RISC FACTORS OF ARM LYMPHEDEMA DEVELOPMENT AFTER BREAST CANCER TREATMENT

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Abstract: *Arm lymphedema represents a major complication in the patients diagnosed and treated for breast cancer, due to both its high frequency of appearance and to multiple implications on the patient's quality of life, with few therapy options of low efficiency. The present article has the objective of determining the main factors involved in the occurence of arm lymphedema subsequent to the treatment of breast cancer through a thorough evaluation of the latest research regarding this pathology.*

Cuvinte cheie: *limfedem, limfadenectomie axilară , mastectomie, radioterapie, cancer mamar*

Rezumat: *Limfedemul braţului reprezintă o complicaţie importantă apărută în cazul persoanelor având cancer mamar, datorită frecvenţei sale de apariţie, a implicaţiilor multiple asupra calităţii vieţii pacientului şi a posibilităţilor limitate de tratament şi a eficienţei reduse a acestuia. Lucrarea îşi propune evidenţierea principalilor factori implicaţi în apariţia limfedemului braţului după tratamentul cancerului de sân prin trecerea în revistă a ultimilor cercetări din acest domeniu.*

Arm lymphedema represents a major problem for clinicians due to its high frequency of appearance in patients diagnosed and treated for breast cancer, its multiple implications on the patient's quality of life and also secondary to the existence of few therapy options of low efficiency.

Lymphedema refers to the swelling of an anatomical segment (hand, arm, foot, abdominal wall, thorax, neck etc.), with ≥5% compared to the contralateral segment, through lymph accumulation in the interstitial tissue, when the lymph system is damaged or has a default in development. Classically, lymphedema can be classified as primary and secondary. Primary lymphedema can have an hereditary component, occurring since birth or since the first years of life (type I hereditary lymphedema or Milroy syndrome – caused by a mutation of the VEGFR 3 gene on chromosome 5), since puberty (type II hereditary lymphedema, Meige disease, lymphedema praecox, lymphedema-Distichiasis caused mainly by a mutation of the FOXC2 gene) or since adult age (type III hereditary lymphedema, lymphedema tarda)(1,2) multiple genes implicated in the onset of primary lymphedema were identified: VEGFC3, FOXC2,CCBE1, FLT4(VEGFR 3),GATA2,GJC2 and SOX18.(3) Lymphedema may also occur as part of a phenotype and within some conditions, as yellow nail syndrome, Turner syndrome, Noonan syndrome, lymphedema-lymphangiectasia syndrome (Hennekam syndrome), Proteus syndrome etc.(4)

Secondary lymphedema occurs due to obstruction, injury or any other cause that leads to the interruption of lymph flow through lymph vessels and nodes.

There is no concordance within the data regarding incidence of arm lymphedema after breast cancer treatment, probably due to: the difficulty of its diagnostic in incipient stages, the identification of patient-specific risk factors, the post-therapeutic control methods and due to the insufficient specialized medical staff. Lymphedema was reported starting with 5 days from the surgical procedure up to 30 years.(5) Petrek et al. showed in a study from 2001 that 80% of female patients may present with varying symptoms of lymphedema in the first 3 years following breast cancer surgery. The rest may develop lymphedema with a 1% per year rate.(6) In another study, Paskett et al. showed in 2007 that the incidence of lymphedema may vary from 8% to 56% in the first two years from the surgical procedure (depending on the extension of the axillary lymphadenectomy and depending on whether or not the patient underwent radiation therapy).(7)

The main risk factors of arm lymphedema onset after breast cancer treatment are: axillary lymphadenectomy, postoperative radiation therapy, obesity, history of lymphangitis affecting the superior limb in question and repeated infections of the particular limb.(8)

Prior studies also mentioned the following as risk factors: mastectomy, the number of positive axillary nodes removed (9), the degree of effort realized by the affected limb (10), surgical intervention on the dominant hand side, age.(11)

Axillary lymphadenectomy

Mastectomy followed by the extended dissection of axillary nodes was proven to significantly increase the risk of arm lymphedema through the major changes that are made to the loco-regional lymphatic circulation.(12) Thus, in Liljegren's et al. study, the female patients with ten or more nodes extracted presented with signs and symptoms of lymphedema in a higher percentage than the patients with fewer nodes extracted (53% versus 33% one year after surgery).(13) Following studies showed similar results.(14) Some particular situations, like

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tumor excision with en bloc resection of adherent lymph nodes englobing the axillary vein, the presence of fluid collection adjacent to the axillary vein, of excess perivenous adipose tissue, of perivenous fibrosis, of a residual tumor, or of the pre- and postoperative thrombosis of the axillary vein (with tumor thrombi or hematic thrombi) may constitute favorable premises for the onset and development of lymphedema.(15) Likewise, axillary vein injury must be avoided since most arm lymphatic vessels and sympathetic nerve fibers are located in its vicinity.

Regarding the number of removed positive axillary lymph nodes, it was believed for a long time that it represents an important risk factor for the onset of lymphedema (9,16), but recent do not approach this subject anymore.

In 2011, Bevilacqua et al. elaborated three mathematic models ("nomograms") with the purpose of aiding clinicians in establishing the probability of arm lymphedema development in 5 years after the surgical procedure, and in initiating prevention measures and adequate treatment.(17)

In 2013 Kim et al. estimated the risk of appearance of arm lymphedema at 5 years post-surgical procedure, taking into consideration the number of lymph nodes removed, adjuvant chemotherapy and supraclavicular irradiation. Thus, in patients with no risk factors or one risk factor the risk of lymphedema development is 3%, in patients with 2 risk factors 19% and in those with 3 risk factors 38%. (18)

Sentinel lymph node biopsy

It associates a risk of lymphedema between 0% and 6%, according to the study published by Barranger et al. in 2005.(19) The clinical trial ALMANAC showed a rate of appearance of lymphedema in case of sentinel lymph node biopsy significantly lower compared to classic axillary lymphadenectomy (5% vs. 13%). (20) Following studies confirmed this finding.(21,22,23,24,25)

Also, the clinical trial ACOSOG Z0011 showed that patients with stage I and II of breast cancer with sentinel lymph node biopsy presented with a significantly lower rate of lymphedema compared to patients with classic axillary lymphadenectomy.(26)

The onset of lymphedema in some cases of sentinel lymph node biopsy could be due to the fact that the lymphatics of the upper limb may be located near the sentinel node and the axillary vein. Therefore in 2007, considering that the upper limb lymphatic drainage is distinct to the breast lymph drainage, a technique was developed (Axillary Reverse Mapping, ARM) that highlights and keeps the upper limb drainage during axillary lymphadenectomy or sentinel node biopsy, in order to try to reduce the risk of lymphedema onset.(27,28) Current studies revealed a series of dysfunctionalities of the technique that led to a reduced technique efficiency regarding lymphedema onset risk reduction.(29,30,31,32)

External radiation therapy

The most important late adverse reactions of irradiation in case of breast cancer are due to the fact that the heart, lungs, shoulder mobility are affected by irradiation leading to an increased risk of brachial plexopathy and decrease in quality of life.(33) Irradiation could contribute to the onset of lymphedema through lymph vessels obstruction, mainly caused by fibrosis of these vessels walls and of the surrounding connective tissue.(8)

A large amount of studies have evaluated the association between different irradiation modalities and different surgical techniques. Towards example, a study by Ozcinar et al. concludes that axillary lymphadenectomy followed by irradiation leads to the onset of lymphedema in a greater manner than sentinel node biopsy followed by irradiation. Furthermore, proceeding with axillary irradiation after sentinel node biopsy increases the risk of lymphedema in comparison with the situation in which the irradiation is left out.(34) Other studies have shown that postoperative axillary irradiation leads to lymphedema in a greater manner than just breast or thoracic wall irradiation.(35,36)

Obesity

Both breast cancer and obesity represent two affections whose worldwide incidences are continuously increasing, represent a major public health concern.(37) The close bond between the two affections is also well known, numerous studies indicated that the risk of developing breast cancer, as well as, the complications after the treatment for breast cancer are significantly greater for obese patients (with an high body-mass index) especially post menopause.(38,39,40) In this context, multiple studies have shown an predisposition in obese patients after breast cancer treatment of developing lymphedema (5,41,42) and even correlated the degree of lymphedema and obesity (5), still the mechanism through which obesity favors the onset of lymphedema is not yet fully known.

Infections

Cellulitis

Cellulitis is defined as an acute diffuse and edematous infection of the dermis and subcutaneous tissue caused mainly by staphylococcus aureus, group A streptococci, pneumococci, cryptococci, gram negative bacilli.

Erysipelas is an acute infection of the superficial subcutaneous tissue (superficial cellulitis) with lymphatic vessels involvement produced by group A ß-hemolytic streptococci and rarely by staphylococcus aureus.

The onset is generally sudden with signs such as fever, shivers and malaise. Locally, cellulitis is characterized by the appearance of an erythematous plaque that is painful, imprecisely delimited with bullae or erosions, while erysipelas appears as a precisely delimited erythematous plaque, warm with a well-defined border. In both cases painful loco-regional adenopathy may appear.

Lymphangitis, a lymphatic vessel infection, most often is caused by a streptococcal skin infection. Reticular lymphangitis is characteristic for small lymphatic vessels involvement, it appears as a painful erythematous induration of the skin that outlines the lesion (the germ's entry site). The affected vessels paths may become visible, appearing as red stripes. Troncular lymphangitis, as a result of a large vessels being affected, appears as an erythematous induration spreading through the length of the vessel and sometimes it reaches all the way to the first node in its path, which it infects. Both types of lymphangitis may cause local pain, fever and malaise, requiring antibiotic, antalgic and anti-inflammatory medication.

There is a close relationship between the presence of lymphedema and cellulitis/ erysipelas that leads to the development of an vicious circle: each episode of cellulitis affects the lymph vessels while the presence of lymph (rich in protein), stagnating at the soft tissue level, constitutes a favorable medium for the growth of the germs that have reached this level through skin lesions.

Baddour et al. showed that bacterial toxins that stagnate at the level of a tissue with poor lymphatic drainage are responsible for the systemic symptomatology of cellulitis, these toxins lead to the production and accumulation of cytokines in the affected tissue.(43)

Another study, by Mortimer et al. stated, that once the bacteria has reached an edematous tissue, its eradication becomes difficult and the risk of developing new episodes of cellulitis is elevated due to the impaired local immunity. This explains the need of prophylactic antibiotic treatment for patients with repeated episodes of cellulitis.(44) Therefore, the

study PATCH I (Prophylactic Antibiotics for the Treatment of Cellulitis at Home) has shown that prophylactic administration of phenoxymethylpenicillin reduces the risk of recurrent cellulitis.(45)

Conclusions:

The risk factors certainly involved in the occurrence of upper limb lymphedema after breast cancer treatment are: axillary lymphadenectomy, postoperative radiation therapy, obesity, history of lymphangitis of the affected upper limb and repeated infections of it. Their association increases the risk of lymphedema occurrence and development even more. There is a group of factors that may have some contribution in the development of lymphedema, like mastectomy, the number of positive axillary lymph nodes that were extirpated, the degree of effort realized by the affected limb, surgery on the dominant side and age but these factors are of low importance.

Some mechanisms implicated in the development of lymphedema can be intuited, like surgery and irradiation. Other mechanisms present with a uncertain character (obesity).

The optimization of surgical procedures and radiation therapy, as well as knowing the risk factors specific to every patient in order to apply the adequate prevention measures and treatment, could decrease the risk of lymphedema development.

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