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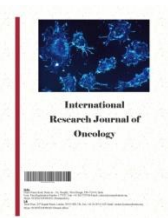
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Lymphatic Injury and Peripheral Lymphedema as Complications of Central Venous Catheter: A Case Report and a Literature Review

**Luis Lopez Montoya^{1*}, D. Yucari Lopez¹, Joceline Sandoval¹,
Angel Lopez Montoya¹, Roberto Garcia Valadez^{1,2},
Claudia Paz Luna¹ and Itzel Alcaraz Arevalo¹**

¹*Fi Fisioterapia Integral S. C. Research Group, Calle San Juan Bosco 1333, Col. Camino Real,
C. P. 45040 Zapopan, Jalisco, México.*

²*Hospital Militar Regional de Especialidades de Guadalajara Jalisco, Av. del Ejército 100,
C. P. 44890, Colonia Reforma, Zapopan, Jalisco, Mexico.*

Authors' Contributions

This work was developed in collaboration among all authors. Author LLM assessed the patient, performed the study and wrote first draft of manuscript. Author DYL designed the study and managed the literature research. Author JS performed the statistical analysis. Author ALM wrote the protocol. Author RGV assessed the statistical analysis and edited the study. Authors CPL and IAA collected data and managed the literature review. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Secondary lymphedema is defined as a chronic-progressive disease which causes a rich protein edema of the limbs, this may be caused due to the damage or obstruction of lymphatic structures; secondary peripheral lymphedema may be considered a complication of central venous catheter procedures.

Objective: To describe a clinical case of upper extremity lymphedema as venous port catheter related complication and present a review of literature of lymphatic complications of central venous catheter.

*Corresponding author: E-mail: lopzmontoy@figdl.com;

Case Presentation: A 57-year-old woman received previous medical attention between 2019-2020 due to Hodgkin lymphoma; the patient was diagnosed by left cervical lymph node biopsy and received 12 chemotherapy cycles through right subclavian catheter. The patient arrived to our facilities in March 2021 to assess her case due to increased right arm volume related to progressive edema that did not improve with rest or elevation and began to limit movements and basic activities; the situation began after a previous right catheter infection and a change of it in January 2020 with no evidence of venous thrombosis and identified a worsening tendency with time since last chemotherapy in May 2020. After clinical history, physical examination and ICG NIR lymphography study, lymphedema was confirmed as a result of subclavian catheter related complication. We decided to present the case along a literature review on the topic.

Conclusion: Lymphatic injury and peripheral lymphedema related to Central Venous Catheter procedures and its complications is a clinical reality that might be underrecognized and underdiagnosed by scientific literature and clinicians; this condition should be properly studied and deeply considered with the adequate assessment strategies in patients undergoing CVC procedures in the mid and long term to avoid its undertreatment.

Keywords: Peripheral lymphedema; central venous catheter; lymphatic injury; lymphatic imaging.

1. INTRODUCTION

According to Pubmed's MeSH database and the International Society of Lymphology, lymphedema is defined as a chronic-progressive disease that causes rich protein edema, it occurs due to the obstruction of lymph vessels, lymph nodes or lymphatic function disorders [1,2], this produces chronic fibrosclerotic changes in tissues and a chronic inflammatory response [3], its progression affects the quality of life [4] and the social context and economic framework of patients [5] affecting more than 250 million people worldwide [6].

Lymphedema is classified mainly into primary and secondary, the first is related to congenital anomalies of lymphatic structure and function [7] while secondary lymphedema is caused by events that affect lymphatic structures and function such as: neoplasm, cancer related treatments like lymph node removal surgeries, radiotherapy, direct trauma, parasite infection or repetitive skin infection that insult lymphatic integrity. [8] Secondary lymphedema is not caused only by direct offence to lymphatic structures but also by their progressive decay of them due to obesity, venous disease and aggression, including the long term sequelae of deep vein thrombosis and advanced chronic venous insufficiency, being all of them risk factors of lymphedema development [9,10].

Structural damage of lymphatic deep structures had been reported as complication of interventions like central venous catheter [11]; the most reported complications described are mainly chylothorax and chylous ascites [12], nonetheless, anatomically the involvement of

deep lymphatic and venous structures may be not limited to cavity but also to peripheral lymphedema [13-17].

We present a case of peripheral secondary upper extremity lymphedema in clinical stage II, according to the ISL lymphedema clinical staging system, related to right subclavian catheter port complications.

Given the lack of reports of peripheral lymphedema described as a complication related to central venous catheter or its proper complications, we decided to perform a literature review about the topic.

2. CASE PRESENTATION

A 57-year-old multiparous woman, height 1.47 m, 82 kg weight, normal heart rate and respiratory frequency, 110/80 arterial tension, hypothyroidism present but under control, other comorbidities denied and not identified; retired, sedentary lifestyle, married. The patient received previous medical attention in public health services due to Hodgkin lymphoma since may 2019, diagnosed by left cervical lymph node biopsy; patient received 12 chemotherapy sessions which included doxorubicin, vinblastine, bleomycin and dacarbazine cycles through right subclavian catheter (last in April 2020); at assessment, cancer appeared to be asymptomatic, responded favorable to treatment and stable, not progressing, according to February 2021 PET study and medical reports.

Patient arrived to our facilities in Fi Fisioterapia Integral S.C. Zapopan, Jalisco, Mexico in March 2021 in order to receive assess and evaluate her

case due to increased arm volume related to progressive edema that didn't improve with rest or elevation that began to hinder movements and basic activities that demanded continuous efforts like preparing food and completing house chores, the patient identified a worsening tendency in time since last chemotherapy in May 2020; the beginning of right limb edema and increasing volume was reported after right subclavian infectious event in December 24th, 2019, this caused a catheter change in same site in January 2020.

Medical file included venous duplex ultrasound study performed the day after the infectious acute event in December 25th, it does report integrity, normal behavior of mechanical characteristics of veins and an absence thrombosis of catheter, subclavian, axillar, median and cephalic veins of right limb; medical file and ultrasound reported infectious local subclavian phlebitis and limb, thorax and right neck edema; infection was treated successfully with a 15 days scheme of cephalexin and clindamycin. In February 2020, PET reports no affection of cervical, supraclavicular, or right axillary lymph nodes related to cancer, only reports a higher intensity of contrast in catheter area due to local inflammatory response.

Historically, the patient observed a tendency of the arm increasing volume through the day during activities and mild improvement at night or during rest, but never close to normal volume; fatigue of arm and heaviness during activities was also present and begin to cause difficulties to develop some daily activities.

Right arm presented thicker skin panicles (Stemmer sign) than left arm due to the presence of mild edema, nonetheless godet sign was not present during exploration and skin showed mild fibrosclerotic changes after palpatory exploration in the forearm.

Comparative anthropometric circumferential measurements were performed for upper limbs: in hands, wrists, elbows, 5cm above and 5cm below elbows (Fig. 1).

Circumferential measures showed a significant average difference of 2.8cm (Table 1).

Clinically it is suspected a case of secondary lymphedema due to deep lymphatic detriment as complication of four factors that may be related to deep lymphatic insult: a first right subclavian catheter implantation, the catheter site infection,

a second catheter re-implantation in the same place and chemotherapy delivery. Anatomically, peripheral and deep right upper limb lymphatic vessels (right arm, thorax, right head and neck) once draining in axillar and/or supraclavicular lymph nodes penetrate the thoracic fascia into thoracic cavity anastomosing to subclavian trunks that at the same time drain into the terminus of right great lymphatic duct which ends up draining into right subclavian vein, [18-20] insults to this specific anastomoses or pedicle site due to central subclavian installation, especially in the presence of complications of it, such as infection and its inflammatory process, catheter thrombosis or even possibly chemotherapy delivery such as doxorubicin [21] may contribute to the development of chylothorax, segmental and upper limb edema and also peripheral lymphedema [22].

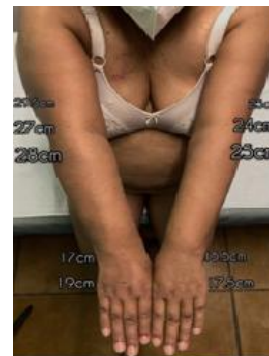


Fig. 1. Upper limbs and circumferences, note right subclavian double catheter incisions

Table 1. Circumferential details

Circumferences	Right arm	Left arm	Difference
5 cm above elbow	29.5	25	4.5
Elbow	27	24	3
5 cm below elbow	28	25	3
Wrist	17	15.5	1.5
Hand	19	17.5	2
		Average	2.8

It was decided to perform a comparative ICG Near Infrared Lymphatic Imaging Lymphography study in both arms which allows an economic, ambulatory, and secure assessment of any possible lymphatic impairment, lymphatic function, and structural integrity of lymphatic system with detail [23] employing our low-cost NIR lymphatic imaging device [24]; 0.2mg of ICG was administered between three interdigital spaces of each hand. Four sequential images of each arm were attained and then integrated to get a sole image of complete limbs (Fig. 2).

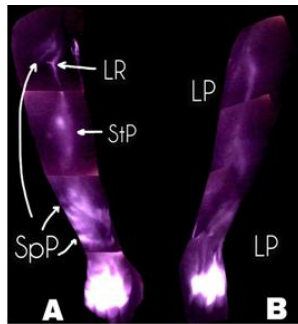


Fig. 2. A-Right arm ICG NIR lymphography; B-Left arm ICG NIR lymphography
LP: Linear Pattern; SpP: Splash Pattern; StP: Stardust Pattern; LR: Lymphatic Rerouting Pattern

Lymphatic imaging evidenced a clear impairment in lymphatic absorption patterns of ICG photophore; left arm (B) showed a normal linear pattern (LP) and lymphatic function from hand to shoulder, allowing good visibility of lymphatic vessels and its pathways, we identified the posterior radial, the posterior ulnar and cephalic lymphatic vessels and until its terminus in deltoid area and axilla without any dermal backflow. In right arm it was clearly evidenced a diminished lymphatic function from hand to shoulder with different dermal backflow pathological patterns described in literature.[25-28] In hand and forearm mainly Splash Pattern (SpP) that shows and represents the initial ectasia in lymphatic disfunction with no clear definition of lymphatic vessels pathway; in elbow and medial arm, along the cephalic lymphatic vessel, there was a clear initial stardust pattern, which is related to contraction behavior of lymphatic vessels and prior to total sclerosis of vessels which represent a major lymphatic disfunction; in deltopectoral sulcus, the proximal pathway of cephalic lymphatic vessel, showed lymphatic rerouting (LR) and again a splash pattern along this area; all of these are typical findings in secondary peripheral lymphedema.

These findings, clinical history and clinical examination confirmed secondary lymphedema at a clinical stage II according to ISL staging system in progression according to lymphatic NIR-ICG pattern, even if right superficial cervical, supraclavicular and axillar lymph nodes were not affected at all; this pattern shows a similarity to those developed after lymphadenectomy, which represent a deep lymphatic injury and a decaying peripheral lymphatic function; this lymphedema was onset as late complication of subclavian catheter events, specially related events, like local infection and chemotherapy delivery; the

patient was programmed to receive physiotherapy treatment in our facilities based on multilayered compression therapy, compression sleeve, strength and resistance functional exercises, weight control and education on selfcare and risk reduction habits to avoid associated complications and progression of limb volume.

3. LITERATURE REVIEW

We researched for similar cases in scientific literature but found a lack of reports of lymphedema or lymphatic injury related to central venous subclavian catheter; the aim of this literature review was to analyze the reports of lymphedema, chylothorax, chylorea, chylous ascites and peripheral edema associated to lymphatic injury related to central venous catheter.

Mesh terms keywords and phrases in English and Spanish were employed in medical scientific search engines such as PubMed, Cochrane, Cinhal, Scielo, Scopus, and Google Scholar. Phrases and keyword included "lymphedema", "lymphatic", "chylothorax", "chylorea", "chylous ascites", "lymphoedema" plus "central line catheter", "catheter port", "central venous catheter" or "subclavian catheter" or "catheter" or "catheter injury", "subclavian catheter complications", "catheter port complications", "central venous catheter complications".

28 studies met the research criteria and were reviewed, nonetheless, only 7 reported explicitly some kind of edema in face, neck, upper limb, chylothorax, chylous ascites, lymphatic injury or lymphedema related to central venous catheterization with precise patient's data.

The first accurate report was made by Wright et al. in 1994 [16]; he reported a patient with massive edema in the left hand and breast after subclavian vein catheter placement and long term complications, this is relevant considering that breast and arm share superficial lymphatic drainage and then deep trunk lymphatics before draining in left subclavian vein, the catheter site; he even explains this may be related only to venous motives. He reports a delayed and chronic situation of more than a year of duration, and as he states, "*the relationship between the left breast edema and the left pleural effusion is speculative.*" Wright tries to explain pleural effusion to venous compromise, but clinically and anatomically this presentation implies and makes more sense considering a deep lymphatic injury and the anatomopathological implications of

catheter placement complications as explained previously in this document. It is required to consider that the patient had end stage renal disease and her edema was from a dialysis catheter placement. The authors state '*arm edema is a well-described complication of subclavian vein dialysis catheter placement*'; nonetheless it is not stated if it evolved to lymphedema due to the lack of medium- and long-term follow-up nor received any lymphatic assessment or screening.

In 2000, Scharff et al. presented a case study of a child (19 months old) who experienced a lymphocutaneous fistula after SVC syndrome, thoracic duct injury or both after CVC placement; patient had three episodes of sepsis, which are considered as lymphatic insults. [11]; Turfe et. al, in 2016, reported a case study of a 65-year-old woman who experienced lymphedema after she developed seroma at her port site necessitating excision and port removal. This patient previously had axillary lymph node dissection on the side of the port and had a BMI >30 (high risk of lymphedema), in this context, it must be understood that catheter may play a role as a lymphatic aggression factor considering its seroma complication.[15] While Kylat et al. in 2017 [14] reported similar clinical situations in different characteristic patients, they explicitly reported a lymphatic injury or lymphedema associated to central venous catheter. Explanations to these cases reported that the injury of lymphatic vessels can occur during insertion of central venous catheter, it can also occur secondary to venous thrombosis (not considered in this study, but relevant), thrombophlebitis, extravasation, infiltration, and specially in populations with comorbidities.

Lymphatic suffering related to CVC implant and or its complications can result in peripheral edema, lymphedema, chylothorax, chylopericardium and chylous ascites.

Greater cohort studies both prospective and retrospective Seo et.al in 2014 [29], Ruchan et.al. in 2017 [13] and Isom et.al. in 2019 [30], reported lymphedema ranging from 0.5% up to 20% in limbs with venous catheter port in site in between a total of 711 patients considering these three studies; most of them in oncological context. Nonetheless Seo described that the patient who developed lymphedema in this series

had also developed venous thrombosis and thrombophlebitis; edema resolved with anticoagulation. In this case, there is no evidence the swelling progressed to lymphedema, but in fact resolved with anticoagulation in the short term, but again, the lack of follow up and proper lymphatic assessment makes it impossible to discard a midterm or long-term lymphedema development. Also, Ruchan et al. explained that the patient who developed lymphedema in this series had also undergone ipsilateral axillary lymph node dissection for breast cancer, like in Turfe's report, placing her at high risk of lymphedema, timing of lymphedema development after port was not given, and was via patient report.

Isom et.al concluded that there was no difference in direct port complications or upper extremity lymphedema rates between patients that underwent breast cancer treatment with contralateral or ipsilateral to cancer catheter implantation; but it was reported that the highest lymphedema rates in patients with venous port (20%) also addressing that age, type of axillary surgery and radiation treatment were statistically associated with developing lymphedema. The study pretended to identify if side of CVC placement matters in terms of complications with ipsilateral port placement. They found that 21% of patients developed lymphedema, however, this incidence is in line with the literature (see Disipio 2013), which is also stated by the author. Nonetheless, the research methodology made it impossible to assess prevalence of lymphedema in limbs with CVC ports, in the mid-term and with high sensibility and specificity assessment of lymphatic function such as NIR-Lymphatic imaging, which helps to identify lymphatic impairment function even in no presence of clinical volume increasing, which limits its conclusions.

The time span between these studies was 25 years, 1994 to 2019; 4 case reports, 2 cohort retrospective studies and 1 prospective study. A total of 715 patients are considered in this study with a mean age of 43 years; included reports of patients with kidney disease, pulmonary disease, premature children, and cancer who underwent central venous catheter procedure as part of their treatments.

Table 2. Reports about lymphedema or lymphatic injury relating to CVC or its complications

Author	Date	Type of study	Intervention	Report	Characteristics
Robert S. Wright, M.D, et.al	1994	Case report	Left subclavian vein catheterization because of a clotted arteriovenous fistula in the left forearm.	Massive edema in the arm and left breast of a year evolution.	38 year-old woman with type 1 diabetes mellitus and end stage kidney disease and left-sided pleural effusion.
Robert P. Scharff, MD, et.al	2000	Case report	3 right subclavian Broviac tunneled CVC and right internal jugular CVC with difficulties to remove because of adhesions.	Lymphocutaneous fistula, chylothorax, upper extremity and head and neck edema.	19-month-old boy
Tae-Seok Seo PhD, et.al	2014	Retrospective study	Single-incision technique via the axillary vein	One patient complained of left upper extremity edema 196 days after port placement via the left axillary vein.	Patients included 112 men and 104 women with a mean age of 58.2 years. All patients had malignancies.
Zaahir Turfe et.al	2016	Case report	Chemotherapy port was positioned in the right deltopectoral groove.	Stage 2 lymphedema on the same side	A 65 year-old woman with a BMI of 30.9 underwent a right mastectomy and axillary lymph node dissection for breast cancer at the age of 27.
Anbar Ruchan, et.al.	2017	Clinical study	Subclavian venous port catheter implantation	Lymphedema was also developed in one case (0.8%). Port infection was observed in once case (0.8%). Thrombotic event or port thrombosis in 18 patients.	114 patients who had undergone subclavian venous port catheter implantation. The median age was 56 years (range: 21-82 years). Port into the right subclavian vein 96.5% and left subclavian vein 3.5% of patients
R.I. Kylat, PhD. et.al	2017	Case report	Placement of percutaneous intravenous central catheters through the axillary and proximal subclavian veins	Massive edema initially over the upper half of the body and the anasarca, predominantly in the head, neck, trunk, and genitalia.	A 3-day old male infant born at 39 weeks gestation.

Author	Date	Type of study	Intervention	Report	Characteristics
Chelsea Isom MD, PhD. et.al	2019	Retrospective study	Placement for central venous ports	Lymphedema occurred in 8 patients (20%) with ipsilateral mastectomy ports.	202 patients had ports placed in the left subclavian vein compared with 179 patients had them placed on the right.

A total of 13 (1.8%) patients out of 715 reported lymphedema and lymphatic injury symptoms such as chylothorax, chylous ascites, peripheral chronic edema (acute onset or delayed onset after catheter placement) with a prevalence of 1.82% calculated by SPSS.

4. DISCUSSION

Central venous catheter is a worldwide common procedure for many medical conditions, mainly but not limited to Intensive Care Unit and Oncological treatment context, this procedure includes patients from all ages and gender; it is estimated that more than 5 million central venous catheters are inserted in the USA annually with a similar rate in Europe [31]; frequent complications include central venous catheter thrombosis, catheter skin or site infection, phlebitis, catheter de-insertion or detachment, acute or chronic edema related to venous and/or lymphatic suffering and in minor rate but anatomically possible: chylothorax, chylous ascites, and peripheral lymphedema as consequence of deep lymphatic injury due to catheter misplacement. Complexity of factors involved into the development of lymphedema should be considered in all cases, especially in those manifesting lymphatic complications.

It should be considered that: the studies presented in which patients developed edema or lymphedema, all patients had either co-morbidities putting them at risk (previous node dissection, infection, Trisomy 21, end stage renal disease with AV fistula, chemotherapy infiltration), or significant complications of catheter placement (infection or thrombosis), increasing the risk of developing lymphedema and contributors of lymphatic detriment. Given this, it is not conclusive that peripheral lymphedema is a direct consequence of CVC, but rather that CVC frequent complications and CVC misplacement may be considered factors of lymphatic insult that put patients in risk of developing lymphatic dysfunction symptoms. Our review estimates a prevalence of lymphatic injury and peripheral lymphedema of 1.82% in a

span of 25 years and 715 patients, which is a concerning rate considering the lack of reports and the potential impact of lymphedema or lymphatic injury in quality of life and function for patients who may develop it, especially in the mid and long term, after a highly practiced procedure with a certain rate of complications, specially may result in lymphatic detriment, particularly in populations with co-morbidities that contribute as factor for lymphatic function impairment.

From our research, this is the only review and presentation addressing this clinical problem considering historical scientific data. It has more than obvious limitations such as heterogeneity of population, amounts of precise studies available, studies variability, different study types and methodology, lack of proper lymphatic assessment after CVC complications, quality of reports documenting peripheral lymphedema or lymphatic injury as multifactorial entity; the fact of being a problem with an increasing amount of reports would make us ask if we are properly considering or opportunely identifying lymphedema or lymphatic injury after CVC or its complications, especially in complex clinical situations with co-morbidities that put patients at risk of developing lymphedema.

As a result of estimations, we may have a prevalence of 80,000 cases of lymphedema or lymphatic injury each year only in the United States related to CVC complications; considering the lowest rate of lymphedema related to CVC reported in literature reviewed (0.8%).

We suspect peripheral lymphedema and lymphatic injury related to Central Venous Catheter (CVC) and its complications may be an underdiagnosed, underreported, and underrated complication of CVC probably due to different factors, such as:

- 1- Follow-up of patients undergoing CVC procedures: this, considering that largest follow-ups reported go from few weeks up to 24 months. We suggest clinical prospective studies with a larger follow-

up, nonetheless it is understandable the difficulty to perform this kind of studies.

- 2- Clinical skills to identify and diagnose lymphedema in clinical practice. We suggest clinicians to become familiar with lymphatic pathology.
- 3- Lack of precise and accessible diagnostic tools for lymphatic function such as NIR lymphatic imaging to identify differential causes of "edema" additional to duplex venous ultrasound; this lack of tools may be leading to inaccurate reports of "chronic edema", unspecific "edema" or the assumption that it has a venous origin with no clear definition of etiology. We suggest the use of NIR lymphatic imaging as a tool for clinical practice, as it is easy to use, ambulatory, economic, secure, and easy to develop imaging technique, with high sensitivity and specificity to assess peripheral lymphatic function.
- 4- Poor- and low-quality evidence reporting this complication; most reports are based on highly heterogeneous populations and case reports, only estimations can be done regarding epidemiology of peripheral lymphedema and lymphatic injury related to CVC and its complications. We suggest developing new studies considering strategies to identify lymphedema along other complications of CVC, not only in the short term but also in the mid and long term.

5. CONCLUSION

Lymphatic injury and peripheral lymphedema related to Central Venous Catheter procedures and its complications is a clinical reality that might be underrecognized and underdiagnosed by scientific literature and clinicians, this condition should be properly studied and deeply considered with the proper assessment strategies in patients undergoing CVC procedures in the mid and long term to avoid its undertreatment.

CONSENT

Authors declare that written informed consent was obtained from the participant for publication of this study and accompanying images.

ETHICAL APPROVAL

Hereby, all authors declare that all interventions have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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