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Lymphoscintigraphic Investigations for Axillary Web Syndromes

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Abstract

Background: Axillary web syndrome (AWS) is a frequent complication after surgery for breast cancer, but its lymphatic involvement is not definitively established. Here we report the results of lymphoscintigraphic investigations in patients with AWS.

Methods and Results: We conducted a retrospective, single-center review of lymphoscintigraphic investigations performed in 46 patients with AWS that was either clinically obvious or suspected. Of this group, 23 patients had two investigations with a mean interval of 19 weeks between them (range, 6–98 weeks). Results of the lymphoscintigraphic investigations, which were performed according to a well-standardized protocol, were classified into four patterns: normal; functional lymphatic insufficiency only (no lymphatic vascular morphologic abnormality); lymphovascular blockade without collateralization; and vascular collateralization and/or dermal backflow. Of the 46 patients, on the first lymphoscintigraphic investigation, four (8.6%) had a normal pattern, seven (15.2%) had functional lymphatic insufficiency only, four (8.6%) had lymphovascular blockade without collateralization, and 31 (67.3%) had vascular collateralization and/or dermal backflow. Among patients who underwent two investigations, four of the five who had only functional lymphatic insufficiency at the first investigation had developed vascular collateralization and/or dermal backflow by the second. The three patients who had lymphovascular blockade without collateralization at the first examination had also progressed to collateralization and/or dermal backflow at the second. None of the 15 patients who initially had vascular collateralization and/or dermal backflow showed any reversal at the second examination.

Conclusions: Our analysis confirms the lymphatic nature of AWS and shows the lymphoscintigraphic patterns and evolutions of the lymphatic lesions with potential therapeutic implications. The retrospective review of our database is approved by the institutional ethics committee under number 2048.

Keywords: cording, rehabilitation, axillary lymphadenectomy, axillary web syndrome, lymphoscintigraphy, breast cancer

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Introduction

AXILLARY WEB SYNDROME (AWS) is a common but often overlooked condition that most frequently occurs following axillary lymph node surgery for breast cancer (complete axillary lymph node dissection or sentinel lymph node [SLN] biopsy).^{1–4} It also occurs in patients with other shoulder and axillary pathology, including trauma, infection, and melanoma surgery with axillary lymphadenectomy.^{5,6} Some cases of AWS have been related to infection and strenuous activity.^{5,7–9}

Several synonyms have been used for AWS, including “cording,” “lymphatic cording,” “fibrous banding,” and “Mondor’s disease.” Moskovitz et al. first described AWS in 2001, but the use of “Mondor’s disease,” which characterizes thrombophlebitis of a superficial vein, bears witness to the controversy about the pathogenesis of the condition.³ Included in the unknowns about AWS is the level of involvement of the lymphatic system.

Lymphoscintigraphy is now considered the gold standard for investigation of the lymphatic system in patients with a benign lymphatic disease,¹⁰ but we were unable to identify reports describing its use to investigate AWS. Furthermore, the evolution of AWS has been described thus far only in clinical terms and not referenced to functional imaging findings. For these reasons, here we conducted a retrospective review of cases in our center to track lymphoscintigraphic patterns observed in those with AWS and describe their evolution.

Materials and Methods

The retrospective review of our database (approved by the institutional ethics committee under number 2048) identified 46 patients with AWS (mean age, 52.9 years; range, 29–78 years; median body mass index [BMI], 25.4; range, 18.14–38.7). Of these, 45 developed AWS after complete axillary lymph node dissection and one after SLN biopsy for breast cancer, and eight patients had no post-operative irradiation.

AWS was suspected and/or diagnosed in the affected extremity (23 right and 23 left upper limbs) when at least two of the following symptoms were present: localized edema, as reported by the patient (77% of cases), or edema confirmed by perimetry (41% of cases had a sum of the perimetries measured every 4 cm from the wrist to the axilla at the level of their operated limb, 5% greater than the corresponding sum for the opposite limb); pain, either spontaneously reported (55% of cases) or when moving the arm (93%); limited function and range of motion, either spontaneously reported or when moving the arm or forearm, found in 51% for abduction of the upper arm and in 33% for extension of the forearm; and cord visible (63%) or palpable (88%). A venous thrombotic phenomenon was usually excluded by an echo-Doppler investigation of the affected arm. The median interval between intervention and the first symptoms was 6.43 months (range, 1 day to 145 months).

Lymphoscintigraphic technique

Radionuclide upper limb lymphangiography was performed according to a well-standardized protocol.⁶ One-tenth

of a vial of human serum albumin nanosized colloids (Nanocoll R; GE Healthcare, Belgium) labeled with 2 mCi (74 MBq) of ^{99m}Tc in a volume of 0.2 mL was injected subcutaneously into the first interdigital space of each hand. Using a dual-head, single-photon gamma camera equipped with a parallel-hole, all-purpose, low-energy collimator, images (anterior and posterior views) were obtained from the hands to the head after a succession of three phases (Fig. 1), as follows: after 30 minutes, with limbs in resting position (phase 1); after 15 minutes of exercises (alternating rotations of the thumbs and opening and closing of the hands; phase 2); and after 1 hour of normal activity (phase 3). Dynamic images centered on the axillary areas during phases 1 and 2 and one single-photon emission computed tomography examination after phase 3 were also performed as part of the protocol.

The median interval between clinical symptoms and the first examination was 9 days (range, 0–148 days). The median time between the intervention and the first examination was 220.5 days (range, 21–4305 days). A total of 23 patients had two examinations, with a median interval of 116 days between them (range, 43–1700 days); nine of them had an interval greater than 116 days. The remaining 23 patients had only one examination for one of several reasons: they did not receive in-house physical therapy, they were told that the outcome was normal and required no follow-up, or they had presented already at the first examination with collateralization.

Statistical analysis

For statistical analysis, we used GraphPad and applied unpaired *t* tests (or the Mann–Whitney *U* test if the data distribution was not normal) to evaluate the possible statistical differences among patients with different patterns on lymphoscintigraphy. Data normality was verified using the Kolmogorov–Smirnov test, D’Agostino and Pearson omnibus normality test, and the Shapiro–Wilk normality test. For $p \geq 0.05$, we assumed that no significance was reached and that the null hypothesis was not rejected. $p < 0.05$ to ≤ 0.01 indicated statistical significance, $p < 0.01$ to ≤ 0.001 indicated high significance, and $p < 0.001$ was taken to indicate the highest level of significance; in all cases of significance, the null hypothesis was rejected.

Results

Comparisons of imaging of affected and unaffected arms revealed four patterns, suggesting sequential evolution of AWS. Similar findings between the operated and contralateral arm were considered to represent a normal pattern (4 cases; 8.7%). An early-stage AWS pattern that we detected showed no major morphologic lymphovascular abnormality in the affected arm, but decreased lymphatic function during phases 1 and 2 (7 cases; 15.2%), sometimes with one “lymphostatic” feature (e.g., either localized or extensive increased activity in the lymphovascularity) (Figs. 1, 2, and 6). The next or middle stage in this apparent evolution was the appearance of a lymphatic blockade without collateralization (4 cases; 8.7%; Figs. 3–5). The final, late-stage pattern (31 cases; 67.4%; Figs. 1–6) we detected consisted of lymphovascular collateralization

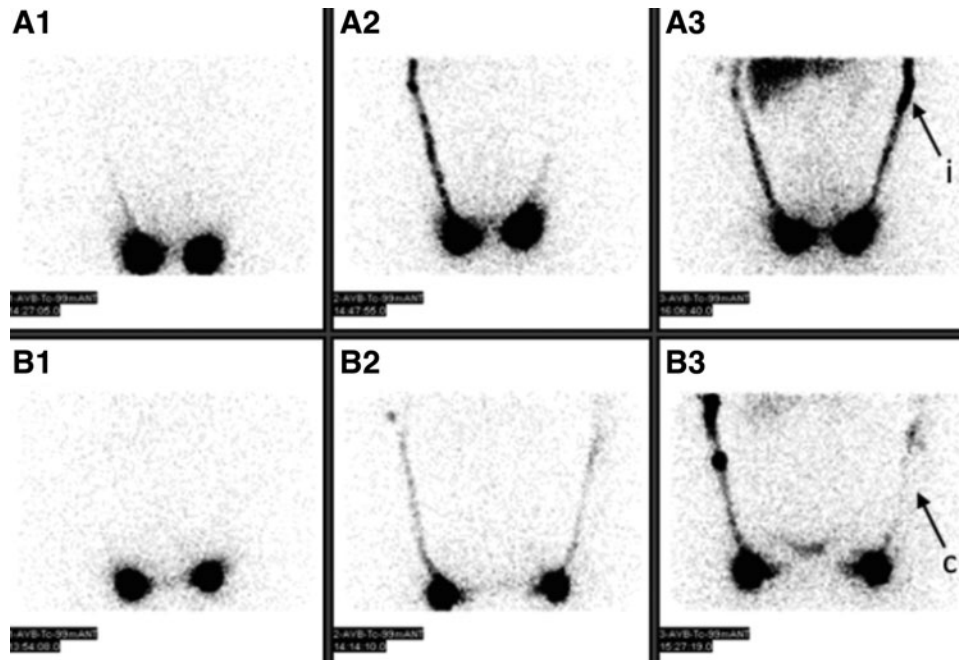


FIG. 1. Anterior lymphoscintigraphic views of the hands, forearms, and elbows at diagnosis (series **A**) and after physical treatment (series **B**) in a patient who complained of one palpable cord on the *left side* after lumpectomy with axillary lymph node dissection. Before treatment in the first phase (1), one lymph stasis was observed on the *right side* with no lymph drainage from the hand on the *left side*. After phase 2 (2), the situation was normal on the *right side*, but the tracer had flowed only into the distal and radial parts of the lymph vasculature on the *left*. After phase 3 (3), left lymph vessels were seen, but activity was higher on the *right*, corresponding to the early AWS pattern of decreased lymphatic function (i). After treatment (and 174 days after the first investigation), the situation remained unchanged on the *right side*. On the *left*, the lymph vessel seen on the first examination could still be seen, but one collateral lymphatic vessel appeared at the level of the external-cubital part of the forearm, corresponding to the late-stage pattern of lymphovascular collateralization with lymphovascular and/or dermal backflow (c). AWS, axillary web syndrome.

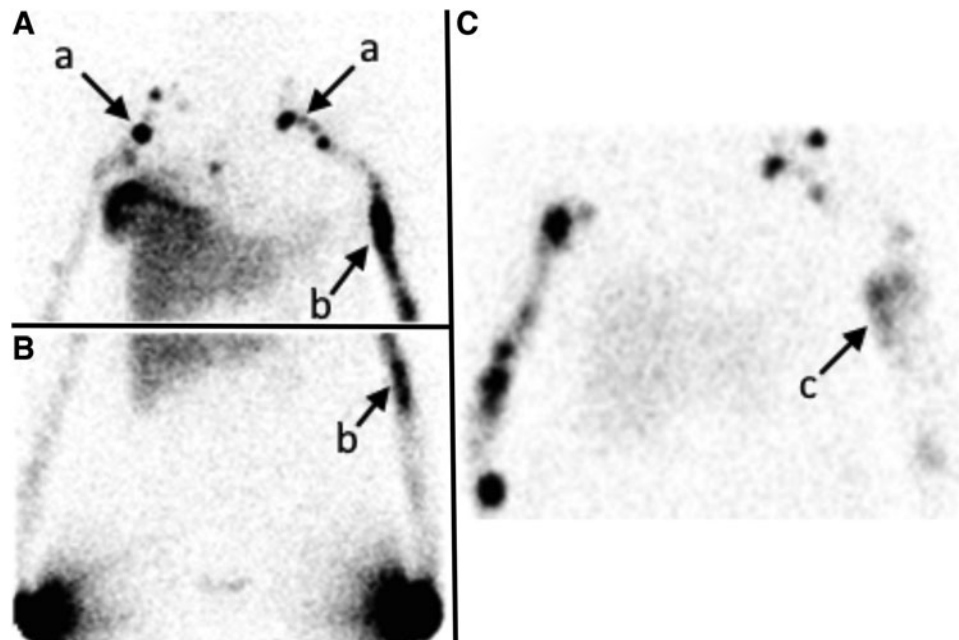


FIG. 2. Images obtained after phase 3, centered on the arms and axilla at diagnosis (**A**), after treatment (**C**), and centered on the hands and forearms at diagnosis (**B**), in a patient who complained of one palpable cord and presented with lymphedema on the *left side* after mastectomy with axillary lymph node dissection. Before treatment, the left lymph vessels could be seen, but with one showing higher activity at the level of the elbow and arm, corresponding to the early AWS pattern of decreased lymphatic function (b). After treatment (and 116 days after the first investigation), the lymph vessel could no longer be seen, and dermal backflow (c) was observed at the level of the midpart of the arm, with signs of Mascagni's pathway, corresponding to the late-stage pattern of lymphovascular collateralization with lymphovascular and/or dermal backflow.

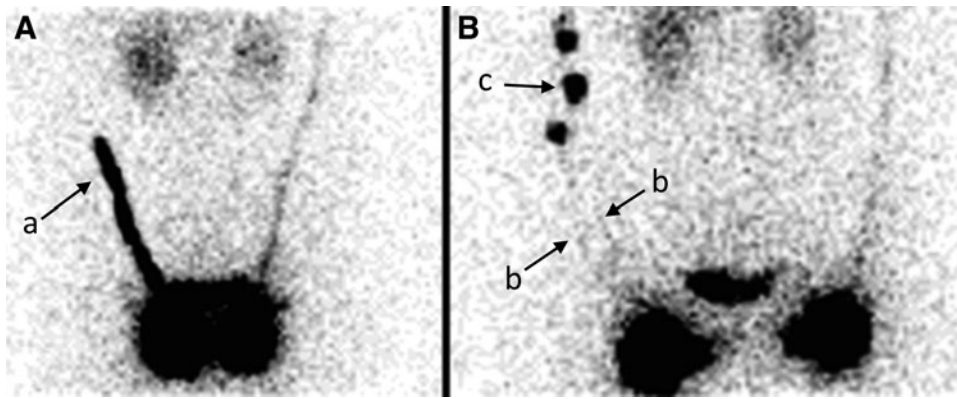


FIG. 3. Images centered on the hands and forearms obtained after phase 3 at diagnosis (**A**) and after treatment (**B**) (no data on history). Before treatment, high activity in one lymph vessel could be observed at the level of the right wrist and distal part of the forearm, corresponding to a midstage pattern of lymphatic blockade without collateralization (a). After treatment (and 138 days after the first investigation), the lymphatic vessel could no longer be seen, but at least three lymph nodes were visible (c) with very faint activity in one deep lymphatic vessel and in one superficial one (b). This result corresponded to the late-stage pattern of lymphovascular collateralization with lymphovascular and/or dermal backflow.

(collateral vessels and/or deep lymph node) with lymphovascular and/or dermal backflow (in half of these cases).

Patients who had normal findings or showed only decreased lymphatic function in the affected arm tended to have had a shorter interval between the intervention and the examination (median, 80 days) compared with those with the other two more extensively involved AWS patterns (median, 317 days; $p=0.005$). In addition, among patients who had a second examination, four of five who had only decreased lymphatic function at the first examination had gone on to develop collateralization with lymphovascular and/or dermal backflow (Figs. 1, 2, and 6). Likewise, three patients who had lymphatic blockade without collateralization on their first examination experienced a progression to this late-stage pattern of collateralization with lymphovascular and/or dermal backflow (Figs. 3–5). Finally, in the 15 patients who already had the late pattern at the first examination, the second examination showed no signs of amelioration.

Discussion

The diagnosis of AWS is based mainly on clinical symptoms.^{5,11} The reported incidence ranges from 6% to 86% following breast cancer surgery and depends on the type of surgery and length of follow-up.^{1,4,12,13} Incidence is higher in surgery with axillary lymph node dissection (36%–72%)^{1,2,4,12–14} compared with surgery for SLN biopsy (11%–58%).^{1,4,12,14} In one recent prospective study, AWS prevalence was 50% at 18 months,² and in a second recent report, there was a 51% incidence in the 8 weeks¹⁵ following surgery.

Since Moskovitz et al. described the syndrome in 2001, controversy has persisted about its pathogenesis.³ In their series of five biopsied cases, this group found dilated lymphatics in two (with a fibrin clot in one) and venous thrombosis in three. A previous report by Marsch et al.¹⁶ of biopsies in three cases described an occluded vessel in two that was consistent with thrombosis and a dilated perineural lymphatic

vessel with inspissated material in the third case. Johansson et al.¹⁷ described seven cases involving venous tissues, with an inflammatory process in four. Later, however, they reported on one case with a dilated vessel with a thickened wall and a lumen occluded by organized thrombus, within which new vessels were forming, suggesting recanalization.¹⁸ Others later reported similar findings^{19–21} implicating the lymphatics in AWS.

In 2009, Leduc et al. linked the cord path in a patient to the superficial radial lymphatic pedicle path of the forearm and the bicipital pedicle path of the arm.²² Later, using 17-MHz ultrasound imaging, the same group found different echographic patterns associated with lymphovascular structures²³ in 12 of their 15 patients. They described the axillary cord as an anechogenic structure that may correspond to the lymphovascular lumen with a hyperechogenic edge probably representing the vessel wall. They found this hyperechogenic structure, probably corresponding to cord fibrosis, in seven cases, three of them involving intraluminal thrombus. In addition, in eight cases, they found an anechogenic area with hypoechoic content that suggested the presence of an endoluminal thrombus.

Adding our current findings to this background, we believe that the lymphatic nature of AWS is clear. The midstage pattern of lymphatic blockade without collateralization that we identified corresponds obviously to thrombosis of one lymphatic vessel, with a downstream accumulation of the radiocolloid that appears to correspond to the pathologic observations that Marcus et al. and Josenhaus et al. described.^{7,24} The evolution toward the late-stage lymphovascular collateralization involving vessels or deep lymph nodes with lymphovascular and/or dermal backflow suggests that these cases do not evolve toward recanalization (as described by Johansson and Reedijck) but rather toward collateralization. Based on the present limited series, when these collaterals are established (the late-stage pattern), no further lymphoscintigraphic changes seem to manifest.

Although we detected the pattern of the earliest stage, decreased lymphatic function, in only five patients in our



FIG. 4. Images centered on the hands and forearms obtained after phase 3 at diagnosis (**A**) and after treatment (**B**) in a patient who presented with a palpable cord and lymphedema on the *left side* after mastectomy with axillary lymph node dissection. Before treatment, high activity could be observed in only one lymph vessel at the level of the left wrist and distal part of the forearm, corresponding to a midstage pattern of lymphatic blockade without collateralization. After treatment (and 127 days after the first investigation), at the level of the left wrist, a blockade with localized lymphatic reflux and two lymphatic vessels could be observed at the level of the forearm, corresponding to the late-stage pattern of lymphovascular collateralization with lymphovascular and/or dermal backflow.

series, the presentation and evolution of this apparently early pattern toward collateralization support the hypothesis of a lymphostatic scenario or at least of decreased lymph flow or dilated vessels^{7,9,17} as an initial factor. This onset would then lead to intralymphatic clotting (as noted by Moskovitz et al.³) and thrombosis (as noted by Johansson et al.¹⁸ and Marcus et al.²⁴) or to lymphangitis (as noted by Ichinose et al.²⁵).

Other investigations

Lymphofluoroscopy (near-infrared fluorescence imaging of the lymphatic vessels) with injection of indocyanine green (ICG) may represent a nonirradiating alternative to lymphoscintigraphy.

Indeed, it is used for SLN imaging,²⁶ axillary reverse mapping,²⁷ lymphedema investigation,²⁸ and during surgery for lymphaticovenous anastomosis.²⁹ We were unable to find any reference in the literature regarding its use in AWS. Lymphofluoroscopy may present several limitations in this setting, however. Publications on the technique rely on morphologic rather than functional data. Because 15% of the cases in the present series had only one lymphatic insufficiency, specific lymphofluoroscopic studies with functional evaluation would have to be performed. ICG fluorescence is also difficult to detect in deep lymphatic vessels (>10 mm), and in cases involving a high BMI, detection of the lymphatic vessel abnormalities might be difficult and result in lower sensitivity compared with lymphoscintigraphy. Although lymphofluoroscopy has been approved for SLN imaging in patients with cervix and corpus uteri carcinomas,³⁰ it has not been approved for other cancers or for benign entities such as lymphedemas or for lymphatic vessel imaging. Controversy also persists regarding its potential toxicity to functioning lymphatic vessels, with one group reporting “a profound dose- and diluent-dependent influence of ICG on lymphatic contractions that would directly translate to alterations in lymph transport *in vivo*.”³¹

Magnetic resonance imaging (MRI) and ultrasound are also used for lymphatic vessel imaging and investigation and have been proposed by Leduc et al.²³ MRI is expensive and less available than ultrasound, but the latter is operator dependent and has a limited field of view. The ability of ultrasound to recognize the early-stage pattern of decreased lymphatic function in AWS would have to be established.

Clinical and therapeutic implications

Based on our findings, lymphoscintigraphy may be said to return a false negative in only four cases, or 8.7% of the series. The examination thus might be proposed in patients to confirm clinical suspicions.

Based on results from several studies,^{4,20,32–39} physical therapy is recommended as a safe and effective primary treatment for AWS. However, our study supports the hypothesis that physical therapy has no effect on the thrombotic evolution of the disease.

If AWS is accompanied by edema, physical therapy using adjunctive manual lymphatic drainage may significantly reduce arm volume and pain compared with physical therapy alone.³⁴ Our results suggest that reduced edema is related to the development of collateralization of the lymphatic pathways and supports the use of manual lymph drainage to favor this development.

Nonsteroidal anti-inflammatory drugs and opioids have also been recommended based on the severity of associated pain.⁴⁰ These data and our results open the question of also using antithrombotic drugs (possibly administered topically) to act on the intralymphatic clotting.

The proposed lymphoscintigraphic patterns might thus present a rationale to guide physical and/or pharmaceutical therapies.

Limitations of the work

Our work is retrospective and single center. It is based on human serum albumin nanocolloids, and if other

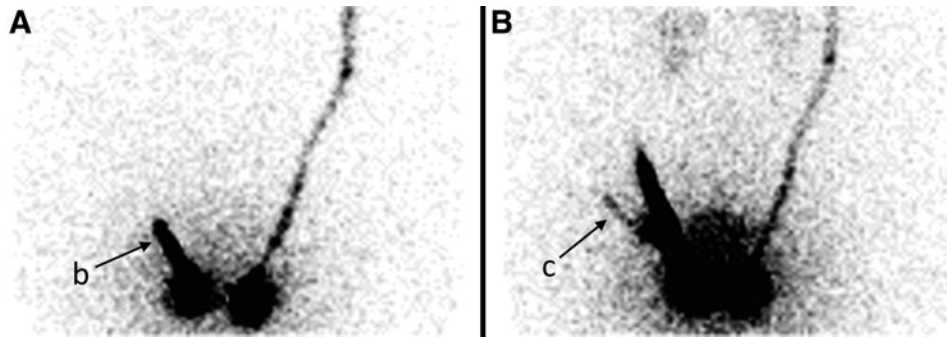


FIG. 5. Images centered on the hands and forearms obtained after phase 2 (**A**) and phase 3 (**B**) at diagnosis in a patient who presented with multiple cords and lymphedema of the right upper limb after mastectomy and axillary lymph node dissection. On phase 2 pictures, high activity could be observed only in one lymph vessel at the level of the wrist, corresponding to a midstage pattern of lymphatic blockade without collateralization (b). After phase 3, however, at the level of the left wrist, a blockade with localized lymphatic reflux and lymph stasis in two lymph vessels could be observed at the level of the distal part of the forearm, corresponding to the late-stage pattern of lymphovascular collateralization with lymphovascular and/or dermal backflow (c).

radiocolloids are used, further evaluation for the earliest stage pattern might be needed because of differing characteristics and kinetics among the colloids. Only half of the patients in this study also had a second examination, and the numbers of patients with the first two patterns were small. A prospective study with enrollment

of all patients with clinical signs of AWS would offer important insight. Trials in which lymphographic controls are systematically performed after complete axillary node dissection would also have to be reviewed and evaluated with regard to the presence or not of the proposed patterns and their evolution(s).

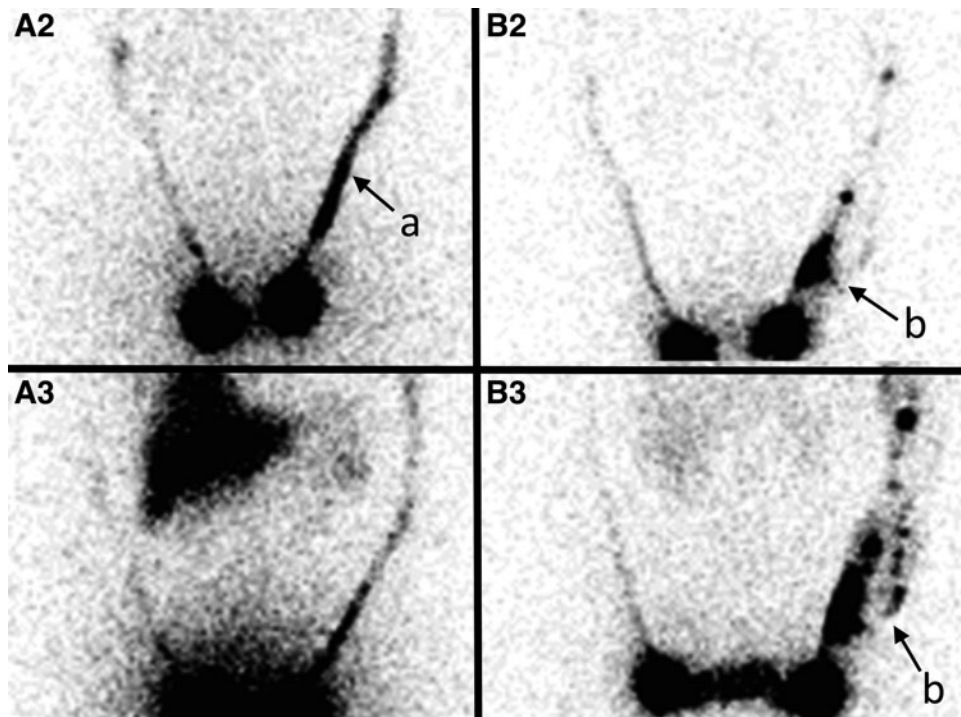


FIG. 6. Images centered on the hands and forearms obtained after phase 2 (2) and phase 3 (3) at diagnosis (**A**) and after treatment (**B**) in a patient who presented with a palpable cord on the *left side* after lumpectomy with axillary lymph node dissection. Before treatment, one lymph stasis could be observed on the *left side*, with activity higher than in the right arm, corresponding to an early-stage pattern of decreased lymphatic function (a). After treatment (and 174 days after the first investigation), the situation remained unchanged on the *right side*. On the *left*, however, there was a lymph blockade at the level of the wrist, with lymphatic reflux and collateralization in the lymphatic vessel at the level of the forearm after phase 2, and dermal backflow after phase 3. This pattern corresponded to the late-stage presentation of lymphovascular collateralization with lymphovascular and/or dermal backflow (b).

Conclusions

AWS is a common condition following breast cancer surgery with axillary lymph node dissection. Lymphoscintigraphy was normal in only 8.7% of our series, and our results suggest that these situations begin with a lymphostatic presentation evolving toward lymphatic thrombosis and collateralization. If these findings are confirmed, such an evolution would need to be considered in the management of patients undergoing surgery for breast cancer.

Author Disclosure Statement

No competing financial interests exist.

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