Gynecologic Oncology Reports 65 (2026) 102132

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

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

# Improvement in chronic lymphedema in a gynecologic cancer survivor after starting GLP-1 receptor agonist therapy: A case report

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ARTICLE INFO

*Keywords:*
Lymphedema
GLP-1 receptor agonist
Cervical cancer

ABSTRACT

BACKGROUND: Lower extremity and pelvic lymphedema is a difficult-to-treat and often debilitating sequela of gynecologic cancer treatment. Management has traditionally relied on lymphedema therapy, home manual massage drainage, compression garments, and pumps. These treatments can be time and labor intensive, and often fail to adequately manage symptoms. Patients with poorly controlled lymphedema are at increased risk of skin breakdown, infection, pain, and impaired mobility, all of which negatively impact quality of life. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are new medications being used for the treatment of type 2 diabetes and obesity, but there are reports of benefits for lymphedema as well. Thus far, most case reports have focused on patients with upper extremity lymphedema.

CASE PRESENTATION: Here, we present a case of chronic severe lower extremity and pelvic lymphedema which was reversed with use of a GLP-1 RA. Previously our patient had severe, debilitating lymphedema for almost two decades. On starting a GLP-1 RA, she had marked improvement in her lymphedema symptoms, function, and quality of life.

CONCLUSIONS: GLP-1 RAs show promising benefit as a new treatment for chronic, uncontrolled lymphedema; however, there are currently no reported uses in lower extremity edema. This case report provides one example of GLP-1 RA effectiveness for lower extremity and pelvic edema and supports the case for further dedicated research.

## 1. Background

Lower extremity lymphedema is a chronic, debilitating, and costly condition that substantially impairs quality of life and often necessitates lifelong management. Lymphedema may be classified as primary, resulting from congenital or hereditary abnormalities of the lymphatic system, or secondary, arising from acquired disruption due to infection, obesity, cancer, surgery, or diabetes. While infection remains the leading cause of secondary lymphedema globally, malignancy and cancer-related treatments are the predominant etiologies in the United States (Dessources et al., 2020).

Lymphedema affects an estimated 10 million individuals in the United States and over 200 million worldwide (Bernas et al., 2023). Cancer survivors, particularly those with gynecologic malignancies, are at high risk. Local tumor mass effects, surgical alterations to lymphatic flow (e.g., lymph node dissection), and radiation-induced fibrosis are all contributing factors. A systematic review reported that lymphedema was present in up to 45% of gynecologic and urologic cancer patients within 24 months of treatment, with incidence rates reaching up to 66.7% in vulvar cancer (Letellier et al., 2024).

Elevated body mass index is a well-established risk factor for the development and progression of lymphedema (Brown et al., 2024; Chaput et al., 2020; Shimizu et al., 2013). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have gained widespread use for the treatment of type 2 diabetes and obesity. Several reports have noted improvement in lymphedema among patients initiated on GLP-1 RAs for metabolic indications (Brown et al., 2024; Crowley et al., 2024). Emerging mechanistic evidence suggests that GLP-1 RAs may exert direct effects on lymphatic endothelial function through modulation of adiponectin, improved glycemic control, and anti-inflammatory pathways (Brown et al., 2024; Shimizu et al., 2013).

The existing literature is limited and largely confounded by

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https://doi.org/10.1016/j.gore.2026.102132
Received 15 April 2026; Received in revised form 2 June 2026; Accepted 3 June 2026
Available online 5 June 2026

concurrent weight loss and metabolic improvement. Only one prior case report has described improvement in lymphedema in a non-obese, non-diabetic breast cancer survivor treated with a GLP-1 RA (Crowley et al., 2024). To our knowledge, no studies have reported the use of GLP-1 RAs as a primary treatment for lower extremity lymphedema in gynecologic cancer survivors. We therefore present a case of a non-obese, non-diabetic patient with gynecologic cancer who experienced marked improvement in treatment-refractory lower extremity lymphedema following initiation of GLP-1 RA therapy.

## 2. Clinical course

This is an otherwise healthy 51-year-old patient who was diagnosed with Stage IB-1 adenocarcinoma of the endocervix in 2006. Available records of exact treatment were not available, but per patient report included radical hysterectomy, chemotherapy, and external beam and brachytherapy radiation. Six months following radiation treatment, she developed swelling in her bilateral thighs and labia leading to recurrent episodes of cellulitis treated with long-term suppressive antibiotics.

She underwent complete decongestive therapy (CDT) five times since her original diagnosis which included manual lymphatic drainage, compression, exercise, and skin care. During this time the patient visited Mayo Clinic and University of Michigan hospitals for multiple lymphoscintigraphies to seek out lymphatic surgery, for which she was declined both times.

She first presented to the University of Michigan Health Lymphedema Clinic in 2023 with initial total girth of 360.7 cm in the RLE and 379.2 cm in the LLE. Her weight was 76 kg and her BMI was 28.6 kg/m$^2$, though with minimal abdominal fat. Her primary complaints were swelling in her bilateral lower extremities and occasional weeping in her lower abdomen, upper thighs and perineal region. She completed the Lymphedema Life Impact Scale (LLIS) with 17/17 questions answered (Weiss and Daniel, 2018). Patient's raw score was 40 for an impairment rating of 58%.

During this intensive course of CDT she had reduced to 350.5 cm in RLE and 357.5 cm in the LLE. This course included constant compression bandaging, daily exercise, manual lymphatic drainage, and meticulous skin care. She received custom compression day and night garments during this time. She returned for additional CDT every six months in 2024. She was consistent with wearing compression, using pneumatic compression pump, MLD, and exercise with minimal change despite compliance.

In May 2024, she was started on tirzepitide 2.5 mg weekly. She initially learned of GLP-1 RAs potentially being beneficial for lymphedema through online patient forums and requested her primary care physician prescribe it. During this time she remained consistent with her lymphedema care. She continued with daily exercise and changed to a plant-based diet.

At her next visit to the lymphedema clinic in 2025, her weight had decreased to 58 kg. Her girth measurements totals were 307.7 cm in the RLE and 325.2 cm in the LLE, demonstrating a 15% girth reduction from her initial visit in 2023 in both right and left lower extremities. Her LLIS score went down to 20%, demonstrating a 38% reduction in perceived functional impairments due to lymphedema. She reported significant reductions in pain and improvements in quality of life. Due to improvements in her lymphedema, she was able to engage in pelvic floor physical therapy, which had previously been very painful, and was able to increase her physical activity considerably including running 5 K races.

## 3. Discussion

The lymphatic system plays a critical role in immune surveillance and fluid homeostasis (Jiang et al., 2018). The pathophysiology of cancer-related lymphedema is multifactorial and most often initiated by disruption of lymphatic drainage following pelvic or inguinofemoral lymph node excision, a routine component of surgical management for many gynecologic cancers. Lymphatic injury leads to impaired fluid return resulting in lymph stasis, chronic inflammation, and progressive tissue remodeling characterized by fibrosis, smooth muscle proliferation, and pathological adipose deposition (Brown et al., 2022; Dessources et al., 2020). Radiation therapy further exacerbates lymphatic dysfunction through sclerosis of lymphatic vessels and nodes, while additional risk factors, including tumor compression, obesity, chemotherapy, deep vein thrombosis, and advanced-stage disease, contribute to disease severity and progression (Chaput et al., 2020).

The clinical burden of lower extremity lymphedema extends well beyond limb swelling. Complications such as recurrent cellulitis, skin breakdown, and ulceration arise from impaired immune cell trafficking and compromised skin integrity (Brown et al., 2024; Dessources et al., 2020). Gynecologic cancer survivors face unique challenges, including genital lymphedema, which predisposes patients to lymphorrhea, pruritus, discomfort, and infection, further compounding physical and psychosocial distress (Lau et al., 2024). Lymphedema has been consistently associated with reduced mobility, loss of independence, chronic pain, anxiety, depression, altered body image, sexual dysfunction, and social isolation. The condition also imposes a significant financial burden on both patients and healthcare systems due to chronic treatment needs and infection-related hospitalizations (Bowman et al., 2023; Lau et al., 2024; Letellier et al., 2024).

Current management strategies for lymphedema focus primarily on symptom control rather than disease modification. CDT remains the standard of care; however, it is resource-intensive, physically demanding, and difficult to sustain long-term (Bernas et al., 2023; Chaput et al., 2020; Lau et al., 2024). Surgical approaches, including lymphovenous bypass, vascularized lymph node transfer, and debulking procedures, have demonstrated variable success and are invasive, costly, and not widely available (Bernas et al., 2023; Dessources et al., 2020). Importantly, these interventions primarily address structural lymphatic damage and fail to target the chronic inflammatory processes that perpetuate disease progression (Bernas et al., 2023; Brown et al., 2022; Brown et al., 2024; Dessources et al., 2020).

Emerging evidence suggests that GLP-1 RAs may represent a novel adjunctive therapeutic approach to treating lymphedema by targeting underlying metabolic and inflammatory mechanisms central to lymphedema pathophysiology. While elevated body mass index is a well-established risk factor for lymphedema, weight loss alone has not consistently resulted in disease improvement, suggesting that the benefits of GLP-1 RAs extend beyond adiposity reduction (Brown et al., 2024; Chaput et al., 2020; Shimizu et al., 2013).

Mechanistically, GLP-1 RAs improve glycemic control and insulin sensitivity, which may enhance lymphatic endothelial cell integrity and function. In addition, these agents exhibit direct anti-inflammatory effects, including inhibition of CD4$^+$ lymphocyte migration, an important contributor to chronic inflammation, fibrosis, and lymphatic dysfunction (Brown et al., 2024). GLP-1 RAs also modulate adipokine signaling, increasing adiponectin levels while reducing leptin concentrations. Adiponectin has been shown to promote lymphangiogenesis and improve lymphatic repair, whereas elevated leptin levels disrupt lymphatic endothelial cell organization and proliferation (Sato et al., 2016; Shimizu et al., 2013; Simental-Mendía et al., 2021).

Although most reported cases of lymphedema improvement with GLP-1 RA therapy involve patients with comorbid obesity or diabetes, this case contributes to a growing body of evidence suggesting a direct lymphatic effect independent of metabolic disease. Notably, the patient described was neither obese nor diabetic, rendering treatment experimental and not covered by insurance. To our knowledge, only one prior case report has described a similar response in a non-obese, non-diabetic breast cancer survivor (Crowley et al., 2024). Together, these observations support further investigation into GLP-1 RAs as a potential disease-modifying therapy for lymphedema.

Safety considerations remain paramount when introducing GLP-1

RAs to cancer survivors. Gastrointestinal adverse effects are the most reported side effects (Brown et al., 2024; Nagendra et al., 2023). A large systematic review found no increased overall cancer risk, including pancreatic or thyroid malignancies, associated with GLP-1 RA use, though long-term data remain limited and largely confined to patients without prior cancer diagnoses (Nagendra et al., 2023). It is also important to note that GLP-1 RAs are not readily available to all patients. Consequently, prospective studies specifically evaluating safety and efficacy in cancer survivor populations are warranted.

## 4. Conclusion

Cancer-related lower extremity lymphedema is a common and debilitating complication among survivors of gynecologic malignancies. Despite its prevalence, management remains challenging, and long-term morbidity is substantial. This case highlights a marked improvement in refractory lower extremity lymphedema following initiation of a GLP-1 RA in a patient who failed standard conservative therapies. Although there are currently no FDA-approved pharmacologic treatments for the prevention or management of lymphedema, GLP-1 RAs may represent a promising therapeutic avenue through their combined metabolic and anti-inflammatory effects (Brown et al., 2024). Further investigation is warranted to evaluate the efficacy, safety, and optimal dosing of GLP-1 RAs in non-obese, non-diabetic cancer survivors. Given the chronic, progressive nature of lymphedema and the significant limitations of existing treatment strategies, expanding evidence-based medical therapies is critical to addressing the substantial unmet needs associated with this lifelong and resource-intensive condition.

## AI Declaration

During the preparation of this work the authors used ChatGPT in order to assist with formatting and editing. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

## CRediT authorship contribution statement

**Andrea Fromson:** Writing – review & editing, Writing – original draft, Conceptualization. **Christelle David:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Cody C. Andrews:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Subha Hanif:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

## Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

## Declaration of competing interest

The authors of this manuscript do not have any conflicts of interest to declare.

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