR is 9.94.

4. Conclusion

This is the 1st case report that objectively assessed the subcutaneous tissue induration that developed after a non-vesicant anticancer drug extravasation using ultrasonography. Ultrasonography could visualize induration and assess induration that leads to the vein stenosis. Therefore, induration affecting the vein should be prevented. Ultrasonography is a useful method to identify extravasated sites and to detect early degeneration of the tissues surrounding the vein.

Author contributions

Conceptualization: Mari Abe-Doi, Ryoko Murayama.
Data curation: Mari Abe-Doi, Koichi Yabunaka, Chieko Komiyama.
Formal analysis: Mari Abe-Doi.
Investigation: Mari Abe-Doi.
Methodology: Mari Abe-Doi, Ryoko Murayama, Hidenori Tanabe.
Supervision: Ryoko Murayama, Koichi Yabunaka, Hiromi Sanada.
Writing – Original Draft: Mari Abe-Doi.
Writing – Review & Editing: Mari Abe-Doi, Ryoko Murayama, Hiromi Sanada.

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