

MULTICAUSAL LYMPHEDEMA: A NEW FRAMEWORK?

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TRADITIONAL LYMPHEDEMA CLASSIFICATION

- Primary
 - Described as “congenital” even when swelling starts later in life
 - Majority sporadic, smaller subset hereditary, relatively few genes discovered
- Secondary
 - Identifiable cause for lymphatic damage/dysfunction
 - Cancer-related always described as most common cause in US

OUR PATIENTS DON'T FIT THE MOLD!

- Often no definite hereditary pattern although thorough family history may show “tendency” to swell in some relatives
- Onset of lymphedema in patient often hard to pinpoint, patients only notice when it becomes more severe
- No definite identifiable cause for swelling
- Patients often obese, have multiple comorbidities

TYPICAL PATIENT – LET'S CALL HER LINDA

- Mild intermittent swelling in 20's/30s, usually in summer
- Fam hx: some swelling in sister, aunts, also FH of obesity
- Significant weight gain in 30s, especially after children
- Weight increases further in spite of “yo-yo” dieting, swelling progresses
- By 40s swelling constant, usually improves overnight, stage 2
- One episode LE cellulitis responded to oral abx.



LINDA

- By 50s/60s mobility declines, more sedentary → severe morbid obesity
- Multiple comorbidities incl DM, HTN, OA → TKA, DVT/CVI, obstructive sleep apnea (OSA) with pulmonary HTN and possible right heart failure.
- Lymphedema now severe stage 2/3, one episode transient weeping
- Two more episodes of cellulitis, one requires hospitalization
- Three courses of CDT with improvement but limited compliance with self-care



HOW TO CLASSIFY THIS PATIENT?

- Many possible causes for the lymphedema in this individual (e.g. multicausal!):
 - CVI
 - OA, knee surgery
 - Immobility, dependency, sedentary lifestyle (loss of muscle pump)
 - DVT/CVI
 - OSA, pulmonary hypertension
 - Infection
 - DM and HTN – medications can cause edema

BUT WHAT'S THE COMMON FACTOR?

- The common factor that underlies all these disorders is: **Obesity**
- Obesity increases the risk of:
 - OA/lower limb joint surgery
 - Venous disease
 - OSA/pulmonary hypertension/right heart failure
 - Cellulitis
 - DM, HTN

IS MULTICAUSAL LYMPHEDEMA PRIMARY OR SECONDARY?

- **YES!**
- These patients have primary lymphatic "insufficiency", sometimes with apparent familial component
- Probably explains why some obese patients have swelling and others don't ("predisposition").
- Clinical onset of lymphedema is triggered by identifiable secondary factor: obesity
- Exacerbated by associated comorbidities

FOELDI CLINIC EXPERIENCE (PER DR TOBIAS BERTSCH)

- Mirrors our own
- Progressive increase in prevalence of obesity, especially morbid obesity
- Exponential increase in BMIs >40, >50, >60, not much change in BMIs between 30-39
- Decrease in pts with other causes of secondary lymphedema, increase in obesity-related lymphedema
- Obesity worsens all types of lymphedema, whether primary or secondary
- 100% of patients with multicausal lymphedema are obese

OBESITY AND LYMPHEDEMA THE EXTENT OF THE U.S. PROBLEM

- As of 2014 more than 35% of US adults obese, 6% morbidly obese
- Nearly 70% of adults overweight or obese
- Proportion of population with obesity is increasing by 2.1- 4.7% every 10 years
- At the Földi Klinik, 68% of patients with lymphedema are obese, 32% of those are morbidly obese
- In my lymphedema practice, saw about the same percentages

OBESITY AND LYMPHEDEMA

- Morbid obesity can produce lymphedema in absence of other injury to lymph system (Greene et al., N Engl J Med, 2012)
- Adipose tissue plays active role in inflammation, produces hormones, cytokines, and leads to deposition of fibrofatty tissue in affected limb.



"LYMPHEDEMA AND OBESITY: IS THERE A LINK?"

(MEHRARA AND GREENE, PLAST RECONSTR SURG, 2014)

- Adipose deposition is similar in lymphedema and obesity
 - There is both proliferation and hypertrophy of local adipocytes (fat cells)
 - The fat tissue is chronically inflamed
- Fluid stasis activates adipose differentiation genes (stem cells) that preferentially lead to further adipose deposition, decrease ability to form new lymphatic vessels

COMPLICATED ASSOCIATION BETWEEN OBESITY AND LYMPHEDEMA

- Obesity causes increased deposition of adipose (fat) tissue.
- Conversely, lymphedema causes increased deposition of fat tissue in affected limbs → vicious cycle.
- Adipose tissue is in close proximity to precollectors
- Adipose tissue produces hormones and inflammatory modulators (eg cytokines) that:
 - Increase inflammation around lymphatic vessel
 - Decrease lymphatic contractility



ANIMAL STUDIES OF OBESITY AND LYMPHEDEMA

- Obese mice display changes in structure and function of collecting lymphatics
- reduced transport in skin lymphatics
 - reduced frequency of lymphatic contractions in collecting lymphatics
 - reduced response to mechanostimulation of lymphatics (e.g. massage)
 - enlargement of lymphatic collecting vessels
- (Blum et al., PLOS ONE, 2014)

ANIMAL STUDIES OF OBESITY AND LYMPHEDEMA

(SAVETSKY ET AL. AM J PHYSIOL HEART CIRC PHYSIOL, 2014)

- Obese mice in this study
 - Had worse lymphatic function at baseline
 - Developed worse lymphedema after surgery
 - Had increased inflammatory response to skin irritation
 - Had increased adipose deposition, fibrosis and inflammation
- Previous research by same group showed that fibrosis decreases lymphatic function and regeneration, so again → vicious cycle

SKIN AND TISSUE CHANGES IN LYMPHEDEMA EXACERBATED BY OBESITY

- Papillomatosis
- Increased adiposity
- Congestive dermatitis
- Fibrosis, tissue hardening
- Hyperkeratosis
- Fungal rashes in skin folds
- Lymphedematous lobules
- Massive localized lymphedema



SKIN AND TISSUE CHANGES IN LYMPHEDEMA

- Lymph stasis leads to inflammation, fibrosis, and deposition of excess fat tissue - dermatolipofibrosis
- Studies implicate inflammation and fibrosis as key contributors to the pathological cascade in lymphedema, suggesting antifibrotic and anti-inflammatory approaches to treat or prevent lymphedema
- The process of fat accumulation and inflammation in a limb in response to fluid stasis “mimics the events that occur in obesity in general”. Obesity is an area of intense research currently.

TAKE-HOME #1 SUMMARY OF THESE FINDINGS

- Obesity decreases lymphatic function and propensity to inflammation at baseline
- These effects are amplified by lymphatic injury and/or fluid stasis
- Heightened immune responses in obesity promote inflammation, fibrosis, adipose deposition
- These effects further impair lymphatic function and ability to regenerate

MECHANICAL EFFECTS OF OBESITY ON LYMPHATIC FUNCTION

- Overhanging abdomen, large lobules can compress lymphatics
- Decreased muscle pump due to immobility reduces lymphatic contractions
- Large fibroadipose layer can diminish effect of bandaging, compression
- Ability to self-manage impaired



OBESITY AND LYMPHEDEMA TREATMENT

- Obesity reduces effectiveness of CDT, and impedes patient self-care
- Lymphedema/lobules have high fibrofatty content so may not reduce well
- Wound healing often **very** slow
- Lobules can recur if weight is not addressed

WEIGHT MANAGEMENT

- Weight loss in 12 week program significantly reduced arm lymphedema - avg. weight loss of 7.2 lbs, max loss 13 lbs. (Shaw et al, 2007)
- However, "diets" generally counterproductive, about 95% regain the weight
 - "Diets make you fat and sick!" (Dr. Bertsch)
 - Long-term lifestyle changes necessary
- Bariatric surgery for substantial weight loss.
- Otherwise, "Stabilize and Exercise!"
- Caution patients about gaining weight in the first place.

MEETING THE CHALLENGES OF MULTICAUSAL LYMPHEDEMA

- CDT can be amazingly effective in obese patients
- Intensive therapy (5 days/wk)
- Custom, Velcro garments
- Self-care, home help
- Skin care, hygiene
- Activity



MEETING THE CHALLENGES OF MULTICAUSAL LYMPHEDEMA

- Multicausal lymphedema requires multi-disciplinary treatment! (in addition to CDT)
- Weight management
- Physical therapy - mobility, QOL improve
 - Regular exercise decreases inflammation, pain, improves mood, helps decrease edema
- Co-morbidities (diabetes, HTN, heart problems, CVI, sleep apnea) require medical management – refer if necessary
- Assistance at home – may have to hire private aide

MEETING THE CHALLENGES OF MULTICAUSAL LYMPHEDEMA

- Bariatric surgery for severe obesity – long term data prove effectiveness but **ONLY** if multidisciplinary approach
- Lymphedema therapist (CLT)
- MD
- Psychologist
- Bariatric surgeon
- Nutritionist
- Physical therapist (exercise, activity)
- Plastic surgeon for dermatolipectomy (at least 1 to 2 years post weight-loss)

TAKE-HOME MESSAGE #2
MULTICAUSAL LYMPHEDEMA

- The majority of our patients have “multicausal” lymphedema
- Common factor is obesity
- Probable physiologic or genetic “predisposition” in many/most
- Treatment can be very effective but must be multidisciplinary

THANK YOU FOR MEETING
THE CHALLENGES OF
MULTICAUSAL LYMPHEDEMA
EVERY DAY!