VL-DUAL SHORT REVIEW

Lymphatic senescence and possible clinical implications

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Abstract Lower limb edema is a frequent occurrence in the geriatric age. Among the possible causes, the deterioration of lymphatic function caused by its senescence is usually overlooked. There is multiple evidence of aging of the lymphatic system, based on in vivo observations, both in humans and in animal models, and on cadavers. The alterations concern both the morphological and ultrastructural level, as well as functionality. On the basis of the available data, some clinical pictures can be better understood and new areas of investigation envisaged.

Keywords Senescence, Aging, Edema, Lymphatics, Lymphedema

Introduction

Edema of the lower limbs is a frequent occurrence in the geriatric population[1].

The causes can be different, often concomitant: heart failure, chronic venous insufficiency, phlebolymphatic stasis due to obesity, effect of drugs are among the main ones (Fig. 1). The possibility that a degenerative mechanical insufficiency of the lymphatics could be a cause of this disorder is poorly considered in the clinical setting and in the literature.

The organic failure may be the consequence of a chronic overload of the lymphatic network due to excess of fluids in the interstitium, but it could depend at least in part on alterations linked to the senescence of the lymphatic structures (Fig. 2).

Degenerative alterations were actually already demonstrated in the sixties with the finding in the cadavers of elderly subjects of: reduction in the number of lymphatic capillaries throughout the body; specific "varicose swellings" in the muscular walls of the lymphatics of various networks; signs of fibrosis and lipid accumulation, in addition to atrophy of muscle fibers and elastic elements destruction in the wall of the thoracic duct [2,3,4]. In recent years, further observations have been carried out, especially in vivo and in animal models.

Morphological and ultrastructural alterations of the lymphatic vessels

Alterations of the cutaneous lymphatic network resulting from the senescence process were studied by injecting green indocyanine into the ears of young (2 months), middle-aged (7 months) and elderly (18 months) mice. With near infrared fluoroscopy, a significant reduction in lymphatic clearance has been demonstrated in elderly subjects, with the evidence of normal blood capillary filtration. The identified cause is the reduction in the density and complexity of the initial lymphatic network[5].

The aging process also affects the morphology of the collector muscle wall. This is normally made up of muscle fibrocells which are arranged longitudinally at the pre- and valvular level, and circularly in the remaining, longer section. The longitudinal arrangement would play a role in the gating mechanism between adjacent lymphangions. The study of the lymphatic collectors of the mesentery of rats of different ages (3, 9, 24 months) has allowed to observe a progressive depletion of the muscular investiture which occurs only in the pre- and valvular area[6].

Figure 1 - Example of mixed edema in the elderly: causes in this case are venous insufficiency, obesity, inactivity, mild heart failure, mild leg tissues inflammation and, possibly, mechanical insufficiency of lymphatics.

Electron microscopy studies on mesenteric lymphatic vessels of 9 and 24 month old rats demonstrated in the former a connective tissue tight to the adventitia. In old subjects, tissue degeneration and rarefaction of perivascular collagen bundles were observed, with a substantial loss of extracellular matrix proteins, such as fibronectin and cartilage oligomeric protein[7].

Proteomic studies performed on the mesenteric vessels of 9 and 24 month old rats have demonstrated the reduction of numerous muscle contractile and associated cytoskeletal proteins in old subjects. The amount of troponins, myosin, actin, gelsolin, dynein was reduced at least twice compared to what was found in young subjects. Other proteins involved in generating muscle contraction, including Na+, K+, and Ca++ channels, adrenergic receptors, and related kinases were reduced in elderly collectors[7].

The glycocalyx is a structure made up of proteoglycans and glycoproteins, located on the luminal side of the blood and lymphatic vascular endothelia. It has an important function in regulating the permeability of blood capillaries. Studies performed on lymphatics of rats have shown that in young subjects (9 months) the glycocalyx is continuous, intact, electron-dense while in elderly rats (24 months) its reduction in size and continuity is observed. Furthermore, there is a significant reduction in its proteins, such as aggrecans, versicans, proteoglycans, agrin, galectins, brevican, mucins and clusterins[7].

The innervation of the lymphatic collectors of the cervical, mesenteric and femoral regions has been studied. Also these structures are affected by the aging process. The immunohistochemical investigation has demonstrated the presence of both sympathetic and parasympathetic innervation. In elderly subjects, lymphatic collectors show a reduction of all types of nerve fibers[8].

Senescence also has consequences on the morphology, and therefore the function, of human lymph nodes. In fact, a progressive loss of lymphocytes and venules with high endothelium was observed, in addition to fibrous and lipoid degeneration[9].

Alterations in the functionality of lymphatics

As a clear consequence of the morphological alterations described above, the senescence of the lymphatic vessels involves the alteration of their function. Studies on the contractile activity of collectors of the rat mesentery have demonstrated, in elderly subjects, a 20% reduction in the amplitude of contraction but above all a significant reduction (up to 70%) in its frequency. The velocity of systolic lymphatic flow is approximately half of that observed in young subjects[7].

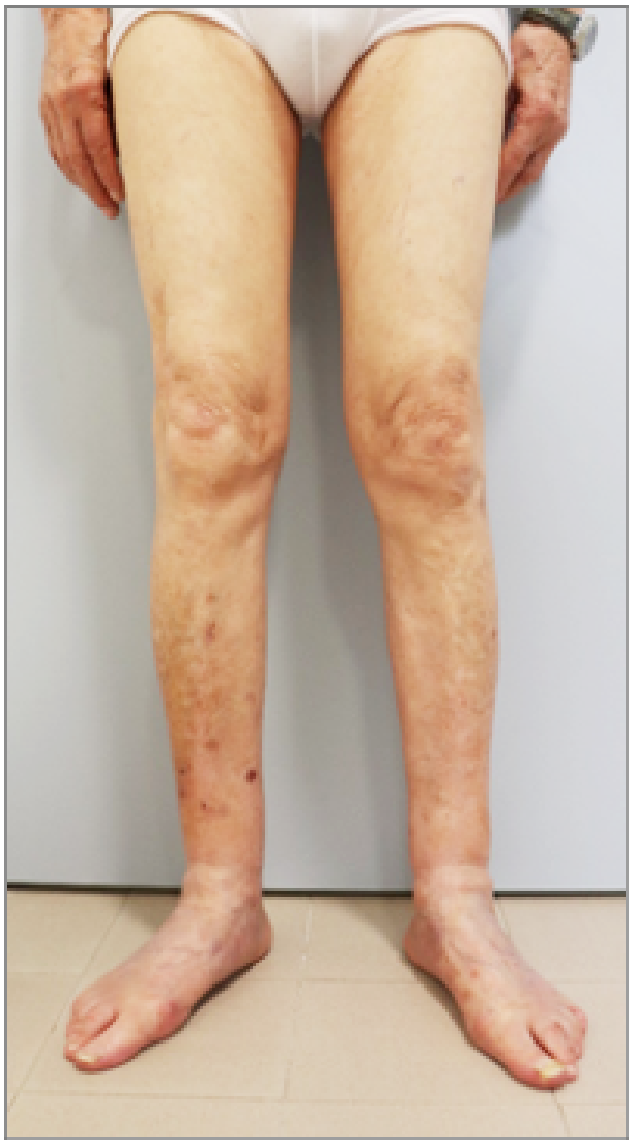

Figure 2 - Active person, 93 y.o. Swelling of the legs, present for about two months, less noticeable in the morning. No swellings before. No actual or previous pathologies of heart, kidneys, liver, thyroid, veins; no medical treatment taken. Is it lymphedema owing to lymphatic senescence?

The contractility of lymphatic vessels is regulated by Nitric Oxide (NO)-dependent mechanisms. The NO that regulates this activity has different sources: endothelial cell synthetases (eNOS), inducible synthetases of vascular muscle fibrocells and immune cells (iNOS), nerve synthetases of lymphatic perivascular nerves (nNOS).

The lymphatic endothelium is highly sensitive to the increase in flow and therefore shear stress, generated during the contraction of the lymphangion. This increase in shear stress involves the production and intravascular release of nitric oxide, with the function of reducing the contractile tone and frequency of the vessel, with consequent increase in the diastolic filling of the lymphatic system. Studies on the contractility of the rat's thoracic duct have shown that, in the elderly subject, this regulatory mechanism is significantly reduced, with failure to regulate the frequency of contraction and the extent of flow.

Furthermore, it has been observed that inflammation leads to an increased activity of inducible synthetases that originate from inflammatory cells (iNOS). The massive production of nitric oxide depresses the activity of the lymphatic vessels, dilating them and reducing their inotropism.

Chronic inflammation of the interstices is often present in elderly subjects[10].

The reduction in the impermeability of the lymphatic collectors can be postulated on the basis of the alterations of the glycocalyx and muscle investment observed in elderly rats[6,7]. A reduction in tight and adherens junctions between lymphatic endothelial cells has also been demonstrated. The adherens junctions would be lost due to upregulation of caspase-3, with fragmentation of the cadherin/catenin complexes[10].

The permeability of the lymphatic collectors of elderly subjects was demonstrated with two experiments.

Evans blue dye was injected into the sole of the hind paw of 4- and 22-month-old mice.

In young mice the dye remained mostly confined to the collectors. In old mice, Evans blue dye was present in both collectors and surrounding tissues[7].

The injection in the same site of Staphylococcus aureus, Cryptococcus neoformans, and Mycobacterium smegmatis allowed to observe in elderly mice (22 months of age) a quantity 100 times higher than in young mice (4 months) of bacteria in the sole of the paw and in the intersitium surrounding the lymphatic vessels. Their unequal distribution along the collectors suggests preferential passage zones for bacteria from inside to outside the lymphatic vessel[7].

Clinical implications

The alterations in morphology, ultrastructure and function of the lymphatics, resulting from the aging process, are poorly considered at the clinical level.

Symmetrical edema of the lower limbs of the elderly is usually attributed to heart or renal failure, venous circulation disorders, use of potentially edema-causing drugs and inactivity. Lymphedemas, primary or secondary, are usually well recognizable by their specific characteristics, first of all their asymmetry[1].

In the clinical setting, the instrumental study of the anatomical and functional alterations of the lymphatic vessels is not easy, essentially depending on the application of lymphoscintigraphy[11]. To date there is no data on its use for the diagnosis of degenerative mechanical insufficiency of the lymphatics in the elderly. For reasons of cost and practicability (long examination requiring demanding motor activity for an elderly person), it can rarely be prescribed if such a condition is suspected. On the other hand, in this population symptomatic treatment is usually rapidly effective: it consists of elastic compression, modulated according to the extent and rhythm of the disorder[12].

However, there are some aspects to considered.

Lymphedema, whether primary or secondary, is established by progressive exhaustion of the functional reserve of the lymphatic collectors. Lymphatic stasis is diagnosed when the limb begins to swell, with the possibility of assessing the increase in volume and the change in consistency. In reality, before this condition is reached, a decompensation of the lymphatic function has already occurred, indicated by a stagnation of fluids of even several decalitres, highlighted with particular instruments (e.g. by measurement of the Tissue Dielectic Constant)[12, 13]. We can hypothesize that the degenerative alterations of the senescent lymphatic vessels may represent a model of the alterations that appear in the early stages of lymphedema. It may therefore be useful to compare animal models in which the lymphatic alterations of old subjects are compared with those highlighted in subjects in whom lymphedema has been artificially produced.

The specific degenerative alterations of the lymphatics, reported in the literature, can become the target of old and new drugs. Among the old products we have all the substances with demonstrated phlebotropic action, which are actually often also used for a possible lymphotropic action, with even decent results[14].

In most cases it must be proven whether they actually have an action on the lymphatic vessels, with which mechanisms they act at a molecular level and in which phase they would be most suitable. It is also possible that the main effect is expressed indirectly on the lymphatic vessels, simply by reducing the lymphatic load for better venous efficiency.

A particular compound, useful in many cases of peripheral edema in the elderly, is mesoglycan. It consists of a polysaccharide complex, extracted from the porcine intestinal mucosa, consisting of heparan sulfate (52%), dermatan sulfate (35%), electrophoretically slow-moving heparin (8%) and chondroitin sulfate (5%). An antithrombotic and profibrinolytic action is documented[15]. It can be hypothesized, given its composition, that the glycocalyx itself can be reconstituted with the administration of mesoglycan, thus improving the barrier effect it exerts on intravascular fluids and solutes.

It is common to find symptomatic swelling of the legs in elderly people, with modest skin erythema. It is a picture of stasis dermatitis[12], although there is often doubt whether it could be subclinical infections. The persistence of bacteria has been demonstrated in lymphedematous tissues, which could be related to the reduced bacterial clearance by an altered lymphatic system, observed experimentally[16]. Bacteria expressing a low local pathogenicity could remain in senescent tissues, for a balance with the host's immune defenses, but interfering with the quality of the interstitium and therefore, for example, determining the upregulation of iNOS and the reduction of the effectiveness of the lymphatic pulsation.

Conclusions

More and more data are available on aging-induced alterations of lymphatic vessels. This knowledge can help us better understand the anatomical and functional changes that occur in the very early stages of lymphedema. It also offers us a broader vision of edema in the elderly, allowing us to act, with old and new remedies, on the pathophysiological aspects of the symptoms and signs complained of.

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