MULTIFACTORIAL ETIOLOGY OF LOWER LIMB EDEMA IN ELDERLY PATIENT WITH HEART FAILURE. CASE REPORT

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MULTIFACTORIAL ETIOLOGY OF LOWER LIMB EDEMA IN ELDERLY PATIENT WITH HEART FAILURE (Abstract): Aging population and increasing life expectancy has led to an exponential increase in the incidence of heart failure. In the elderly patient with heart failure lower limb edema is most commonly considered in the context of decompensated heart disease, causes such as malnutrition, kidney and liver disease or secondary drug effects being rarer. We report two cases of edema of noncardiac origin. In the first case, kidney damage was identified, edema resulting from hypoproteinemia and proteinuria, and in the second case it had an iatrogenic cause, namely the adverse effect of dihydropyridine calcium channel blocker. In the latter case, investigations centered on the assessment of body composition revealed the tendency to dehydration vs. hyperhydration, which led to a different therapeutic approach compared to the general tendency to administer *per primam* a diuretic treatment. The elderly patient with comorbidities that associate heart failure and lower limb edema requires careful investigations of the possible alternative causes. **Keywords:** ELDERLY, HEART FAILURE, LOWER LIMB EDEMA, MULTIFACTORIAL ETIOLOGY.

Symmetrical lower limb edema is a common clinical sign in the elderly, but also a major problem in geriatric medicine (1). This sign is so common in daily clinical practice because it is the symptom of a wide range of acute or chronic illnesses, and therefore particular attention should be given to the differential diagnosis centered on the elderly patient (2).

The cause of lower limb edema in the geriatric patient is frequently multifactorial (2). Although venous insufficiency and heart failure are the most common causes (3), an important role in this issue is given to protein calorie malnutrition and drug-induced edema: dihydropyridine calcium blockers (4), non-steroid anti-inflammatory drugs (2, 5), corticotherapy.

The general trend in an elderly patient with history of heart failure of various causes and lower limb edema is to establish a causal relationship between them, without further investigation of other causes for edema (6). Therefore, additional systematic investigations are not performed, and patients receive routine diuretic treatment (1), with severe functional and metabolic consequences such as secondary falls (2), renal impairment, hypokalemia, alkalosis and volume depletion.

CASES REPORTS

To exemplify, we report two cases of

elderly patients with heart failure in whom lower limb edema detected on physical examination was due to noncardiac causes.

Case 1. An 81-year-old female the medical history of whom revealed, among others, cardiovascular disorders represented by stage 3 essential hypertension, severe aortic valve stenosis, mild mitral regurgitation and heart failure with preserved ejection fraction. She associated vertiginous syndrome and cervical-lumbar spondylosis. For the afore-mentioned conditions the patient followed drug treatment with loop and anti-aldosterone diuretics (fixed-dose combination of spironolactone 50 mg and furosemide 20 mg), beta blocker (bisoprolol 5 mg), dihydropyridine calcium blocker (Amlodipine 5 mg) and betahistine 24 mg.

The patient presented to a geriatric medical ward with lower limbs edema, declaring the onset of symptoms a month earlier.

The cardiovascular exam showed a 4/6 systolic murmur in the aortic valve area and the echocardiographic examination revealed: normal-size heart, pulmonary artery pressure (PAP=27 mmHg) within normal range, normal inferior vena cava size with inspiratory collapse present and left ventricular ejection fraction (EF)=50%, findings inconsistent with a cardiovascular cause. To rule out iatrogenic-induced edema, treatment with amlodipine was discontinued, but with no result.

Further investigations revealed: high creatinine level corresponding to an eGFR of 44 mL/min/1.73m^2, hypercholesterolemia and hypertriglyceridemia, hypoproteinemia and non-specific inflammatory syndrome (erythrocyte sedimentation rate=130 mm/h). Urine tests were suggestive of glomerular nephrotic syndrome with 24-hours urine protein of 6.48 g.

Considering the diagnostic elements of nephrotic syndrome, further investigations were performed to establish its ethology. In this regard, we investigated a possible immunological (pANCA and cANCA antibodies were negative), and infectious cause (Ag HBs, Ac anti VHC negative), paraneoplastic manifestations - pulmonary, digestive, gynecological, hematological (thoracic X-Ray without suggestive lesions, abdominal ultrasound, kappa to lambda light chain ratio, gynecological examination - within normal limits). In the absence of an obvious cause, renal injury was interpreted in the context of a chronic glomerulopathy secondary to cardiovascular damage, and edema was considered secondary to hypoproteinemia and proteinuria. In addition to cardiovascular medication, maximal antiproteinuric treatment with angiotensin converting enzyme inhibitor was initiated, without diuretic dose adjustment. The outcome was favorable, with lower limb edema and serum proteins correction.

Case 2. An 84-year-old female patient with multiple comorbidities: cardiovascular (stage 3 essential hypertension, paroxysmal atrial fibrillation chemically converted to sinus rhythm, ischemic heart disease), renal (single left kidney after right nephrectomy for kidney tuberculosis), gynecological (total hysterectomy), endocrinological (thyroid nodules and total thyroidectomy) and orthopedic (left hip replacement following femoral neck fracture, right coxarthrosis). The patient followed drug treatment with amiodarone 200 mg/day, amlodipine 10 mg/day, carvedilol 12.5 mg/day, apixaban 2.5 mg x 2/day (adapted to renal function), levothyroxine 100 micrograms/day and alfacalcidiol 0.5 mg/day

(with both metabolic and renal protection due to the antiproteinuric effect).

The patient was symptomatic by dyspnea on low physical exertion, fatigability, and physical examination revealed symmetrical lower limb edema.

Cardiovascular examination showed rhythmic heart beats and blood pressure controlled with the current antihypertensive medication. Chest X-ray showed leftward displacement of the left heart border, right basal pachypleuritis. Transthoracic echocardiography revealed a normal-sized heart with preserved left ventricular systolic function (volumetric EF=57%), delayed relaxation diastolic dysfunction, mild tricuspid regurgitation, normal caliber vena cava, and full inspiratory collapse and moderate pulmonary hypertension (PAPs=60 mm Hg). Clinically, varicose veins were not found, and venous echo Doppler revealed some slightly dilated calf perforator veins.

Blood tests revealed atherogenic dyslipidemia, high creatinine levels (creatinine=1.36 mg% from 1.1 mg% a month earlier), with eGFR of 35.6 mL/min/1.73m^2 from 46.1 mL/min/1.73m^2 a month earlier and normal thyroid status. We did not find any possible cause of the acute deterioration of chronic kidney disease: prerenal (absence of nephrotoxic medication, euvolemic status-determined by bioimpedance), intrinsic renal (urine tests with no pathological findings) and post-renal (absence of ultrasound signs of obstruction and absence of radiographic signs of pelvis compression).

The assessment of body composition by bioimpedance revealed a dehydrated patient, and paradoxically, parenteral hydration was initiated with consequent correction of renal function. Discontinuation of dihydropyridine calcium-channel blocker treatment resulted in remission of edema.

DISCUSSION

The diagnosis of heart failure in the elderly can be difficult due to the increased prevalence of atypical signs and symptoms, presence of concomitant diseases (they may alter the classic manifestations of heart failure) and, on the other hand, due to the different perceptions of patients on the changes usually associated with it (7). Confusion, delirium, cognitive deficit, physical and mental asthenia which are a characteristic of the elderly can alter the symptoms or even mask them completely (8).

In the geriatric population, heart failure is the second most common cause of symmetrical lower limb edema after venous insufficiency (1); this aspect is due to the increased incidence of heart failure with preserved ejection fraction of up to 50% (3), being consistent with the two reported cases.

Among the most common - and less investigated - comorbidities in the elderly patients with heart failure are renal dysfunction, frailty and malnutrition (9, 10), polypragmasy and drug-induced edema (6, 11), lower limb edema being a common symptom of these entities (12). The systematic investigation of these entities will lead to a correct identification of the causes for edema onset, avoiding inappropriate administration and disastrous results of diuretic treatment, most commonly injectable furosemide.

In the first presented case, further investigations revealed the presence of a nephrotic syndrome, superimposed on preexisting heart disease. Considering the wide range of nephrotic syndrome causes, exhaustive parallel investigations were

required to avoid omitting a possible causal treatment. Chronic glomerulopathy is a common clinical syndrome in the elderly with chronic kidney disease (13), and this is the type of kidney damage identified in the first reported case.

Another important aspect is the iatrogenic cause of lower limb edema in the elderly. The incidence of drug-induced edema is seriously underestimated (1). Among the incriminated agents, antihypertensive drugs (3) and non-steroidal anti-inflammatory drugs (2) are the most common drugs. It is estimated that 50% of patients receiving dihydropyridine calcium channel blockers develop lower limb edema at different times of treatment (1). Our second case illustrates the situation of amlodipine-induced edema in a patient with stable cardiac failure and concomitant kidney disease. For the accuracy of the diagnosis in this case, the data in the literature demonstrate the superiority of bioimpedance versus clinical assessment (14).

Pulmonary hypertension is an underdiagnosed cause of lower limb edema, especially in the elderly patients. The substrate is sleep apnea, but it can also be secondary to chronic lung disease (1). The echocardiographic assessment in the second reported case revealed moderate pulmonary hypertension, which confirms the frequently multifactorial etiology of lower limb edema in the elderly patient (15).

CONCLUSIONS

In our cases, strict investigation of alternative causes of lower limb edema in the elderly is therefore necessary, beginning with the most common causes such as heart failure, protein-calorie malnutrition, to the least frequent, represented by iatrogenic cause, nephrotic syndrome and pulmonary hypertension. This strategy may reduce diagnostic confusion and may also reduce inappropriate use of diuretics with severe consequences: renal damage, dehydration, hyponatremia/dyselectrolytemia, increased risk of falls and poor life quality.

A direct consequence of this phenomenon is the increased number of patients experiencing symmetrical lower limb edema, the investigation of this clinical sign being a major but neglected problem of geriatric medicine due to its frequently non-cardiac and often multifactorial etiology.

REFERENCES

1. Thaler HW, Wirnsberger G, Piennaar S. Bilateral leg edema in the eldery. Clinical considerations and treatment options. *Europ Geriatr Med* 2010; 1: 353-357.
2. Thaler HW, Pienaar S, Wirnsberger G, Roller-Wirnsberger RE. Bilateral leg edema in an older woman. *Zeitschrift fur Gerontol Geriatr* 2013, 1-3.
3. Clark A, Clelanj J. Causes and treatment of oedema in patients with heart failure. *Nature* 2013; 10: 156-170.
4. Scholler DA, Achilles A, Manekas D *et al*. Segmental Bioimpedance for Measuring Amlodipine-Induced Pedal Edema: A Placebo-Controlled Study. *Clin Therap* 2012; 34(3): 580-592.
5. Alexa ID, Pancu AG, Moroşanu AI *et al*. The impact of self-medication with NSAIDS/ analgesics in a North-Eastern region of Romania. *Farmacia* 2014; 62(6): 1164-1170.
6. Samala RV, Navas V, Saluke E. Heart failure in frail, older patients: We can do MORE. *Cleveland Clin J Med* 2011; 78(12): 837-845.

7. De Freitas EV, Batlouni M, Gamarsky R. Heart failure in the eldery. *J Geriatr Cardiol* 2012; 9(2): 101-107.
8. Ely JW, Osheroff JA, Chambliss LM. Approach to Leg Edema of Unclear Etiology. *J Amer Board Fam Med* 2006; 19(2):148-160.
9. Pîslaru AI, Ilie AC, Pancu AG, Sandu IA, Alexa ID. Detection and prevention of frailty in independently living pre-elderly and elderly in Northeastern Romania. *Med Surg J-Rev Med Chir Soc Med Nat* Iaşi 2016; 120(4): 909-914.
10. Crăcană IM, Ştefăniu R, Mocanu V, Alexa ID. New developments in the approach and diagnosis of sarcopenia. *Rev Med Chir Soc Med Nat Iasi* 2016; 120(3): 491-495.
11. Hitoshi Y, Hitoshi S, Hiroshi S. Renal disease in the eldery and the very elderly Japanese: analysis of the Japan Renal Biopsy Registry (J-RBR). *Clin Experim Nephrol* 2012; 16: 903-920.
12. Lazzarini V, Mentz RJ, Fiuzat M, *et al*. Heart failure in elderly patients: distinctive features and unresolved issues. *Europ J Heart Fail* 2013; 15: 717-723.
13. Richard JG. An Update on Glomerular Disease in the Eldery. *Clin Geriatr Med* 2013; 29: 579-591.
14. Scholler DA, Achilles A, Manekas D, *et al*. Segmental Bioimpedance for Measuring Amlodipine-Induced Pedal Edema: A Placebo-Controlled Study. *Clin Therap* 2012; 34(3): 580-592.
15. Fukazawa R, Koyama S, Kanetaka H, *et al*. Leg edema detected on comprehensive geriatric assessment for eldery outpatients and its associated risk factors. *Nihon Ronen Igakkai Zasshi*. 2013; 50(3): 384-391.

NEWS

IMPACT OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION ON LUNG TRANSPLANTATION

Diastolic dysfunction may influence perioperative outcome, early graft function, and long-term survival. Has been compared the outcomes of double lung transplantation (DLTx) for patients with pulmonary arterial hypertension (PAH) with preoperative left ventricular (LV) diastolic dysfunction with the outcomes of patients without diastolic dysfunction. Fourteen (31.8%) patients with diastolic dysfunction pretransplantation had a higher body mass index (29 [IQR 21.5-32.6] vs 22.4 [IQR 19.9-25.3] kg/m^2) and mean pulmonary arterial pressure (54.6 10 mmHg vs 47 +/- 11.3 mmHg) and right atrial pressure (16.5 +/- 5.2 mmHg vs 10.6 +/- 5.2 mmHg). The patients received extracorporeal life support more frequently, had worse APACHE II scores, and a trend toward worse ventilator-free days. In conclusion, diastolic dysfunction was the only variable that correlated with overall survival and leads to early postoperative morbidity and worse survival in patients with PAH after DLTx (Avriel A, Klement A, Johnson S, *et. al*. Impact of Left Ventricular Diastolic Dysfunction on Lung Transplantation Outcome in Patients with Pulmonary Arterial Hypertension, *American Journal of Transplantation* 2017; 17(10): 2705-2711).

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