Send Orders for Reprints to reprints@benthamscience.net

Endocrine, Metabolic & Immune Disorders-Drug Targets, XXXX, *XX*, 1-7

CASE REPORT

Cardiorenal Syndrome Triggered by Slowly Progressive Drugs Toxicity-Induced Renal Failure along with Minimal Mitral Disease: A Case Report

Carlo Caiati[1,*], Adriana Argentiero[1], Stefano Favale[1] and Mario Erminio Lepera[1]

[1]*Department of Emergency and Organ Transplantation, Unit of Cardiovascular Diseases, University of Bari, Bari, Italy*

ARTICLE HISTORY

Received: XX XX, XXXX
Revised: XX XX, XXXX
Accepted: XX XX, XXXX

DOI:
XX XX, XXXX

Abstract: ***Background*:** We report the case of a 93-year-old patient with normal left ventricular function and severe mitral annulus calcification, with mild mitral steno-insufficiency.

***Case Presentation*:** She had developed creeping drugs-induced renal toxicity that is generally totally overlooked, due mainly to statins, a proton pump inhibitor, and aspirin. The Na and fluid retention, along with hypertension that ensued, although not severe, caused acute heart failure (sub-pulmonary edema) by worsening the mitral insufficiency. This occurred due to a less efficient calcific mitral annulus contraction during systole and an increasing mitral transvalvular gradient, as the transvalvular mitral gradient has an exponential relation to flow. After the suspension of the nephrotoxic drugs and starting intravenous furosemide, she rapidly improved. At 6 months follow-up, she is stable, in an NYHA 1-2 functional class, despite the only partial recovery of the renal function.

***Conclusion*:** Progressive renal failure can functionally worsen even minimal mitral valvulopathy. Drug-induced nephrotoxicity can always be suspected in case of renal failure of unknown etiology. The suspension of the culprit drugs can improve renal function and dramatically improve the clinical symptoms even in a nonagenarian.

Keywords: Renal insufficiency, kidney toxicity, heart failure, mitral annulus calcification, sub-pulmonary edema, nephrotoxicity.

1. INTRODUCTION

Heart failure (HF) is unfortunately on the rise [1]. What is commonly believed is that HF arises from an intrinsic dysfunction of the heart (mainly involving the left ventricle). However, creeping renal failure due to drug toxicity, largely overlooked in the clinical practice [2-5], can have a major role in triggering HF in association with predisposing minimal heart abnormalities like a minimal mitral disease, inducing a cardiorenal syndrome [6]. Renal failure, by causing reduced sodium excretion, in fact, expands circulating volume and enhances blood pressure, increasing both preload and afterload [7]. Degenerative annular steno-insufficient mitral disease [8], even mild, can induce a major functional worsening in this situation. A very similar pathophysiological model is that of worsening of mitral/aortic disease in pregnancy [9]. In this report, we describe a case of a nonagenarian (93 yrs old) that had sub-pulmonary oedema secondary to functional worsening of minimal mitral steno-insufficiency owing to slowly progressive drug toxicity-induced renal failure. After the suspension of the offending drugs, he recovered thanks to the progressive improvement of the renal function.

2. CLINICAL CASE

Four months before admission to our tertiary medical center, a 93-year-old woman started complaining about high blood pressure (170-90 mmHg) and slight paroxysmal nocturnal dyspnoea of 15 minutes duration, which obliged her to stay seated on the border of the bed with her legs dangling for some minutes during the night. This complaint was often associated with pain at the level of the mandible. The crises subsided within 5-10 minutes.

Before complaining of these symptoms, in the previous months, she had been reducing her drinking water intake to no plain water consumption during the day. The patient had a history of coronary angioplasty. At the age of 40 years, she had suffered myxedema. She had been mildly hypertensive for the last 20 years, and for the last ten, she had been taking the following drugs: simvastatin 20 mg on alternate days, aspirin 30 mg /day, metoprolol 25 mg once, losartan 50 1/2 cp a day, and levotiroxine 75 1 cp. The thyroid was perfectly compensated, as assessed a couple of months before the starting of symptoms. Up to the starting of symptoms, she was not aware of any significant renal dysfunction, and the NYHA

*Address correspondence to this author at the Cardiovascular Division, Policlinico di Bari, University of Bari, Bari, IT, Piazza G. Cesare 11, 70123 Bari, Italy; Tel +39-080-5592117; Fax: +39-080-5478796;
E-mail carlo.caiati@uniba.it

1871-5303/XX $65.00+.00

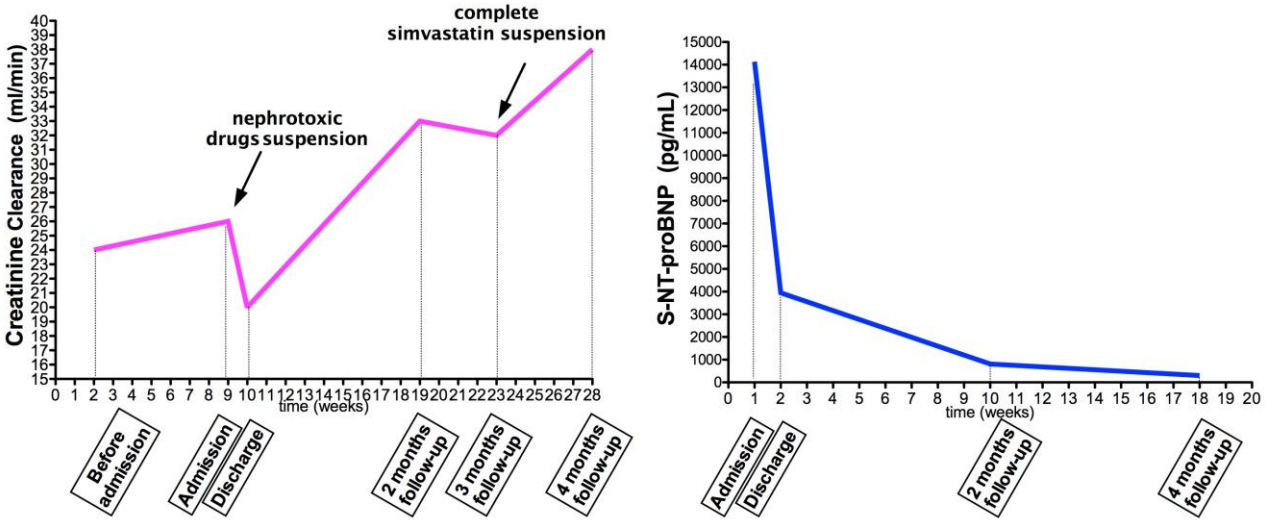

Fig. (1). Time course of creatinine clearance and pro-BNP. The renal function (graph on the left) revealed a significant and unexpected impairment two months before admission. However, there was a certain improvement of renal function after nephrotoxic drugs suspension (indicated by the arrow) at 2 months follow-up even though the improvement was only partial; however, GFR further improved at 4 months follow-up, one month after complete simvastatin suspension. The pro-BNP (graph on the right) showed an exponential, fast normalization and was in normal range within a few months. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

class (1-2) was normal. She was bradycardic with a baseline heart rate (HR) around 60b/m. A previous echocardiogram had shown a normal left ventricle (ejection fraction = 60%) and calcification of the mitral annulus associated with a minimal regurgitation with a centric protosystolic jet.

After the complaints, when the new symptoms developed, she saw a private cardiologist who suggested increasing the antiangina, antilipemia, and antihypertensive therapy and, in addition, prescribed her a full dosage proton pump inhibitor (PPI) as gastric protection. Her new therapy was as follows: pantoprazole 40 mg once a day; simvastatin 40 mg once a day; clopidogrel 75 mg once a day; aspirin 100mg once a day; metoprolol 100 mg once a day; amlodipine 10 mg a day; isorbide mononitrate 20 mg twice a day. No suggestion was given regarding water intake, which remained scarce, and salt was not restricted. This therapy continued for a couple of months. Two months before admission, blood tests showed a compromised renal function (Fig. **1**).

However, the situation progressively worsened. She had been gaining weight at a faster rate in the last months; overall, she gained 10 kgs compared to her standard weight. She developed increasing numbers of paroxysmal nocturnal dyspnoea episodes per night, and the functional class declined sharply (NYHA= 3-4). She developed lower limbs oedema, so a diuretic per os was added (furosemide 25 mg per day). However, the patient started to have dyspnoea at rest and orthopnoea, and finally, she was referred to our tertiary center for recovery. In the hospital, she appeared to be in severe distress and mildly dyspnoic. The vital signs showed the following: high blood pressure = 180/100 mmHg; regular fast radial pulse: >100-110 b/m with a fast rate of rise and normal amplitude; elevated respiratory rate at 30 per min; and normal temperature. Physicals showed that the apex beat was normal in terms of location (=10 cm from the mid sternal line) and duration (no sustained apex beat) with a mildly increased amplitude and no extra humps. The jugular pulse was frankly abnormal with increased jugular engorgement: the vertical distance from the top of the jugular blood column to the sternal angle of Luis was 5 cm, with a markedly positive hepato-jugular reflux. There was a minimal Y descent with no evident X' descent. In the lungs, there was a reduced vesicular murmur at the lung base, and teleinspiratory crackles over most of the lungs but more evident in the mid posterior lung fields. She had marked leg swelling, along with an erythematous rash.

The EKG showed sinus tachycardia with no major morphologic abnormality of the QRS and T waves. Chest X-ray showed interstitial oedema and bilateral mild pleural effusion. The echocardiogram showed a marked fibrotic/calcific degeneration of the mitral annulus with the posterior segment involving the base of the posterior leaflet (Fig. **2**); the left ventricle had an ejection fraction > 60% but a normal end-diastolic volume and normal mitral-E-septum distance. Doppler evaluation showed moderate mitral regurgitation with a centric j*et al*ong with a mild mitral annular stenosis with a peak and mean gradient of 21 and 6 mmHg, respectively, and a valvular area of 2.4 cm^2 (pressure half time) (Fig. **3**), pulmonary hypertension (peak systolic right ventricular pressure = 60 mmHg) (Fig. **4**) and inferior vena cava dilation with minimal (< 30%) inspiratory collapse.

Blood tests showed a markedly abnormally high pro-BNP (B-type natriuretic peptide) and markedly reduced renal function (Fig. **1**) with no casts in urine analysis but with mild proteinuria (<0.5 gr). Thyroid function was in discrete compensation.

The patient was treated with furosemide EV 60 mg per day. Antiaggregants were suspended; the PPI inhibitor was gradually suspended over 7 days [10]. *Enoxaparin* sodium was added 4,000 IU once a day, the dosage of simvastatin

dosage was reduced to 20 mg on alternated days, salt was totally restricted, and she was advised to drink plain spring water 2 liters per day. In 3 days, she markedly improved: she lost 5 kgs, the nocturnal dyspnoea almost disappeared, and her heart rate started to decrease. She was discharged on the 4th day after a drug change to oral furosemide 25 mg twice a day; no antithrombotic medications were suggested, but it was advised to only eat one single clove of garlic a day [11]. A minimal dose (50 mg per day) of metoprolol was also added, and simvastatin was reduced (20 mg 2 days per week). The opotherapy was confirmed. The echocardiogram at the discharge showed a reduction of the mitral regurgitation and tricuspid regurgitation and of the mitral transvalvular gradient (Fig. **3**).

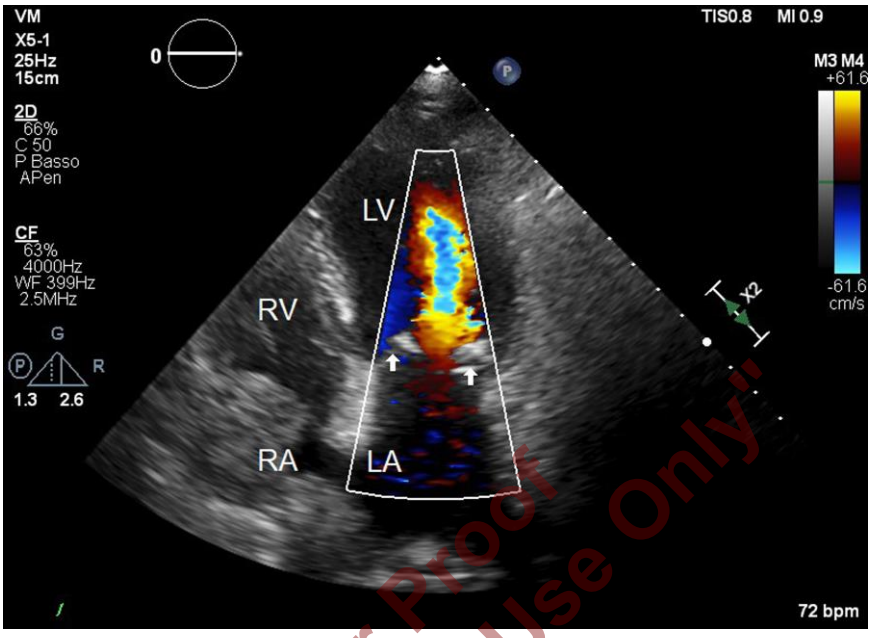

Fig. (2). The color flow of transmitral flow velocities. Flame-like appearance (indicating aliasing of the core of jet) of diastolic transmitral color signal secondary to high flow velocity for mitral stenosis. Arrows indicate the well-evident calcification of the mitral annulus. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

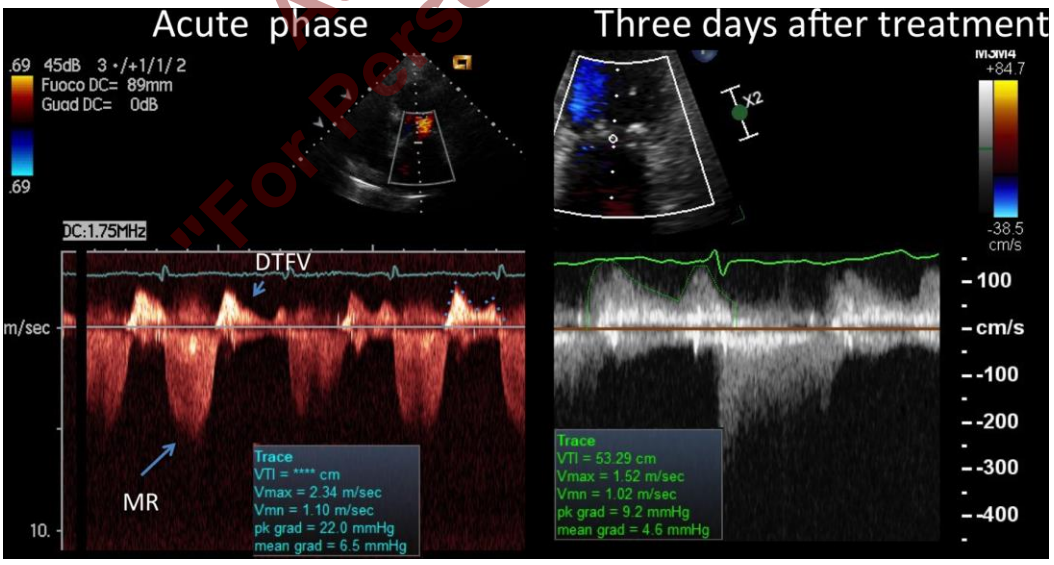

Fig. (3). Color-guided transmitral continuous Doppler recording in the acute phase and after 4 days of therapy. In the acute phase, the regurgitant systolic jet (MR) shows a more intense and better-depicted outline of the curve as compared to the admission phase (after 4 days of therapy), indicating a more severe mitral regurgitation in the acute phase. The regurgitation severity can be graded as moderate in the acute and mild in the recovery phase. Also, the diastolic transmitral flow velocity is higher in the acute phase (in the acute phase, the velocity scale is compressed as compared to at recovery), indicating a higher transmitral gradient: (max peak diastolic gradient is 22 mmHg vs. 9 mmHg; the mean gradient is 6.5 vs. 4.6 mmHg). In particular, the reduced peak diastolic gradient is an expression of the reduction of mitral regurgitation. The mitral valve area, as assessed by the pressure half time, is 2.4 cm^2, indicating mild stenosis that remained constant over time. DTFV= diastolic transmitral flow velocity; MR= mitral regurgitation. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

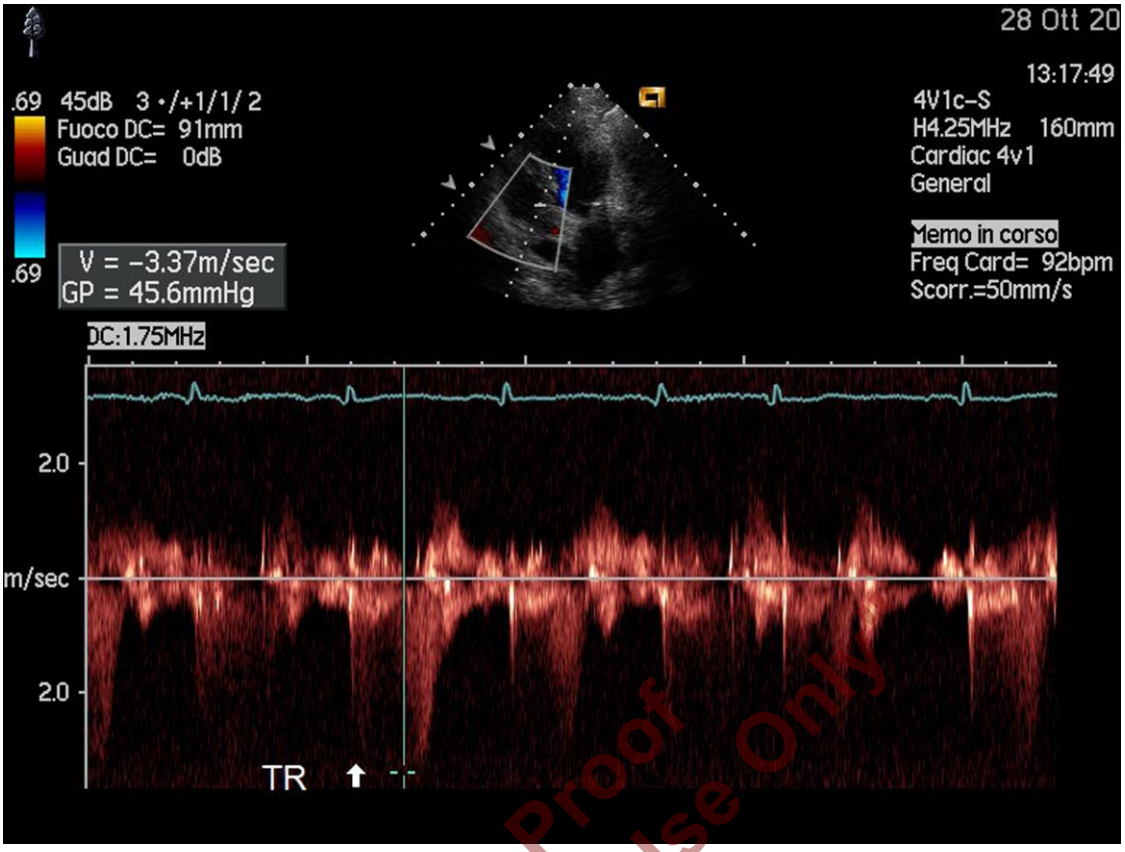

Fig. (4). Color-guided continuous Doppler recording of tricuspid regurgitation flow in the acute phase. The regurgitation is of moderate severity. The pulmonary systolic pressure is high: at 60 mmHg calculated by summing the max systolic pressure gradient between the right ventricle and right atrium (45 mmHg) to the estimated high atrial pressure (15 mmHg), giving the reduced inspiratory collapse (<30%) of the inferior vena cava (not shown). TR = tricuspid regurgitation (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

At home, she continued to lose weight (4 kgs more, reaching her normal weight of 60 kgs in 10 days). The heart rate returned to 60 b/m, the proBNP normalized, and the renal function mildly improved but remained substantially depressed (Fig. **1**. Her NYHA class returned to 1-2, and after 9 months of follow-up, she remained substantially asymptomatic and stable. After 3 months, simvastatin was totally suspended, boosting in one month after suspension a further improvement of GFR (glomerular filtration rate) (Fig. **1**).

3. DISCUSSION

This case underscores the importance of multi drugs renal toxicity in the elderly that is largely underestimated and thus overlooked like in our case. Secondly, renal dysfunction, even if not severe, can have serious adverse consequences on the heart by inducing heart failure in the presence of mild abnormalities like mild mitral disease, which can amplify the intracardiac pressure effect of a non-severe volume overload induced by renal insufficiency. Thirdly and most importantly, eliminating the harmful drugs, along with mild intravenous diuretic therapy, can dramatically ameliorate the cardiorenal syndrome.

This patient lacked a systemic illness associated with glomerulopathy (*e.g.*, diabetes or lupus) and had bland urine analysis findings (no casts) with mild proteinuria (<1 gr/24 hours); therefore, an interstitial disease possibly related to nephrotoxicity is likely [12]. Multi drugs can often induce renal toxicity [5, 13]. The tubular interstitial part of the kidney is prone to become a target for toxicity. The kidneys, although they constitute less than 1% of the total body mass, receive 20% of the total cardiac output. Therefore, the tubules and interstitium are quantitatively more exposed to toxins [14] than other organs [7]. In addition, the reabsorption of 98% of the filtered water can enhance the susceptibility to nephrotoxicity, especially in subjects with a reduced plain water intake like in our case, since toxic compounds (chemicals, drugs, *etc.*) can reach extraordinarily high concentrations in the tubules, far above those in the plasma and other organs. In addition, very active drugs metabolites are formed in the kidney, thanks to the action of cytochrome P450 (CYP) maximally present in the epithelial cells of the proximal renal tubules in order to detoxify the drugs moiety. Drugs biotransformation by CYP (phase 1 detoxification) may play a significant role in establishing or increasing the toxic nature of a xenobiotic by transforming it into a reactive electrophile [15]. These reactive electrophile intermediates, if not promptly conjugated (phase 2 detoxification), may exert toxic effects within the kidneys by covalently binding to structural protein, lipids, and nucleic acids. In addition, since cytochromes are oxidases, they, in the process of biotransormation of xenobiotics, generate reactive oxygen species (potent radicals such as superoxide, peroxide and

hydroxyl radicals, and singlet oxygen) that can exert oxidative damage on renal cells structure (cytoplasmatic macromolecules, cell membranes, cytoplasmatic organelles, *etc*.) [7, 15]. Finally, the genes encoding CYP enzymes are polymorphic, resulting in high variability of drug excretion rates and final serum concentration among different individuals and ethnicities. In the poor metabolizers, higher concentrations of drugs and toxicants in general are present in the interstium and in the plasma, thereby contributing to toxicity [16].

In our patient, the simvastatin, along with aspirin, caused a first progressive, indolent renal damage, which after several years, started to cause sodium retention [2]. After that, because the symptoms were erroneously interpreted as worsening angina, other nephron toxic drugs were added: PPI, clopidogrel, and amlodipine, while aspirin and simvastatin were considerably increased in dosage. At this point, the clinical situation took a rapidly worsening turn as more renal damage occurred and more sodium retention developed. What is clinically relevant was that we did not face a pre-uremic renal insufficiency with critical sodium and water retention [17], but a relatively slow, progressive renal problem that could possibly have been gone unrecognized for a longer period of time in the absence of mitral valve disease, given the patient's normal ventricular function.

In particular, statins are commonly used in the prevention of coronary artery disease. However, they can have serious adverse effects [18] and can also be damaging for the kidneys [19]. Although in some studies (randomized clinical trials), statins were shown to improve GFR in the short term, perhaps by ameliorating endothelial function of the intra-renal vessel network [20, 21], the main long term effect is a progressive worsening of renal function, as shown in two recent population-based studies [19, 22]. In one of these studies conducted in 128,140 older incident statin users treated in a single Canadian province, the authors found a graded, independent association between the intensity of statin treatment and the risk of hospitalization with AKI [22]. In the other retrospective cohort study with a 6.5 years follow-up, statin users had greater odds of acute kidney injury (odds ratio [OR] = 1.30, 95% confidence interval [CI] = 1.14 to 1.48), chronic kidney disease (OR = 1.36, 95% CI = 1.22 to 1.52), and nephritis/nephrosis/renal sclerosis (OR = 1.35, 95% CI = 1.05 to 1.73) [19].

The renal damaging mechanism of statins could be rabdomyolysis, although this did not apply in our case. It can induce tubular epithelial damage [23] or an acute or chronic interstitial inflammation [24], and sometimes epithelial casts could be found in the tubular epithelial but not in the interstitial disease. We did not find any casts, so we think that torpid interstitial damage applies in our case [2]. In our case, the specific torpid nephrotoxic effect of simvastatin is also partially supported by the further improvement of the GFR in one month after complete simvastatin suspension (Fig. **1**).

Aspirin at low doses may affect renal function in elderly patients [25]. Aspirin exerts its main effect by blocking the function of the cyclooxygenase (COX) in producing prostaglandins by non-competitive and irreversible acetylation of a serine residue in the active site of the COX enzyme [26]. In the kidney, such prostaglandins cause vessel vasodilation. So aspirin, by stopping the production of the prostaglandins, can reduce renal perfusion and GFR not in normal subjects but when an intra-renal vasocostrition state is already present (due to a high sympathetic tone and high activation of angiotensin II). Such vasoconstriction state is generally induced by kidney hypoperfusion like in chronic nephropathy (as in our patient), in congestive heart failure, hypovolemia, *etc*. [27]. Moreover, aspirin may cause a transient shedding of renal tubular cells, alterations in urate excretion, inhibition of spironolactone action [25], and may also cause salt and water retention by reducing the prostaglandin-dependent inhibition of the reabsorption of chloride and of the antidiuretic hormone action. In our case, the ongoing renal failure might have magnified the aspirin toxicity after the aspirin dosage increase in the last months.

PPIs had been added in the last 3-4 months before admission to our center. This class of drugs has several toxic effects [28]; however, one of the most serious is nephrotoxicity [29]. PPIs are now considered to be among the most common causes of drug-induced acute interstitial nephritis worldwide [30].

As recently reviewed [31], putting together all the evidence (observational studies, meta-analysis), it seems that PPI use is a likely contributor to the risk for the development and progression of chronic kidney disease even in a relatively short time [29]. In addition, PPI use is associated with an increased risk for death in general cohorts and hemodialysis patients. Only if truly necessary should they be prescribed to the elderly. In our case, the PPI was prescribed for inappropriate indications (for gastric protection), even without checking the renal functional parameters.

Amlodipine, unlike statins, could have impaired glomerular autoregulation by dilating the afferent glomerular artery, thereby eliminating the powerful mechanism that protects the glomerular capillaries against the transmission of systemic pressures [32]. This effect can increase proteinuria (< 1 g in our case) and possibly create over time progressive damage of the glomerular capillaries network, especially when a hypertensive state persists [32]. This glomerular amlodipine effect could have been compounded by the anti-prostaglandinic effect of aspirin, which further compromises intra-renal vessel autoregulation, thereby worsening glomerular filtration. In addition, given the reduced clearance of the drug owing to renal insufficiency, its adverse effect could have been magnified, provoking our patient's scaly rash on the legs. In advanced kidney failure, instead of using vasodilators, hypertension should be managed mainly with diuretics with a potent natriuretic effect [7].

In our case, the main confirmation of the drug toxicity was given by the patient's response to drugs suspension. Her clinical and kidney condition rapidly improved, although a consistent renal insufficiency remained, indicating that irreversible kidney damage had already taken place (Fig. **1**).

Drinking too little water (plain water) could also have fueled the drug's toxicity and sodium and water retention. A higher water intake increases the clearance of sodium, urea, and osmoles [33], and an increased water intake is the most effective therapeutic measure to prevent kidney stones (stones are also associated with loss of kidney function) [33].

5. Renal-cardiac interaction

Since the patient was not in a pre-uremic phase, one would have expected adequate handling of the moderately increased blood volume due to renal insufficiency by the heart [17]. In our case, however, valvular abnormalities triggered a rapid increase in atrial and lung capillaries pressure, inducing a rapid, acute heart failure.

The first major mechanism triggering elevation of the atrial pressure was the rapidly functional worsening of mitral regurgitation. The dilation of the LV (increased preload) in combination with an increased afterload due to hypertension can worsen the efficiency of the annular contraction in systole, already impaired by the extensive calcification [8] and, at the same time, increase the LV-LA systolic gradient, thereby boosting more regurgitant flow [34]. This contributes to heightening the left atrial pressure first by increasing the systolic V wave in the atrium since the regurgitation, although not severe, took place in a relatively short time, making the atrium less compliant to the extra mitral regurgitant flown [35]. This was confirmed by the fact that the atrial chamber size was fairly normal, and the early diastolic flow was markedly increased (Fig. **3**). Secondly, this extra regurgitant flow added up to the normal left atrial filling from the pulmonary veins, thereby further boosting the diastolic pressure gradient through the already mild stenotic valve (Fig. **3**). Pressure gradient through a stenotic valve, in fact, has an exponential relation to flow [36].

Thus, the mean atrial pressure increased with the consequent retrograde transmission to the capillaries and secondary increase of pulmonary arterial pressure (the patient had a 60 mmHg of systolic pulmonary pressure assessed by Doppler echocardiography) (Fig. **4**). The increased systolic overload of the right ventricle triggered by the capillary congestion caused mild right ventricular failure with greater tricuspid regurgitation (Fig. **4**). Both events contributed to causing venous congestion, which finally brought about lower limbs edema. Furthermore, this central venous congestion probably had an independent effect in the final rapid worsening of renal failure by inducing intrarenal venous congestion. Intrarenal venous congestion, in fact, can compress the tubules and increase capsular pressure, thereby opposing filtration and finally reducing the glomerular filtration rate and sodium and water excretion [37, 38].

CONCLUSION

In the era of multi-medications, especially in the elderly, creeping kidney failure can arise, which brings about plasmatic volume expansion. This fluid expansion, even mild, can trigger severe cardiac insufficiency in the presence of predisposing conditions like mitral disease, even mild. Chronic medications, especially if multiple, should be discouraged in the elderly. However, if they are really necessary, close kidney function surveillance is essential, especially when both renal and cardiac function show signs of impairment.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

We did not follow any specific guidelines since no experimentation on human subjects took place.

CONSENT FOR PUBLICATION

Patient study consent was waived because the patient was not enrolled in a study (no clinical study was ongoing). However, per each exam, the patient signed consent for good clinical practice.

STANDARD FOR REPORTING

CARE guidelines and their methodologies were followed

AVAILABILITY OF DATA AND MATERIALS

Since this is a case report, a specific database does not exist. The main material concerning the case is reported in the manuscript.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGMENTS

The authors would like to thank Mary V. Pragnell for her invaluable support in revising the linguistics of the manuscript.

REFERENCES

[1] Roger, V.L. Epidemiology of heart failure. *Circ. Res.,* **2013**, *113*(6), 646-659. http://dx.doi.org/10.1161/CIRCRESAHA.113.300268 PMID: 23989710

[2] Verdoodt, A.; Honore, P.M.; Jacobs, R.; De Waele, E.; Van Gorp, V.; De Regt, J.; Spapen, H.D. Do statins induce or protect from acute kidney injury and chronic kidney disease: An update review in 2018. *J. Transl. Int. Med.,* **2018**, *6*(1), 21-25. http://dx.doi.org/10.2478/jtim-2018-0005 PMID: 29607300

[3] Perazella, M.A. Renal vulnerability to drug toxicity. *Clin. J. Am. Soc. Nephrol.,* **2009**, *4*(7), 1275-1283. http://dx.doi.org/10.2215/CJN.02050309 PMID: 19520747

[4] Perazella, M.A. Toxic nephropathies: Core curriculum 2010. *Am. J. Kidney Dis.,* **2010**, *55*(2), 399-409. http://dx.doi.org/10.1053/j.ajkd.2009.10.046 PMID: 20042257

[5] Pazhayattil, G.S.; Shirali, A.C. Drug-induced impairment of renal function. *Int. J. Nephrol. Renovasc. Dis.,* **2014**, *7*, 457-468. PMID: 25540591

[6] Rangaswami, J.; Bhalla, V.; Blair, J.E.A.; Chang, T.I.; Costa, S.; Lentine, K.L.; Lerma, E.V.; Mezue, K.; Molitch, M.; Mullens, W.; Ronco, C.; Tang, W.H.W.; McCullough, P.A. Cardiorenal syndrome: Classification, pathophysiology, diagnosis, and treatment strategies: A scientific statement from the american heart association. *Circulation,* **2019**, *139*(16), e840-e878. http://dx.doi.org/10.1161/CIR.0000000000000664 PMID: 30852913

[7] Rennke, H.G.; Bradley, M.D. *Renal Pathophysiology. The essentials,* 4th ed; Wolters Kluwer- Lippincot Williams & Wilkins: Baltimore, MD, **2014**.

[8] Massera, D.; Kizer, J.R.; Dweck, M.R. Mechanisms of mitral annular calcification. *Trends Cardiovasc. Med.,* **2020**, *30*(5), 289-295. http://dx.doi.org/10.1016/j.tcm.2019.07.011 PMID: 31402089

[9] Kannan, M.; Vijayanand, G. Mitral stenosis and pregnancy: Current concepts in anaesthetic practice. *Indian J. Anaesth.,* **2010**, *54*(5), 439-444. http://dx.doi.org/10.4103/0019-5049.71043 PMID: 21189882

[10] Lødrup, A.B.; Reimer, C.; Bytzer, P. Systematic review: Symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. *Scand. J. Gastroenterol.,* **2013**, *48*(5), 515-522. http://dx.doi.org/10.3109/00365521.2012.746395 PMID: 23311977

[11] Bordia, T.; Mohammed, N.; Thomson, M.; Ali, M. An evaluation of garlic and onion as antithrombotic agents. *Prostaglandins Leukot. Essent. Fatty Acids,* **1996**, *54*(3), 183-186. http://dx.doi.org/10.1016/S0952-3278(96)90014-9 PMID: 8860105

[12] Rahman, M.; Smith, M.C. Chronic renal insufficiency: A diagnostic and therapeutic approach. *Arch. Intern. Med.,* **1998**, *158*(16), 1743-1752. http://dx.doi.org/10.1001/archinte.158.16.1743 PMID: 9738603

[13] Naughton, C.A. Drug-induced nephrotoxicity. *Am. Fam. Physician,* **2008**, *78*(6), 743-750. PMID: 18819242

[14] Caiati, C.; Pollice, P.; Favale, S.; Lepera, M.E. The herbicide glyphosate and its apparently controversial effect on human health: An updated clinical perspective. *Endocr. Metab. Immune Disord. Drug Targets,* **2020**, *20*(4), 489-505. http://dx.doi.org/10.2174/1871530319666191015191614 PMID: 31613732

[15] Snyder, J.W. Mechanisms of toxic cell injury. *Clin. Lab. Med.,* **1990**, *10*(2), 311-321. http://dx.doi.org/10.1016/S0272-2712(18)30571-7 PMID: 2197051

[16] Zanger, U.M.; Schwab, M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol. Ther.,* **2013**, *138*(1), 103-141. http://dx.doi.org/10.1016/j.pharmthera.2012.12.007 PMID: 23333322

[17] Brenner, B.M.; Lazarus, J.M. Chronic renal failure.*Harrison's principles of internal medicine,* 12th ed; Wilson, J.D.; Braunwald, E.; Isselbacker, K.J.; Petersdorf, R.G.; Martin, J.B.; Fauci, A.S.; Eds.; McGraw-Hill, Inc: New York, **1991**, pp. 1151-1157.

[18] Wolfe, S.M. Dangers of rosuvastatin identified before and after FDA approval. *Lancet,* **2004**, *363*(9427), 2189-2190. http://dx.doi.org/10.1016/S0140-6736(04)16513-6 PMID: 15220045

[19] Acharya, T.; Huang, J.; Tringali, S.; Frei, C.R.; Mortensen, E.M.; Mansi, I.A. Statin use and the risk of kidney disease with long-term follow-up (8.4-Year Study). *Am. J. Cardiol.,* **2016**, *117*(4), 647-655. http://dx.doi.org/10.1016/j.amjcard.2015.11.031 PMID: 26742473

[20] Sarma, A.; Cannon, C.P.; de Lemos, J.; Rouleau, J.L.; Lewis, E.F.; Guo, J.; Mega, J.L.; Sabatine, M.S.; O'Donoghue, M.L. The incidence of kidney injury for patients treated with a high-potency *versus* moderate-potency statin regimen after an acute coronary syndrome. *J. Am. Heart Assoc.,* **2014**, *3*(3), e000784. http://dx.doi.org/10.1161/JAHA.114.000784 PMID: 24786143

[21] Baigent, C.; Landray, M.J.; Reith, C.; Emberson, J.; Wheeler, D.C.; Tomson, C.; Wanner, C.; Krane, V.; Cass, A.; Craig, J.; Neal, B.; Jiang, L.; Hooi, L.S.; Levin, A.; Agodoa, L.; Gaziano, M.; Kasiske, B.; Walker, R.; Massy, Z.A.; Feldt-Rasmussen, B.; Krairittichai, U.; Ophascharoensuk, V.; Fellström, B.; Holdaas, H.; Tesar, V.; Wiecek, A.; Grobbee, D.; de Zeeuw, D.; Grönhagen-Riska, C.; Dasgupta, T.; Lewis, D.; Herrington, W.; Mafham, M.; Majoni, W.; Wallendszus, K.; Grimm, R.; Pedersen, T.; Tobert, J.; Armitage, J.; Baxter, A.; Bray, C.; Chen, Y.; Chen, Z.; Hill, M.; Knott, C.; Parish, S.; Simpson, D.; Sleight, P.; Young, A.; Collins, R. SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): A randomised placebo-controlled trial. *Lancet,* **2011**, *377*(9784), 2181-2192. http://dx.doi.org/10.1016/S0140-6736(11)60739-3 PMID: 21663949

[22] Tonelli, M.; Lloyd, A.M.; Bello, A.K.; James, M.T.; Klarenbach, S.W.; McAlister, F.A.; Manns, B.J.; Tsuyuki, R.T.; Hemmelgarn, B.R. Alberta Kidney Disease Network. Statin use and the risk of acute kidney injury in older adults. *BMC Nephrol.,* **2019**, *20*(1), 103. http://dx.doi.org/10.1186/s12882-019-1280-7 PMID: 30909872

[23] van Zyl-Smit, R.; Firth, J.C.; Duffield, M.; Marais, A.D. Renal tubular toxicity of HMG-CoA reductase inhibitors. *Nephrol. Dial. Transplant.,* **2004**, *19*(12), 3176-3179. http://dx.doi.org/10.1093/ndt/gfh474 PMID: 15575008

[24] Annigeri, R.A.; Mani, R.M. Acute interstitial nephritis due to statin and its class effect. *Indian J. Nephrol.,* **2015**, *25*(1), 54-56. http://dx.doi.org/10.4103/0971-4065.136883 PMID: 25684874

[25] Segal, R.; Lubart, E.; Leibovitz, A.; Berkovitch, M.; Habot, B.; Yaron, M.; Caspi, D. Early and late effects of low-dose aspirin on renal function in elderly patients. *Am. J. Med.,* **2003**, *115*(6), 462-466. http://dx.doi.org/10.1016/S0002-9343(03)00436-4 PMID: 14563503

[26] Meek, I.L.; Van de Laar, M.A.F.J.; E Vonkeman, H. Non-steroidal anti-inflammatory drugs: An overview of cardiovascular risks. *Pharmaceuticals (Basel),* **2010**, *3*(7), 2146-2162. http://dx.doi.org/10.3390/ph3072146 PMID: 27713346

[27] Hörl, W.H. Nonsteroidal anti-inflammatory drugs and the kidney. *Pharmaceuticals (Basel),* **2010**, *3*(7), 2291-2321. http://dx.doi.org/10.3390/ph3072291 PMID: 27713354

[28] Schoenfeld, A.J.; Grady, D. Adverse effects associated with proton pump inhibitors. *JAMA Intern. Med.,* **2016**, *176*(2), 172-174. http://dx.doi.org/10.1001/jamainternmed.2015.7927 PMID: 26751904

[29] Fossmark, R.; Martinsen, T.C.; Waldum, H.L. Adverse effects of proton pump inhibitors-evidence and plausibility. *Int. J. Mol. Sci.,* **2019**, *20*(20), E5203. http://dx.doi.org/10.3390/ijms20205203 PMID: 31640115

[30] Moledina, D.G.; Perazella, M.A. PPIs and kidney disease: From AIN to CKD. *J. Nephrol.,* **2016**, *29*(5), 611-616. http://dx.doi.org/10.1007/s40620-016-0309-2 PMID: 27072818

[31] Al-Aly, Z.; Maddukuri, G.; Xie, Y. Proton pump inhibitors and the kidney: Implications of current evidence for clinical practice and when and how to deprescribe. *Am. J. Kidney Dis.,* **2020**, *75*(4), 497-507. http://dx.doi.org/10.1053/j.ajkd.2019.07.012 PMID: 31606235

[32] Griffin, K.A.; Bidani, A.K. Potential risks of calcium channel blockers in chronic kidney disease. *Curr. Cardiol. Rep.,* **2008**, *10*(6), 448-455. http://dx.doi.org/10.1007/s11886-008-0071-8 PMID: 18950553

[33] Sontrop, J.M.; Dixon, S.N.; Garg, A.X.; Buendia-Jimenez, I.; Dohein, O.; Huang, S.H.S.; Clark, W.F. Association between water intake, chronic kidney disease, and cardiovascular disease: A cross-sectional analysis of NHANES data. *Am. J. Nephrol.,* **2013**, *37*(5), 434-442. http://dx.doi.org/10.1159/000350377 PMID: 23594828

[34] Yoran, C.; Yellin, E.L.; Becker, R.M.; Gabbay, S.; Frater, R.W.; Sonnenblick, E.H. Dynamic aspects of acute mitral regurgitation: Effects of ventricular volume, pressure and contractility on the effective regurgitant orifice area. *Circulation,* **1979**, *60*(1), 170-176. http://dx.doi.org/10.1161/01.CIR.60.1.170 PMID: 445720

[35] Grose, R.; Strain, J.; Cohen, M.V. Pulmonary arterial V waves in mitral regurgitation: Clinical and experimental observations. *Circulation,* **1984**, *69*(2), 214-222. http://dx.doi.org/10.1161/01.CIR.69.2.214 PMID: 6690094

[36] Jawad, I.A.; Ghali, M.H.; Brown, R.L.; Sohn, Y.H. Pressure-flow relations across the normal mitral valve. *Am. J. Cardiol.,* **1987**, *59*(8), 915-918. http://dx.doi.org/10.1016/0002-9149(87)91119-2 PMID: 2950751

[37] Wathen, R.L.; Selkurt, E.E. Intrarenal regulatory factors of salt excretion during renal venous pressure elevation. *Am. J. Physiol.,* **1969**, *216*(6), 1517-1524. http://dx.doi.org/10.1152/ajplegacy.1969.216.6.1517 PMID: 5786741

[38] Mullens, W.; Abrahams, Z.; Francis, G.S.; Sokos, G.; Taylor, D.O.; Starling, R.C.; Young, J.B.; Tang, W.H.W. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J. Am. Coll. Cardiol.,* **2009**, *53*(7), 589-596. http://dx.doi.org/10.1016/j.jacc.2008.05.068 PMID: 19215833