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IATROGENIC SYSTEMIC LYMPHEDEMA FOLLOWING MULTIPLE MYELOMA TREATMENT

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ABSTRACT

Lymphedema is a debilitating disease characterized by abnormal lymphatic drainage, either due to primary maldevelopment of the lymphatic system or to secondary injury. The clinical features of primary and secondary lymphedema differ, with primary lymphedema more often involving progressive bilateral lower extremity disease as compared to secondary lymphedema characteristically having more localized symptoms related to the origin of injury. This case presentation describes a patient who presented with bilateral lower extremity swelling, left greater than the right, with imaging results to support the diagnosis of lymphedema. During the time he was followed in our clinic, our team witnessed rapid progression of his lymphedema despite compliance with conservative management. We believe that the primary mechanism of systemic damage to our patient's lymphatic system is the lenalidomide and bortezomib therapy prescribed to treat multiple myeloma. This review explores the relationship between lenalidomide, bortezomib, and lymphedema in efforts of understanding this unique pathology of iatrogenic lymphedema mimicking primary nature.

Keywords: iatrogenic lymphedema following multiple myeloma

Lymphedema is a debilitating disease characterized by abnormal lymphatic drainage, either due to primary maldevelopment of the lymphatic system or to secondary injury. This pathology results in persistent infiltration of lymph fluid into soft tissues. The clinical features of primary and secondary lymphedema differ, with primary lymphedema more often involving progressive bilateral lower extremity disease as compared to secondary lymphedema characteristically having more localized symptoms related to the origin of injury (1). These variations in presentation correlate with pathophysiology, ultimately requiring different treatment approaches. While the mainstay of treatment for both diseases is compression and conservative therapies, over the past several decades, physiologic surgical approaches have emerged. Lymphovenous bypass (LVA) and vascularized lymph node transfer (VLNT) have been found to be most successful in addressing secondary lymphedema (2).

This case presentation describes a patient who presented to lymphedema clinic with bilateral lower extremity swelling, left greater than the right, with imaging results to support the diagnosis of lymphedema. During the 3 months he was followed in our clinic, our team witnessed rapid progression of his lym-

Fig. 1. *Timeline of clinical course.*

phedema despite compliance with conservative management under the guidance of certified lymphedema therapists (CLTs). We believe that the primary mechanism of systemic damage to our patient's lymphatic system is the lenalidomide and bortezomib therapy prescribed to treat multiple myeloma. The relationship of lenalidomide, bortezomib, and lymphedema has not been previously discussed in literature. Lenalidomide, a more biologically potent structural analogue of thalidomide with less neuropathic side effects, is a common immunomodulator used in the treatment of multiple myeloma (3). Lenalidomide works through various mechanisms of action, including direct cytotoxicity, indirect effects on tumor immunity such as altered cytokine production, and, importantly, anti-angiogenesis activity. While this medication has the theoretic potential to disrupt the pathways involved in lymphatic vessel remodeling, lenalidomide has not been linked to lymphedema in the literature. In a placebo-controlled trial that investigated the efficacy of lenalidomide with dexamethasone in the treatment of refractory multiple myeloma, 1.1% of patients taking lenalidomide developed peripheral edema of unknown cause, compared to 1.7% of patients taking placebo who developed peripheral edema (4). Bortezomib is a proteasome inhibitor also used for the treatment of multiple myeloma that works through inhibition of NF-κB. While this relationship is also not well studied, in a bortezomib pilot trial of 17 patients, one patient discontinued use due to grade 2 lymphedema thought to be possibly related to drug initiation (5). This case aims to explore these relationships further and illustrate the unique pathology of iatrogenic lymphedema that mimics primary nature.

CASE

A 63-year-old man presented to our lymphedema clinic as a referral from Vascular Surgery with 2 years of bilateral lower extremity edema, left worse than right, that first started at the time of initiating lenalidomide therapy status post autologous stem cell transplantation. Medical history was positive for multiple myeloma, asthma, GERD, HTN, sleep apnea, small chronic hemorrhagic cerebrovascular hemorrhages along the motor strip causing persistent weakness of the right hand, and iatrogenic neuropathy. Chemotherapy regimen included 11 cycles of VRD-lite (lenalidomide, bortezomib, and dexamethasone) and one dose of intermediate-dose cyclophosphamide (100mg/m2) (*Fig. 1*). The autologous stem cell transplantation (ASCT) conditioning regime included high-dose melphalan (100 mg/m2) for two days prior to the procedure. The cryopreserved autologous peripheral blood stem cells (415mL) containing 4.09 million CD34-positive cells/kg were infused. Surgical history was significant for bilateral hip replacements 10 years prior to presentation, prostatectomy without lymph node removal, and L5/S1 lumbar fusion. As he previously had post-operative DVTs both with his more recent lumbar fusion and previous hip replacements (on apixaban), he was initially seen by vascular surgery for his swelling. Vascular causes were ruled out and both CT and venous duplexes were found to be normal. On physical exam, the patient had a positive Stemmer sign, nonpitting edema, hyperpigmentation, fibrotic tissue, erythema, impaired ROM, and impaired mobility, placing him at Stage 2 lymphedema.

At the time of presentation, he had

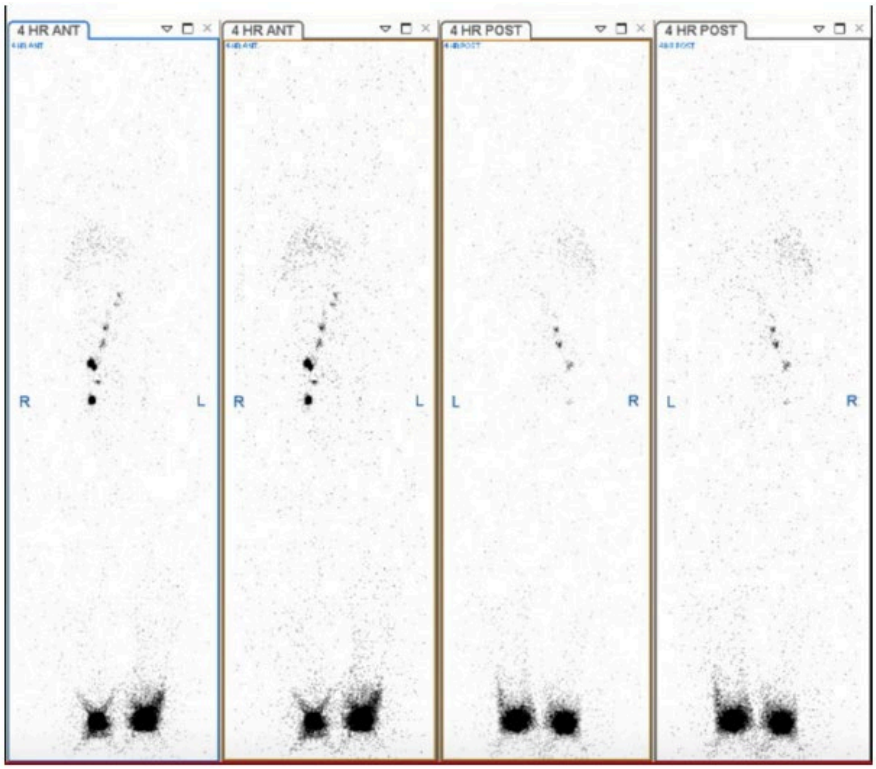

Fig. 2. *Nuclear medicine lymphoscintigraphy revealed normal deep lymphatic drainage of the right lower extremity and significantly impaired lower extremity lymphatic drainage on the left, with no visualization of lymphatic channels and faint uptake in a single left inguinal lymph node at 4 hours.*

already been working with a lymphedema specialized physical therapist for 3 months including custom flat knit compression stockings, manual lymphatic drainage, and educated on lymphedema risk reduction practices. A nuclear medicine lymphoscintigraphy was performed, which revealed normal deep lymphatic drainage of the right lower extremity and significantly impaired lower extremity lymphatic drainage on the left, with no visualization of lymphatic channels and only faint uptake in a single left inguinal lymph node at 4 hours (*Fig. 2*). Dynamic indocyanine green (ICG) lymphography showed Stage I disease on the right with a splash pattern and dermal backflow at the level of the calf, and Stage III-IV on the left with stardust pattern (data not shown). After discussion of these findings, the patient elected to address the less severe right lower extremity lymphedema in an effort to halt disease progression. Approximately 4 weeks later, the patient was taken to the operating room for lymphovenous bypass of the right lower extremity at the time of an already scheduled orthopedic hand operation (right cubital tunnel release and left carpal tunnel release). Under general anesthesia, a SPY Phi camera was used, which revealed residual ICG pooling from the imaging procedure one month prior at the level of the foot, indicating progressive worsening of disease (*Fig. 3*, top). Using anatomic landmarks, a lymphovenous anastomosis was still attempted. Three transverse incisions were made, first at the ankle, then at mid-calf, and finally at the leg at the mid-point between the medial patella and the popliteal fossa. One single linear lymphatic was identified at the mid-calf. A nearby vein was identified, and the lumens were anastomosed using the

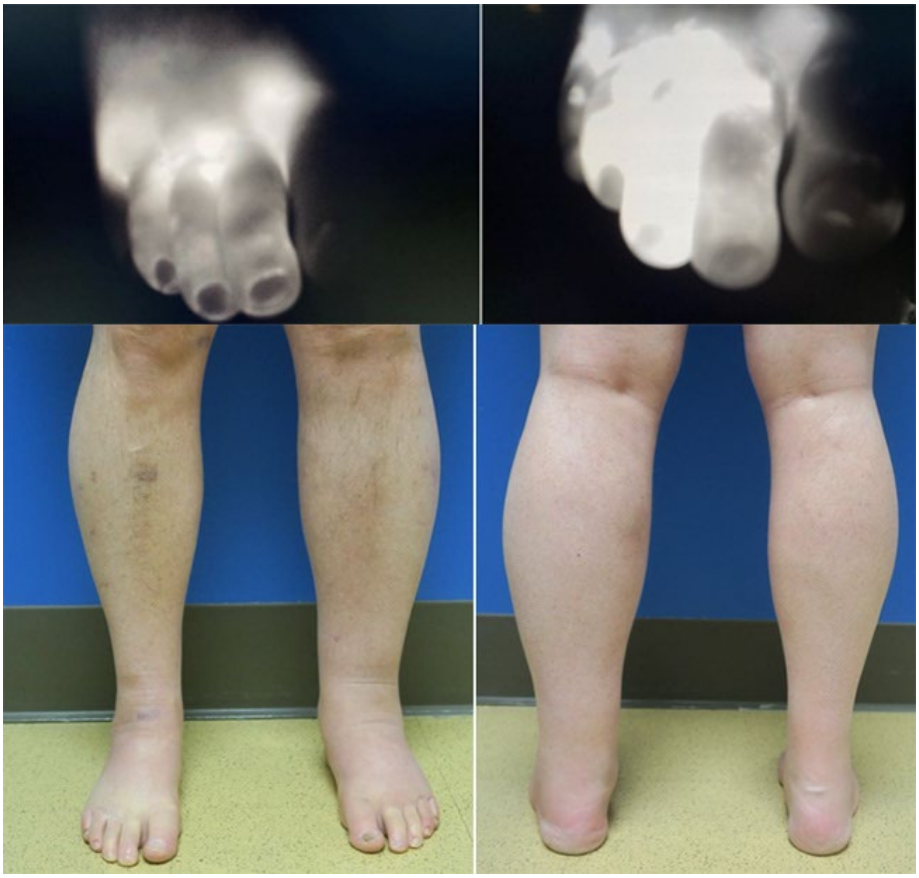

Fig. 3. *(Top) SPY Phi ICG imaging of the right foot demonstrating worsening of disease with pooling of ICG tracer in right forefoot (left) and subsequent pooling of ICG tracer in right digits 3-5 (right). (Bottom) Post-operative anterior (left) and posterior (right) images of the bilateral lower extremities.*

Mitaka MM51 microscope and superfine microinstruments. The patient experienced no complications during the procedure and had an uncomplicated recovery. At a post-operative appointment at 6 weeks, he reported subjective improvement in symptoms on the right side. On physical exam, the patient had non-pitting edema present bilaterally worse on the left lower extremity compared to the right lower extremity. Bioimpedance measurements were taken with a value of 40.7 on the left lower extremity; increased from preoperative value of 35.5 and a value of 16.7 on the right lower extremity which was his baseline. Circumferential measurement (taken 30cm from the base of the foot) on the right lower extremity was 32.1 cm compared to 34.2 preoperatively. Circumferential measurement on the left lower extremity was 49.2 compared to 48.2 preoperatively. Despite his subjective improvements, objectively his measurements remained unchanged.

Due to the progression of his disease, moving forward this patient's treatment will largely focus on optimizing conservative management. This includes continued compression with custom flat knit fitted stockings and continued physical therapy with a specialized lymphedema therapist using manual lymphatic drainage. Previously, liposuction or other debulking options was considered long-term pending lymphedema status stabilization. Though, this is no longer an option due to recent imaging revealing progression of a chron-

ic DVT in the left lower extremity, despite ongoing anticoagulation. Due to the benefits of lenalidomide maintenance therapy after autologous stem cell transplant for multiple myeloma, this patient will likely continue taking lenalidomide as maintenance therapy until recurrence of his disease (6,7).

DISCUSSION

This case presentation illustrates an iatrogenic progressive case of systemic lymphatic damage. The patient presented with a complicated clinical history. Given his history of bilateral hip replacements, which have been shown in limited publications and in the senior author's clinical experience to occasionally cause lymphatic injury, it was thought that the anterior approach to the left side may have been the inciting event. However, lymphedema typically develops in the first two to three years after surgical intervention, and the patient's signs and symptoms emerged 8 years after his last orthopedic operation (8). The patient also had a history of DVT, which may have produced some level of venous hypertension and resultant phlebolymphedema. Venous studies, however, were negative for residual clot and venous reflux. The orthopedic operations and his history of DVT may have predisposed this patient to development of lymphedema, but the temporal relationship between initiation of chemotherapy to treat his multiple myeloma and the onset of progressive lower extremity swelling implicates a systemic culprit for the patient's lymphatic disease. Upon further exploration into the drugs' mechanisms of action, it seems more plausible that lenalidomide effects led to systemic lymphatic injury.

The relationship between lenalidomide and lymphedema has not been previously studied, though general peripheral edema has been noted as a side effect in clinical trials. Notably, in the lenalidomide prescribing information, 26% of myeloma patients who were prescribed lenalidomide/dexamethasone developed peripheral edema compared to 21% of patients prescribed placebo/dexamethasone (9). In a study of patients treated with combination lenalidomide and dexamethasone for refractory multiple myeloma, 1.1% of patients developed peripheral edema of unknown cause (4). All reports linking lenalidomide to peripheral edema have largely been suspected to be linked to tumor lysis syndrome or venous thromboembolic events (10). One case report describes a 61-year-old man with multiple myeloma who was treated with this chemotherapy regimen who presented with persistent right lower extremity edema and pain, had a negative duplex study, and was ultimately found to have Merkel Cell carcinoma (11). While this case could represent a similar presentation of lymphedema related to lenalidomide or bortezomib, the story is complicated by the known relationship between aggressive, bulky carcinoma and lymphedema (12).

One of the possible mechanisms of lenalidomide damage to the lymphatic systems involves its anti-angiogenesis activity. Angiogenesis is the process of new blood vessel development, an important process during fetal development and a critical function gained by tumors as they alter pro-angiogenic and anti-angiogenic factors. Vascular endothelial growth factor (VEGF) and its receptors are at the center of this process during carcinogenesis, embryonic development, wound healing, and lymphovasculargenesis (3). Lenalidomide has been shown to significantly decrease the expression of VEGF, thereby reducing angiogenesis even independent of its immunomodulatory effects (3). VEGF-C is also a central growth factor in lymphangiogenesis, lymphvasculogenesis, and lymphatic remodeling from preexisting lymphatic vessels (13). It is well documented that abnormal regulation of VEGF-C is implicated in lymphatic dysmorphogenesis, characteristic in primary lymphedema pathology, and studies have even explored gene transfer of VEGF in efforts of direct augmentation of lymphangiogenesis (14).

Our patient was also treated with 11 cycles of bortezomib, a drug that has been linked to one case of new onset grade 2 lymphedema in a small pilot study (5). Bortezomib has also been shown to mediate anti-angiogenesis in multiple myeloma via indirect and direct effects on endothelial cells

(15). This drug has been shown to inhibit VEGF secretion and angiopoietin-1 in a study looking at the effects of bortezomib on the angiogenic phenotype of multiple myeloma patient-derived endothelial cells (15).

While this secondary lymphedema is iatrogenic in nature, it notably presented pathologically as a systemically mediated lymphedema, similar to primary lymphedema in its diffuse and bilateral presentation. This is highlighted by the progressive rapid progression of right lower extremity disease in the one month between ICG lymphography to the attempted LVA.

CONCLUSION

This case presentation and review illustrates an iatrogenic progressive case of systemic lymphatic damage in a patient with a complex medical history. In exploration of the relationships that led to the unique pathology of iatrogenic lymphedema that mimics primary nature, we believe that lenalidomide may have been responsible due to its known interactions with the lymphatic system. If these chemotherapeutic agents are truly responsible for the development of lymphedema, and it is well-established that damage to the lymphatic system causes derangements in both regional and systemic immunity, patients treated with this regimen are at higher risk of infectious complications than previously understood (16).

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

CONTRIBUTIONS OF AUTHORS

Each of the authors contributed and meet criteria for authorship by writing and editing this manuscript. There is no funding information to declare.

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