Massive localised lymphoedema: a review of published literature on this unique entity


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Massive localised lymphoedema (MLL) is a unique presentation of lymphoedema in morbidly obese patients, located most commonly in the medial thigh. MLL presents as a localised painless mass of lymphoedematous tissue. However, it is more generalised condition than the name implies, since it restricts patient's activities of daily living and significantly impairs quality of life. The authors conducted a systematic review of the literature on MLL. The search yielded 53 articles, with a total of 105 patients documented. MLL has been reported in association with Hashimoto's disease, hypothyroidism and diabetes. There is a low quality of evidence and a lack of rigorous studies on MLL. It is possible that prevalence of MLL will increase with the rising incidence of morbid obesity. It is essential to increase clinicians' awareness of MLL, since this complex condition is more easily managed in its early stages.

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Massive localised lymphoedema (MLL), a rare unique presentation of lymphoedema, is characterised by a large, benign, painless usually unilateral mass that develops in morbidly obese people. MLL was first described by Farshid and Weiss in 1998 in a series of 14 patients, all morbidly obese (Farshid and Weiss, 1998).

MLL is most commonly located on the medial thigh (*Figure 1*), but is not restricted to thighs, and can develop on the lower leg, suprapubic or mons pubis region, the genitals or the groin, the popliteal fossa and even the upper arm. MLL is generally considered a rare condition in morbidly obese patients. Since the prevalence of morbid obesity is on the rise, with 5.7% of Americans 20 years and older considered to be extremely obese (BMI≥40 kg/m^2), it is likely that the true prevalence of MLL is underestimated (Ogden and Carroll, 2010).

Recurrent infection and ulceration is a common complication of MLL. Considering the huge annual healthcare cost for skin wounds and ulcers that runs into the billions ($6,398 million, and $5,442 million respectively in the US in 2013), increased awareness regarding these conditions is a priority (Lim et al, 2017).

The authors suggest that higher awareness of MLL is needed, and a multidisciplinary approach to manage these patients is critical. Moreover, this condition is more easily managed in its earlier stages, so monitoring the morbidly obese population for MLL is essential.

Methods

To gather the literature for this review, PubMed, EMBASE and MEDLINE were searched from inception to November 2017. The keywords used were "massive localized lymphedema/lymphoedema", "lymphedema/lymphoedema" and "pseudosarcoma". The inclusion criteria were full text original articles in English related to the search terms.

Search results were analysed. There have been no clinical trials relating to MLL. Case reports were defined as those studies with one or two patients with MLL in any location, whereas case series were defined as those with three or more patients. We also located one case-control study.

Results and discussion

A total of 53 articles were found, 12 review articles, seven case series, 15 case reports and one case-control study, with a total of 105 patients documented. The review articles were excluded. *Table 1* provides a summary of the included publications.

Morbid obesity is not new to modern medicine, and it is plausible that MLL is not a new entity at

Table 1: Clinical summary of case series and case reports about massive localised lymphoedema (MLL).

Study	Sample size	Gender	Location of MLL	Unilateral vs bilateral	Bx taken	Medical history
Farshid and Weiss (1998)	14	9 females; 5 males	Thigh (*n*=12); arm (*n*=2)	Unilateral	Yes	None
Barr (2000)	1	Female	Lower abdominal wall	N/A	Yes	None
Wu et al (2000)	6	4 females; 2 males	Thigh, abdomen, penis, popliteal fossa, scrotum, suprapubic, inguinal region	Both	Yes	Hypothyroidism (*n*=2)
Goshtasby et al (2006)	1	Male	Thigh	Unilateral	Yes	DM, Kasabach-Merritt syndrome
Modolin et al (2006)	4	2 females; 2 males	Thigh (*n*=3); hypogastrium (*n*=1)	Unilateral	Yes	None
Weston and Clay (2007)	1	Female	Thigh	Bilateral	Yes	None
Asch et al (2008)	1	Male	Lower abdominal wall	N/A	Yes	Hypothyroidism
Manduch et al (2009)	22	15 females; 7 males	Thigh (*n*=17) NOS (*n*=6), lower leg (*n*=4), hip (*n*=1)	Unilateral	Yes	None
Wang et al (2010)	2	2 females	Lower abdomen, suprapubic area	N/A	Yes	Hypothyroidism (*n*=1)
Bogusz et al (2011)	2	1 female; 1 male	Genitalia, thigh	Unilateral	Yes	None
Evans and Scilley (2011)	2	2 females	Lower leg, thigh	Unilateral	No	None
Fadare et al (2011)	2	2 females	Genitalia	N/A	Yes	None
Brewer and Singh (2012)	1	Male	Mons pubis	N/A	No	DM
Narayanarao et al (2012)	1	Female	Mons pubis	N/A	Yes	Hypothyroidism
Lee et al (2013)	6	6 males	Genitalia	N/A	Yes	Crohn's disease (*n*=1)
Fife (2014)	1	Female	Thigh	Bilateral	No	Hashimoto's disease
Heller et al (2014)	1	Female	Genitalia	Bilateral	Yes	DM, hypertension, asthma, bipolar disorder
Bahrami et al (2015)	1	Male	Medial thigh	Unilateral	Yes	HIV positive, DVT right lower extremity
Jabbar et al (2015)	6	5 females; 1 male	Thigh (*n*=3), calf (*n*=1), abdomen (*n*=2)	Unilateral	Yes	None
Kotidis et al (2015)	1	Female	Lower abdominal wall	N/A	Yes	None
Wisenbaugh et al (2016)	11	11 males	Genitalia	N/A	Yes	Unknown
Hilerowicz et al (2017)	1	Female	Medial thigh	Unilateral	Yes	None
Maclellan et al (2017)	17	9 females; 8 males	Thigh (*n*=16; bilateral = 10, unilateral = 6), genitalia (*n*=3), suprapubic area (*n*=2)	Both	No	None

DM=diabetes mellitus; DVT=deep vein thrombosis; N/A=not applicable; NOS=not otherwise specified.

all, but rather was only brought to the attention of clinicians since it was first reported two decades ago (Farshid and Weiss, 1998). Despite subsequent reports in the literature, MLL is still considered uncommon.

Morbidly obese patients, with a history of trauma to the leg, long-standing leg swelling or hypothyroidism are at high risk for the gradual development of MLL (Maclellan et al, 2017).

MLL presents as localised disproportionate swelling of tissue that gradually increases in size. Secondary lymphoedematous changes of the skin lead to cobblestone appearance, erosions, oozing and subsequent ulceration (*Figure 1*).

MLL significantly affects the activities of daily living; it leads to restriction in mobility, difficulty in finding appropriate wear, and challenges with personal hygiene. More gravely, MLL can be complicated with recurrent deep tissue infection and, rarely, angiosarcoma, which has a high mortality rate (Requena and Sangueza, 1998).

There is no clear-cut explanation of the exact pathophysiology of MLL. The assumption is that morbid obesity leads to disruption in the lymphatic flow and drainage due to excessive adipose tissue deposits (Bogusz et al, 2011;

Figure 1. Massive localised lymphoedema on posterior thigh.

Fife, 2014). This in turn might lead to a vicious cycle and more comprised lymphatic flow until the formation of these fatty masses. However, this process is ignited by a trigger, either prior infection or surgery that leads to an obstruction of efferent lymphatic flow (Wu et al, 2000; Evans and Scilley, 2011).

Localised ischemia is caused by the tension and weight on the affected tissue may also contribute to MLL. Ischemia may in turn lead to recruitment of growth factors to the affected area, leading to fibrosis and accentuation of adipose lobules (Wu et al, 2000).

Morbid obesity triggering MLL was shown in a recent study of 17 patients, none of whom had primary or secondary lymphoedema, and whose median body mass index (BMI) was 66 kg/m^2 (Maclellan et al, 2017).

Although MLL is a benign process *per se*, secondary tumours have been reported to develop in MLL tissues, including angiosarcoma, a malignant sarcoma observed in 13% of cases reported in literature (Chopra et al, 2015). MLL has also been reported in association with Hashimoto's disease and hypothyroidism in 5.7% (6/105) of cases (Wu et al, 2000; Asch et al, 2008; Wang et al, 2010; Narayanarao et al, 2012; Fife, 2014).

Other interesting associations that were found in our literature search include diabetes mellitus in 2.8% (3/105), but we suspect that this associated disease has been underreported, since obesity is linked to diabetes.

In another case report, the patient also had the consumptive coagulopathy Kasabach-Merritt syndrome (KSM), a potentially life-threatening condition (Goshtasby et al, 2006). KSM syndrome, which is associated with massive haemangiomas, has been classically reported in the paediatric population (Hall, 2001). Although KSM is rare, the conclusion from this case is that it might be cost-effective to include laboratory studies for complete blood count to assess for infection or haematoma formation.

Delay in diagnosis of MLL until the advanced stages is a common clinical scenario. Therefore, it is important for clinicians to perform a thorough medical history and physical examination to identify any masses obscuring the normal anatomy and to document their growth over time. The term pseudosarcoma was coined and used interchangeably with MLL in some published articles due to the pathological similarity noted in some case reports (Goshtasby et al, 2006; Narayanarao et al, 2012).

Histologically, MLL is characterised by an expanded dermis with lymphangiectasis, increased dermal collagen and reactive fibroblasts. The adipose lobules of mature fat are interrupted by expanded fibrous septa, with lymphatic and vascular proliferation and ischemic changes such as infarction and fat necrosis (Kotidis et al, 2015).

MLL is essentially a clinical diagnosis, and biopsy is neither required nor recommended in the vast majority of cases. However, it may be a relatively "easy" diagnostic tool in selected cases, considering that in many cases the size of these masses restricts them from imaging with an MRI machine.

Dercum's disease (adiposis dolorosa) presents with multiple painful lipomas mainly in overweight, postmenopausal females with mental or emotional disturbances (Dercum, 1892). A recent retrospective review of the imaging in 17 cases found that although the imaging findings assisted in ruling out infection or malignancy, they were unable to clearly distinguish between MLL and Dercum's disease (Petscavage-Thomas et al, 2015).

Tissue biopsy, can be beneficial in some cases, particularly when there is concern regarding malignancy. The histological features of MLL are characteristic and aid the diagnosis by ruling out other options (Manduch et al, 2009). MLL evolves over several years. A rapidly growing mass is more suggestive of malignancy. Therefore, careful history taking is imperative and will suffice in most cases.

The core therapy for lymphoedema involves complete decongestive physiotherapy, which consists of manual lymph drainage, lymphoedema bandaging, exercise and skin care (Fife and Carter, 2008; Tan et al, 2011). Pneumatic compression device can be a valuable in addition to the regimen both to reduce MLL volume and maintain reductions long-term (Adams at al, 2010). However, due to the size of the MLL collections and their often-awkward locations (e.g. suprapubic or abdomen), standard pneumatic compression devices are unlikely to fit and may have inadequate compression cycles to effect improvement. A novel pneumatic compression device system has been designed to treat morbidly obese patients. It applies therapy to the abdominal, genital and proximal thigh areas and the lower legs, utilising a compression profile designed for these larger patients. A randomised controlled study of this system for lymphoedema patients compared it to arm treatment alone and showed no additive benefit (Ridner at al, 2012).

Undoubtedly, surgery is the best therapeutic option for MLL, and has curative potential, but it is

not free of risks and complications. Intraoperative complications include compromising delicate anatomical regions, such as when removing MLL from the genital regions (Wisenbaugh et al, 2018). Postoperative complications are expected especially as MLL patients have morbid obesity and high BMI (Thejeswi et al, 2012; Wisenbaugh et al, 2018).

Conclusion

MLL, a unique form of lymphoedema, is relatively new entity, since it was not recognised until 1998. It is a debilitating condition, encountered in morbidly obese patients, sometimes with associated conditions as well. It is expected that the prevalence of MLL will rise with the increase in obesity globally.

Prevention of MLL is only possible when closely monitoring morbidly obese patients, and alerting them of the high risk of the condition developing. More studies are required to understand the pathophysiology of this disorder and to optimise treatment protocols. WINT

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