Current Problems in Cancer 44 (2020) 100538

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Is the risk of lymphedema life-long following treatment for gynecologic cancer?—A case report

Evelyn S. Qin, Mindy J. Bowen, Wei F. Chen*

Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Iowa Hospitals and Clinics, Iowa City, Iowa

A B S T R A C T

Lymphedema is a common complication following oncologic surgeries and is classically described to occur months to a few years after these procedures. A 64 year-old woman with history of total abdominal hysterectomy and bilateral salpingo-oophorectomy developed right-sided lower extremity lymphedema 7 years after the surgeries. Lymphographic imaging performed approximately twenty years after the original surgeries revealed development of subclinical, asymptomatic lymphedema on the contralateral lower extremity. This delayed presentation of lymphedema after initial injury, is the first described case of subclinical lymphedema without detectable lymphatic injury, making it important to continuously monitor patients at risk for lymphedema long-term.

Abbreviations: ICG, Indocyanine green; LLE, Left lower extremity; LVA, Lymphaticovenular anastomosis; RLE, Right lower extremity.

☆ Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

☆☆ Declaration of Competing Interest: None of the authors have any conflicts of interest to declare, financial or otherwise.

★ Ethical statement: The patient involved in this case report provided written informed consent authorizing the use and disclosure of her protected health information. A copy of the written consent remains available upon request for review.

* Correspondence to: Wei F. Chen, MD, FACS, Division of Plastic and Reconstructive Surgery, Department of Surgery, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, 1537 JCP, Iowa City, Iowa 52242-1086.

E-mail address: wei-chen@uiowa.edu (W.F. Chen).

https://doi.org/10.1016/j.currproblcancer.2020.100538
0147-0272/

ARTICLE INFO

Keywords: Lower extremity lymphedema; Subclinical lymphedema; Gynecologic cancer; Indocyanine green lymphography; Hysterectomy; Salpingo-oophorectomy

Introduction

Lymphedema is a common complication of cancer therapies such as breast and gynecologic cancer surgeries,[1] and involves swelling of the limbs due to damage or insufficiency of the lymphatics. This swelling can significantly reduce limb function and quality of life, which is why early diagnosis and continual disease tracking is important for improved outcomes. Lymphedema severity can be classified into clinical[2,3] and lymphographic[4] stages. Currently, clinical lymphedema is defined as symptomatic cases with detectable lymphatic injury (eg dermal backflow patterns on lymphographic imaging[5]). Subclinical lymphedema is defined as asymptomatic cases with detectable lymphatic injury. This report details the first described case of subclinical lymphedema without detectable lymphatic injury.

Case presentation

A 64 year-old female with suspected cervical cancer underwent bilateral salpingo-oophorectomies, total abdominal hysterectomy, and pelvic lymphadenectomy approximately 30 years ago. She was clinically stable for a decade until she developed lymphedema in her right leg. After years of lymphedema refractory to therapy and disease progression, she presented to our department in 2015 for surgical management.

Initial assessment in our department included a history and physical exam, a validated lymphedema-specific quality-of-life survey, bioimpedance spectroscopy, limb circumference measurements, and indocyanine green (ICG) lymphography. Disease severity was staged using the Campisi criteria[2] and ICG lymphography (Table 1A). On exam, the patient demonstrated a bulky right lower extremity (RLE), and gross asymmetry between both legs. Exam further

Table 1
Lymphedema staging (A) The patient's Campisi, ISL, and Lymphographic stages from 2015 to 2019 (B) Proposed classification of lymphedema which takes into consideration both clinical and diagnostic findings.

(A)	Year	Leg	Campisi stage	ISL stage	ICG stage
	2015	Right	III	II	III
		Left	0	0	0
	2016	Right	III	II	III
		Left	–	–	–
	2017	Right	IA	0	III
		Left	–	–	–
	2018	Right	IA	0	III
		Left-	-	-	–
	2015	Right	IA	0	III
		Left	IA	0	III

(B)	Classification	Lymphatic injury	Lympho graphic imaging	Symptoms
	No lymphedema	Negative	Negative	Negative
	Presub clinical lymphedema	Positive	Negative	Negative
	Subclimcal lymphedema	Positive	Positive	Negative
	Clinical lymphedema	Positive	Positive	Positive

ICG, indocyanine green; ISL, International Society of Lymphology.

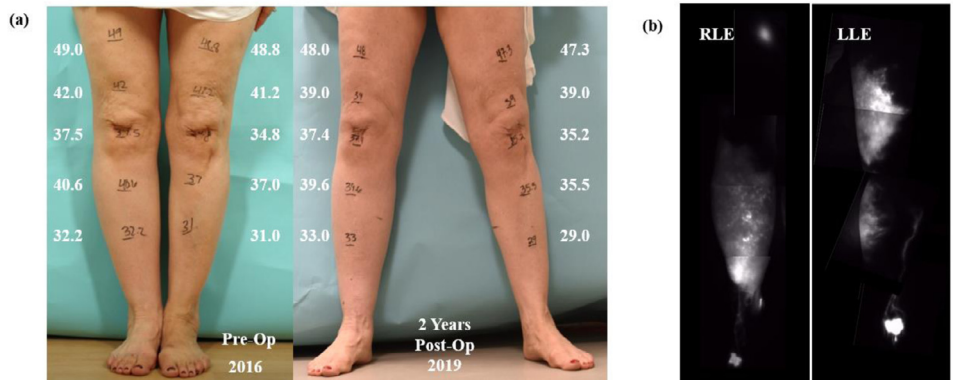

Fig. 1. Physical exam and imaging findings (A) Circumference measurements in 2016 before the RLE lymphaticovenular anastomosis (LVA), and in 2019 after the RLE LVA. The patient's right lower extremity is visibly larger than the left lower extremity in both images but shows reduction in circumference measurements over time. (B) 2019 ICG lymphography study demonstrating a stardust pattern of the right and left lower extremities. The stardust patterns in the left calf and mid-thigh were not present in 2015. LVA, lymphaticovenular anastamosis; RLE, right lower extremity.

showed an abundance of lipodystrophy and edema consistent with Campisi stage III (Fig 1A). The left lower extremity (LLE) was clinically normal (Campisi stage 0). Both legs were imaged with ICG lymphography. While the right leg showed pathologic stardust patterns (ICG stage III), the left leg showed normal linear pattern suggestive of intact lymphatic function (ICG stage 0).

In 2017, the patient underwent RLE lymphaticovenular anastomosis (LVA) successfully. In addition to subjective symptom improvement, correlating improvements were seen in all metrics, including ICG lymphography. Since the patient was symptomatic in the RLE only, and initial imaging of the LLE was normal, clinic visits from 2016 to 2018 focused on her RLE. In 2019, our clinic changed our protocol to continue imaging both legs postoperatively in patients with lymphedema caused by pelvic surgery/radiation. Therefore, in 2019, both of the patient's legs were imaged (Fig 1B). At that time, the patient was 2 years out from her RLE LVA, and doing well (Campisi Ia, ICG stage III). However, ICG scans of her asymptomatic (Campisi IA) LLE revealed advanced signs of lymphedema (ICG stage III). Following these findings, she decided to undergo prophylactic LVA of the LLE (ie Lymphatic Microsurgical Preventive Healing Approach[6]) to prevent further disease progression and symptom development. She responded favorably to surgery and showed improvement in post-op ICG scans.

Discussion

Current studies have found subclinical lymphedema days to months after lymphatic insult.[5,7] Lymphedema can remain latent months to years before becoming symptomatic. Because of the risk of disease progression, providers focus on patients with pathologic findings in the early postoperative period. Conversely, patients with normal lymphographic patterns, are presumed to be normal and considered low risk for lymphedema. This case demonstrates a unique presentation of subclinical lymphedema in which lymphatic injury was not detectable until decades after gynecologic surgery.

The most plausible explanation for this patient's presentation is our current technology being inadequate to detect mild lymphatic injury. While ICG lymphography has superior sensitivity than other diagnostic tools such as bioimpedance[8] and lymphoscintigraphy,[9] and is favored for its ability to diagnose bilateral lymphedema, all technologies have their limitations. Upon presentation, the patient likely already had left leg lymphatic injury, but ICG lymphography was insufficiently sensitive to detect it. To our knowledge, no acquired lymphedema has been reported to occur 3 decades after triggering lymphatic injury. Relevant questions are if patients with

iatrogenic lymphatic injury are at life-time risk of lymphedema, and when is a patient considered risk free? While these remain unanswered questions given our current understanding of lymphedema pathogenesis, the unexpected delayed pathogenesis in this case obliges us to consider a structured lymphedema surveillance program following high-risk oncologic procedures.[10]

Other explanations to the case are (1) de novo lymphedema in the left leg, which was previously healthy, and (2) left leg lymphatic injury as a result of LVA-related lymph flow changes in the right leg. De novo disease is unlikely considering the patient's history of high-risk oncologic intervention which is known to cause lymphatic injury. Development of contralateral leg lymphatic injury secondary to LVA in the right leg is also unlikely as the patient responded favorably to LVA, suggestive of lymph drainage improvement.

Conclusion

It is debatable what should be called lymphedema. Is it the mere presence of lymphatic injury based on history? Does it need to be lymphatic injury that is detectable? Or should it be lymphatic injury that is both detectable and symptomatic? Relevant terminology includes presubclinical lymphedema, subclinical lymphedema, and asymptomatic lymphatic injury (Table 1B). Regardless of classification, it is important for patients and providers to be aware of the risk factors of lymphedema and that our current diagnostic tools may not detect the earliest stages of lymphedema. This makes it important to monitor high-risk patients longitudinally.

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