

A Case of a 42-year-old Filipino Male with Bilateral Lower Extremity Swelling

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ABSTRACT

A 42-year-old male was admitted at the University of the Philippines-Philippine General Hospital (UP-PGH) for a 3 month history of a non-healing wound in the medial side of his right leg in spite of multiple antibiotics. The wound worsened with multiple ulcerations and draining sinuses. The wound was shown to have suppurative and granulomatous infiltrates that yielded *Mycobacterium tuberculosis*. An algorithm in the approach to a chronic or non-healing wound is discussed.

Key Words: lymphedema, tarda, edema. lower extremity, bilateral, filariasis

Introduction

This is a case of a 42-year-old male admitted at the University of the Philippines-Philippine General Hospital (UP-PGH) for non-healing wounds over both lower extremities which have been relentlessly enlarging over the past 9 years. This paper will discuss the possible etiologies, diagnostic pearls, and management of swelling of extremities.

Case Presentation

A 42-year-old male was admitted to this hospital because of non-healing wounds over his lower extremities. He presented with a 9-year history of progressive swelling of the right ankle and foot initially, followed by the left side, spreading proximally to the legs and thighs, after a seemingly innocuous minor right ankle sprain. Initially there was no pain, but there was eventual ulceration beginning in the toes of the right foot and decrease in sensation of the both limbs.

Upon consultation at a private institution, the patient was told that he had a problem with his veins and underwent removal of superficial leg veins. The ulcerations

were treated with systemic antibiotics. However there was continued swelling of the extremities. He again sought consultation at another private institution where his Doppler studies showed absence of deep venous thrombosis or reflux. No additional treatment, except for physical therapy, was advised. His bipedal enlargement progressed. He had to stop working as a pedicab* driver but was still ambulatory.

In the interim, he was diagnosed with diabetes mellitus and was prescribed Metformin and Gliclazide with poor compliance.

He went to our institution on the sixth year of his ailment. At this time, both lower limbs had grade 2-3 non-pitting edema and had decreased sensation. His right lower extremity was described to have verrucous epidermal change, while the left limb had a 12 x 3 cm ulceration at the medial aspect with skin thickening and scaling. Microfilarial smears done twice were negative. Duplex scan showed deep venous insufficiency of both lower extremities. He was started on topical keratolytics, systemic antibiotics, and compression therapy, with note of improvement of symptoms. Upon discharge, the patient was lost to follow up.

In the interim, there was continued enlargement of both lower limbs, with progression of verrucous nodules and plaques and eventual ulceration associated with seropurulent foul-smelling discharge and subsequent formation of draining sinuses. He then returned to our institution on the ninth year of his illness.

He did not have fever, jaundice, heart failure symptoms, or changes in urination or defecation. He denied hypertension, heart ailment, or thyroid problems. There was no similar illness in the family. Notably, he had history of travel to Catbalogan, Samar once, although this was a year after the swelling initially started. He was a high school graduate and had no vices.

On physical examination, he was alert, not in distress, and was not ambulatory. He was overweight. There was no facial dysmorphism observed. Vital signs were within normal and he was afebrile. He had no lymphadenopathy, no adventitious breath sounds, and no apparent cardiomegaly or murmurs. There was also absence of

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*A type of local means of transport consisting of human-powered tricycle designed to carry passengers on a for hire basis.

scrotal edema. Nailbeds of the upper extremities were pink. Pulses on all four extremities were full.

Both lower extremities, from the mid third of the thighs down to the feet, exhibited elephantiasis, with brawny, non-pitting edema (Figure 1). There were overlying verrucous skin-colored to hyperpigmented plaques and nodules with cobblestone-like appearance, and draining sinuses with yellowish foul-smelling discharge on both legs. There was deformity of the toes, and black discoloration, onycholysis, and subungual hyperkeratosis of the toenails. The assessment was: Primary Lymphedema, probably Lymphedema Tarda stage III, with secondary bacterial infection; secondary Chronic Venous Insufficiency; and Type 2 Diabetes Mellitus.



Figure 1. Patient's lower extremities on examination.

The patient was admitted in the wards and started on insulin, meropenem and clindamycin. He was eventually co-managed with Dermatology, Cardiology, Endocrinology, Infectious Disease, Orthopedics, and Vascular Surgery. He was also referred to Psychiatry for evaluation and support, and was assessed to have mental retardation.

Wedge biopsies done showed suppurative dermatitis and scar formation. Fungal stains (Periodic Acid-Schiff, Gomori Methenamine Silver, Fite Faraco) were all negative. Bacterial cultures of wound discharge showed moderately heavy growth of *Edwardsiella tarda* while bacterial tissue culture was positive for *Klebsiella pneumoniae*. Fungal and Acid Fast Bacillus (AFB) tissue cultures were negative. Filariasis antigen test was also negative. X-rays of both lower extremities showed no bone involvement and revealed only soft tissue swelling of thighs, legs, and feet. Pelvic computerized tomography scan showed lymphedema with focal fluid accumulation in the left thigh, but there was absence of masses, enlarged nodes, or abnormal vascular

structures/channels. Lymphoscintigraphy showed non-visualization of lymphatics in the right lower extremity and patent lymphatics in the left lower extremity up to the level of the inguinal area with stasis in the left leg. (Figures 2A, 2B, 2C, 2D)

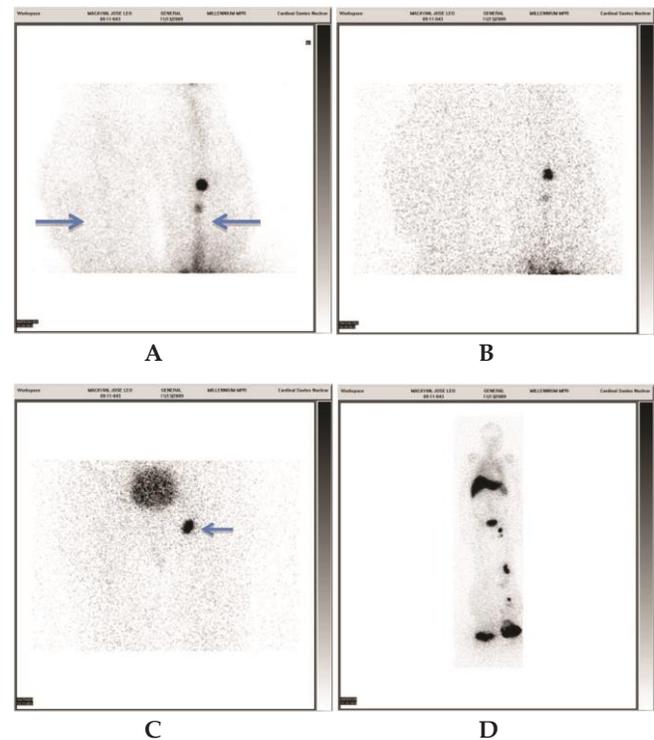


Figure 2. Lymphoscintigraphy results. **A.** Calves, immediately after injection: Note the complete absence of flow on the right leg. **B.** Calves at 1st hour: Absent flow on the right **C.** Thighs at 1st hour: lymphatic collection on the left (arrow), as well as the bladder (big dark round collection at the upper center); absent flow on the right. **D.** Whole body at 4th hour

Since the limbs were beyond salvage and there was danger of sepsis, all services agreed that the best treatment option was bilateral above-knee amputation. The patient underwent surgery on his 27th hospital day and tolerated the procedure well. Intra-operative specimens sent for fungal and TB cultures were negative. Bacterial culture showed heavy growth of *Proteus vulgaris*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. The gross specimen of the left leg was described to be edematous (greatest leg circumference of 56.5cm), with 7.4 cm-thick dermis and subcutaneous fat, while bone and muscle were grossly unremarkable. Histopathology showed diffuse lymphangiectasia, dermal fibrosis, hyperkeratosis, and abscess with draining sinus. Table 1 is a summary of pertinent examinations done. Intravenous antibiotics were continued post-operatively. The patient was discharged on his 15th post-operative day. He is currently on regular follow-up at the outpatient department.

Table 1. Summary of pertinent laboratory examinations done

Test	Result
Blood Chemistry	HBA1c – 5.7 mmol/L BUN – 2.7 mmol/L Creatinine – 70 umol/L Sodium – 133 mmol/L Potassium – 3.8 mmol/L Calcium – 2.09 mmol/L Albumin – 18 g/L ALT – 30 u/L LDL – 2.5 mmol/L HDL – 1.32 mmol/L Cholesterol – 4.07 mmol/L Triglycerides – 0.5 mmol/L
Urinalysis	Color – yellow Transparency – Clear SG – 1.030 pH – 6 Sugar – Negative Albumin – Negative RBC – Negative WBC – 1-4/HPF Casts – Hyaline 0-2 Crystals – Negative Bacteria – few
CBC	WBC – 9.05 x10 ⁹ /L (Neutrophils 0.603; Lymphocytes 0.260) RBC 3.61 x10 ⁹ /L Hb – 97 g/L Hct – 0.31 % MCV – 85 fL MCH – 27 pg MCHC – 317 g/L Platelets – 380 x10 ¹¹ /L
Filarial (microfilariae) smear	Twice negative
Filarial antigen test	Negative
Wound D/C CS	(+) <i>Edwardsiella tarda</i>
Tissue (from lymphedematous leg) GS/CS	PMN 0-5 Gram-negative bacilli 3-6 Gram-positive cocci in chain 0-1 (+) <i>Proteus vulgaris</i> (+) <i>Klebsiella pneumoniae</i> (+) <i>Acinetobacter baumannii</i>
Wound AFB smear x 3	Negative
Tissue AFB culture	Negative
Tissue KOH and other fungal stains	No hyphal elements
Tissue fungal cultures	Negative for pathogenic fungi
Blood CS	No growth after 5 day
Chest X-ray PA	No significant chest findings
Thighs, legs, feet APL	The cortical outlines are intact. The joint spaces are maintained. There is marked soft tissue swelling with irregularities in both legs and feet with associated splaying of the metatarsals and phalangeals. Soft tissue swellings with displaced fascial planes are also seen in both thighs. There are no lytic bone changes noted.
CT of the pelvis (lower abdomen)	Lymphedema with focal fluid collection at the left thigh. (Thickening of subcutaneous tissues of the pelvis and visualized proximal thighs; unenlarged nodes; no vascular structures/channels are appreciated)
2D-echo with Doppler	EF: 71% Concentric left ventricular hypertrophy with good wall motion contractility and preserved overall systolic function. Trivial tricuspid valve regurgitation. Mild pulmonary arterial hypertension.
Venous Duplex scan of both LE	Deep venous insufficiency of both lower extremities. No DVT.
Lympho-scintigram	Nonvisualization of lymphatics in the right lower extremity. Patent lymphatics in the left lower extremity up to the level of the inguinal area with stasis in the left leg.

Discussion

Our patient presented with a 9-year history of progressive bilateral lower extremity swelling with eventual ulcerations, secondary bacterial infection, deformity, and debility.

The Swollen Leg

A swollen leg, the initial consideration for this case, may be due to systemic or local etiologies. Systemic origins include congestive heart failure (CHF), renal failure, myxedema, pregnancy, hypoalbuminemia from cirrhosis, protein-losing nephropathy, or other causes.^{1,2} These lead to bilateral affection of the extremities. Local etiologies include lymphedema, lipedema, chronic venous insufficiency, thrombosis in the deep leg or portal veins or the inferior vena cava, cellulitis, popliteal cyst, and post-operative complications.²⁻⁶ These may present with either unilateral or bilateral swelling. A thorough history and physical examination is the mainstay in excluding many of the above-mentioned.

Along with normal serum biochemical analyses, we were able to eliminate all of the systemic, and many of the local, causes in our patient. The initially painless edema, progressive nature, and non-pitting appearance of the limbs led us to diagnose it as lymphedema. Absence of similar diseases in the family and other secondary causes make it probable that the patient's condition may be a non-familial primary lymphedema. The main reason for investigating further is not only to confirm the diagnosis, but also to exclude a potentially lethal condition, such as deep venous thrombosis (DVT).^{1,2}

Lymphedema Versus Edema

The lymphatics parallel the venous drainage system. Lymph, dependent on compressive forces, moves through the lymphatic capillaries to the major lymphatic vessels in a one-way direction passing through lymph nodes to return protein, colloids, and debris to the systemic venous circulation.^{7,8} One-way valves support this unidirectional flow. Lymphedema is thus a regional excess of protein-rich interstitial volume due to failure of lymph drainage in the face of normal capillary filtration. Patients with complete absence of lymphatics have a history of long-term swelling, compared to those with impaired lymph drainage, which have a shorter history.⁹

In contrast, in generalized edema states, edema is interstitial fluid overload that occurs with disruption in the Starling forces across capillaries. There is resulting imbalance between capillary filtration and lymph drainage, with an excess of the former. Edema that resolves with elevation of the affected area is likely due to increased capillary filtration, such as in CHF.^{8,9}

Lymphedema is a less common form of edema and is generally irreversible.

Clinical manifestations of Lymphedema

The initial symptom of lymphedema is usually painless swelling.¹ Lymphedema can be graded based on the severity of the swelling as seen in Table 2.¹⁰ Two-thirds of lymphedema are unilateral.¹¹ At the outset, the distal part of the extremity is affected with proximal extension occurring later. Edema is pitting initially but chronic lymphedema is characterized by non-pitting enlargement due to fibrosis in subcutaneous tissues. The clinical hallmark of more severe lymphedema is fibrosis, *peau d'orange*, and a positive Stemmer sign, which refers to the examiner being unable to lift the skin at the base of the upper surface of the digits, usually the second toe or finger in the affected extremity.¹² With time, the skin becomes thicker, rougher, and can break down, with lymph exuding through. Since protein-rich lymph provides a good medium for bacterial growth, there is compromise in healing which leads to a vicious cycle of recurrent infection, further lymphatic drainage dysfunction, and worsening edema.

Table 2. Grading of Lymphedema¹⁰

Grade	Edema	Involvement
1	Mild	Distal parts of extremity
2	Moderate	Entire limb or quadrant of trunk; with tissue changes
3a	Severe	Entire limb and quadrant
3b	Massive	Same as 3a, with \geq 2 extremities
4	Elephantiasis	Huge extremities due to almost complete blockade of lymph drainage

Lymphedema Classification and Staging (Table 3)

Primary lymphedema is due to a congenital abnormality or inherent defect of the lymphatic system and can be further classified according to age at initial examination. It is more common in females. The Praecox type is the most common variety with around 71% of the cases and onset particularly around menarche.¹ On the other hand, clinical manifestations of the less common Lymphedema Tarda, caused by a mutation in the FOXC2 gene, may not be evident until 30 years of age,^{13,14} such as in our patient. Primary lymphedema most often involves the lower limbs (80% of cases), but can also occur in the arms, face, trunk, or even the external genitalia.¹⁵ As in our patient, symptoms may be linked to minor trauma, suggesting that the abnormal lymphatics were able to cope under normal circumstances but were not capable of meeting the challenge of increased tissue fluid from inflammation brought about even by seemingly innocent trauma.¹⁶

Secondary lymphedema is caused by a reduction of lymph flow by an acquired cause, and is based on two basic principles: lymphatic interruption and lymphatic obstruction.⁹ These underlying causes can vary widely from obesity to lymphatic fibrosis due to radiation therapy.^{9,17} Malignancy, including its treatment, is the most common etiology in industrialized countries, while Filariasis

(parasitic infection with the nematode *Wuchereria bancrofti*) is the most common cause in developing countries and worldwide. Filariasis can affect up to 11%^{18,19} of the population in endemic areas, which are in tropical areas throughout the world.

Table 3. Classification of Lymphedema¹⁰

Primary
Congenital (detected at birth or first year of life)
Praecox (adolescence)
Tarda (adulthood)
Secondary
Lymphatic damage (trauma, surgery, radiation, etc)
Malignancy
Infection (filariasis)
Connective tissue disease or rheumatoid arthritis
Recurrent infection or cellulitis
Chronic venous stasis
Obesity

Lymphedema is also classified according to its severity in terms of staging. The Fifth WHO Expert Committees on Filariasis defined the most common method.^{20, 21} (Table 4)

Table 4. Staging of Lymphedema^{20, 21}

Stage	Characteristic
0	- "Subclinical" - Asymptomatic, or with feeling of limb heaviness - Exists for months or years before onset of overt lymphedema
1	- "Spontaneously reversible" - Accumulation of protein-rich fluid; - Subsides within 24 hours of limb elevation; - soft, pitting edema
2	- "Spontaneously irreversible" - 24-hour limb elevation alone rarely reduces swelling - Not as pitting
3	- "Lymphostatic elephantiasis" - Absent pitting - Trophic skin changes (fat deposits, acanthosis, verrucous overgrowths)

Complications of Lymphedema

As mentioned above, there is a vicious cycle of skin infection, deterioration of lymph drainage, and worsening edema. Cellulitis, erysipelas, or lymphangitis can occur. Lymphangiosarcoma is a rare and aggressive malignancy that may arise in chronic congenital nonhereditary lymphedema, although it is still most frequently associated with post-mastectomy lymphedema (Stewart-Treves syndrome).²² It is actually a misnomer because it is a vascular neoplasm and hence an angiosarcoma.

Diagnosis

Like any other disease, establishing the diagnosis of lymphedema begins with a thorough history and physical examination. Filariasis is the most common cause worldwide and should be excluded. In the Philippines alone, there are reported 7.7 cases per 1,000 population in endemic provinces.²³ It is endemic throughout most of the

southern half of the Philippine archipelago.²⁴ Figure 3 illustrates the endemic provinces in the Philippines. Antigen testing is now recognized as the test of choice for detection of *Wuchereria bancrofti* infections. Unlike tests that detect microfilariae, which have to be done at night because of the nocturnal nature of the parasites, antigen tests can be performed with blood collected at any time.²⁵

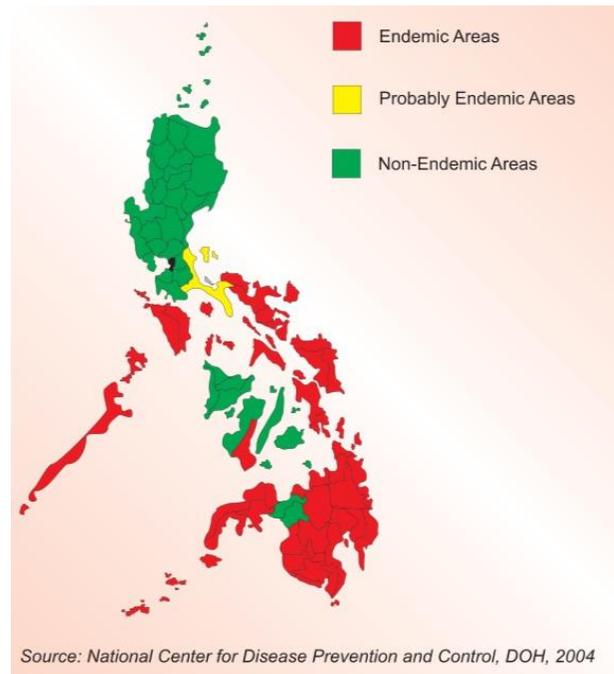


Figure 3. Classification of filariasis-endemic provinces in the Philippines.

Imaging

Imaging of the lymphatics may not be necessary if the diagnosis is obvious. Lymphoscintigraphy (radionuclide imaging) is the gold standard in cases where imaging is warranted.^{1,15,26} It can gauge lymphatic function, lymph movement and drainage, and response to treatment. Radiotracers (usually technetium 99m sulfur colloid, as was used in our patient) are injected subcutaneously or intradermally in the web space of the upper or lower extremities, and imaging is performed at 30 to 60 minutes after injection. The patient then performs extremity exercises and is followed by another imaging. Findings of absent or delayed radiotracer transport, absence or paucity of lymphatic collectors, dermal diffusion (backflow), and poorly visualized or absent regional lymph nodes establish the diagnosis of primary lymphedema in the absence of secondary causes.¹³ This procedure is minimally invasive, easy to perform, and does not damage the lymphatic endothelium. With a sensitivity of 73-97% and specificity of 100%,^{27,28} it has largely replaced the much more invasive and time-consuming lymphangiography, which involves direct

cannulation of the lymphatics, hence with increased risk for emboli, infections, and further fibrosis.²⁹ This, however, may still be indicated if there are plans for surgical intervention, such as by-pass procedures, to address the lymphedema.¹³

On the other hand, lymphoscintigraphic features of secondary lymphedema are distinct in that there are prominent lymphatic trunks, in contrast to attenuation or absence in primary lymphedema.

Lymphoscintigraphy can also differentiate between lymphedema and edema of venous origin. In patients with chronic venous insufficiency and venous leg ulcers, there is significantly reduced lymph drainage in both the affected and non-ulcerated leg. In those with post-thrombotic disease, there is decrease in the subfascial lymph flow. In lymphedema, aside from those mentioned above, both epifascial and subfascial lymphatics are abnormal.^{1,30} In lipedema, the peripheral lymphatics are normal although the flow may be a little slower.³¹

Other imaging methods that may be indicated are as follows:

- Ultrasound, MRI, or CT scan of the lower abdomen – these provide anatomic and nodal details and may complement information gathered from lymphoscintigraphy, as these can rule out obstructive causes of lymphedema. MRI may also differentiate primary lymphedema from other causes such as lipedema. Our patient's pelvic CT scan was essentially free from enlarged nodes and other masses that may cause obstruction of lymph flow.^{1,14}
- Doppler ultrasound – this is useful when DVT is a possibility. In our patient, there was initially no venous insufficiency, although deep venous insufficiency was detected on repeat ultrasound a few years later. There was no DVT in both extremities.

Our patient's lymphoscintigram showed non-visualization of lymphatics in the right lower extremity, and patent lymphatics in the left lower extremity up to the level of the inguinal area with stasis in the left leg. Coupled with the pelvic CT scan and venous Doppler results, we concurred that he had primary Lymphedema Tarda on the right. The resulting chronic venous insufficiency from the massive lymphedema led to secondary lymphedema on the left, and also aggravated the original primary lymphedema on the right.

Histopathology may be indicated only in patients suspected of secondary lymphedema based on clinical presentation and lymphoscintigram.

Management of Lymphedema

There is no known cure for primary lymphedema.² However, management can be successful in most patients, and is usually conservative. It is rooted on returning

lymphatic fluid to the venous circulation through the remaining or functional lymph vessels by several methods (Table 5) which should be used together to achieve therapeutic effect.⁸ Secondary lymphedema may also be addressed as such, in addition to removal of the obstruction, if this is possible.

Table 5. Key Components in Management of Lymphedema

Elevation
Skin and nail hygiene
Exercises (flexibility; weight training; strengthening)
Compression (garments or devices)
Manual lymph drainage massage
Patient education
Psychological support

Uncomplicated mild lymphedema may simply be addressed by avoidance of prolonged standing and elevation of the affected limb, along with good skin care to decrease risk of infections.²⁶ Exercises are utilized for both weight control and fluid mobilization. The rest of the components in management may be added on to address more severe cases. Intermittent pneumatic pumps assist lymphatic flow by external pressure exerted by a device attached to the extremity.

Diuretics and coumadin have not found their place in the management of lymphedema and are therefore not recommended.²⁶

When medical management fails, surgical alternatives may be palliative. These include bypass to improve lymph flow, or debulking procedures to remove subcutaneous lymphedematous tissues.^{1,2,26} These may improve the patients' quality of life.³² Long term prognosis is excellent if the type and cause of lymphedema is identified early and treatment begins immediately once the diagnosis is made.

Since our patient's limbs were no longer salvageable, with superimposed severe bacterial infections that may lead to sepsis should the service wait any further, bilateral above knee amputation was performed. He is now on physical therapy to continue his exercises and manual lymphatic drainage of the thighs.

Conclusion

Lymphedema may be primary or secondary, with the former subclassified according to age of symptomatology. History and physical examination are the cornerstones in the diagnosis. The role of imaging studies are limited, however, lymphoscintigraphy is the gold standard to reliably differentiate the type of lymphedema as well as to distinguish it from edema of venous insufficiency. DVT should be ruled out in all patients with the use of non-invasive studies such as Doppler scans. Management entails meticulous adherence to a program of rerouting of lymph flow through elevation, compression, and exercise, along with good skin care, to prevent complications.

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