Use of Abnobaviscum to treat refractory seroma after breast reconstruction with a latissimus dorsi flap: A case report

Jong Seong Kim¹, Pil Seon Eo¹, Joon Seok Lee¹, Jeong Woo Lee¹, Ho Yun Chung¹, Byung Chae Cho¹, Kang Young Choi¹, Ho Young Park², Jung Dug Yang¹

Departments of ¹Plastic and Reconstructive Surgery, and ²Surgery, School of Medicine, Kyungpook National University, Daegu, Korea

This article was presented at the 8th Research & Reconstruction Forum on April 19–20, 2018, in Jeonju, Korea.

INTRODUCTION

With advances in diagnostic techniques for breast cancer, the number of mastectomies has increased over the last few decades, and alongside growing cosmetic interest, this has led to an increase in the frequency of breast reconstruction surgery. The latissimus dorsi (LD) musculocutaneous flap is often used in breast reconstruction, because it enables a natural-looking reconstruction that maintains symmetry with the contralateral side. Although LD flap breast reconstruction has become more common, refractory donor site seroma has been established to be a difficult postoperative complication. Currently, various methods are used to treat seroma, including needle aspiration, compression therapy using bandages, arm fixation, triamcinolone injection, and capsulectomy [1-5].

Surgical treatment of refractory seroma using capsulectomy is invasive and provokes anxiety in patients. Therefore, interest has emerged in methods of whole-capsule sclerotherapy for use before considering surgical methods. In the field of thoracic surgery, Abnobaviscum is used to treat adhesions in cases of malignant pleural effusion, and an attempt has been made to use this product to treat seroma [6]. Some studies have reported Abnobaviscum to be effective against malignant pleural effusion, and its efficacy as a sclerosing agent has also been recognized [7-9]. Similarly, there have been continual efforts to treat refractory seroma after malignant pleural effusion treatment or LD flap breast reconstruction using fibrin glue, triamcinolone, anti-inflammatory drugs, or phenytoin [10-14]. At Kyungpook National University Hospital, we have observed positive outcomes when using Abnobaviscum, which has been demonstrated to be safe when used as an anticancer agent, to treat refractory seroma that did not respond to compression dressing using elastic bands, triamcinolone injection, and needle aspiration. Herein, we introduce Abnobaviscum as a potential method to resolve seroma, which is a common complication of LD flap breast reconstruction.
CASE REPORTS

This was a retrospective, single-center study including three Korean patients who underwent LD flap breast reconstruction and had a refractory seroma between September 2016 and May 2018. The study protocol was approved by the Institutional Review Board on December 31, 2018 (IRB No. 2018-12-017) at Kyungpook National University Chilgok Hospital.

The procedure in this study was performed by a single plastic and reconstructive surgeon. The patient group was limited to patients with refractory seroma that persisted for at least 3 months after LD flap breast reconstruction, and that did not respond to conventional methods, such as compression dressing using elastic bands, needle aspiration, or triamcinolone injection (Table 1). In this patient group, consent was obtained from three patients, who decided to receive treatment with Abnoba Heilmittel GmbH (Pforzheim, Germany) after a thorough explanation. The protocol for using Abnoba Heilmittel GmbH is shown in Table 2. A safe dose with regard to adverse effects was determined based on the patient's body weight and the site of administration [5,6], and treatment proceeded according to the method presented below. In patients who showed no response to triamcinolone therapy, 1 mg/0.5 mL of Abnoba Heilmittel GmbH was mixed with 10 mL of normal saline and administered to the patient. Thereafter, the patient lay in the supine, decubitus right, and decubitus left positions for 10 minutes each, and the Abnoba Heilmittel GmbH was removed by aspiration 30 minutes later. Outpatient follow-up was performed 3 days after the procedure; if seroma was observed, the patient visited twice a week for outpatient aspiration, following by compression therapy using elastic bands. After 2 weeks, if the seroma still had not resolved, an identical dose of Abnoba Heilmittel GmbH was administered, and for refractory seroma, the Abnoba Heilmittel GmbH was administered at a higher dose.

Case 1

A 56-year-old female patient was diagnosed with invasive ductal carcinoma (IDC) of the right breast. The department of surgery decided to perform total mastectomy, and referred her to the department of plastic and reconstructive surgery for breast reconstruction. Following an outpatient consultation at the department of plastic and reconstructive surgery, the patient underwent volumetry, and LD flap breast reconstruction was selected as a suitable method for moderate-sized breasts. Following total mastectomy, the patient underwent LD flap breast reconstruction at the department of plastic and reconstructive surgery. On the 13th postoperative day, the daily output drainage was confirmed to be less than 30 mL, and the back drain was removed. No seroma was observed in outpatient follow-up at 3, 4, 6, 8, and 10 weeks postoperatively. At 12 weeks postoperatively, the patient developed refractory seroma and aspiration was performed (Fig. 1). Triamcinolone injections were injected twice in 1 month and, since the seroma did not resolve, according to our institutional protocol, we decided to treat the patient with Abnoba Heilmittel GmbH. At 4 months postoperatively, 1 mg of Abnoba Heilmittel GmbH was administered, and a second dose of 4 mg was administered at 18 weeks postoperatively. The seroma had completely resolved at 19 weeks postoperatively, and thereafter the patient showed no refractory seroma for a further year after treatment. The total treatment duration was 19 days.

Case 2

A 50-year-old female patient showed clustered microcalcifications in seven locations in her left breast, and was diagnosed with IDC. The department of surgery decided to perform left nipple-sparing mastectomy with sentinel lymph node biopsy, and referred the patient to the department of plastic and reconstructive surgery for breast reconstruction. After consultation with the patient, we decided to perform LD flap breast reconstruction. On October 18, 2016, the patient underwent nipple-sparing mastectomy followed by LD flap breast reconstruction. There were no notable events during surgery. On the 13th postoperative day, the daily output drainage was confirmed to be less than 30 mL, and the back drain was removed. At follow-up, a seroma was observed at the back-donor site, measuring 8 and 6 mL, respectively, on the 10th and 14th days after discharge. Following needle aspiration and triamcinolone injection, back donor site seroma was not observed during four follow-up examinations at 4, 6, 8, and 12 weeks after treatment. At 18 weeks postoperatively, the patient developed a refractory seroma. During the next 12 weeks postoperatively, the patient

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.73</td>
<td></td>
</tr>
<tr>
<td>Flap size (width×length, cm²)</td>
<td>5.7×16</td>
<td></td>
</tr>
<tr>
<td>Flap weight (g)</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Breast volume (mL)</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>Right breast</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>Left breast</td>
<td>260</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean.

Table 2. Protocol for Abnoba Heilmittel GmbH use at KNUH

| Abnoba Heilmittel GmbH treatment protocol (KNUH) |
|-----------------------------|-----------------------------|
| 1st                         | Abnoba Heilmittel GmbH, 1 mg |
| 2nd                         | Abnoba Heilmittel GmbH, 2 mg |
| 3rd                         | Abnoba Heilmittel GmbH, 4 mg |
| 4th                         | Abnoba Heilmittel GmbH, 3 mg |
| 5th                         | Abnoba Heilmittel GmbH, 5 mg |

The seroma is extracted with a syringe, the mixed fluid is injected into the empty space, and the mixture is withdrawn after 30 minutes.

KNUH, Kyungpook National University Hospital; NS, normal saline.
underwent triamcinolone and needle aspiration therapy, as well as compression therapy using elastic band dressings, but an 11-mL seroma continued to be observed up to 30 weeks postoperatively. Triamcinolone therapy was judged to have failed, and so, according to the protocol, we decided to use Abnobaviscum to treat the refractory seroma. The patient received a 1-mg dose of Abnobaviscum at 30 weeks postoperatively, and when the seroma continued to be observed, received another dose of 4 mg at 34 weeks postoperatively. The seroma was cured at 34 weeks postoperatively, after which the patient showed no refractory seroma for a further year after treatment. The total treatment duration was 33 days.

Case 3
A 51-year-old female patient visited the outpatient department complaining of a mass, and was diagnosed with multiple microcalcifications in her left breast; after core needle biopsy, the patient was diagnosed with invasive carcinoma with ductal and lobular features. From October 8, 2016 to January 31, 2017, the patient underwent six rounds of neoadjuvant chemotherapy using docetaxel, Neoplatin, Herceptin, and Perjeta, and showed complete remission; the patient was then scheduled for surgery. The department of surgery decided to perform total mastectomy, and referred the patient to the department of plastic and reconstructive surgery for breast reconstruction. Following an outpatient visit to the department of plastic and reconstructive surgery, the patient underwent volume try, and after consultation with the patient, we decided to perform LD flap breast reconstruction. Surgery was completed with no particular incidents. The patient then underwent radiotherapy and hormonal therapy (Herceptin) from March 13, 2017 to October 2, 2017, under the joint care of the departments of radiation oncology and hematology and medical oncology. At six subsequent follow-up consultations, no seroma was detected at the back-donor site. At 24 weeks postoperatively, the patient developed refractory seroma, which we decided to treat with Abnobaviscum. The patient was administered 2 mg of Abnobaviscum at 25 weeks postoperatively, and since no effect was observed, the dose was increased to 4 mg for subsequent administration at 26, 28, and 31 weeks postoperatively. The seroma had still not resolved; therefore, the dose was increased

Fig. 1. A 56-year-old woman presented 3 months after breast reconstruction with an extended latissimus dorsi flap. (A) The seroma was checked using ultrasonography and a physical examination. (B) The area was covered with potadine ointment. (C) Aspiration with a needle and syringe. (D) Abnobaviscum injection.
Fig. 2. [A] Graph of seroma severity over time for the case 1, a 56-year-old woman. (B) Graph of seroma severity over time for the case 2, a 50-year-old woman. (C) Graph of seroma severity over time for the case 3, a 51-year-old woman. POM, postoperative month.
again and the patient was administered 8 mg at 36 weeks postoperatively. The seroma had resolved at 41 weeks postoperatively, and no refractory seroma occurred in 28 weeks after treatment. The total duration of treatment was 130 days.

For the three patients in this study, the mean time until use of Abnobaviscum was 5.6 months, the mean duration of treatment was 60.6 days, the mean number of doses was 3, and the patients showed a 100% cure rate with a mean follow-up period of 7 months. The 56-year-old patient developed a mild fever of 38.3°C the day after Abnobaviscum administration, which lasted for about 2 days. This complication has also been mentioned several times in thoracic surgery cases using Abnobaviscum, with mild fevers of less than 39°C that subsided spontaneously (Fig. 2).

DISCUSSION

Abnobaviscum binds to cell membrane receptor proteins, on which it exerts an antitumor effect by dissolving ribosomal RNA, blocking protein synthesis, and inducing cell death. In addition, it promotes macrophage colony-stimulating factor production by lymphocytes; increases levels of interferon, interleukin, tumor necrosis factor, and natural killer cells; enhances immune function; and promotes endorphin secretion [15]. Among the side effects of Abnobaviscum, we focused on the fact that it tends to induce adhesion, and we anticipated that it could be effective when used in patients with a refractory seroma at the donor site after LD flap harvesting for breast reconstruction.

We implemented sclerotherapy, using the method described above, in three patients with refractory donor site seroma that persisted for at least 3 months after LD flap surgery, and that did not respond to conventional methods of compression dressing using elastic bands, needle aspiration, or triamcinolone injection. The three patients showed a 100% full recovery rate with a mean of 60.6 days of treatment and three doses of Abnobaviscum. One patient experienced the adverse effects of a tingling sensation and a mild fever of 38.3°C, but these subsided within 2 days.

For patients in whom conventional treatment failed, adding sclerotherapy using Abnobaviscum before capsulectomy (surgical treatment) could provide a good alternative in patients who experience fear or anxiety related to capsulectomy.

This study has some limitations. First, the injection was processed with a different capacity among patients. Our hospital’s treatment method differed from the suggested method. We attempted to optimize the dosage considering patients’ body mass index, the amount of seroma, and complications, and we succeeded, with a cure rate of 100% using our method. On this basis, an institutional protocol was established, and patients with the complication of refractory seroma have been treated with this protocol.

Second, limitations of this study include the small number of patients and the short follow-up period. In addition, there was a lack of observations of clinical outcomes regarding adverse effects when the drug was administered to treat seroma. One 56-year-old female patient showed a mild fever of 38.3°C after Abnobaviscum administration, as well as a tingling sensation. Abnobaviscum has been reported to cause adverse effects of fever, lymph node swelling, and rarely, diarrhea and an increased urge to urinate. Of these, fever is the most common adverse effect, but antipyretic medication should be avoided. If the fever lasts longer than 3 days, differential diagnoses must be considered. Thus, if the reaction exceeds a tolerable level, the subsequent injection should only be given when the fever has regressed, with a reduced concentration and dose. In the context of ongoing research into mechanisms of resolving seroma and pathological changes, as well as treatments and interventions, Abnobaviscum shows the potential to be easy and convenient to use in patients who show no response to conventional therapy or steroid infiltration, but who do not fit the indications for surgical treatment. Abnobaviscum can be a good option to try before surgical treatment, since it reduces patients’ anxiety, has only relatively minor complications (such as fever), and is effective at curing refractory seroma.

NOTES

Conflict of interest
No potential conflict of interest relevant to this article was reported.

Ethical approval
The study was approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital (IRB No. 2018-12-017) and performed in accordance with the principles of the Declaration of Helsinki.

Patient Consent
The patients provided written informed consent for the publication and the use of their images.

ORCID
Jong Seong Kim https://orcid.org/0000-0002-4725-9277
Pil Seon Eo https://orcid.org/0000-0003-1909-7298
Joon Seok Lee https://orcid.org/0000-0002-1580-0487
Jeong Woo Lee https://orcid.org/0000-0003-4903-6066
Ho Yun Chung https://orcid.org/0000-0001-7359-3044
Byung Chae Cho https://orcid.org/0000-0002-9395-8896
Kang Young Choi https://orcid.org/0000-0002-7735-1939
Ho Young Park https://orcid.org/0000-0003-2318-9806
Jung Dug Yang https://orcid.org/0000-0002-9040-4724

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