RESEARCH PAPER

LYMPHO-SCINTIGRAPHIC LOCALISATION OF OBSTRUCTIONS IN PRIMARY LYMPHOEDEMA OF LOWER LIMBS IN THE CENTRAL PROVINCE OF SRI LANKA FROM 1990 TO 2003

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Abstract

Introduction: Primary lymphoedema constitutes the bulk of cases among those seeking treatment in the Central province¹. The underlying pathophysiological mechanics at presentation have not yet been established in Sri Lanka.

Objective: To describe the location of the sites of obstruction to lymphatic flow in primary lymphoedema among Sri Lankan patients related to their clinical level of lymphoedema at presentation.

Method: Eighty consecutive patients with primary lymphoedema, with varied levels of clinical lymphoedema were studied by isotope lympho-scintigraphy to ascertain where the block occurred, for each level of clinical lymphoedema of the lower limb.

Results: The location of scintigraphic obstruction was always located more proximal in the limb, to the level of clinical lymphoedema. The site varied for each clinical level. Sites were related to the anatomical location of lymph nodes except for, a very common site in the medial knee. Such blocks were associated with rapid entry to the blood stream suggestive of the existence of lympho-venous shunting at this level. In most, the presenting level of lymphoedema was reached within 24-months of onset.

Conclusion: Lymph nodes are probably the site of obstruction in most cases of primary lymphoedema. Presenting clinical level of lymphoedema is a dynamic of, site of lymphatic blockage and the presence of lympho-venous shunting.

Key words: Primary lymphoedema, lower limbs, Lympho-scintigraphy

Introduction

Lymphoedema where a secondary cause is not identified, i.e. primary lymphoedema, is the most common form of lymphoedema in the Central Province of Sri Lanka¹. Lympho-scintigraphic studies on primary lymphoedema have not been published from Sri Lanka. The prevalence of Filarial infection in the Central Province during the years of study (1990-2003) was thought to be low (not endemic) ².

The level of lymphoedema at presentation in primary cases depends on the dynamics of many factors. The degree and location of congenital mal-development of the lymphatic system, the availability and functionality of lymphatic...
collaterals in the skin, the existence of lympho-venous shunting and the duration related damage that has occurred to the lymphatic system by recurrent attacks of lymphangitis, and peri-lymphangitis. These factors need to be evaluated to understand the extent degree of lymphoedema in each clinical presentation.

Clinical features and lympho-scintigraphy of an affected lymphoedematous limb affords an opportunity to detail all this data. We hoped that this would further establish a body of morphological data as per affected limb, enabling us, to some extent visualise and hopefully work out, what could be done for the limbs of patients with primary lymphoedema.

Lympho-scintigraphy is an established method of assessing the lymphatic system. Its dynamic form using a SPECT Gamma camera (Single Photon Emission Computerized Tomography) is a modern-day sophistication of this facility and gives more resolution to the time related flow of the tracer isotope within the lymphatic system. At the time of the study we had only static lympho-scintigraphy. Flow and its features are assessed by many qualitative and quantifiable assessments. Lymphatic transport can be assessed by quantitative clearance, as depicted on time activity curves (Figure 1), which can show hold up of the transit of the tracer compared to the unaffected limb. Time based qualitative visual interpretation, (Figure 2), of the distribution patterns of the labelled colloid on scintigrams, can by their accumulation highlight the location of obstruction on the limb and the existence of collaterals that have since, developed. However, it has been shown that reliability and reproducibility is best (a high order of sensitivity and specificity) obtained by a combination of assessments i.e. a transport index being used for evaluation. Timed uptakes by the liver will allow us to work out the rate of entry of the isotope tracer to the systemic (venous) circulation which can occur via the thoracic duct in the neck or via lympho-venous shunts that maybe present or have developed.

![Figure 1: Time activity curve of normal vs lymphoedematous limb](image1)

The time activity curve highlights the delay in lymphatic tracer transport in the lymphoedematous limb compared to a normal limb.

![Figure 2: Lymphatics of the normal lower limb](image2)

Figure highlights the normal distribution of lymphatic trunks and lymph nodes in the lower limb.

**Methods**

80 consecutive new patients (53 female and 27 male) with lymphoedema of the lower limb on whom no secondary cause was found were studied by lympho-scintigraphy. They presented to the Vascular clinic of the Teaching Hospital
Peradeniya, Sri Lanka from 1990 to 2003. Clinical details as to the demography, the extent of involvement, its duration, complications were recorded as a prospective audit. Investigations that included filarial antibody titre (FAT) smears for microfilaria and latterly microfilaria antigen titres, were performed. Only those with what we believed to be, primary lymphoedema\textsuperscript{1}, were taken into account.

Patients, when the affliction was bilateral, those with different levels of clinical lymphoedema in their two lower limbs at presentation were excluded from the study group as they would not be able to provide the requisite information or the unaffected limb for comparison.

Patients were explained as to the procedure, it’s minimally invasive nature and those who consented, recorded. Those who consented and fell within the criteria of selection were scintigraphed. Their clinical details were correlated with the location of the scintigraphic block.

The lymphoscintigraphy was done using freshly prepared radioactive (148 Bq-ie 4 mCi) \textsuperscript{99m} Technetium (Tc\textsuperscript{99}) Sulpha Colloid (American Hepatolite) with a particle size of 40-50nm was drawn into two tuberculin syringes in a volume of less than 0.25 ml in each and injected into the subcutaneous tissue of the first web space of both feet, which had been thoroughly cleaned with methyl spirit. The time recorded. A 30 second massage of the site and 10 min walk subsequently were strictly timed. The radioactivity of the contents in the syringe before and after the administration recorded, Local anaesthesia was not used.

15 minutes later, the supine patient was scanned using a LFOV (large field of view) Gamma Camera (Searl-Medex) fitted with a low energy high resolution collimator, attached to a Nuclear Medicine Computer, which was used for scanning the distribution of isotope.

Attempt was made to visually identify the location of the site of obstruction to the lymph flow in the limb, the existence of collaterals, the time of entry to the systemic circulation by the hepatic uptake of tracer and see its correlation to the level of clinical lymphoedema.

160 lower limbs were studied. Irrespective of unilateral or bilateral involvement of the lymphoedematous process. 105 were affected limbs and 55 were clinically normal limbs. The customary precautions as to an absence of a pregnancy and a history of allergies to drugs were taken and appropriately avoided.

Ethical clearance was obtained from the Faculty of Medicine, Peradeniya, Committee for Ethical clearance.

Statistical package used was SPSS for Windows 8.0.2.

Results

Demography (age and gender) of patients studied is shown in Figure 3. Average age of the patients was 37.7 years (range 0.5-75 year). The male (M): female (F) ratio was 1:1.96. Level of lymphoedema of the limbs studied is shown in table 1. Age structure of each level of lymphoedema studied is shown in table 2.
Figure 3: Age and gender distribution of patients

Table 1: Presentation of cases of primary lymphoedema of the lower limb

| Gender  | No:  | Below Knee* | Above Knee | Both Limbs | Left Limb | Right Limb |
|---------|------|-------------|------------|------------|-----------|------------|
| FEMALE  | 53   | 46          | 7          | 18         | 18        | 17         |
| MALE    | 27   | 20          | 7          | 7          | 10        | 10         |

*includes below ankle.

Table 2: Age and gender stratified presentations of primary lymphoedema of the lower limbs

| PRESENTATION     | GENDER | AGE GROUPS IN YEARS |
|------------------|--------|---------------------|
|                  |        | 0-10    | 11-20   | 21-30   | 31-40   | 41-50   | 51-60   | 61-70   | 71-80   |
| BELOW ANKLE      | F      | 0       | 0       | 4       | 4       | 0       | 0       | 0       | 0       |
|                  | M      | 0       | 0       | 2       | 1       | 1       | 1       | 0       | 0       |
| BELOW KNEE       | F      | 0       | 3       | 14      | 7       | 12      | 2       | 1       | 0       |
|                  | M      | 1       | 3       | 1       | 2       | 4       | 2       | 0       | 1       |
| ABOVE KNEE       | F      | 0       | 1       | 3       | 2       | 1       | 0       | 0       | 0       |
|                  | M      | 1       | 1       | 1       | 2       | 1       | 0       | 1       | 0       |
| TOTALS           | F      | 0       | 4       | 21      | 13      | 13      | 2       | 1       | 0       |
|                  | M      | 2       | 4       | 4       | 5       | 6       | 3       | 1       | 1       |
Number of affected Limbs with the level of lymphoedema (Unilateral/Bilateral) at each clinical level by gender is shown in table 3.

The unilateral cases had their unaffected limb also scintigraphed as according to the protocol i.e. 55 normal limbs.

The familial cases. % prevalence of familial cases was 12/80 (15%) and the number of bilateral diseases in this group was 9/12 (75%). In males (n=3) all three had bilateral BK lymphoedema. In females (n=9), six had bilateral lymphoedema of which five were BK and one was AK. Two females had unilateral BK disease while one other had BA lymphoedema.

Duration of lymphoedema as per clinical level of lymphoedema is shown in Figure 4. It highlights that ascent of the lymphoedema does not seem to be duration related, as the Above knee lymphoedema does not show greater prevalence with longer duration of affliction.

### Table 3. Gender, level and extent (unilateral/ bilateral) of lymphoedema

| Gender | BA   | BK   | AK   | TOTAL |
|--------|------|------|------|-------|
|        | BIL  | UNIL | BIL  | UNILAT| BIL  | UNILAT|       |
| Female | 2    | 7    | 28   | 24    | 6    | 4     | 71    |
| Male   | 4    | 3    | 10   | 10    | 0    | 7     | 34    |
| Total  | 6    | 10   | 38   | 34    | 6    | 11    | 105   |

BA-below ankle, BK- below knee, AK- above knee, BIL – bilateral, UNILAT - unilateral

![Duration of Primary Lymphoedema as per clinical level at presentation](image)

**Figure 4:** Duration of lymphoedema as per clinical level of lymphoedema
Figure 5: Lymphoscitigrams highlighting the location of obstruction.
Figure 6: Collateralization

Figure 6-A Shows scintigraphic collateralisation. Fig: 6-B via the five layers of valveless collaterals found in the skin, to overcome obstruction to main lymph trunks. Fig:6-C When collaterals are gross, leads to lymphatic vesicles on the skin, proximal to the clinical levels.

Collateralisation

Collateralisation highlighted by lymphoscintigraphic data shown in figure 6.

Level of clinical lymphoedema relationship to location of lymphoscintigraphic obstruction

Table 4: Location of scintigraphic obstruction at different clinical levels of lymphoedema

| Location of Scintigraphic obstruction | BA (n=16) % | BK (n=72) % | AK (n=17) % |
|--------------------------------------|------------|------------|------------|
| EXTERNAL ILIAC                       | 0          | 1.39       | 17.65      |
| INGUINAL                             | 18.75      | 25         | 52.94      |
| FEMORAL                              | 31.25      | 26.39      | 29.41      |
| MID THIGH                            | 0          | 1.39       | 0          |
| MEDIAL KNEE                          | 31.25      | 33.33      | 0          |
| POP:FOSSA                            | 0          | 8.33       | 0          |
| CALF                                 | 12.5       | 0          | 0          |
| ANKLE                                | 6.25       | 1.39       | 0          |
| INJECTION SITE                       | 0          | 2.73       | 0          |
Detailed breakdown of the levels lymphoedema seems to stabilise at about 48 months. Scintigraphic obstruction per clinical level of lymphoedema done up to that time period is found representative and shows scintigraphic obstructions proximal to the clinical levels. Further it highlights that collateralisation through the skin lymphatics are not very effective within the less than 48-month period when most were seen. But for medial knee obstructions, the other obstructions seem to have occurred in areas where lymph nodes are present.

Systemic uptake

The rate of tracer uptake, based on time activity curves on tracer reaching the liver from the period post inoculation to the web space is highlighted in the fig: 7a-e. Isotope uptake by the liver implying it’s systemic spread is muted in cases of bilateral lymphoedema even at four hours but shows significant uptake by the liver in unilateral below knee lymphoedema.

Though patients with BK lymphoedema caused by upper vertical inguinal set block, showed a slow uptake by the liver, those with similar level of lymphoedema (BK) be they unilateral or bilateral, in
those patients with medial knee scintigraphic obstruction the uptakes show a rapid systemic entry of tracer, in 1-2 hours Fig 7-d and more so in 7-e. This suggests lympho-venous shunting at this level.

**Discussion**

In this study of 105 lower limbs with lymphoedema, in 103 limbs the isotopic tracer was shown up to be held up at some site, either in lymphatic trunks or lymph nodes in their course in the affected limb. In the remaining 2 patients it did not proceed beyond the injection site of the tracer confirming that we were indeed dealing with Primary lymphoedema.

The distribution of patients based on the gender ratio, of female dominance in the 20-50 years, the equal gender prevalence in the very early years (0-19) years and the presence of familial cases confirm that we are studying limbs affected with Primary lymphoedema.

That the extent of lymphoedema after the obstructive lesion, was significantly reached within 2 years in most cases of below ankle or below knee lymphoedema and possibly slightly later in above knee lymphoedema is shown in Fig: 4.

That the percentage site of isotopic obstruction was always more proximal to the level of clinical lymphoedema is highlighted in table 4. That very rarely, even a very proximal block, for example, external iliac region (probably a lymph nodal block) can precipitate below knee lymph oedema in the first year and half is worth noting.

We have shown that the extent of proximal ascent of clinical lymph oedema is associated with a more proximal obstruction of isotopic tracer as seen in table 4. It also could be deduced that the degree of collateral development is good in below ankle clinical lymphoedema where some blocks are in the femoral group as seen in table 4. If collaterals were a factor in any dominant way, as shown in, Fig: 6, A,B,C, they would have been seen to be of frequent occurrence in the scintigrams (Figure 5) and would not show the depressed uptake with time in the hepatic scintiscans, as shown in Figure : 7 (a-c), which highlight this fact.

The location of obstructed tracer Table 4, Figure 5 (1-6), is consistent compatible with the distribution of lymph nodes in the subcutaneous of the lower limb as is seen Figure 2., The only exception being the medial knee blocks , Table 4, Figures:5-3, in below ankle (n= 5 of 16 ) and below knee (n= 24 of 72 ) limbs with lymphoedema. The possible mechanisms for this feature could be mal development of lymphatics in this locality, or to argue that it is due to a ‘distal die back’ from the sentinel node for the leg, i.e. the lowermost of the vertical set of inguinal nodes. That is to say that it a die back of more than 25 cm’s which seems unlikely. The other arguments that can be adduced for this unusual location (medial knee) is that the lymphatics are mal developed as in a primary distal hypoplasia. It is in an anatomically prominent site, it is where the lymphatic trunks which do not increase their bore as they ascend the lower limb become, from approximately <5 in number in the leg, meet up with lymphatics coming from the lateral thigh and form more than 15 lymphatics ascending the thigh. This area maybe more exposed due to its prominence (because of the underlying condyles of the knee) and sensitive to the damage from episodes of trauma.

Further if lymphangitis or perilymphangitis had supervened, secondary to minor trauma of barefoot walking the scintigraphic obstructions would be more, where the lymphatics are close to the foot.
on the leg. One needs to contemplate an alternative mechanism. It is possible that the below-knee or ankle oedema with medial knee scintigraphic obstructions, amounting to a third of the cases in this clinical category, could be characterized by a lympho-venous shunt at the level of the knee. This hypothesis is mostly confirmed by the rapid hepatic uptakes in this group i.e. it’s not a block but a shunt around the knee. Figure 7-e.

A fair percentage of those with below ankle lymphoedema have shown very proximal lymphatic blocks, (table 4), but review of the hepatic uptakes on those with these proximal lymphatic blocks reveal a high uptake by the liver within a short time. Such systemic entry may also be facilitated by a lympho-venous shunt.

Taking those at the other extreme, those presenting with Above knee lymphoedema the hepatic uptakes in them, both in the unilateral cases as well as the bilateral cases, were low. Perhaps such individuals have no lympho-venous shunts, the fact that even the unilateral cases show a poor uptake signifies that such a dynamic plays a part in presentation.

In those with below knee lymphoedema, those with medial knee, lower vertical and upper vertical blocks, the dominant rapid entry to the systemic circulation suggest they have lympho-venous shunts. Also suggest that these shunts are located in the region of the knee. Hence even with a high block of lymph they do not present with Above knee lymphoedema as these individuals possess shunts.

That this is not the entire mechanism is suggested by the presence of a few cases with upper vertical blocks and no evidence of shunting, with below knee lymphoedema.

Conclusion

We conclude that the level of lymphoedema in primary lymphoedematous patients are a result of a dynamic between lymphatic nodal blockage (? due to mal-development) and lympho-venous shunting. The relative prevalence of these mechanisms on a cohort of 80 patients with primary lymphoedema is presented.

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