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# CLINICAL AND GENETIC STUDY OF ITALIAN FAMILIES WITH PRIMARY LYPHHEDEMA

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## ABSTRACT

Primary lymphedemas are often determined by the mutation of a gene that prevents the receptor of the cell membrane to recognize the growth factors normally circulating. The authors studied the possible genetic mutations present in patients suffering from primary lymphedema, suitably selected from the clinical point of view.

Nine genetic mutations have been identified on the genes VEGFR3 and FOXC2. Some of them had never been described in literature.

The study is in progress and aims to study the entire families into account that the disease is autosomal dominant with incomplete penetrance.

KEYWORDS: primary lymphedema, genetics.

## INTRODUCTION

Primary lymphedema is a disease with autosomal dominant inheritance and incomplete penetrance. By definition, it may therefore have gene mutations and a normal phenotype. Although the presence of primary lymphedema in ancestors, collaterals and descendents of certain families has stimulated genetic studies for many years, many anatomical and functional aspects are still unclear<sup>(1-5)</sup>.

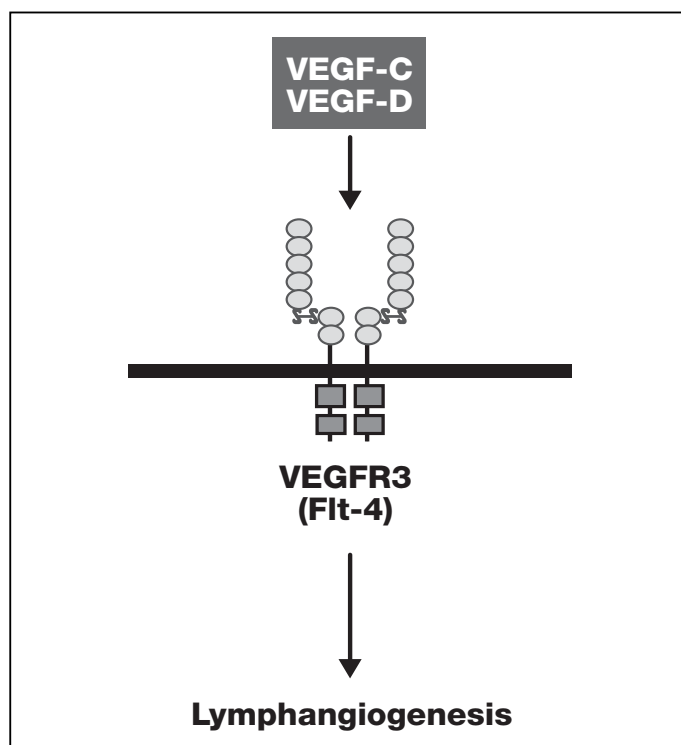
Primary lymphedema is a chronic disease, often connatal, that mainly affects the lower limbs. It consists essentially of accumulation of largely proteic (> 5mg/dl) fluid in affected tissues. Because the proteins stimulate fibroblasts to produce collagen fibres and sclerotic tissue, this sooner or later leads to fibrosis. The disease often causes relative functional impotence with psychological repercussions (Fig. 1).



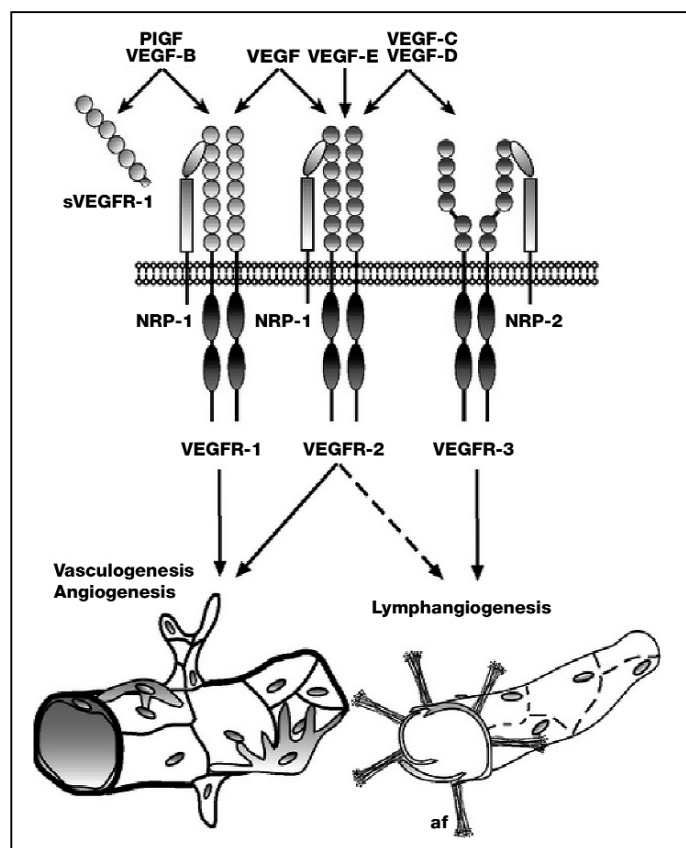
**Figure 1 - Connatal primary lymphedema of the right lower limb and genitals.**



Regular local and regional development of the lymphatic system depends on the response of membrane receptors on replicating lymphatic cells to vascular growth factors circulating in the extracellular environment. Cell response triggers transmission of information to the cell nucleus and organelles, enabling cell replication and migration to their anatomical site (Fig. 2)<sup>(6-11)</sup>. A membrane receptor may not recognise the growth factor due to a gene mutation, which may often be hereditary. Thus lymphatic development may be incomplete in certain body regions and lymph nodes may be defective or absent<sup>(12-18)</sup>. The greater the underlying genetic and consequently functional defect, the greater and sooner the lymph transport defect manifests as edema. The aim of the present study was to create a network of lymphologists with the purpose of selecting patients with primary lymphedema and studying new genetic mutations, in order to obtain insights into incidence, penetrance and prevalence of the disease. Forty mutations in the gene VEGFR3 (also known as FTL4) are documented in the literature (Fig. 3). All pathological mutations are located in two intracellular tyrosine-kinase domains, the coding sequence of which goes from exon 16 to 27. This gene is important for lymphangiogenesis and structural maintenance of the lymphatic endothelium. When activated it binds to growth factors VEGF-C and VEGF-D (Fig. 3). The FOXC2 gene has important functions in angiogenesis, lymphangiogenesis and vascular remodelling. It is also implicated in the development of metastases and rapid proliferation of breast cancer. Mutation of the gene may be associated with speech defects in children.



**Figure 3 - VEGFR3 membrane receptor binds growth factors triggering cell replication and migration (lymphangiogenesis).**



**Figure 2 - Lymphatic vascular growth factor meets cell receptor.**

## MATERIALS AND METHODS

### Patient population

A network of lymphology experts was created to select patients to undergo genetic testing for the two genes most frequently linked to primary lymphedema: VEGFR3 and FOXC2. It included recognised centres in different parts of Italy so as to gather groups of patients representing the various regions (Fig. 4). Enrolment criteria were as follows:

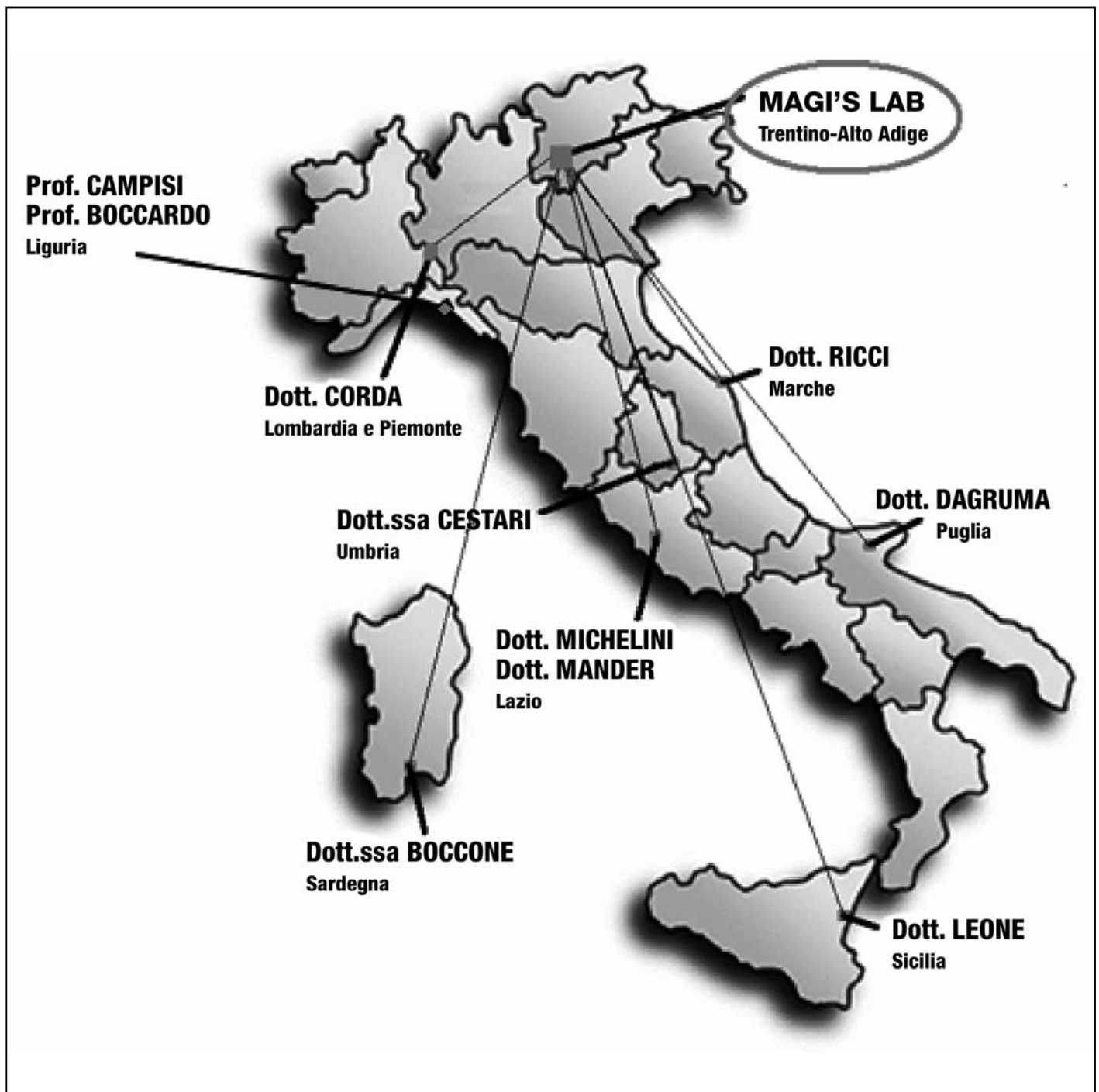
- lymphedema of the limbs diagnosed clinically and/or by lymphoscintigraphy;
- primary lymphedema;
- clinical manifestation at birth or subsequently [before 30 years of age?];
- family history positive or otherwise for primary lymphedema;
- clinical signs of lymphedema.

Written informed consent to the study was obtained in all cases.

The population of lymphedema patients enrolled for this preliminary study numbered 111, 23 with phenotypically documented cases in the family and 88 with ostensibly negative family history. Fourteen patients had lymphedema from birth, 11 from the first decade and 86 from the second or third decade.

### Genetic analysis

DNA was extracted from at least 3 ml of whole blood samples using a kit based on “salting-out” method (Blood DNA kit E.N.Z.A.,



**Figure 4 - Distribution of medical centres from which patients were selected.**

Omega Bio-tek, Inc. Doraville, GA, USA). PCR and direct sequencing of amplified fragments (Thermo PX2 thermocycler, Beckmann Coulter CEQ 8000 sequencer) were used to find mutations in VEGFR3 (exons 17-26, Ref. Seq. NG\_011536.1) and FOXC2 (Ref. Seq. NG\_012025.1) genes. Assembly of PCR reactions, cycling, primer sequences and sequencing conditions are available on request. The “blast 2 sequences” tool was used to compare electropherograms of all amplified fragments with the

on-line reference sequences (<http://blast.ncbi.nlm.nih.gov>); the nucleotide blast and blastx algorithm were then used to analyse all fragments containing sequence variations; a final search for known mutations was performed using the HGMD database (<http://www.hgmd.cf.ac.uk>) and the dbSNP database of the NCBI (<http://www.ncbi.nlm.nih.gov/snp>). All tests were performed in the MAGI's Laboratory (MAGI'S Lab S.r.l. – Diagnostics of Rare Genetics Diseases, Rovereto, Italy).

## RESULTS

Nine mutations were identified in our population, five in the gene VEGFR3 and four in the gene FOXC2. These mutations affected 8.1% of the population. For VEGFR3, 2/5 mutations were already documented in the literature and the other three were detected for the first time (Fig. 5). For FOXC2, none of the four mutations found were documented in the literature (Fig. 6).

Many polymorphisms in the protein sequence of DNA, already reported in the literature but listed as “non pathological”<sup>(19-22)</sup>, were also found. We also discovered three new polymorphisms, the phenotypical significance of which is being studied.

Four of the nine mutations (three VEGFR3 and one FOXC2) were found in subjects with positive family history affecting more than one relative<sup>(23-27)</sup>, while five (two VEGFR3 and three FOXC2) were encountered in subjects with no known family history of the disease. Two cases manifesting in the neonatal period, with mutations in the FOXC2 gene<sup>(28-30)</sup>, had speech disorders associated with lymphedema, as reported in the literature. The two cases were referred for treatment of both problems.

## DISCUSSION AND CONCLUSIONS

This multicentric study found mutations in the genes VEGFR3 and FOXC2 correlated with phenotypic manifestations of primary lymphedema. The percentage of patients positive to the genetic test is much lower than in populations published by North American authors, suggesting that the distribution of the disease is subject to ethnic and other differences.

A second phase of the present study will consider other genes that could be implicated in the disease: TIER1, TIER2, CCBE1, SOX18, GJC2, CCBE1 and COUP-TF2<sup>(31-36)</sup>, initially in cases with positive family history of lymphedema.

A further step will be to extend the study to relatives (ancestors, collaterals and descendants) of patients positive in the present study, and to perform lymphoscintigraphic studies to detect any subclinical developmental deficits indicating clinically latent lymph transport anomalies in cases of genotypic but not phenotypic positivity. This will provide insights into various aspects of this debilitating disease, which is underestimated by the national health system<sup>(37-42)</sup>.

Exon	cDNA Nomenclature	Protein Nomenclature	Alleles	References
18	c.2560 G>A	p.Gly854Ser	wt/mt	Evans (2003) J Med Genet 40, 697
18	c.2575 G>A	p.Val859Met	wt/mt	<b>New mutation</b>
23	c.3122 G>A	p.Arg1041Gln	wt/mt	Evans (2003) J Med Genet 40, 697
19	c.2740 G>T	p.Gly914Trp	wt/mt	<b>New mutation</b>
20	c.2777 T>C	p.Ile926Thr	wt/mt	<b>New mutation</b>

Figure 5 - Genetic mutations identified in the gene VEGFR3.

cDNA Nomenclature	Protein Nomenclature	Alleles	References
c. 826_827del2	p.Met276AspfsX185	wt/mt	<b>New mutation frameshift</b>
c. 1109 G>C	p.Ser370Thr	wt/mt	<b>New mutation</b>
c.8 C>G	p.Ala3Gly	wt/mt	<b>New mutation</b>
c.1460 T>C	p.Leu487Pro	wt/mt	<b>New mutation</b>

Figure 5 - Genetic mutations identified in the gene FOXC2.



The final aim is to determine the potential for correcting the lymphatic system developmental defect by synthesis of specific recombinant proteins from among normally circulating growth factors and cell membrane receptors<sup>(43-50)</sup>.

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# HOW TO LIMIT LYMPHATIC MORBIDITY IN BREAST CANCER TREATMENT

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## ABSTRACT

Authors report anatomical and pathophysiologic aspects concerning lymphedema following breast cancer treatment. They underline clinical and lymphoscintigraphic criteria to define lymphedema-risk patients, in whom preventive measures are indicated. They propose a surgical primary prevention, by performing direct lymphatic-venous anastomosis at the same time of axillary nodal dissection (LY.M.P.H.A. – Lymphatic Microsurgical Preventing Healing Approach).

## ANATOMICAL AND PATHOPHYSIOLOGIC ASPECTS

A side-effect of axillary lymph node excision and radiotherapy for breast cancer is arm lymphedema in about 25% (ranging from 13 to 52%). Sentinel lymph node (SLN) biopsy has reduced the severity of swelling to nearly 6% (from 2 to 7%) and, in case of positive SLN, complete axillary dissection (AD) is still required. That is why ARM method was developed aiming at identifying and preserve lymphatics draining the arm. It consists in injecting intradermally and subcutaneously a small quantity (1-2 ml) of blue dye at the medial surface of the arm which helps in locating the draining arm lymphatic pathways. ARM technique allowed to find variable clinical anatomical conditions from what was already generally known, that is the most common location of arm lymphatics below and around the axillary vein. In about one-third

of the cases, blue lymphatics can be found till 3-4 cm below the vein, site where SLN can easily be located, justifying the occurrence of lymphedema after only SLN biopsy. ARM procedure showed that blue nodes were almost always placed at the lateral part of the axilla, under the vein and above the second intercostals brachial nerve. Leaving in place lymph nodes related to arm lymphatic drainage would decrease the risk of arm lymphedema, but not retrieving all nodes, the main risk is to leave metastatic disease in the axilla. Conversely, arm lymphatic pathways when they enter the axilla, cannot be site of breast tumoral disease and their preservation would certainly bring about a significant decrease of lymphedema occurrence rate<sup>(1-4)</sup>.

## LYMPHANGIOGENESIS AND OTHER LOCAL CHANGES

Another important aspect to point out is that, in the axilla, new lymphatic vessel formation (lymphangiogenesis) occurs in response to the ligation of lymphatic vessels involved in lymph node retrieval. Lymphangiogenesis and lymphatic hypertension were demonstrated experimentally in case of lymphatic drainage obstruction. And, in response to lymphatic hypertension, lympho-venous shunts open and provide alternative lymphatic pathways when the main ones are obstructed. These mechanisms represent an adaptive response to lymphatic hypertension but are not enough to restore normal flow parameters. Furthermore, chronic obstruction to lymph flow

progressively leads to a reduced lymphatic contractility, lymphatic thrombosis and fibrotic changes, at a different degree according to variable constitutional predisposition <sup>(5,6)</sup>.

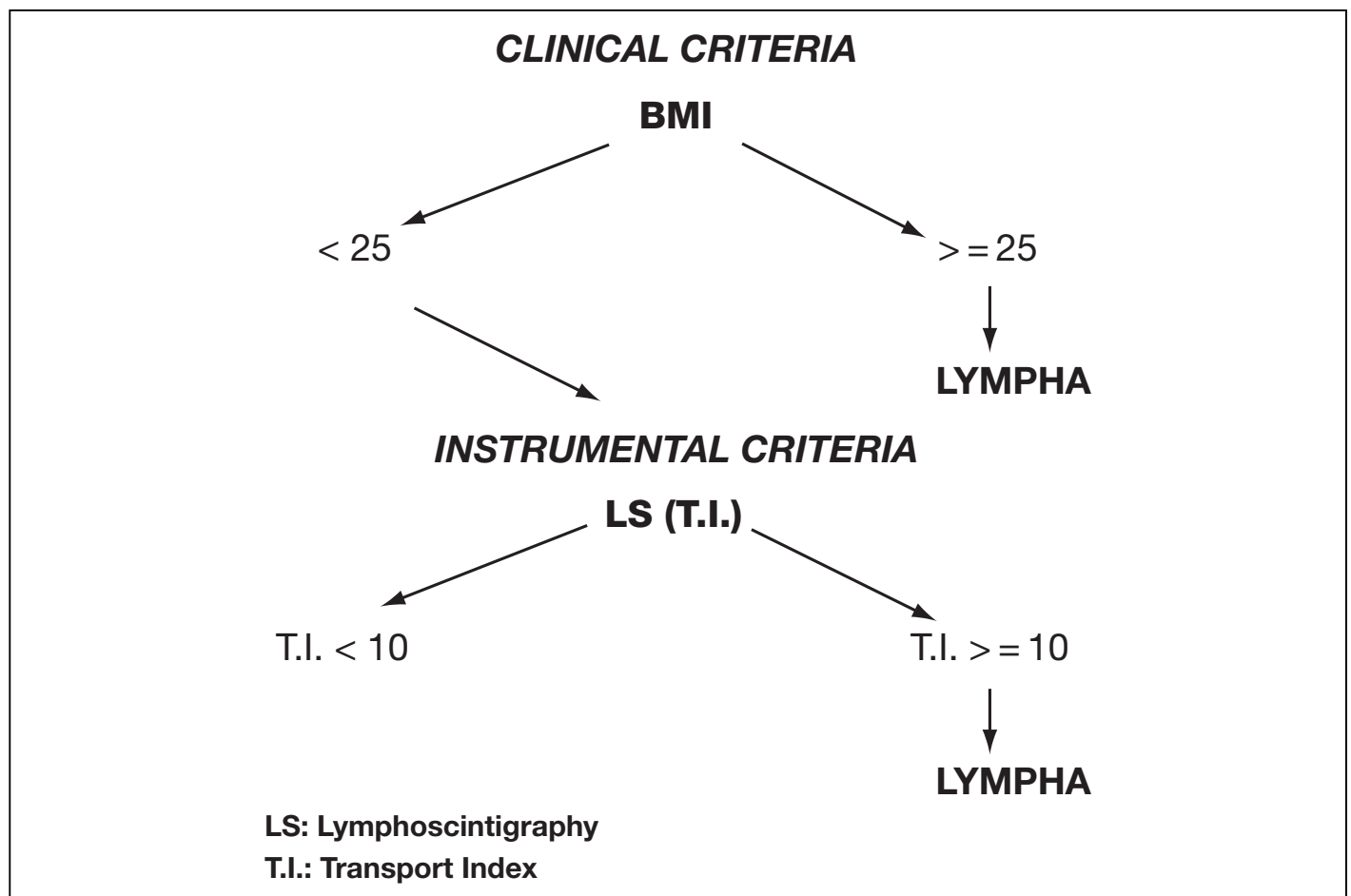
## SURGICAL PREVENTIVE PROCEDURES

Recent advances in the treatment of breast cancer, specifically as concerns the prevention of lymphatic complications following sentinel lymph node biopsy and axillary dissection brought to the proposal of a new technique to primarily prevent lymphedema by microsurgical lymphatic-venous anastomoses. ARM technique allows to identify arm lymphatics and lymph nodes which can therefore be preserved even though there is the risk to leave undetected metastatic disease in the axilla. But, it is almost impossible to preserve efferent lymphatics from the blue nodes because they join the common axillary nodal basin draining the breast. Thus, not preserving efferent lymphatics makes practically impossible to preserve arm lymphatic flow. So, on the basis of our wide experience in the treatment of lymphedema by microsurgical lymphatic-venous anastomoses (LVA), we thought to perform LVA immediately after finishing nodal axillary excision. The surgical technique proposed for patients with operable breast cancer requiring an axillary dissection consisted in carrying out

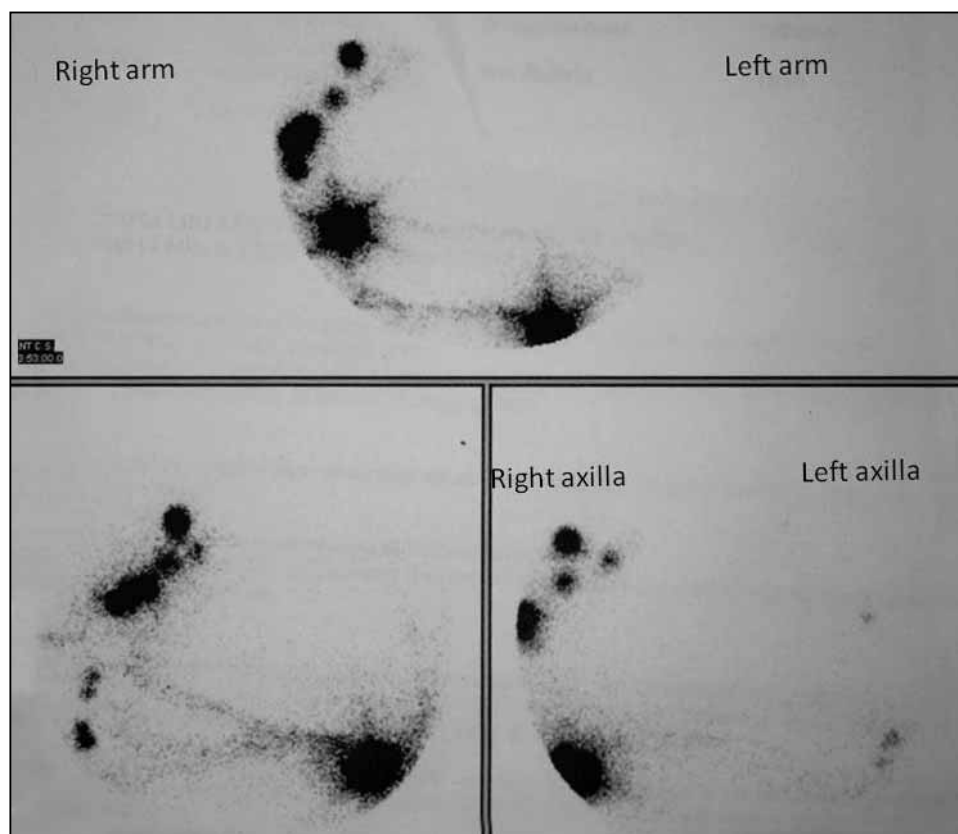
LVA between arm lymphatics identified by injecting blue dye in the arm and an axillary vein branch simultaneously (Lymphatic Microsurgical Preventive Healing Approach – LY.M.P.H.A.) <sup>(7)</sup>. It is almost always possible to find blue lymphatics and also to find a vein branch long enough to be connected to arm lymphatics which are usually locate very laterally (Figs.1-4).

Patients are followed up both clinically by volumetric assessment and by lymphangioscintigraphy performed before surgery and after 18 months. Blue nodes in relation to lymphatic arm drainage can be identified in almost all patients after blue dye injection at the arm. All blue nodes must be resected and 2 to 4 main afferent lymphatics from the arm can be prepared and used for anastomoses. Lymphatics are introduced inside the vein cut-end by a U-shaped stitch. Other few stitches are given to fix the lymphatic adventitia to the vein wall.

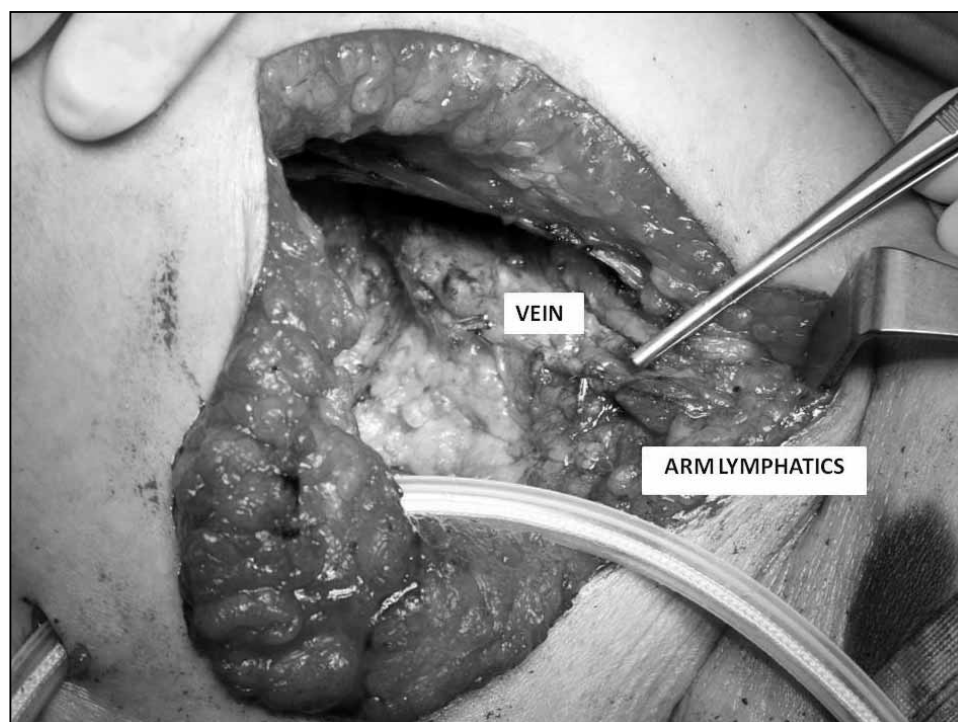
The operation takes only 15-20 minutes averagely, since both lymphatics and the vein are prepared during nodal dissection. LVA proved not only to prevent lymphoedema but also to reduce early lymphatic complications (i.e. lymphorrhea, lymphocele) thanks to the reduced regional intralymphatic pressure. Drain tubes can be removed after about 7-10 days at the utmost. Post-op lymphangioscintigraphy allowed to demonstrate the patency of microvascular anastomoses after over 1 year and half from operation.



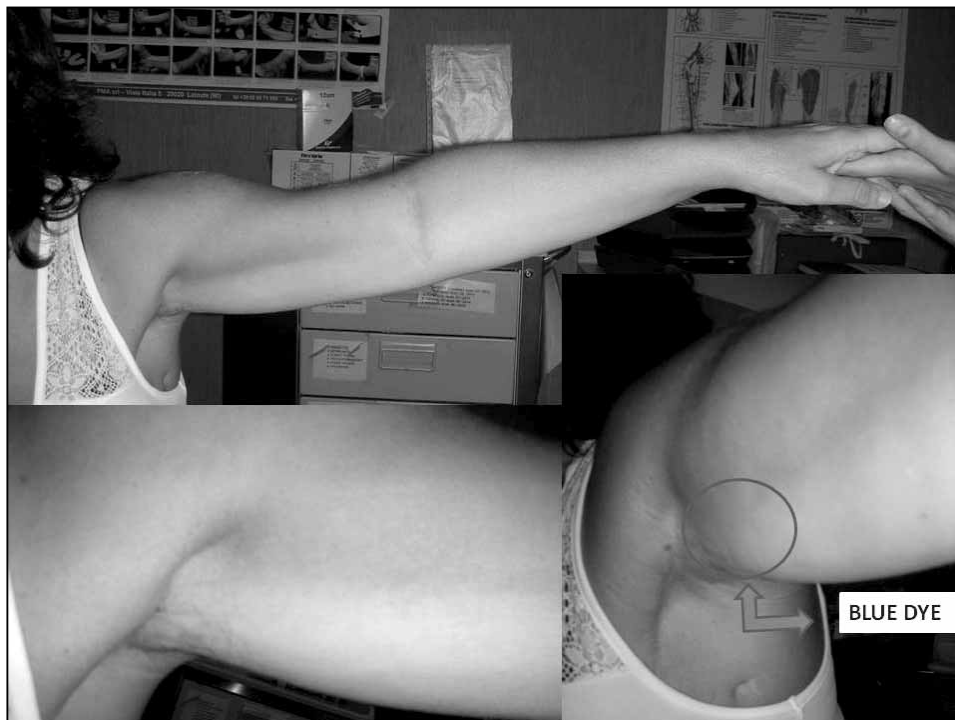
**Figure 1 - Clinical and lymphoscintigraphic criteria to select lymphedema-risk patients in whom LYMPHA technique is indicated.**



**Figure 2 - Lymphoscintigraphy performed before breast cancer treatment which shows an impaired transport index at the left side, site of the tumour and of the axillary nodal dissection.**



**Figure 3 - LYMPHA technique which consists in performing lymphatic-venous multiple anastomosis between arm lymphatics, pointed out in blue by BPV, and a collateral branch the axillary vein.**



**Figure 4 - Long term clinical follow-up in a patient after 3 years from breast cancer treatment, axillary nodal dissection and LYMPHA. Of note, no arm edema, notwithstanding radiotherapy, disappearance of the blue dye and good axillary scar without skin retraction or cording.**

## FINAL CONSIDERATIONS

Disruption of the axillary nodes and closure of arm lymphatics can explain the significantly high risk of early and late lymphatic complications after axillary dissection, especially the most serious complication, that is arm lymphedema. The use of the blue dye and of LVA helps to solve the problem of preventing secondary arm lymphedema even maintaining the oncological radicality. LYMPHA, therefore, might represent a rational approach to the prevention of lymphedema and reduce other lymphatic complications after axillary surgery in the therapy of breast cancer.

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# ROLE OF LYMPHOSCINTIGRAPHY IN PRIMARY PREVENTION AFTER BREAST CANCER TREATMENT

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## INTRODUCTION

In our lymphological study center, we focused our attention on 166 all subclinical stage patients (126 lymphadenectomy and 40 sentinel lymph-node biopsy), which includes patients at risk of developing lymph stasis in the homolateral arm without clinical evidence of edema, who had undergone surgery between 6-12 months before arriving at our centre for examination.

## MATERIALS AND METHODS

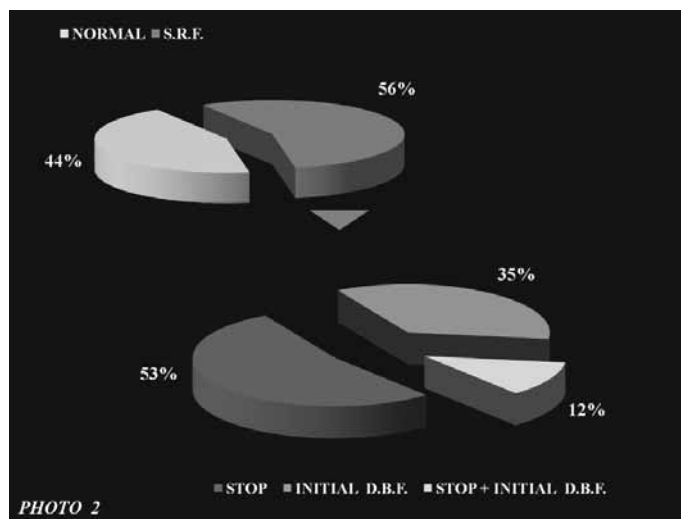
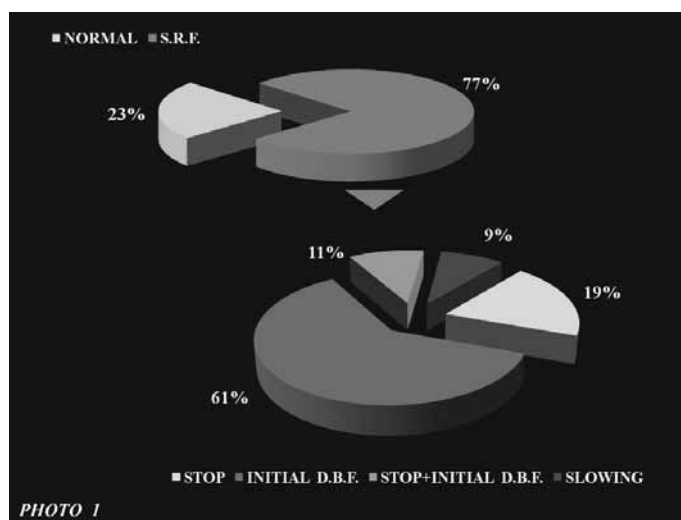
Patient evaluation had led to a clinical report where anamnesis and clinical examination were included as well as the centimetrical evaluation of compared arms (every 5 centimeters from wrist) and relative volumes calculated by using the volume of a truncated cone and the difference expressed as a percentage.

A physiatric evaluation was also fundamental for eventual subsequent specific physiotherapy.

When we talk about primary prevention however, lymphoscintigraphy has the main importance because it allows us to identify patients at risk of edema onset, those who present slower radiotracer flow, which might not otherwise be identified. In this study nuclear M.D. had performed the exam by bilateral subcutaneous injections (needle 28 G) of 99mTc-nanosized colloid (80 nm) in interdigital spaces, without additional proximal injection, (185 MBq-2,035 mSv).

With regards to lymphadenectomy, 44% of the patients refused the exam: including patients who had undergone surgery recently, because they were not ready to perform other exams outside the oncological field, but, above all, because the exam was against medical advice (in oncologists' opinion lymphoscintigraphy is useless, and lymphedema is not a relevant pathology). In the exam carried out (56%) lymphoscintigraphy highlighted a normal radiotracer flow in 23% of the cases and a slower radiotracer flow in 77% of the cases (lymph-node stops 19%, initial dermal back flow 61% or both 11%, slowing 9%). Photo 1.

Furthermore, lymphoscintigraphy with homolateral slower radiotracer flow also highlighted contralateral stops in 29% of the cases. With regards to sentinel lymph-node biopsy, 38%, of the patients refused to undergo the exam, because it was against medical advice (sentinel lymph-node is equal to no edema), while in the exam carried out (62%) lymphoscintigraphy highlighted a normal radiotracer flow in 44% of the cases and slower radiotracer flow in 56% (lymph-node stops 53%, initial dermal back flow 35% or both 12%). Photo 2.



Furthermore, lymphoscintigraphy with homolateral slower radiotracer flow also highlighted contralateral stop in 23% of the cases.

With regards to no lymphoscintigraphy or no evidence of slower radiotracer flow, only follow-up was requested (one check a year), while in homolateral slower radiotracer flow, after the opening of a rehabilitative project, patients were included in the early treatment which consisted in respiratory training, manual lymph drainage, activation of alternative pathways and isotonic

gymnastics (3 times a week for 4 week) and a follow-up was requested (one check a year).

All patients included in the study were informed on preventive measure through individual settings whose end-point was information on lymphedema and the acceptance of preventive measures, intended not as prohibitions, that could lead to anxiety or depression, but as a fundamental behavioural strategy. Until two years ago, we used to organize the informative group which included patients with subclinical stage and patients affected with lymphedema: the lymphologist talked about lymphedema, a physiotherapist explained the anatomy-physiology of the lymphatic system and highlighted the importance of the hygienic-behavioural rules and at the end, the psychologist who listened to the women's problems and became available for eventual individual sittings.

At present, we inform on preventive measures through individual sittings because we realize patient compliance was insufficient using the former method. A brochure, which contains the above-mentioned rules, is also given to the patients.

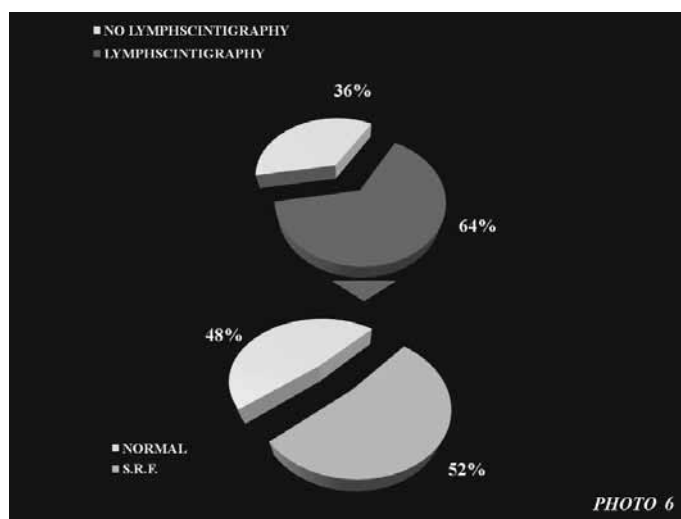
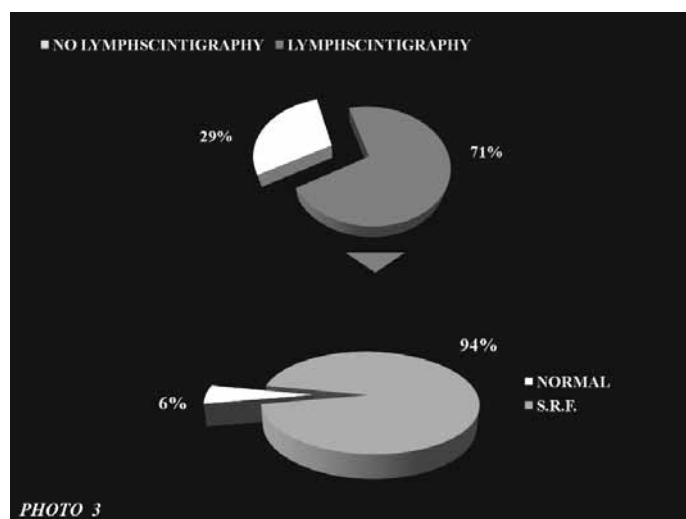
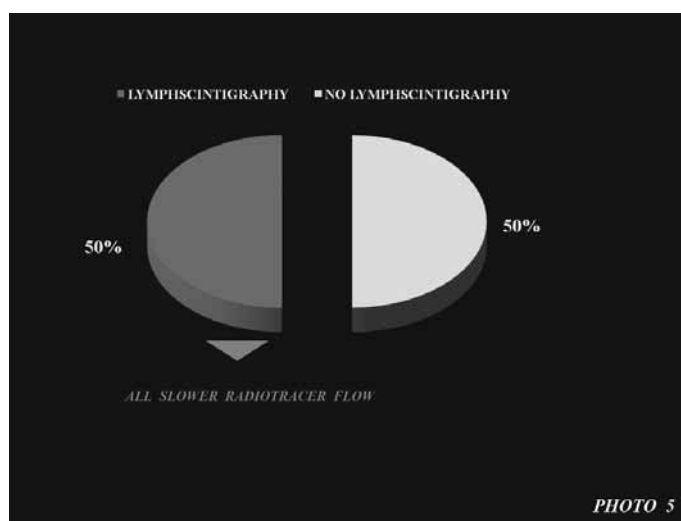
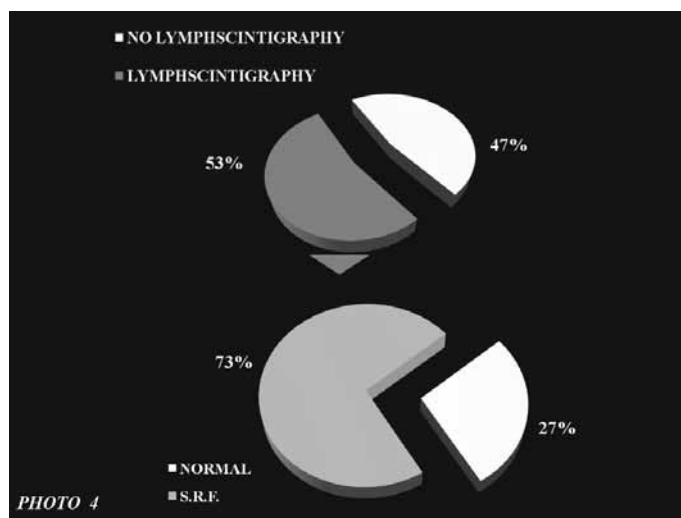
## RESULTS

With regards to lymphadenectomy we observed lymphedema onset in 20% of patients: 71% had undergone lymphoscintigraphy that highlighted normal exam in 6% of the cases and slower radiotracer flow in 94% of the cases. Photo 3. In cases of no edema (80%): 47% refused the exam while 53% had undergone lymphoscintigraphy that highlighted normal exam in 27% and slower radiotracer flow in 73%. Photo 4.

With regards to sentinel lymph-node biopsy, we observed lymphedema onset in 10% of patients: 50% had undergone lymphoscintigraphy that had highlighted slower radiotracer flow in all cases. Photo 5.

In cases of no edema (90%): 36% refused the exam while 64% had undergone lymphoscintigraphy that highlighted normal exam in 48% and slower radiotracer flow in 52%. Photo 6.

In both cases edema onset was always secondary to accidental or



avoidable event in previously informed patients: with regards to lymphadenectomy, edema onset after lymphangitis (insect bite, gardening without protection), heavy work (long window cleaning session, long session ironing or cooking), sunburn or burn removing dishes from oven, while with regards to sentinel lymphnode biopsy, edema onset always after lymphangitis (cat scratch, local wound).

## CONCLUSION

This study highlights the main importance of lymphoscintigraphy in primary prevention, because it allows us to identify patients at risk of edema onset, but also underlines the necessity to attain the complete compliance of the patients who have to interpret the preventive measures, particularly highlighted in the case of slower radiotracer flow, as a fundamental strategy in primary prevention. Moreover, as a rehabilitative team, we continue to have a dream: not to treat lymphedema, but to prevent it through the identification of patients at risk.... also we know that primary prevention should start immediately after the post-surgical period.

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**Prof. Dr. Etelka Földi**

# DIAGNOSIS AND TREATMENT OF CHYLOUS DISORDERS

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## ABSTRACT

Authors report their clinical experience in the treatment of chylous disorders due to congenital dysplastic malformation or secondary to oncological operations with nodal dissection.

They report proper diagnostic investigations including above all traditional oil contrast lymphangiography associated with CT scan. A sequential therapeutical sequence is finally described including conservative procedures, laparoscopic approach and microsurgical methods.

## HISTORICAL BACKGROUND

Abnormal retrograde transport of lymph or reflux can derive from outside the intestine (non-chylous) or arise in the intestine (chylous or milky in appearance). The phenomenon was recorded as far back as Cruikshank<sup>(1)</sup>, who considered it a post-mortem phenomenon in cadavers. Busey in 1878<sup>(2)</sup> described patients with chylous and non-chylous reflux syndrome with accompanying lymphedema and expressed his frustration with inability to improve their condition. Because cholesterol and long-chain triglycerides as chylomicra are absorbed exclusively by the lymphatic system, disruption, compression, obstruction or fistulization of mesenteric lacteals, the cisterna chyli, and the thoracic duct directly relates to chylothorax, chylous ascites, chyluria, and chylous reflux in other sites. In some patients with severe obstruction to intestinal lymph flow, the peripheral lymphatics gradually dilate, valves become progressively more incompetent, and lactescent lymph refluxes into the soft tissues of the pelvis, scrotum, and lower extremities (chylous vesicles), and even manifests as generalized subcutaneous chyledema in newborns. A variety of genetic mouse models mimic this condition with diverse developmental defects of the intestinal-thoracic duct lymph system. Dynamic imaging of both chylous and non-chylous lymph reflux can usually be obtained by adjusting the whole body protocol for lower and also rarely upper limb lymphangioscintigraphy and can be applied to newborn infants as well as adults to identify the source, timing and location of the lymph reflux and tailor further evaluation and management accordingly<sup>(3-9)</sup>.

## PATHOPHYSIOLOGY

From the etiopathological point of view, primary forms of chyloperitoneum are basically correlated with congenital dysplastic alterations<sup>(10-15)</sup> and more or less extended malformations of chyloferous vessels, cisterna chyli, and/or of the thoracic duct, as well as of regional lymph nodes in this region or in affected regions. These conditions account for approximately 70% of all cases. Conversely, “secondary” forms due to mechanical causes or obstructions of various types or disruptions, including trauma, are less common.

It should be pointed out that from a pathophysiologic point of view, malformation-related dysplastic alterations act as actual obstacles to antigravity lymph drainage, just like mechanical obstruction. A malformation affecting the thoracic duct, Pecquet cyst, and/or chyloferous vessels illustrates this concept and represents a significant obstacle to lymph drainage and, in particular, to intestinal drainage. Accordingly, chyloferous vessels along the walls of the small intestine and of the mesentery become significantly dilated and abnormally stretched due to chylous stasis. The disease also features lymphatic megacollectors with more or less extensive chylous lymphangiectasia, often associated with lymphangiomyomatosis. These are not only located right below the visceral peritoneal layer with a mesh-like arrangement, but also throughout the small intestine and more specifically at the level of intestinal villi. Hence, dysplastic chyloferous megalymphatics may rupture due to a localized swelling (the so called “mesentery chylous cyst”) or anywhere along the wall of an extremely ectatic collector, sometimes through a two-step process, that is, once the peritoneum is opened up by chyle with subsequent development of a “chyloma”, chyle begins to flow into the abdominal cavity. Also, in other cases, the chyloferous vessel at the center of the villus breaks into the intestinal lumen, thereby causing the loss of proteins, lipids, lipoproteins, and even calcium and glucose, which leads to metabolic disorders that are typical of so called “Protein Losing Enteropathy” (PLE).

Owing to the direct link between the septic intestinal environment and the inner lining of chyloferous vessels, there may be recurrent attacks of acute lymphangitis and acute mesenteric lympho-angioadenitis which, in some cases, may even lead to septic shock or, at best, to a chronic process, while triggering a vicious circle

with further worsening of the intestinal lymphatic drainage. Chyloperitoneum and PLE may often be combined. Also, it should not be forgotten that, apart from intestinal lymphatics, also lumbar lymphatics – collecting the lymph from the lower limbs, external genitalia, intra-abdominal organs, kidneys, adrenal gland, and the abdominal wall – flow into the cisterna chyli. Further, considering the thoracic-mediastinal catchment basin of the thoracic duct and that lymphatic dysplasias can affect even one or more extra-abdominal sites, due to bizarre malformation combinations, chyloperitoneum can also be associated with a whole range of different pathologic pictures: mono or bilateral chylothorax; chylous cyst, mediastinal chyloma or chylomediastinum; chylopericardium; chyluria; chylo-colpometrorrhea; chyloedema of external genitalia and/or of one or both lower limbs, with chylo-lymphostatic verrucosis and subsequent chylo-lymphorrhea; and chylous joint effusion

The wide ranging extension of the foregoing malformations and the complexity of their association with dysplasia of chylo-lymphatic vessels, thoracic duct, and chylous cyst explain why, in the newborn, sometimes these conditions affecting multiple sites are incompatible with life<sup>(16)</sup>. Further, upon clinical onset of the most severe cases, effective treatment may be difficult to achieve later in life, thereby leading to more or less complex prognostic implications involving “quoad valetudinem” as well as “quoad vitam” issues.

## TREATMENT

For a rapid restoration of proper metabolic balance, total parenteral nutrition (TPN) is recommended early on in order to significantly limit the chylous leak volume.

In the initial approach to this complex problem, especially in acute and sub-acute onset cases, a videolaparoscopy can be useful and also indicated to help in the proper positioning of one or more peritoneal drains of correct size. These will be used to drain the effusion in one or more steps, depending on its volume, while taking care not to cause “ex vacuo” hemorrhages and keeping in mind that chyle is a dense fluid. This procedure is preferred over the ultrasound or CT guided positioning of smaller drains, which are more likely to become closed over time.

Once in place, these drains can be used “on demand”, also for washings with a Trémollières sterile solution (concentrated lactic acid) combined with an antibiotic (250-500 mg of sodium rifampicine). The sclerosing effect of this drug has proven beneficial, especially in the treatment of post-surgical chyloperitoneum (mostly occurring after lymph node resections performed close to the mesenteric root). Also, in these cases of surgical origin where the onset of chylorrhagia occurs in the early days after surgery and can be observed through the same drains placed upon surgery completion, in the great majority of cases, washing with Trémollières associated with a rigorous total parenteral feeding has proved to be successful in resolving this condition in two or maximum three weeks. Actually, the great majority of chylorrhagia cases have been due to extended lymphadenectomy in kidney cancer surgery. In this way, timely treatment of chylorrhagia as a post-operative complication can help prevent the onset of secondary chyloperitoneum. This complication is common in oncological surgery particularly when abdominal drains are removed too early.

On the other hand, primary chyloperitoneum caused by dysplasia or malformations is a much more complex condition. An accurate diagnostic assessment is required for proper treatment, depending on associated clinical features, namely:

- <sup>51</sup>CrCl<sub>3</sub> test, to gain evidence of any major abdominal protein leak (>2% of fecal radioisotope disposal within 5 days following intravenous – 30 ΦCi – administration of this substance. Especially in children, care must be taken not to mix feces with urine since ~ 30% of this isotope is excreted in the urine.
- Small intestine barium enema, to demonstrate any notable thickening due to lymphedema, which is generally greater in the submucosa of the intestinal wall, and subsequent protrusion of intestinal folds and villi;
- Small intestine endoscopy, in particular with biopsy of the duodenum-jejunum segment, which shows significantly stretched chyliferous vessels at the centre of villi;
- Lymphoscintigraphy, with evidence not only of tracer leak into the peritoneal cavity, but also of a more or less severe dysplasia involving also other compartments, like external genitalia and the lower limbs. This method is an excellent tool to assess microsurgery outcome (as we illustrate below);
- Standard lymphangiography with liposoluble ultrafluid contrast medium injected with microsurgical technique after isolation and cannulation of the lymphatics of the extensor digitorum muscle. If coupled with a CT scan, LAG allows a more accurate assessment of disease extension, as well as the site of the obstacle and source of chylous leak;
- Magnetic resonance which, by digital subtraction method of the fatty tissue, offers a more in depth demonstration of dysplasia-related impairment of the lymph vessels (lymphangiomagnetogram)<sup>(17)</sup>.

In order to demonstrate a concurrent Protein Losing Enteropathy (PLE), albumin labeled (<sup>99m</sup>Tc) scintigraphy may be quite useful for a more complete diagnosis. PLE can be observed inside the intestinal lumen in scans taken 1-24 hours after intravenous administration of 740 mBq.

Finally, in case of even more complex pictures associated with more or less widespread hemangiodysplasias, selective digital angiography of the compartments affected by vascular visceral and/or peripheral malformations, and angio-CT are helpful complements to the aforementioned instrumental diagnostic process. At this point, surgical intervention depends on the outcome of the various conservative treatments already implemented, namely, hyperprotein and hypolipidic diet (e.g., exclusively based on medium-chain fats and triglycerides) and total parenteral nutrition (TPN); proper antibiotic protection, which is necessary to prevent and treat the not uncommon septic complications; and even serial paracentesis, which mainly aims at gradual chylous effusion drainage and subsequent reduction in intra-abdominal pressure. In this as well as in subsequent treatment phases, the intravenous, intramuscular, and/or subcutaneous administration of somatostatin or octreotide (the synthetic form) can be useful in reducing chylous effusion – in some cases remarkably successful – likely related to their pitressin-like effect and even as anti-proliferation agents in vascular and, more specifically, lymphatic cells and endothelium<sup>(18)</sup>.



## SURGICAL APPROACHES

Therefore, surgery should be designed on a case by case basis, depending on the primary or secondary nature of chylous effusion, clinical severity, and the number of chylous leaks. The following types of surgical approaches can be performed to treat this disease depending on the specific clinical condition and prior response<sup>(19-21)</sup>:

- Chyloperitoneal drainage;
- Identification of the site or sites of chylous leakage;
- Removal of chylous cysts and/or chylomas;
- Resection of lymphangiectatic -lymphangiodysplastic tissue, which can also be combined with other ad hoc solutions;
- “Spaced-out” antigravity ligatures of incompetent and ectatic chyliferous lymphatic vessels, in order to treat gravitation chylous reflux – following the techniques of Servelle and Tosatti – and if necessary, also
- CO<sub>2</sub> Laser: When applied at low power, this technique has a welding effect on lymphatics and many other tissues and blood vessels up to one mm diameter;
- Derivative (lymphatic-venous anastomosis) or reconstructive (lymphatic-venous-lymphatic plasty) microsurgery: When applicable, efficacy has been extensively documented. With well demonstrated techniques, functional solutions can be fashioned allowing for anti-gravitational discharge into lumbar, iliac-pelvic, and inguinal lymph nodes – depending on each case – and, when suitable, ectatic collectors can be harvested.
- In the most difficult cases and those affected by repeated recurrences, a peritoneo-jugular shunt (Denver, Le Veen type), which, however, has major limitations in children and is susceptible to thrombosis from the viscous chylous lymph.
- In extreme cases, entero-mesentery lymphangiectasia may be so severe that a full resection of the intestinal segment prominently affected by dysplasia may be required and, in the extreme, intestinal transplantation performed.
- Videolaparoscopy as a support to laparotomy: When the former cannot be performed as an exclusive procedure – and often associated with CO<sub>2</sub> Laser assisted microsurgery –this approach has been particularly helpful. For better recognition of chyliferous vessels, the administration of a fatty meal (60 g of butter in a cup of milk) is useful 4-5 hours before surgery.

## SURGICAL TREATMENT OUTCOME

Sixteen patients (14 males, 2 females) at the University of Genoa have been treated surgically for primary chylous ascites. The group consisted of 6 children between 9 months and 12 years old (median, 8 years) and 10 adults from 23 to 56 years old years (median, 35 years). All patients were initially treated by a medical approach alone. They were fed by TPN for a mean of 2 weeks and depending on the presence of the chylous ascites, one or two peritoneal drainages were placed into position by laparoscopy. After draining all chylous ascites, the open surgical procedure began by removing all dysplastic tissues at the site of the chylous leakage by multiple lymphatic and chylous ligatures using nonabsorbable suture material and CO<sub>2</sub> laser welding effect.

Afterwards, suitable lymphatic or chylous vessels were used to perform lympho-venous shunts on mesenteric or iliac veins. Three drainage tubes were left inside the abdomen, two in the parietocolic area and one in the pouch of Douglas. TPN was extended for 10 days and afterwards, appropriate oral feeding was progressively introduced. Drainage tubes were removed 10 to 15 days after surgery (Figs. 1-5).

Early relapse of chylous ascites was observed in only one case, which required a peritoneo-jugular shunt, which produced a good outcome. All patients must follow an appropriate diet. Bowel resection was not required in any of the patients. One patient with chyluria was treated by resection of the perirenal lymphatic vessels. Median follow-up was 5 years (range, 3 to 7 years). Nine patients did not present with relapse of the ascites or protein-losing enteropathy, and six patients showed persistence of a small quantity of ascitic fluid with no protein imbalance or hypoproteinemia. Eight patients underwent postoperative lymphoscintigraphy, which confirmed an improvement in lymph flow and a decrease in lymph reflux.



**Fig. 1 - Voluminous chylous ascites causing also double abdominal hernias in patient with congenital chylous dysplasia.**



**Fig. 2 - Surgical findings in the same patient confirming the dysplastic nature of the disease.**



**Fig. 3 - Long term outcome after surgical operation of drainage of the chyle, excision of dysplastic tissues, antigravitational multiple ligatures of dilated chyloferous vessels and chylous-venous microsurgical shunts.**



**Fig. 4 - Chylous ascitis secondary to lymphnodal retroperitoneal dissections for renal tumor. Several liters of chyle were drained from the abdomen.**



**Fig. 5 - Long term result after surgical laparoscopic and microsurgical combined approach.**

## FINAL REMARKS

From the immunological point of view, it is important to avoid the leakage of immunoglobulins and lymphocytes into the ascitic fluid in order to maintain immunologic competence. Lymph in the thoracic duct contains from ~2,000 to 20,000 lymphocytes per mm<sup>3</sup>, i.e., a concentration of lymphocytes 2-10 times higher than in the blood. This lymphocytosis varies according to the number of lymph nodes, temperature, digestive phase and endocrine conditions. It is, therefore, easy to understand the importance of restoring normal drainage of the intestinal lymph circulation. In case of an isolated picture of chyloperitoneum, it should be pointed out that, owing to the primary nature of the disease especially in children and young adults, the presence of extended

cutaneous hemangiomas in the chest or the limbs – normally flat, of a cafe au lait or port wine color – may be a sign of the disease. No familial tendency has yet been confirmed for these malformations.

Clearly information about the patient's medical history and a clinical examination are fundamental for diagnosis and must be conducted in a comprehensive fashion<sup>(22)</sup>.

According to some authors, the definition of "acute chylous peritonitis" is not accurate, since pain is caused by the rapid swelling related to chylous leak into the peritoneal cavity rather than to direct chylous action irritating or inflaming the peritoneum. However, intraoperative findings as well as peritoneal biopsies have shown the presence of significant acute inflammation process. This finding would confirm the typical clinical picture of

an acute abdomen, which, in about half of cases could initially lead to an incorrect diagnoses of “perforated gastroduodenal ulcer”, “acute appendicitis”, or acute “cholecystitis”. These acute forms are unlikely to be complicated by septic shock. Subacute and chronic forms are more subtle, where chylous leak is slow and progressive, with practically no pain, which the patient feels rather an annoyance or burden due to abdominal distension. Distension, in turn, raises the diaphragm, with subsequent significant breathing capacity reduction and related subjective and objective symptoms. Vomiting is frequent in children.

In case of slow chylous leak, adult patients can show a greater adjustment capacity for even for longer periods (weeks, months, even years) depending on the severity and cause of chyloperitoneum until some sort of spontaneous, probably unstable balance is reached.

In the majority of cases, malnutrition is present, with significant hypoproteinemia – specially affecting the albumin fraction – and weight loss. Respiratory problems and steatorrhea are also often present in PLE-associated forms.

The chylous nature of the effusion can be confirmed not only from its peculiar milky color, but also by chemical analysis which will show a high fat concentration (cholesterol, lipoproteins, chylomicrons). For a proper differential diagnosis, paracentesis is fundamental: this procedure allows verification of the nature of the effusion and confirmational clinical and imaging (US and CT) results. It is generally employed to confirm clinical assumptions, while laboratory tests are useful to show the presence of leukocytosis and related lymphopenia. Particularly in acute onset forms, bacteriological analysis coupled with antibiotic sensitivity is useful to implement a targeted antibiotic therapy when necessary.

In our opinion, all of these patients, even those with acute onset, should not undergo operation prematurely until at least a proper diagnosis has been made as to the nature and site of the likely leak. During this period, the patient should be properly metabolically compensated through an appropriate diet with protein integration and limited lipid input confined only to medium chain triglycerides (MCT). MCTs, rather than being absorbed through intestinal chyliferous lymphatic roots, use the portal venous pathway. The addition of water-soluble vitamins (ADEKs tablet) should also be considered.

In conclusion, considering the etiopathogenesis as well as the nature and complexity of chyloperitoneum, the treatment of these difficult pictures and the outcome significantly depend on the skills of the physicians/surgeons and on the available technology and equipment. For this reason, it is highly recommended that these patients be referred to the few centers that have a specific surgical experience in the treatment of this disease.

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# DIFFERENTIAL DIAGNOSIS IN RECURRENT INTESTINAL PERFORATION: CHRONIC INFLAMMATORY DISEASE WITH INTESTINAL LYMPHEDEMA OR ANTIPHOSPHOLIPID SYNDROME?

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## ABSTRACT

Authors report a clinical case of recurrent intestinal perforation in whom the diagnostic assessment was particularly tricky and required the global evaluation of clinical and laboratory data, accurate diagnostic imaging, histopathological findings and the response to therapy. All this diagnostic and therapeutical approach allowed Authors to get to the correct diagnosis and proper treatment.

**KEYWORDS:** Recurrent intestinal perforation, chronic inflammatory disease, crohn's disease, intestinal lymphedema, antiphospholipid syndrome.

## INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by a state of hypercoagulability potentially resulting in thrombosis of all segments of the vascular bed<sup>(1,2)</sup>, fetal loss, and moderate thrombocytopenia<sup>(3,4)</sup>. APS is associated with elevated titers of antiphospholipid antibodies (aPL) and/or lupus anticoagulant (LAC)<sup>(5,6)</sup>. Gastrointestinal manifestations are rarely observed (about 1.5% of patients) and intestinal infarction, resulting from mesenteric vessel thrombosis, has been infrequently reported<sup>(3)</sup>. The presentation may be acute (acute abdomen), often preceded by intestinal anginal. Rarely, thrombosis of large vessels (aorta and inferior vena cava) has also been reported in association with aPL<sup>(7)</sup>.

We describe a case of recurrent intestinal perforation and thrombosis of the inferior vena cava occurring as APS presentation.

## CLINICAL CASE

A 33-year-old man developed an acute abdomen treated with laparoscopic appendicectomy in February 2006. In March 2006 he was admitted again to the local hospital for a second episode of acute abdomen.

Abdominal computed tomography (CT) scan demonstrated the presence of ascites, and emergency laparotomy was performed. Small bowel perforation was found and was treated by segmental resection. Abdominal pain and fever (38°C) persisted after surgical treatment and a further abdominal CT scan confirmed the suspicion of another intestinal perforation. A second laparotomy was performed and 20 cm of jejunum were resected.

Histological examination of operative specimens showed intestinal mucosal necrosis with perforation, congestion, and infiltration of lymphocytes, plasmacytes and multinucleated giant cells. The diagnosis of chronic inflammatory bowel disease, such as Crohn's disease, was made and treatment with oral budesonide ileal-release capsules (9 mg once a day) and 5 aminosalicylic acid (ASA; Pentasa, 4 g once a day) was started.

Unfortunately, abdominal pain and intermittent fever (38°-38.5°C) were always present and in June 2006 the patient was admitted again to the local hospital for another acute abdomen. Emergency

laparotomy demonstrated an ileal perforation and a further segmental resection was performed. Treatment with oral budesonide and 5-ASA was continued. Nevertheless, he reported progressive worsening of the abdominal pain, and sometimes fever, anorexia, nausea, vomiting, and weight loss. In December 2007 he presented another acute abdomen and emergency laparotomy demonstrated a further small bowel perforation, which was resected as well. Budesonide was stopped and oral prednisone (50 mg once a day) was started. He was admitted to our department in February 2008 for the onset of right abdominal pain and melena. Abdominal CT scan demonstrated a right-colon covered perforation and partial thrombosis of the inferior vena cava. Celiac and superior and inferior mesenteric artery angiographic studies proved the abnormal origin and course of the splenic artery from the abdominal aorta, of the hepatic artery from the superior mesenteric artery, and of the left gastric artery from the splenic artery, but excluded arteritis and/or arterial thrombosis. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, and anti-Saccharomyces cerevisiae antibodies of IgG and IgA class were negative. At that time, results of the search for aPL showed elevated titers of IgM anticardiolipin (> 120 UPL/ml) and antiphosphatidylserine (> 120 RU/ml) antibodies, but not anti-β glycoprotein I antibodies. The aPL positivity was confirmed in May 2008. LAC activity and serological tests for syphilis were

negative. Serum levels of protein C, protein S, and antithrombin III were in the normal range. The search for HLA-B27 and HLA-B51 antigens was also negative. Moreover, our patient was a heterozygous carrier of methylenetetrahydrofolate reductase (MTHFR) C677T gene mutation, but factor V Leiden and prothrombin G20210A gene mutations were absent. Plasma homocysteine level was in the normal range. Finally, the histological reexamination of jejunum operative specimens confirmed intestinal mucosal necrosis with perforation, congestion, and infiltration of lymphocytes, plasmacytes and multinucleated giant cells, suggestive of an inflammatory granulomatous foreign-body reaction to a point of suture, and also showed intestinal small-vessel thrombosis without signs of vasculitis.

Therefore, the previous diagnosis of Crohn's disease (CD) was questioned. Apart from the clinical characteristics of the disorder, which were not typical for a chronic bowel disease, CT scan did not pointed out a clear thickness of intestinal wall and of mesentrium neither any regional lymphadenopathy, as usually found in CD (Fig. 1). Moreover, intestinal perforations are not common in CD.

Clinical, immunological, and imaging data were suggestive for the diagnosis of recurrent intestinal perforations in association with partial thrombosis of the inferior vena cava as presentation of primary APS.

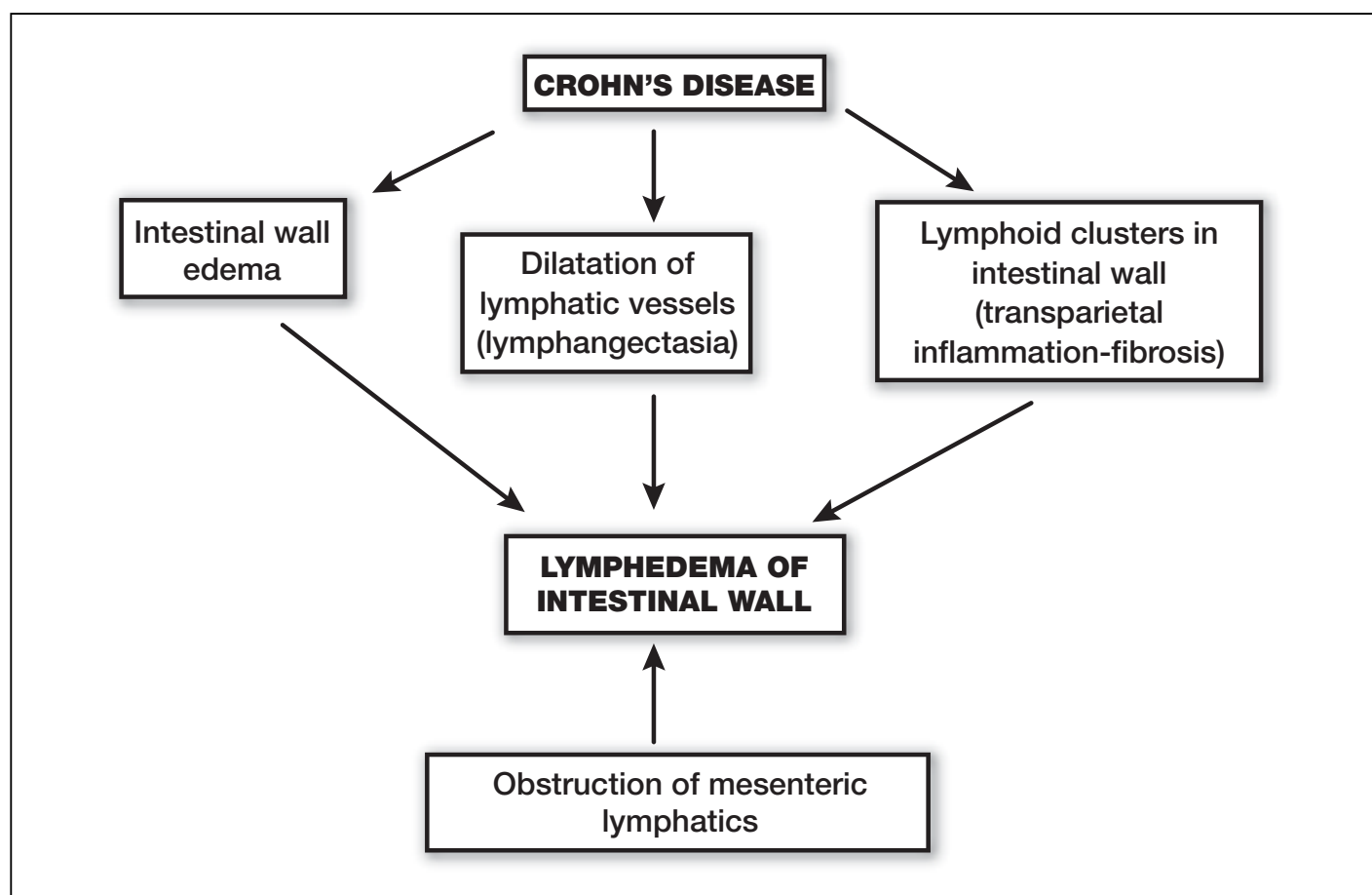


Figure 1 - Theory of intestinal lymphedema in Crohn's disease..

From the surgical point of view, clinical assessment of abdomen revealed no signs of peritonitis, patient complained general abdominal pain and manual compression at the lower right quadrant caused worsening of the pain, but there was no muscular abdominal wall contraction, and Blumberg sign was negative. Considering the good general condition of the patient, the absence of fever and a relative leucocytosis and a regular intestinal function, it was decided not to perform any emergency surgery, but a total parenteral nutrition was started. Blood parameters and clinical conditions were followed up. Thus, total parenteral nutrition was administered and treatment with low-dose aspirin (100 mg/day), low molecular-weight heparin (4000 IU twice a day), and oral warfarin was started. After 10 days of total parenteral nutrition, abdominal CT scan demonstrated remission of the right-colon covered perforation, but not of the partial thrombosis of the inferior vena cava. Total parenteral nutrition was stopped. Finally, aspirin and low molecular-weight heparin were stopped when international normalized ratio reached a value between 2 and 3. At present, the patient feels well and is treated with oral warfarin.

## DISCUSSION AND CONCLUSIONS

Elevated levels of aPL are associated with increased risk of venous and arterial thrombosis<sup>(5,8)</sup>. APS was first defined as a triad of thrombosis, fetal loss, and thrombocytopenia, but the definition soon evolved into that of a systemic condition that may be even more systemic than lupus<sup>(6)</sup>. According to the recently revised Sapporo criteria, APS is diagnosed if at least one of the clinical criteria and one of the laboratory criteria are met<sup>9</sup>. In our patient, the diagnosis of APS was made on the basis of the presence of recurrent intestinal perforation and partial thrombosis of the inferior vena cava associated with elevated aPL levels. Intestinal infarction due to thrombosis of mesenteric vessels has been infrequently reported in patients with aPL<sup>(1)</sup> and, to our knowledge, only 1 case of recurrent intestinal perforations as a presentation of APS has been reported<sup>(10)</sup>. Our patient did not present superior mesenteric, inferior mesenteric, and celiac artery thrombosis, but intestinal small-vessel thrombosis and partial thrombosis of the inferior vena cava. Large and small-vessel thrombosis are considered the cause of multiple organ ischemia and dysfunction, including gastrointestinal involvement, in patients with APS<sup>(1,11-13)</sup>. Finally, our patient was a heterozygous carrier of MTHFR C677T gene mutation with normal plasma homocysteine level; these are not associated with risk of venous thrombosis<sup>(14-16)</sup>.

We hypothesize that our patient had recurrent intestinal perforations that were not initially diagnosed as intestinal manifestations of APS.

Therefore, we propose that any abdominal disease of uncertain diagnosis should be considered as a suspicious manifestation of APS, and accurate histological examination and/or reexamination of intestinal biopsy or operative specimens should be made to assess the presence of thrombotic microangiopathy. Finally, as the true incidence of intestinal involvement in APS is probably underestimated, screening for aPL should be carried out in patients who present unexplained signs of intestinal angina.

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# ANALYSING THE FACTORS OF THE VARIABILITY OF THE RESPONSE TO DECONGESTIVE LYMPHATIC THERAPY

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## ABSTRACT

The efficacy of Decongestive Lymphatic Therapy (DLT) in reducing the excess volume of the lymphedematous limb has been reported between 22% to 73%. The aim of this paper is to review the literature about the factors predicting the outcomes of DLT. The influence of patient's weight and the body mass index in the result of DLT is controversial. The extension of lymphadenectomy is related with a worse response to DLT. Excess Volume is a proved factor that negatively affects the results. Patient's compliance to the bandage is one of the most important predictive factors of response to DLT.

**KEYWORDS:** Decongestive Lymphatic Therapy, lymphedema, physiotherapy, predictive factors, multivariate analysis.

## INTRODUCTION

Lymphedema, defined as the abnormal accumulation of protein-rich fluid in soft tissues, results from a dysfunction of lymphatic system<sup>1</sup>. In the case of breast-cancer-related lymphedema (BCRL), it develops when lymph transport is impaired due to damage or resection of lymph nodes as a result of surgery and/or radiation<sup>2</sup>.

The incidence of BCRL ranges from 6 to 56%, depending on different studies<sup>3-9</sup> due to the lack of standard diagnostic and assessment criteria<sup>10</sup>. As it has been described, BCRL is associated with disability of the arm<sup>11</sup> with lower levels of quality of life<sup>11,12,13</sup> and with psychological as well as social sequels<sup>14,15</sup>. Nevertheless, lymphedema has been one of the adverse effects of cancer treatment that has received less attention in the literature<sup>16</sup>. The wide variety of therapies and schedules employed in each centre, the lack of uniformity in the insurance coverage of treatments and the isolation of the research groups complicate even more any research in this field.

The "golden standard" in the treatments for lymphedema is the Decongestive Lymphatic Therapy (DLT)<sup>17</sup> that includes Manual Lymphatic Drainage with or without intermittent pneumatic compression, multilayer bandages compression, exercises and skin care.

Several studies have reported the benefits of DLT in patients

suffering BCRL with a reduction in the excess volume between 22% to 73%<sup>1,18-21</sup>.

As it has been postulated, oedema reduction is an important part of what influences quality of life<sup>22</sup>, so we should wonder why the outcomes of this treatment present this important variability. Some of the reasons for this variability may be the different therapies used during this DLT, the frequency and schedule of the treatment, the number of sessions and its duration, and the characteristics of the patients included in the studies.

Risk factors must not be confounded with prognostic factors. A risk factor of lymphedema is any variable that increases the probability that a subject in a population without lymphedema, develops this disease. A prognostic factor is a variable that indicates a better or worse evolution of the disease. If the presence or absence of this factor produces a change in the prognosis with an etiologic sense, the prognostic factor is explicative. If the presence or absence of this factor only indicates a change in the prognosis without an etiologic sense, the prognostic factor is predictive. Therefore, a predictive factor of response to DLT is any variable whose presence or absence produces a significant change in the degree of response to the treatment. Predictive factors of response to DLT have been poorly investigated. The aim of this paper is to review the reported predictive factors influencing the DTL outcomes.

## MATERIAL AND METHODS

The aim of this review was to describe the published predictive factors of response to DLT. Searches of electronic databases were conducted to identify articles that reported factors associated to the response to DLT in lymphedema patients. Eligible studies were preferably longitudinal in design with a multivariate analysis. Nevertheless, both cross-sectional and univariate analysis studies were also included for identification of prognostic factors, because of scarce research in this field. The review identified 15 relevant studies.

The factors can be classified according to the nature of the variable: patient-related factors, cancer treatment-related factors, lymphedema-related factors and factors related to the Lymphedema treatment.

## RESULTS

### *Patient-related factors:*

- **Age:** despite an older age at diagnosis of breast cancer (BC) is related with the incidence of lymphedema<sup>23</sup>, it had not influence in the outcome of the DLT in a multivariate analysis study<sup>24</sup>.
- **Body Mass Index (BMI):** In a retrospective study, BMI was found to be negatively associated with reduction in edema<sup>25</sup>. Afterwards, VIGNES *et al.* were the first to study the predictive factors of response to decongestive treatment in a wide prospective cohort of BCRL patients<sup>26</sup>. They found that the BMI was a predictive factor of response when the response was measured in absolute values of reduction in lymphedema volume. They found that a higher BMI was related to a larger absolute reduction of lymphedema volume. Nevertheless, BMI was not found to be significant when assessing the relative percentage of oedema reduction<sup>26</sup>. On the contrary, the patient's weight has been associated with a worse response to treatment in the univariate analysis in a prospective study<sup>27</sup>, but was not found to be an independent predictive factor of response in a posterior multivariate analysis study<sup>24</sup>. The weight gain was found to be a negative predictive factor of response in a multivariate analysis, with a mean difference of -9.3% in the results of DLT<sup>28</sup> and the weight loss is correlated with a reduction in excess volume (EV)<sup>29</sup>.
- **The history** of peripheral nervous impairment, upper limb traumatism and surgical complications have not been related to the results of DLT<sup>24</sup>.
- **Venous insufficiency in lower limbs:** A multivariate linear regression study showed that when the patient suffered from venous insufficiency in lower limbs diagnosed by a vascular surgeon by duplex ultrasonography, the result of DLT was more important<sup>24</sup>. This can be explained by the fact that a part of the excess volume (EV) can be a venous stasis that could drain more easily with decongestive treatment and so, giving a better result.

### *Cancer treatment-related factors*

- **Lymphadenectomy:** As to the effects of the degree of lymph node dissection, the outcomes of DLT tended to be greater for patients with narrow lymphadenectomy compared to broad lymphadenectomy<sup>30</sup>.
- **Chemotherapy:** Adjuvant chemotherapy was related with a worse response to treatment in a univariate analysis but it was not found to be a predictive factor of response to DLT in the multivariate analysis<sup>24</sup>.
- **Radiotherapy:** Axillary radiation and the administered dose of radiotherapy were negatively affecting the results of the DLT in a univariate analysis, but were not found in multivariate analysis probably due to the small number of patients in the non-radiated group<sup>24</sup>.

### *Lymphedema- related factors:*

- **Excess volume:** RAMOS *et al.* found that the factor that was associated with a good response to DLT was not the chronicity of the lymphedema but the volume it had reached. The group of

patients with less oedema showed a better response to decongestive treatment (a mean reduction of 78%) and the patients with more oedema showed a worse response (58.9%)<sup>31</sup>. In another prospective study, the Percentage of Excess volume at baseline was found to be a predictive factor of response after multivariate regression<sup>24</sup>; the lower was the Excess Volume, the more important was the reduction after the treatment. This data support the idea that more severe lymphedema patients have a worse response to treatment. As other authors recommend<sup>1,17</sup>, decongestive treatment in early stages can bring better results.

- **Chronicity:** The association between the chronicity of lymphedema and the response to DLT is not clear. VIGNES *et al.* found that longer duration of DLT was related to a larger reduction in the absolute lymphedema volume<sup>26</sup>, although some other authors failed to find a significant association<sup>30,31,32</sup>. Lymphedema is a progressive disease and it has been demonstrated that patients reach higher levels of severity along the time<sup>6,33,34</sup>. This may be due to the stimulation of fibroblasts, keratinocytes and adipocytes<sup>35</sup> with the onset of dermal complications as fibrosis, hyperkeratosis and increased deposition of subcutaneous fat<sup>36</sup>.
- **Fibrosis:** Other factors that have been associated with a poor response to treatment have been fibrotic consistency of lymphedema<sup>28</sup>.

### *Factors related to the Lymphedema treatment*

Despite the fact that lymphedema is treated by several means, it is not the aim of this paper to analyse the efficacy of each of these therapies that are applied in different settings.



- **Compliance to bandages:** Multi-layer bandages are effective in reducing the volume of the lymphedematous limb<sup>37-42</sup>. Bandages is the component of the DLT that shows the higher degree of recommendation in the existing systematic reviews<sup>43-49</sup>. The compliance to bandages was found to be the most important predictor of response in a multivariate analysis<sup>24</sup>. This prospective cohort study with 171 patients reported that a good compliance to the bandages, that was maintained  $\geq 90\%$  of the time, the percentage of reduction of EV showed an increase of 25% compared to fair or bad compliance (60-89% and  $<60\%$  of the time, respectively). Previous studies have reported the important role of low-stretch compression bandages in the reduction of lymphedema volume<sup>50-52</sup>. The pressure with the bandage is done by the tissues against the resistance of the multilayer bandage when the muscles are contracting. The amplitudes between pressures in rest and activity are the base of its efficacy<sup>50</sup>.

- **Weather conditions during the treatment:** The local climate has emerged as an important factor related to the bandage compliance. When the weather is humid and warm adds an additional difficulty in the treatment of lymphedema patients. It is very difficult to convince them to wear the multilayer bandages 24 hours between physiotherapy sessions, as most of them receive decongestive therapy in an outpatient regime. The season of treatment was an independent predictive factor of response to DLT in a multivariate analysis<sup>24</sup>. The patients treated in autumn obtained better outcomes than during the rest of the year. The reason can be that after the summer patients show an increase in the volume of their arm due to high summer temperatures and the bad compliance to garments<sup>53</sup>. This oedema is probably a recent and non structured lymphatic fluid that can be reduced more easily with treatment during autumn when bandages are better tolerated.
- **The pressure under the bandage:** While it has been suggested that bandages were more effective when they exert more pressure on the lymphedematous limb, a randomized trial showed that inelastic, multi-layer bandages with lower pressure (20-30 mmHg) achieved the same result in volume reduction as bandages applied with higher pressure (44-58 mm Hg)<sup>54</sup>. Moreover they were better tolerated by the patients. Further research is warranted.
- **Number of sessions:** The traditional DLT consists of 4-5 weeks of daily therapy, but data are controversial. A study stated that an increased number of DLT sessions provides marked improvements in volume, but results in poorer compliance<sup>55</sup>. Another study reports that from days 4 to 6 of therapy, volume changes were slight, ranging from 0.1 to 1.0%/day<sup>56</sup>.

## CONCLUSIONS

The influence of patient's weight and the BMI in the result of DLT is controversial.

The extension of lymphadenectomy is related with a worse response to DLT; in these fields, some efforts have to be done to improve the conservative approach in breast cancer surgery. As excess volume is a proved factor that negatively affects the results, DLT should be performed in early stages to avoid the progression of the disease.

Concerning DLT, patient's compliance to the bandage is one of the most important predictive factors of response. Therefore, patient motivation and involvement is essential in the treatment.

Further research is needed to clarify what factors can predict the results of DLT, in order to optimize the outcomes of the treatment when these factors could be controlled.

**Table 1. Factors associated to response**

<i>Factors</i>	<i>Type of stud, Type of analysis</i>	<i>N.</i>	<i>Effect on outcome</i>
<b>PATIENTS CHARACTERISTICS</b>			
<i>Body mass index and weight gain (yes/no)</i>			
Hinrichs <sup>25</sup>	Retrospective study, Univariate analysis	14	negative
Vignes <sup>26</sup>	Prospective cohort study, Univariate analysis	357	positive
Bertelli <sup>28</sup>	Prospective cohort study, Multivariate analysis	120	negative
Forner-Cordero <sup>27</sup>	Prospective cohort study, Univariate analysis	161	negative
Forner-Cordero <sup>24</sup>	Prospective cohort study, Multivariate analysis	171	No predictive factor
<i>Venous insufficiency in lower limbs</i>			
Forner-Cordero <sup>24</sup>	Prospective cohort study, Multivariate analysis	171	positive
<b>CANCER TREATMENTS</b>			
<i>Broad Lymphadenectomy</i>			
Yamamoto <sup>30</sup>	Prospective cohort study, Univariate analysis	82	negative
<b>LYMPHEDEMA CHARACTERISTICS</b>			
<i>Chronicity</i>			
Vignes <sup>26</sup>	Prospective cohort study, Univariate analysis	357	positive
<i>Baseline EV (ml)</i>			
Ramos <sup>31</sup>	Prospective cohort study, Univariate analysis	69	negative
Forner-Cordero <sup>24</sup>	Prospective cohort study, Multivariate analysis	171	negative
<i>Presence of Fibrosis</i>			
Bertelli <sup>28</sup>	Prospective cohort study, Multivariate analysis	120	negative
<b>LYMPHEDEMA TREATMENT</b>			
<i>Compliance to bandages</i>			
Forner-Cordero <sup>24</sup>	Prospective cohort study, Multivariate analysis	171	positive
<i>Season of treatment: autumn</i>			
Forner-Cordero <sup>24</sup>	Prospective cohort study, Multivariate analysis	171	positive
<i>Pressure under the bandage</i>			
Damstra <sup>54</sup>	Prospective randomised trial	36	negative
<i>Number of sessions</i>			
Mondry <sup>55</sup>	Prospective cohort study	20	positive
Yamamoto <sup>56</sup>	Prospective cohort study	83	No predictive factor

EV: excess volume.

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# DIAGNOSTIC ASSESSMENT AND THERAPEUTICAL STRATEGY IN A CASE OF INTESTINAL INVAGINATION DUE TO BOWEL LIPOMA WITH MESENTERIC LYMPHADENOPATHY

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## ABSTRACT

Authors report the diagnostic assessment and the therapeutical strategy in a case of intestinal intussusception with bowel occlusion arising from a lipoma of the colon with regional mesenteric and mesocolic lymphadenopathy.

## EPIDEMIOLOGY

Lipomas of the large intestine are the most common benign neoplasms after adenomatous polyps<sup>(3)</sup> and their prevalence varies from 0.035% to 4.4% of all benign tumors of the gut<sup>(1)</sup>. Lipomas of the colon can be single or multiple (20%)<sup>(5)</sup>, sessile or pedunculated, subserous (10%)<sup>(3)</sup>, intramuscular<sup>(8)</sup> or submucosal, as it happens in 90% of cases<sup>(1,3)</sup>. They affect mainly the fifth-seventh decade of life and with slight preference for females (1,5-2:1)<sup>(1,3,8)</sup>. The size varies from few millimeters up to several centimeters<sup>(1)</sup>. With the increase of the diameters, the tumor presses and cause ischemia of the overlying mucosa, which is also damaged by the passage of stool<sup>(3)</sup> and by transient episodes of invagination<sup>(4,7)</sup>. The pathophysiological mechanisms described above are responsible of the appearance of small superficial ulcers that can cause chronic bleeding resulting in anemia<sup>(7)</sup> and inflammation and infections determining a lymphatic-lymphnodal local reaction. Differential diagnosis with malignant tumors is demanded, considering also the possible association of important intestinal hemorrhages. In about 20-30% of patients, mucosal lesions can determine injuries of small arterial vessels of the intestinal wall with consequent serious enterorrhagia<sup>(3,7)</sup>. As concerns the site of lipomas, location is in 10-15% of cases in the stomach, 20-25% in the ileum and 60-65% in the colon<sup>(3)</sup>. It is possible to assess a higher prevalence of colic lipomas in the right side (caecum and ascending colon) than in the transverse and

descending-sigmoid colon<sup>(1,3,5,8)</sup>. As regards macroscopic aspects of lipomas, sessile and smaller lipomas are usually found in the right colon, while peduncolated and greater lipomas are most common in the left colon<sup>(3)</sup>. These larger lipomas are most frequently responsible for clinical manifestations. The cut-off size for the occurrence of symptoms is a diameter greater than 2 cm<sup>(1,5,7,8)</sup>. Usually lipoma of the colon is asymptomatic and it is discovered accidentally during diagnostic investigations performed for other reasons.

## CLINICAL CASE

A woman, 68 years old, arrived in the Emergency Department complaining of abdominal pain with intestinal obstruction which started about 24 hours before. Physical examination revealed asymmetric abdominal distention, above all in the upper-right quadrant, no signs of abdominal wall muscle contracture neither of peritonitis. Deep palpation caused pain and revealed a mobile and non pulsating epigastric mass. A naso-gastric tube was placed with the evidence of 1 liter of gastric and ileo-biliary fluid. There were no relevant data in patient's clinical history apart from arterial hypertension and depression.

The patient underwent abdominal x-ray, which showed significant intestinal distension with clearly evident air-fluid levels. Abdominal echo-scan allowed to find a mass at the descending colon, with a characteristic image of possible colo-colonic invagination, with the classical image of a "target" in cross section, and an initial vascular impairment of the intestinal loops. Angio-CT scan permitted to confirm the pattern of bowel obstruction due to probable colo-colonic intussusception, intestinal vascular ischemic signs and involvement of mesenteric and mesocolic lymphnodal structures, but without giving any useful information about the nature of colic lesion causing this acute

occlusive abdomen. Thus, on the basis of clinical and diagnostic parameters, the patient was addressed to emergency surgery, including explorative laparotomy and the treatment of the intestinal lesion. After a medium supra-umbilical pubic laparotomy, a bulky mass could be felt in left iliac fossa. Based on pre-operative diagnostic findings, and with the suspect of an intestinal invagination, through proper surgical maneuvers it was found that the invaginated part of the intestine included transverse and descending colon and the cause was a mass at the middle of the transverse. Not being sure of the nature of the mass, a proper segment of trasverse including the mass was excised together with regional mesocolic lymphnodes. Intestinal transit was healed with colo-colonic anti-peristaltic latero-lateral anastomosis with GIA 80 and closing the stumps with TA 60. A proper prevention of internal hernias and of further episodes of invagination was done by putting some peritoneal stitches. Postoperative course was favorable with prompt and efficient recovery of the canalization from the same II post-op day. Surgical drainage was removed after 7 days post-op. Histopathological findings revealed the mass to be a lipoma (about 7 cm in diameter), with mature elements, partially encapsulated, which compressed and ulcerated overlying mucosa, and there were no neoplastic lesions neither in the intestinal wall nor in the corresponding lymph nodes (Fig. 1).

## DISCUSSION AND CONCLUSIONS

Most patients affected from intestinal lipoma complain of vague abdominal pain, limited sub-occlusive crisis resulting from transient invaginations, nausea, vomiting, constipation, abdominal distension, diarrhea and repeated episodes of rectal bleeding. These symptoms represent vague and nonspecific expressions and clinical sets are unclear but, starting from a probable diagnosis of malignancy, a proper diagnostic assessment is mandatory. Diagnostic investigations include: abdominal radiography,

ultrasounds, angio-CT and endoscopy, that in some cases represents also the cure being able to solve the invagination and the obstructive clinical condition.

Moreover, endoscopy can help in understanding the nature of the lesion by proper biopsies<sup>(3)</sup>. The association of colon cancer with lipomas<sup>(1, 2, 3, 5)</sup> is frequent and the differential diagnosis of a colic lesion is often difficult.

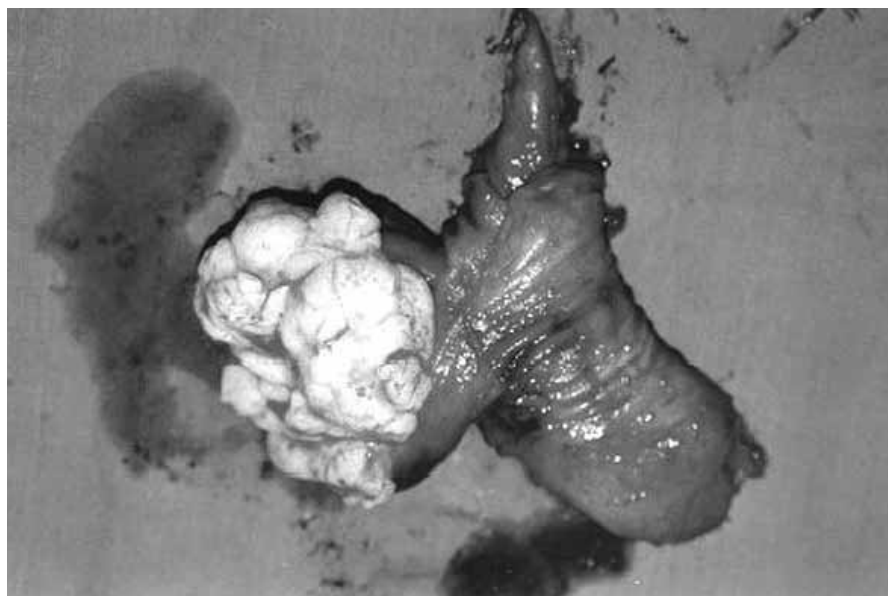
In emergency surgery the problem of differential diagnosis of intestinal mass that causes an acute event such as an intestinal occlusion is relative.

In emergency, you need to solve the acute situation firstly, but anyhow it could be important to know the nature of the mass in order to establish the extension of lymphnodal dissection or the need to do it. Adult patients who come to the emergency room with a clinical picture of intestinal obstruction are approximately 25% of all admissions<sup>(6)</sup>. In these cases, a rapid and simple diagnostic assessment is performed, starting from the clinic evaluation to radiologic and CT investigations.

In our case, a possible pitfall could have been that of cutting the colon before solving the wide intestinal invagination, thus excising an excessively long segment of colon, from transverse to sigma. In this case, pre-operative diagnostics played a central and important role. Another aspect to point out is the decision of how much extensive nodal dissection should be and this depends on several parameters such as clinical general conditions of the patients, macroscopic aspect of the mass, including consistency and surface, and lymph nodal characteristics. Anyhow, it is important to keep in mind that in case of colon cancer, 12 lymph nodes excised are commonly enough for a proper staging of the pathology.

Data arising from Literature are the following: locations at the transverse are rare (13-16% of all colic lipomas)<sup>(3)</sup>; an acute presentation with invagination represents 5% of all adult intestinal occlusions<sup>(2)</sup>; diagnosis of colic lipoma is made at the operating table on the occasion of an acute event in 50-60% of cases<sup>(3)</sup>. On the other hand, it is known that lipomas over than 2 cm are the main cause of colic intussusception in adults.

Intussusceptions are a tipical aspect of pediatric surgery but, as it happens in 5% of all intestinal occlusions, it could be found in adults, too. The presence of a sub mucous mass of the intestinal wall is a frequent cause of bowel invagination and if it is a lipoma it should be at least over than 2 cm. in diameter. Lipomas in the digestive tube are usually in the right side of the colon. In case of emergency, clinical and instrumental diagnostics allow to get a generic diagnosis. Patient's conditions bring us to diagnostic assessment and emergency surgery. Nowadays, with the development of laparoscopic approach<sup>(9,10)</sup>, it is possible to perform abdominal surgery even by laparoscopy instead of laparotomy, also in emergency, thus reducing surgical trauma and favoring recovery of intestinal function, reduce pain, infections and time of hospitalization (fast-track surgery).



**Figure 1 - Operative specimen of the trasverse segment with the big lipoma of its wall.**

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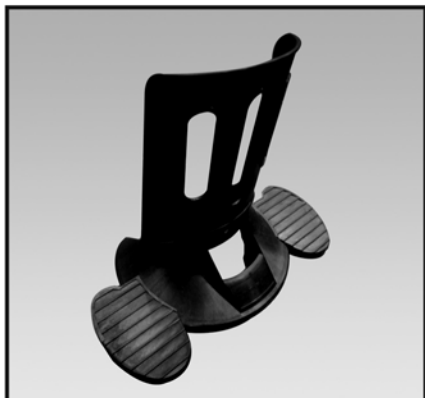
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