

## Review articles

**Lymphoedema in Advanced Cancer**

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*From Palliative Care and Rehabilitation Department, National Cancer Institute (IRCCS Foundation), Milan, Italy***ABSTRACT**

Lymphoedema is a common complication in several advanced cancer (breast, uterine cervix, ovary, prostate, rectum, melanoma). The condition may be extremely severe and often incurable. Several causes contribute to development lymphoedema: lymph nodes and/or dermal and subcutaneous lymphatic vessels infiltration, deep vein thrombosis, extrinsic venous and lymphatic compression.

The clinical feature of malignant lymphoedema may appear suddenly with quick exacerbation on few weeks. In many cases pain and neurological symptoms may precede arise of lymphoedema. This distinguishes malignant lymphoedema from post-surgical. Also skin condition (thin, fragile, lucid, tight) is a characteristic sign as well as dilated collateral veins around shoulder or on abdominal wall.

Signs and symptoms are mostly sufficient to diagnose malignant lymphoedema. Radiological investigation as CT, RMI, and PET may provide further information about disease status.

The treatment is decided each time on the base of clinical feature, local or general conditions of patient and is especially focused to easy the symptoms, control pain, reduce swollen limb volume, prevent further exacerbation, maintain function and limb abilities and to prevent inflammation, infection an thrombotic complications.

Lymphoedema is a common symptom in advanced cancer patients. In particular, breast, uterine, ovarian, prostate, bladder, rectum metastatic cancers, as well as metastatic melanoma, may lead to malignant lymphoedema, which can be very severe and particularly difficult to be treated. Many factors contribute to the development of oedema: these may schematically be classified into local and general factors. The former group includes lymph flow obstructions due to the cancer infiltration to loco-regional lymph nodes or cutaneous or sub-cutaneous lymphatics, venous obstructions due to the presence of neoplastic deep thrombosis or migrating thrombophlebitis, extrinsic lymphatic or venous compressions, caused by neoplastic or lymph node masses, superior or inferior vena cava infiltration and/or compression (1).

General factors are represented by hypoproteinemia, which develops in case of liver metastases, neoplastic cachexia or nutritional deficits, by immobility, by severe hypostenia due to neurologic lesions or bone metastases, by long lasting bed- rest (1-2). The use of non-steroidal anti-inflammatories, calcioantagonists and corticosteroids, too, may become a favouring factor, such drugs being responsible for hydric retention, hyponatremia, peripheral va-

sodilatation and, consequently, oedema (1).

**Clinical features**

Malignant lymphoedema typically manifests as acute, it progresses quite rapidly within a few days or weeks and it is often accompanied or preceded by pain or neurologic symptoms (3-4). Oedematous limb presents tense, subtle and translucent skin. Skin colour is usually erythematous or subcyanotic and it is due to the venous vessels involvement. Lymphatic blisters and lymphorrhea, sometimes even abundant, as well as ulcerations in advanced stages, may be present.

Oedema generally has a soft consistency, with a marked and persistent fovea, due to the elevated hydric retention in the limb tissues. Pain is a constant symptom, to be found in 70% of patients. It is neuropathic and it is due to brachial and lumbosacral plexus infiltration or compression by metastatic lymph nodes or neoplastic masses. Such pain is usually felt through the whole length of the limb as a burning, sharp pain, as an electric shock. It is also intense, continuous and may have worsening at night. In most patients it is associated with proximal-distal hypostenia of the involved limb, functional limitation of the scapular and pelvic girdle, peripheral paresthesias or allodyny (5-6).

In case of severe oedema, the limb weight may cause shoulder pain, hip pain or lumbar back pain, and it may impair walking or the daily routinary activities. Cutaneous recurrences, especially if ulcerated, as well as superficial or deep thrombosis, may either cause or worsen pain.

Venous obstruction presents with dilated collateral vessels and teleangectasias around the shoulder and at chest wall, in case of up-

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per limb involvement; at the abdominal wall and hips, when the lower limb is involved (4). The superior vena cava involvement typically presents with facial, neck, trunk or upper limb oedema, neck vein distension, cyanosis and dyspnoea. Lower limb oedema, associated to superficial collateral veins at abdominal wall, is observed when the inferior vena cava is involved.

Clinical examination often shows cutaneous recurrences, as well as metastatic lymph nodes at the lymphatic stations above the oedematous limb, or a neoplastic lymphangitis that may involve limb, back, thoracic wall and abdomen.

Malignant lymphoedema may easily be diagnosed, especially if an extensive clinical evaluation has been carried out, and the most characteristic symptoms (pain, skin colour, marked fovea, rapid progression of the sthenic deficit) have carefully been assessed. Diagnostic doubts can be solved by means of radiological investigations. CT and MRI are the most largely used techniques, which provide the most reliable data on the extent of the metastatic involvement. Colour Doppler ultrasound may show obstructions or compressions of the venous circle.

## Treatment

Treatment of malignant lymphoedema is quite similar to that of post-surgical one but, unlike this latter, more than reducing oedema itself, it aims at relieving accompanying symptoms, in particular pain, lymphorrhoea, infections, as well as preventing further limb volume increase and preserving and recovering oedematous limb function (7-8).

Manual, containment, pneumatic compression, exercise and drug therapies can all be used, but therapeutic modalities should be individualized and modified, according to different limb local conditions, as well as patient's general conditions. Skin care is very important in advanced cancer patients. Skin is generally very thin, dry and weak. It is, therefore, important to wash and clean it carefully every day, and keep it hydrated and soft by applying proper creams (emollient, moisturizing) (9). Any kind of traumatism should be avoided in order to prevent excoriations, lesions or infections. For this reason, compression garments are often not recommended, due to the cutting pressure exerted on the limb each time the support is worn.

When vesicles, small ulcerative lesions, are present, antibiotic drugs may be very useful for local flogosis and pain control.

In case of large lymphoedema, orthotic devices can be used: for upper limbs, when oedema is associated with brachial plexopathy, an arm support is indicated during standing position, in order to avoid overload to the neck and scapulo-humeral joint, or pillows placed under the arm when the patient is in bed. Declivious positions are to be avoided both for upper and lower limbs, as well as those forced prolonged positions (e.g., with a flexed elbow or knee), in order to prevent oedema worsening, articular impairment or block. Crutches or wheelchairs may be used whenever needed, in order to allow patient move either inside or outside home.

Exercises should be agreed with the patient, based on patient's general health conditions and abilities. For in-bed patients, the passive exercises of the oedematous limb, including those for hand, foot and fingers, may prevent and/or reduce articular rigidity, and it may favour lymphatic flow and venous return and avoid pressure ulcers. For more active patients, exercise mainly aims to maintain articular function and muscle trophism. Large oedema may, in fact, reduce the articular excursion, worsen a pre-existing hypostenia caused by a neurological damage, till a total limb impairment, that makes deambulation particularly difficult, thus confining patients to either bed or armchair.

Manual lymph drainage and a mild massage are indicated for malignant lymphoedema, although some Authors assume that they should absolutely be avoided in case of disease recurrence (10). As for all the other mentioned therapies, session times, interval among sessions and total treatment length should be tailored to limb conditions, as well as patient's general health status. Manual drainage is only counter-indicated in case of massive cutaneous spread and ulcerative lesions.

Bandages are particularly useful to reduce patient's discomfort due to the excessive weight and tension onto the limb, in order to avoid further increase in lymphoedema size, and to control lymphorrhoea. Monoelastic short- or middle-stretch bandages are to be preferred, worn as either single- or multi-layer. As for lower limbs, particularly for in-bed patients, long-stretch bandages can be used, as they can exert the highest compression at rest. In any case, bandage should be light, in order to avoid excessive patient's discomfort. If well tolerated, bandage can be worn all day long, by regularly controlling tolerability. For intolerant patients, double-layer tubular elastic bandages can be used, which can easily be worn, are soft and do not damage skin.

Besides taking into consideration limb size, prescription of elastic sleeve or stocking should also take into consideration the skin status and the presence of pain. Whenever feasible, low-stretch garments should be prescribed (class I-II), which should be worn so as not to create folds or strings, in order to prevent pain in the narrowing point and oedema further worsening.

Extremely controversial is the employment of pneumatic compression therapy (lympho press) in the treatment of malignant lymphoedema. Some Authors support its efficacy, mainly to soften stiff lymphoedema or to reduce the sensation of limb tension and patient's discomfort (11-12). In such cases, treatment must be performed by means of multi-chamber sequential therapy machines, using low-pressure regimens (20-30mmHg) and applications of up to 20-30 minutes per session. According to our experience, pneumatic therapy is not indicated for malignant lymphoedema, because it causes pain recrudescence and oedema worsening, particularly in those patients with metastatic lymph nodes in the station above the involved limb.

Pharmacological treatment should take into consideration lymphoedema etiology, as well as clinical and symptomatic picture. The most used drugs include corticosteroids, diuretics, antico-

agulants, profibrinolytics, analgesics (1). Thanks to their anti-inflammatory action, corticosteroids are indicated in those cases, in which lymphoedema is associated with neurologic symptoms, neuropathic pain or pain induced by the compression on soft tissues and lymphatic or venous structures. Dexamethasone (4-8 mg/die) represents the drug of choice. Posology and treatment length may be modified according to the clinical response. Unlike post-surgical lymphoedema, the malignant one may benefit from the employment of diuretics, in particular if it is due to drug-induced hydric retention, to heart failure or venous involvement. The choice of drug (furosemide, spironolactone) and dosage depend on the electrolytic conditions, renal function and the presence of concomitant symptoms (e.g., ascites). Non-steroidal anti-inflammatory drugs (naproxen, diclofenac, ketoprofen, ketorolac) are indicated for the treatment of pain induced by soft tissue infiltration or bone metastases. Due to their platelet inhibiting action, particular care should be taken when administering such drugs to patients with plateletpenia. Among anticoagulants, low-molecular-weight heparins are largely used in the treatment of venous thrombosis, both superficial and deep. Dosage may vary from 4000 IUs to 8000 IUs, depending on the degree of venous involvement. Since these drugs have a compliance good enough to allow self-medication and since they cause no side effects, treatment may be carried on for long periods without needing any hematologic monitoring. Profibrinolytics (mesoglycan, defibrotide, sulodexide) are to be preferred when an antithrombotic action on the peripheral blood circulation is required. Opioids (tramadol, codeine, buprenorphine, methadone, oxycodone, morphine) should be prescribed in those cases, in which no response can be obtained with any other analgesic treatment.

## Conclusions

In the light of the above, our conclusions are as follows:

- \* For most patients, malignant lymphoedema represents a severe problem, which is often very hard to be managed and treated.
- \* Lymphoedema induces severe pain, cutaneous complications (lymphorrhea, mycotic and bacterial superinfections, ulcerations, etc.), limb function impairment, causing patient discomfort, leading to a progressive deterioration of patient's activities of daily life and

social relationships.

\* Lymphoedema should always to be suspected in presence of a sudden-onset oedema, with a rapid size increase, especially when it associated with pain or symptoms of venous involvement.

\* Lymphoedema can, and it must, always be treated: the choice of treatment (manual, compressive, drug treatment, etc.) should be based on limb local conditions, progression degree (either local or distant) and on prognosis.

\* The aims of treatment must be symptom control and the improvement of patient's quality of life.

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## References

1. Keeley V. Oedema in advanced cancer. In: Twycross R, Jenks K, Todd J, eds. Lymphoedema. Oxon: Redcliffe Medical Press 2000: 338-58.
2. Badger C, Regnard DC. Oedema in advanced disease: a flow diagram. Pall Med 1989; 3: 213-5.
3. Badger CM. Pain in the chronically swollen limb. Progress in lymphology 1988; 11: 243-6.
4. Twycross R. Pain in lymphoedema. In: Twycross R, Jenks K, Todd J eds. Lymphoedema. Oxon: Redcliffe Medical Press 2000: 68-88.
5. Vecht CJ. Arm pain in the patient with breast cancer. J Pain Symp Manag 1990; 5: 109-17.
6. Kori SH. Brachial plexus lesions in patients with cancer. 100 cases. Neurology (NY) 1981; 31: 45-50.
7. Gray RC. The management of limb oedema in advanced cancer. Nurs Times 1987; 73: 504-6.
8. Badger C. Lymphoedema: management of patients with advanced cancer. Prof Nurse 1987; 2: 100-2.
9. Newman V. The use of metronidazole gel to control the smell of malodorous lesions. Pall Med 1989; 3: 303-5.
10. Wittlinger H, Wittlinger G. Absolute contraindications. In: Gunther Wittlinger, Hildegard Wittlinger, eds. Textbook of Dr Vodder's manual lymph drainage. Brussels: Haug International 1995: 74.
11. Gray R. The management of limb oedema in patients with advanced cancer. Physiotherapy 1987; 73: 504-6.
12. Casley-Smith JR, Casley-Smith JR. Venous disease, ulcers, palliative and geriatric care and acute injuries in moder treatment of lymphoedema. 5th edn. The Lymphoedema Association of Australia 1997: 280-1.