

VARIOUS CLINICAL SCENARIOS IN SECONDARY MALIGNANT LYMPHEDEMA

I. Forner-Cordero, L. Herrero-Manley, R. García-Marcos, J. Muñoz-Langa

Lymphedema Unit (IF-C), Hospital Universitari i Politècnic La Fe. University of Valencia; Physical Medicine and Rehabilitation Service (LH-M), Hospital Arnau de Vilanova; Interventional Radiology Department (RG-M), Hospital Universitari i Politècnic La Fe; Oncology Department (JM-L), Hospital Arnau de Vilanova, Valencia, SPAIN.

ABSTRACT

Diagnosing malignant lymphedema is a challenge in daily clinical practice. Clinically, patients may show clear signs of malignancy, but this is not always the case, and at times the diagnosis is not straightforward. In some patients, pain, hardness of the tissues, joint stiffness, proximal involvement, collateral circulation, or an acute onset will provide the clue to determining malignancy. Our aim is to describe several diverse scenarios of Secondary Malignant Lymphedema (SML) with the etiopathogenesis. One possible cause is lymphatic obstruction due to extrinsic compression of lymphatic vessels and/or nodes by either the primary tumor or metastatic masses. Lymphatic obstruction can also be caused by tumoral infiltration. This infiltration can affect both deep and regional nodes as well as cutaneous and subcutaneous vessels and is commonly known as lymphangitis carcinomatosa. Malignant lymphedema can also be secondary to obstruction of the venous flow due to tumoral venous thromboembolism or to extrinsic compression of the veins by tumors or adenopathic masses. Nevertheless, the most frequent cause of this illness is a mixed mechanism of compression of the lymphatic and venous systems. Frequently, SML is the first manifestation of relapse. When lymphedema

appears abruptly, is progressive, with intense pain, associated with collateral circulation, or with hard and infiltrated skin or joint stiffness, SML must be ruled out with an urgent referral to the oncologist and an imaging evaluation.

Keywords: malignant lymphedema, lymphangitis carcinomatosa, tumoral lymphatic obstruction, advanced cancer disease, decongestive lymphatic therapy

Lymphedema is defined as the abnormal accumulation of protein-rich interstitial fluid. However, there is no clear and widely accepted definition of Secondary Malignant Lymphedema (SML). Some authors only use the term when cutaneous lymphatics are infiltrated by the tumor (lymphangitis carcinomatosa). Others prefer not to use the expression "malignant" because the lymphedema is not malignant per se, but it can be provoked by the obstruction of the lymphatic system due to cancer (1). We prefer to use the term "Secondary Malignant Lymphedema" to refer to secondary lymphedema that is produced by altered lymphatic flow due to infiltration, obstruction, or compression of the vessels and/or lymph nodes by the direct action of an active malignant tumor.

This concept is different from secondary lymphedema that occurs as a result of

cancer treatments including primary tumor resection, regional lymphadenectomy, or radiation therapy. This type of lymphedema is designated currently as "Cancer-Related Secondary Lymphedema" or "benign lymphedema." In patients with advanced neoplastic disease, secondary lymphedema is a frequent complication and various types of edema have been reported to affect as many as 85% of patients at the end of life (2,3).

According to retrospective series (1,4,5), it is estimated that the global incidence of SML due to tumor skin infiltration is 0.7-9% of patients with malignant neoplasms, and presenting more frequently in patients with breast, melanoma, head and neck, and gynecological tumors. Approximately 50% of patients with recurrent gynecological cancer develop malignant lymphedema. Malignant lymphedema is also more common in patients with advanced or metastatic cancer and is more severe and difficult to treat than other cancer-related lymphedema (3).

SML can occur in the setting of advanced neoplastic disease and unfortunately can be associated with an unfavorable prognosis (6). Therefore, it is important to take this into account when confronted with illness as an early diagnosis and consequently prompt treatments could improve survival, and also provide better quality of life for the patient. When SML is detected in the early stages of the disease, quality of life and disease prognosis can be positively influenced (1).

The diagnosis of SML can be a challenge in medical practice impacted by the lack of awareness among the medical community. Unfortunately, this can lead to a delay in achieving the appropriate diagnosis and timely treatment of SML (7). Therefore, the main objectives of this study are first to increase awareness of importance of early diagnosis and management of SML and secondly, to emphasize the need for urgency in selecting the appropriate radiological studies.

**SECONDARY MALIGNANT
LYMPHEDEMA CAUSED BY LYMPHATIC
OBSTRUCTION**

Tumoral infiltration

SML is an aggressive form of lymphedema due to invasive cancer. The causes are often complex, including lymphatic obstruction secondary to tumoral infiltration in deep and/or regional nodes. It can also cause lymphangitis carcinomatosa from tumoral infiltration of cutaneous and subcutaneous vessels. Two examples are outlined with clinical photos and MRI images.

1) Deep nodes and regional nodes

A 73-year-old woman, with a history of breast cancer treated with a mastectomy, chemotherapy, and radiotherapy, presented one year later with upper limb lymphedema. It was painful, had a hard consistency, and with proximal involvement (circumference differences of 7 cm at the wrist and 20 cm at the upper arm). Physical examination revealed an indurated breast with areas of necrosis and wounds and a bad odor. A diagnosis of lymphatic relapse was made (*Fig. 1*). A CT scan showed a mass that was infiltrating the thoracic wall with areas of necrosis, tumor growth into subcutaneous fat, and metastasis in the liver (*Fig. 1*).

2) Cutaneous and subcutaneous vessels: lymphangitis carcinomatosa

A 39-year-old woman complained of leg swelling which had been diagnosed by a general practitioner as venous insufficiency. The edema had been increasing and evolving over a period of several months into a progressive lymphedema in her left lower limb. She was admitted to the hospital with acute abdominal pain and imaging techniques determined diagnosis of an advanced ovarian cancer with peritoneal carcinomatosis. Characteristics of lymphedema in this case that would lead us to suspect malignancy were: 1) the hard consistency of the lymphedema, 2) genital and proximal involvement, 3) fibrotic skin on the abdomen, 4) extreme pain, and 5) joint stiffness. MRI images show dilated



Fig. 1. Secondary Malignant Lymphedema presenting in a patient with breast cancer. CT images (left, center) depict an infiltrating tumor with necrosis, tumor spread into subcutaneous tissue, and metastasis to the liver. Clinical image (right) displays a severely lymphedematous right limb.

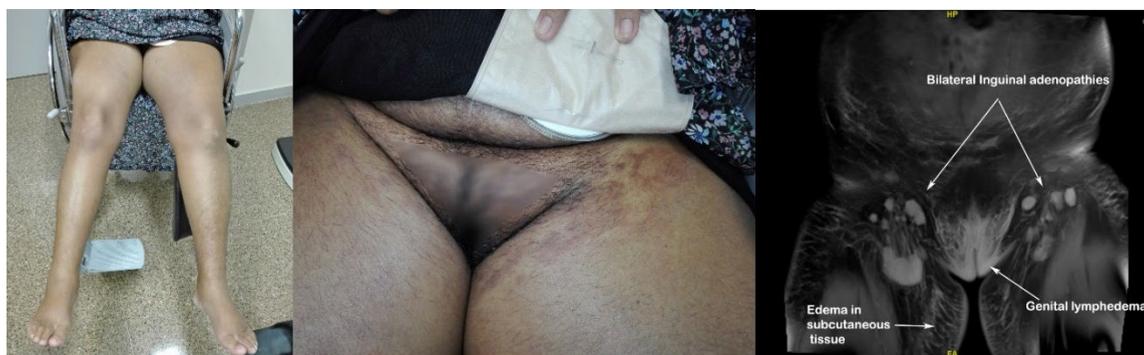


Fig. 2. Secondary Malignant Lymphedema presenting in a patient with ovarian cancer. Clinical images (left, center) display left lower limb and genital lymphedema and coronal T2-weighted MRI image (right) demonstrates dilated lymphatics and bilateral adenopathy.

lymphatics and bilateral inguinal adenopathy associated with both genital lymphedema and lymphedema in subcutaneous tissues (Fig. 2).

Extrinsic Compression of Lymphatic Vessels and Nodes by Primary or Metastatic Masses

Another possible scenario of SML is extrinsic lymphatic obstruction caused by obstruction of lymphatic vessels and nodes by the primary tumor or metastatic masses. In this example, a 43-y-o man with pelvic chondrosarcoma was treated with radical surgical excision. One year later, he suffered a local pelvic relapse which required operation. He subsequently was sent to the Lymphedema Unit presenting with a lower limb lymphedema from the ankle to the hip which was hard and very painful. Circumferential

differences were: 4.4 cm on the foot, 5.6 cm at the ankle, 11 cm on the leg, and 31 cm on the thigh. Requirements of the colostomy hindered the management of the swelling and the prescription of compression garments. A coronal CT image shows that the retroperitoneal lymphatic chain close to the inferior cava vein was compressed by the mass (Fig. 3).

SECONDARY MALIGNANT LYMPHEDEMA CAUSED BY THE OBSTRUCTION OF THE VENOUS FLOW

SML can also be caused by obstruction of the venous flow due to tumoral venous thromboembolism or extrinsic compression of the veins by tumor or adenopathies. Two examples are described.

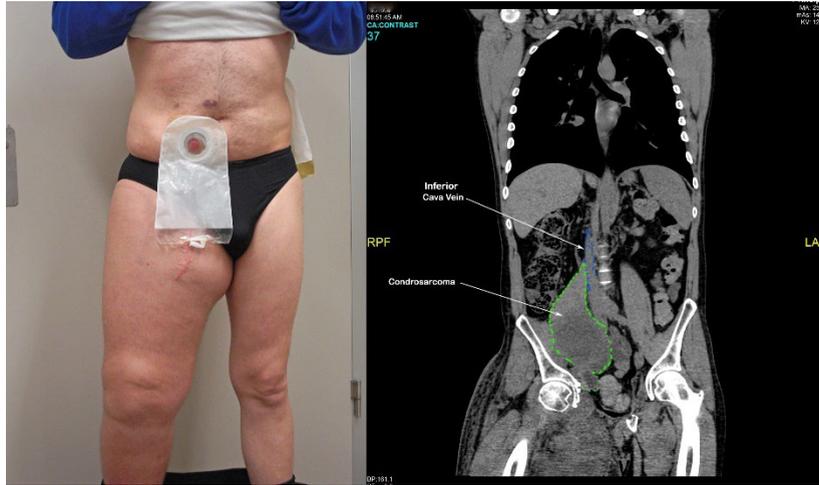


Fig. 3. Secondary Malignant Lymphedema presenting in a patient following earlier treatment for a pelvic chondrosarcoma. Clinical image (left) displays a lymphedematous left lower leg. CT image (right) depicts the chondrosarcoma compressing the retroperitoneal lymphatic chain adjacent to the inferior vena cava.



Fig. 4. Secondary Malignant Lymphedema due to tumoral venous thromboembolism in a patient with breast cancer. Clinical images demonstrate prominent venous collateral due to deep venous thrombosis.

Tumoral Venous Thromboembolism

A 50-year-old woman with a history of breast cancer (2005), who had been treated with mastectomy, lymphadenectomy, chemotherapy, radiotherapy and hormone therapy was referred to the Lymphedema Unit with an acute lymphedema which had dramatically increased over several weeks and was very painful. Physical examination revealed skin that was under tension and appearance of

collateral circulation in the arm and the chest (circumferential measurements were not obtained). On suspicion of deep venous thrombosis, she was sent to the Emergency Room. She was diagnosed with deep vein thrombosis (DVT) at the distal subclavian and axillary vein and treated with heparin (Fig. 4). As DVT is related to the progression of oncological disease, she was referred to the oncologist who subsequently found a progression of distant metastasis.



Fig. 5. Secondary Malignant Lymphedema due to compression of the veins by metastatic masses in a patient with breast cancer. Clinical images (left and right-top) display a mild lymphedema with venous collateral circulation on the right chest/shoulder. CT images (right, bottom) depict extrinsic compression of veins by an adenopathic mass and the collateral circulation.

Physical therapy for lymphedema was started once the DVT was under control and the oncologist authorized the treatment. Manual lymphatic drainage was difficult to perform due to pain.

Extrinsic Compression of the Veins by Tumor or Metastatic Masses

A 71-year-old woman diagnosed with breast cancer-related lymphedema was referred to the Lymphedema Unit with swelling and pain in the upper limb. She had been disease-free for 6 years but had been suffering from pain in the shoulder and upper limb for one year which was not responding to analgesics. She also reported numbness and weakness of the upper limb. Physical examination demonstrated mild lymphedema with a soft consistency and a collateral venous circulation on the proximal part of the limb and on the chest (*Fig. 5*). The CT scan revealed an adenopathic mass that was compressing the

veins extrinsically and impairing the venous flux, mimicking a thrombosis.

SECONDARY MALIGNANT LYMPHEDEMA CAUSED BY A MIXED MECHANISM

Many cases of SML show a mixed mechanism with compression of both the lymphatic and venous systems.

A 25-year-old man with alveolar rhabdomyosarcoma with axillary and supraclavicular involvement presented progression after an initial response to chemotherapy. He was suffering from a Stage III lymphedema in the right upper limb, thorax, and supraclavicular region that was erythematous, under tension, and with severe spontaneous pain (*Fig. 6*). Circumferential difference showed a predominance of proximal involvement. The skin was shiny, with signs of pitting, and collateral circulation was present. Upper limb function was severely impaired not only due to



Fig. 6. Secondary Malignant Lymphedema due to a mixed mechanism of compression of lymphatics and veins by metastatic masses in a patient with rhabdomyosarcoma. Clinical Image (left) demonstrates stage III lymphedema of the whole right upper limb. CT images (Right top and middle) depict a large adenopathic mass in the axillary region and metastatic growths on the right thoracic wall. Duplex ultrasound image (right, lower) depicts a hyperechogenic image inside the right jugular vein which was not compressible.

pain, but also to significant stiffness of the hand and elbow joints, which was not justified given the amount of the edema. A CT scan showed an adenopathic conglomerate in the axillary region displacing right axillary vessels and also metastatic growths in subcutaneous tissue of the right thoracic wall (Fig. 6).

DISCUSSION

The Importance of Early Diagnosis

As pointed out by Shallwany and Towers (7), there appear to be a lack of awareness in the medical community regarding the appropriate and timely diagnosis

and treatment of malignant lymphedema. Furthermore, as survival rates among cancer patients have risen, the prevalence of lymphedema and malignant lymphedema has also increased.

Lymphedema can result in cosmetic deformity, loss of function, physical discomfort, recurrent episodes of erysipelas, and psychological distress. Secondary malignant lymphedema is also a sign of recurrence. It is for these reasons that early diagnosis is essential to the patient's survival.

SML should be particularly suspected in patients who have a previous oncological clinical history. When treating these patients, the physician should consider whether the

origin of the lymphedema is secondary to a malignant recurrence and a thorough examination should be undertaken (1).

On occasion, malignant lymphedema may be the first sign of a tumor recurrence or it may represent the first manifestation of the growth of a hidden or unknown cancer. Among the 10-25% of patients treated for breast cancer who have lymphedema, this is the first sign of tumor recurrence or relapse (8,9). About 1-2% of malignant lymphedema cases are generally secondary to previously unidentified tumors. In three of the six case studies described in this paper, secondary malignant lymphedema was the first symptom of relapse. The average survival rate for patients with lymphedema from malignant infiltration is poor, though early detection and prompt onset of treatment can make an essential difference.

Suspect Clinical Signs of SML

When new or worsening lymphedema occurs in patients with a history of cancer, SML should be suspected. This medical condition usually develops quickly and can be associated with intense pain, which is generally absent in benign lymphedema. Other important signs that suggest SML are: tissue firmness, cutaneous or subcutaneous fibrosis (peau d'orange/ orange peel skin), and visible dilated veins. When cyanosis, ulceration, necrosis of the skin, or dilated veins appear, SML should be highly suspect (10). Malignant lymphedema is often characterized by the rapid onset and progression of edema and may be associated with skin changes and general weakness (11). In the current series, the alarm signs and symptoms of a lymphedema were: 1) acute onset of symptoms, 2) rapid progression of edema, 3) proximal involvement of the limb with progression from the center to periphery, 4) intense and disabling pain with a neuro-pathic component, 5) tension of the skin (tissues cannot adapt as quickly to the increased pressure), 6) collateral circulation that may indicate venous obstruction, 7) hard and infiltrated skin, and 8) joint stiffness that reduces mobility and cannot be explained by

the size of the edema. If these characteristics occur, a tumor recurrence or a hidden or unknown cancer must always be ruled out.

Neurologic manifestations as neuro-pathic pain, weakness, or limitation of joint range of motion can be clues to diagnose metastatic plexopathy. Among the patients with metastatic brachial plexopathy in breast cancer, 66% of the patients exhibited malignant lymphedema (12).

Diagnostic Imaging

Complementary multimodal imaging techniques should be employed since they provide detailed accurate and highly relevant information for diagnosis. SML requires imaging confirmation of the obstruction of lymphatic flow by the primary or secondary tumor. The type of imaging technique depends on tumor type, affected region, and suspicion of locoregional and/or distant recurrence of the tumor disease. Modalities include: 1) Ultrasound, 2) computed tomography (CT), 3) magnetic resonance imaging (MRI), and 4) lymphoscintigraphy.

The use of FDG-PET can also be very useful in the diagnosis since detection of malignant causes by means of anatomical imaging tests can be challenging, given the alterations produced by surgery and/or radiotherapy (1). Urgent referral to an oncology unit is of utmost importance to confirm the diagnosis and optimize treatment management.

Aims of Rehabilitation Treatment

Once the therapeutic approach has been decided, rehabilitation objectives should be categorized according to the clinical and functional characteristics of the individual. These objectives are classified in the following way (13): 1) Preventive- when treatment is carried out prior to the development of an expected potential disability in an attempt to lessen its severity or shorten its duration. 2) Restorative – when the patient can return to their premorbid condition without a lasting disability or known residual disease and resume their occupation. 3) Supportive – when

the disease can be controlled and the patient remains active and to some degree, productive, without residual disease or progression but accompanied by disability. 4) Palliative – when disability increases due to the progression of the disease and a program is proposed to prevent or reduce some of the complications that may arise.

The objective of the treatment of malignant lymphedema depends on the situation in which the neoplastic disease is found, and the oncological treatment prescribed. There are three possible scenarios: 1) The patient has a neoplastic disease refractory or not subsidiary to active cancer treatment- treatment of lymphedema has a palliative objective of relief of symptoms and improvement of functional impotence. 2) The patient has an active neoplasm and is starting or already undergoing antineoplastic treatment -lymphedema treatment is co-adjutant to antineoplastic treatment to improve the clinical status of the patient and allow maintenance of this treatment. 3) The patient was free of tumor at last follow-up visit – a recurrence of the neoplastic disease must always be ruled out: refer to the oncologist for a diagnostic study before considering any treatment for lymphedema case or – rule out other possible causes of lymphedema such as deep vein thrombosis, cancer-related lymphedema, lymphangitis, etc.

Most patients are referred to the Lymphedema Unit for palliative purposes, and therefore controlling the disease is not an option. In these cases, the goals to: reduce the volume of the limb, reduce pain, improve joint mobility, and prevent lymphangitis, in order to improve the overall functionality and quality of life of the patient.

Specific Aspects of SML Treatment

Several published studies show no negative effects when using Decongestive Lymphatic Therapy (DLT) on patients with active cancer (14-19). In addition, these studies indicate that physical therapy can improve health, feelings of well-being, and quality of life of people with cancer and lymphedema. Early treatment is important

because malignant lymphedema tends to progress and causes discomfort and psychological stress in patients (13,15).

DLT can be started during cancer treatments, with previous authorization from the oncologist, scheduling it in accordance with the patient's needs in order to minimize hospital transfers and to avoid days when patients may be dealing with the secondary effects of chemotherapy. In the case of patients with locoregional disease, which is curable with radical treatment, DLT should be postponed until the completion of cancer treatment (16). In short, Decongestive treatment must be adapted according to the patient's condition and to the objectives of the treatment.

Manual Lymphatic Drainage has generally been considered contraindicated in active neoplastic disease due to the theoretical risk of disseminating the tumor, but no evidence of this has been reported. On the contrary, some authors state that it does not contribute to cancer spread and need not be avoided when treating patients with metastasis (20,21). In general, malignant spread depends on the genetically determined capacities of tumor cells, not on their mechanical disconnection, be they individual cells or groups of cells. Since lymphedema caused by the cancerous obstruction of lymphatic vessels occurs in advanced disease and when most patients are receiving antineoplastic drugs, concern about possible DLT-induced spread is over-blown (22).

The response to DLT in patients with SML is positive, although it differs from that in patients with benign lymphedema. Pinnel et al states that the volume reduction was similar in both groups, although patients with SML required more treatment sessions (14). In the Liao study, the patients with malignant lymphedema improved in volume, pain, heaviness sensation, tension, and range of motion categories with the DLT program (20). The response to DLT was a percentage reduction of excess volume of 50.5% which was lower than in other studies and likely related to a worse compliance to the bandages during treatment (20,23).

The inconvenience of complete DLT is that it is a time-consuming technique that can be needed for a long period, and resources are limited. Sometimes Manual Lymphatic Drainage can be poorly tolerated in cases of neuropathic pain (14). It should also be noted that treatment without manual lymphatic drainage can be effective in reducing volume and symptoms, as shown by Hwang (16). We recommend a modified DLT, avoiding or reducing the time spent on manual lymphatic drainage and increasing the use of bandages.

Though self-management interventions in lymphedema have been barely explored, such approaches can potentially improve patients' adherence to and success with treatment (7). These approaches play an especially significant role in managing malignant lymphedema when changes in volume are challenging to control due to factors such as treatment side effects and variations in tumor response. It can be argued that self-management approaches can offer patients more readily available solutions for coping with their lymphedema symptoms, thereby improving physical ability and psychological well-being (7). Self-management options can be adjusted to comply with the individual medical and physical needs of each patient while also taking into account their economic and social situation (7).

Physiotherapists are familiar with the proximal obstruction of the lymphatic system and should apply bandages with mild compression, ensuring good tolerance and compliance on the part of the patient. Compression can be progressively increased if the patient is able to tolerate this.

Limb volume can be vastly reduced by using compression bandages, although the correct pressure must be applied by an experienced physiotherapist. Furthermore, a compression garment can improve the patient's quality of life, making daily life easier.

The use of compression garments during the intensive phase of the DLT has shown good results in reducing the edema volume and is more practical than traditional compression bandaging in patients who are unable to attend the hospital or who are not in

a condition to receive DLT (24).

Velcro devices can be of help if the patient is not attending the hospital daily and the caregiver can adapt the compression to the needs of the patient after instructions for good management (25).

Aquatic activity is highly recommended in forms of swimming or subaquatic training to increase physical activity and avoiding high intensity activities that could cause or aggravate pain. Despite the scarce research in this field, a specifically designed aquatic protocol has shown a positive impact on chronic leg swelling (26). Water density, temperature, hydrostatic pressure, and buoyancy can be exploited to work on effects related to gravity, resistance, and joint impact. Exercises in the water can stimulate the neuromuscular and metabolic systems, with a positive psychological impact.

For maintenance treatment, Velcro devices could be useful and preferable to elastic garments as they are easier to don and doff, can be of help to caregivers in cases of dependency, and are more suitable to frequent volume changes that occur in secondary malignant lymphedema.

Medical and psychological treatment aside, attention to the physical comfort and well-being of the patient can contribute not only to their state of mind but also perhaps to slowing advance of the condition. Focus must therefore be placed on finding the source of the lymphedema and on reducing discomfort. This can take the form of personalized palliative care providing not only essential psychological and physical end of life support, but also incorporating physical activity tailored to the needs of each patient and including permanent light compression of the area in question to hinder enlargement and so impede physical deterioration and discomfort as much as possible.

CONCLUSIONS

Among the 6 cases, in 3 of them Secondary Malignant Lymphedema was the first manifestation of relapse.

The alarm signs and symptoms of a

lymphedema are: 1) acute onset of symptoms, 2) progression, 3) intense and invalidating pain with a neuropathic component, 4) collateral circulation that makes us suspect venous obstruction, 5) Hard and infiltrated skin, and 6) joint stiffness that reduces mobility and cannot be explained by the edema. When these characteristics are noticed in a patient with lymphedema, we should *ALWAYS* investigate the possibility of tumor recurrence or the first sign of an unknown cancer. It is essential to send the patient to the oncologist urgently in order to confirm the diagnosis, by means of an anatomical imaging testing.

PATIENT PERMISSION

All patients provided consent for the use of their clinical data for each of their case reports.

CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that the current study does not have a commercial sponsorship, this material does not have any source of funding, and no financial conflicts of interest exist.

REFERENCES

1. Damstra, RJ, EA Jagtman, PM Steijlen: Cancer-related secondary lymphoedema due to cutaneous lymphangitis carcinomatosa: Clinical presentations and review of literature. *Eur. J. Cancer Care (Engl)*. 19 (2010), 669-675.
2. Cheville, AL, K Andrews, J Kollasch, et al: Adapting lymphedema treatment to the palliative setting. *Am. J. Hosp. Palliat. Care* 31 (2014), 38-44. doi: 10.1177/1049909112475297.
3. Towers, A, P Hodgson, C Shay, et al: Care of palliative patients with cancer-related lymphoedema. *J. Lymphoedema* 5 (2010), 72-80.
4. Krathen, RA, IF Orengo, T Rosen: Cutaneous involvement as the initial presentation of metastatic breast adenocarcinoma - Case report. *South Med. J.* 96 (2003), 164-167.
5. Marcoval, J, A Moreno, J Peyrí: Cutaneous involvement as the initial presentation of metastatic breast adenocarcinoma - Case report. *J. Am. Acad. Dermatol.* 57 (2007), 577-580.
6. Rockson, SG, V Keeley, S Kilbreath, A Szuba, A Towers: Cancer-associated secondary lymphoedema. *Nat. Rev. Dis. Primers* 28 (2019), 22. doi: 10.1038/s41572-019-0072-5.
7. Shallwani, SM, A Towers A: Self-management strategies for malignant lymphedema: A Case report with 1-year and 4-year follow-up data. *Physiother. Can.* 70 (2018), Summer, 204-211. doi: 10.3138/ptc.2016-94.
8. Schuchhardt, C, E Foldi, M Foldi: Diagnostic-therapy long term observation of lymphedema following cancer treatment. *J. Exper. Clin. Hematol.* 51 (1985), 175.
9. Soucek-Hadwiger, B W Döller: Das sekundäre maligne Lymphödem. *Wiener medizinische Wochenschrift* 56 (2006), 309-313.
10. Williams, AF, PJ Franks, CJ Moffatt: Lymphoedema: Estimating the size of the problem. *Palliative Med.* 19 (2005), 300-313.
11. Weissleder, H, C Schuchhardt, RGH Baumeister: *Lymphedema: Diagnosis and Therapy*. Bonn, Germany: Kagerer Kommunikation; 1997.
12. Kim, J, JY Jeon, YJ Choi, et al: Characteristics of metastatic brachial plexopathy in patients with breast cancer. *Support Care Cancer* 28 (2020), 1913-1918. doi: 10.1007/s00520-019-04997-6.
13. Instituto Nacional de Cancerología ESE. Guía de práctica clínica (GPC) para la detección temprana, tratamiento integral, seguimiento y rehabilitación del cáncer de mama. 2013 - Guía No. GPC-2013-19.
14. Pinell, XA, SH Kirkpatrick, K Hawkins, TE Mondry, PAS Johnstone: Manipulative therapy of secondary lymphedema in the presence of locoregional tumors. *Cancer* 1 (2008), 950-954
15. Clemens, KE, B Jaspers, E Klaschik, P Nieland P: Evaluation of the clinical effectiveness of physiotherapeutic management of lymphoedema in palliative care patients. *Jpn. J. Clin. Oncol.* 40 (2010), 1068-1072.
16. Hwang, KH, HJ Jeong HJ, GC Kim, YJ Sim: Clinical effectiveness of complex

- decongestive physiotherapy for malignant lymphedema: A pilot study. *Ann Rehabil Med.* 37 (2013), 396-402.
17. Ruger, K: Diagnosis and therapy of malignant lymphedema. *Fortschr. Med.* 30;116 (1998), :28-34.
 18. Cobbe, S, K Nugent, S Real: Pilot Study: The effectiveness of complex decongestive therapy for lymphedema in palliative care patients with advanced cancer. *J. Palliat. Med.* 2018;21(4):473-8.
<https://doi.org/10.1089/jpm.2017.0235>
 19. Preisler, VK, R Hage, F Hoppe: Indications and risks of manual lymph drainage in head-neck tumors. *Laryngorhinootologie* 77 (1998), 207-212.
 20. Mena-Flor, E, E Mena-Flor, A Mena-Flor: Manual Lymphatic drainage in patients with tumoral activity. *J. Phleb. Lymphology* 2 (2009), 13-15.
 21. Godette, K, TE Mondry, PA Johnstone: Can manual treatment of lymphedema promote metastasis? *J. Soc. Integr. Oncol.* 4 (2006), 8-12.
 22. Liao, SF: Lymphedema characteristics and the efficacy of complex decongestive physiotherapy in malignant lymphedema. *Am. J. Hosp. Palliat. Care* 33 (2016), 633-637.
 23. Forner-Cordero I, Muoz-Langa J, Forner-Cordero A, Demiguel-Jimeno JM. Predictive factors of response to decongestive therapy in patients with breast-cancer-related lymphedema. *Ann. Surg. Oncol.* (2010), 17, 744-751.
 24. Campanholi, LL, JMT Baiocchi, FP Mansani: Use of compression garment in the treatment of malignant lymphedema in a patient with recurrent breast cancer: case report. *Mastology* 29 (2019), 47-51.
 25. Pujol-Blaya, V, S Salinas-Huertas, ML Catasus, et al: Effectiveness of a precast adjustable compression system compared to multilayered compression bandages in the treatment of breast cancer-related lymphoedema: A randomized, single-blind clinical trial. *Clin. Rehabil.* 33 (2019), 631-641. doi: 10.1177/0269215518821785.
 26. Giancesini, S, M Tessari, P Bacciglieri, et al: A specifically designed aquatic exercise protocol to reduce chronic lower limb edema. *Phlebology* 32 (2017), 594-600.

Isabel Forner-Cordero, MD, PhD
Lymphedema Unit. Rehabilitation Department.
Hospital Universitari i Politecnic La Fe.
Valencia. (Spain).
Associate Professor, University of Valencia.
(Spain)
Phone number: +34-961244000 (ext 411157)
E-mail: ifornercordero@gmail.com
ORCID Number: 0000-0003-2778-037X