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Case Report

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Arterial hypertension in a kidney transplanted patient

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Abstract

Hypertension occurs in up to 80% of renal transplant recipients. Blood pressure values are higher in the first period after transplantation, possibly as a result of immunosuppressive treatment initiation. Even though long-term blood pressure should be easily controlled when patients achieve a good glomerular filtration rate, in most this is not the case. They associate multiple comorbidities and need many medications, and thus their therapeutic management requires careful consideration of drug interactions, medication excretion pathway and drug side effects. We present the case of a 49 years old woman with kidney transplant for autosomal dominant polycystic kidney disease, with chronic allograft rejection, stage 5 KDIGO renal failure upon admission, who associates acutely decompensated chronic heart failure and hard to control blood pressure values during hospitalization, as a result of comorbidities and drug interactions.

Keywords: kidney transplant, chronic kidney disease, immunosuppressive therapy, hypertension in renal patients

A 49 years old woman presented to the emergency room with moderate effort dyspnea, fatigue, bilateral lower limb and abdominal wall pitting edema. Her symptoms occurred two weeks before presentation and became progressively aggravated during the previous three days.

Her medical history is relevant for autosomal dominant polycystic kidney disease (ADPKD) diagnosed over 25 years before, complicated with progressive renal failure, and a decline in estimated glomerular filtration rate (eGFR, CKD-EPI) from 59 ml/min/1.73 m^2 in 2005 to 8 ml/min/1.73 m^2 in 2015. Three years before current presentation the patient started hemodialysis on a brahiocephalic fistula and after four months she received a renal transplant. One year later the left native kidney was removed due to compression on the donated kidney.

Immunosuppressive therapy was initiated with prednisone, tacrolimus and mycophenolate mofetil, a regime under which the patient developed plantar Kaposi sarcoma, which required interruption of tacrolimus and replacement with sirolimus and local radiotherapy – to which it was responsive. However,

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Table 1. Blood tests upon admission.

Parameters	Results	Normal range	Units
Hematology			
Erythrocytes	3.46x10^6	3.8-5.3 x10^6	µL
Hemoglobine	9.9	11.7-16.0	g/dL
Hematocrit	32.80	35-47	%
MCV (Mean corpuscular volume)	96.1	82-96	fL
MCH (Mean corpuscular hemoglobin)	28.3	27-32	Pg
MCHC (Mean corpuscular hemoglobin concentration)	29.2	31-36	g/dL
Leukocytes	5.89x10^3	4-9 x10^3	µL-1
Neutrophil	65.60	56-68	%
Lymphocytes	20.70	20-40	%
Monocytes	12.4	4-8	%
Eosinophils	0.8	1-3	%
Basophils	0.5	0-1	%
Platelets	158x10^3	150-350 x10^3	µL
APTT (Activated partial thromboplastin time)	27.3	24-36.5	S
Fibrinogen	272	150-350	mg/dL
PT (Prothrombintime)(s)	10.4	11-14.5	S
INR (International normalized ratio)	0.86	0.81-1.16	
Lipids			
Cholesterol	250	140-200	mg/dL
Triglycerides	151	30-150	mg/dL
Gastrointestinal function			
ALT (Alanine aminotransferase)	45	9.0-52.0	U/L
AST (Aspartat eaminotransferase)	34	14.0-50.0	U/L
Total proteins	4.4	6.30-8.20	g/dL
Albumins	2.77-3.0	3.50-5.0	g/dL
Total bilirubin	0.44	0.20-1.30	mg/dL
Cardiac enzymes			
CK (Creatine kinase)	62	30-135	U/L
CK-MB (Creatine kinase MB)	14	05-25	U/L
Highsensitive Troponin	47.94	<14	pg/dL
Troponin I	0.09	< 0.1	ng/mL

Table 1. continued.

Parameters	Results	Normal range	Units
Reno-urinary function			
eGFR CKD-EPI	15-13.59	90-120	ml/min/1.73m2
Creatinine	3.42-3.71	0.6-1.2	mg/dL
Urea	126-140	15-37	mg/dL
Uric acid	7.9	2.0-7.0	mg/dL
Urinary creatinine	42.4	90-300	mg/dL
Urinary potasium	16.4	20-80	mmol/L
Urinary sodium	98	54-150	mmol/L
Urinary ureea	867	847-2967	mg/dL
Proteinuria	5.4	<0.15	g/24h
Electrolytes			
Potassium	4.19-5.4	3.5-5.0	mmol/L
Sodium	142	137-145	mmol/L
Glucose	87 -102	65-105	mg/dL
Miscellaneous			
LDH (Lactate dehydrogenase)	568	313-618	U/L
CRP (C-reactive protein)	3	<5	mg/dL
VSH	5	< 10	mm/h

under sirolimus, the patient developed nephrotic range proteinuria (~ 5.8 g/24 hours), which required interruption of sirolimus, with progressive improvement of proteinuria (5 months later the proteinuria was ~ 1.5g/24 hours). Over the 2 years previous to the current presentation, immunosuppressive therapy included mycophenolate mofetil 360 mg bid and Prednisone 5 mg od.

At the time of presentation in our clinic the patient also had documented moderate mitral regurgitation and probable pulmonary hypertension (PAPs 45 mmHg), normal left ventricle ejection fraction (LVEF) at 55%, and no wall motion abnormalities. She was on metoprolol succinate 100 mg od and rilmenidine 1 mg bid.

Upon current presentation the patient was afebrile, conscious, with skin pallor and a functional right brahiocephalic arteriovenous fistula (allowing dialysis whenever necessary). Her vital parameters were unremarkable – O_2 saturation in room air 96%, blood pressure (BP) 165/90 mmHg, heart rate 80 bpm, diuresis was present at 1000 ml/24h hours. Clinical examination revealed fine basal bilateral crackles on pulmonary auscultation, along with other clinical signs of stasis – slight jugular vein distension and bilateral lower limb and abdominal wall edema. Her abdomen was increased due to enlarged size of liver and native right kidney. There were no other pathologic signs on examination.

Blood tests revealed nitrogen retention with a serum creatinine level of 3.42 mg/dl corresponding to an eGFR of 15 ml/min/1.73 m^2 – a slight decrease from the last recorded eGFR of 20 ml/min/1.73m^2

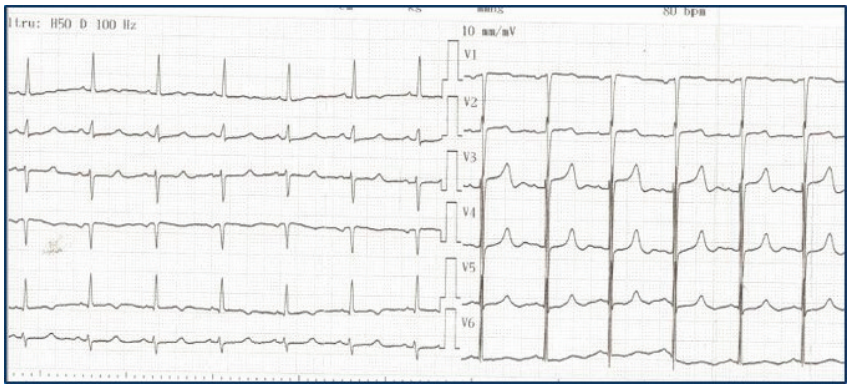

Figure 1. ECG upon admission: Sinus rhythm, 80 beats/minute, left ventricular hypertrophy with minimal secondary repolarization abnormalities.

eight months prior. The serum urea level was 126 mg/dl with no accompanying clinical signs of uremia. Serum protein and albumin level were 4.4 g/dl and, respectively, 3 g/dl. She had high serum lipids – total cholesterol 250 mg/dl and triglyceride 153 mg/dl. Nephrotic range proteinuria was documented at 5.4 g/24 hours. Whole blood count showed mild normocytic normochromic anemia (hemoglobin 10 g/dl, hematocrit 32.8 %). Her NTproBNP level was 43000 pg/ml (Table 1).

There were no significant changes on the electrocardiogram, apart from those found on previous recordings – left ventricle hypertrophy with discrete nonspecific repolarization changes (Figure 1). Echocardiography showed concentric left ventricular hypertrophy, with mid-range systolic function (LVEF 45%) and diastolic dysfunction (E/E'=20.5), a dilated left atrium (indexed volume 54 ml/m2), moderate-severe mitral regurgitation, probable severe pulmonary hypertension (PAPs 95 mmHg) and mild interventricular septum hypokinesis.

The chest X-ray revealed cardiomegaly and pulmonary congestion.

The abdominal ultrasound showed multiple well defined transonic thin walled liver cysts, with severe alteration of kidneys architecture, fully occupied by cysts sized over 20 mm (Figure 2).

Corroborating the available data, the intricate case was interpreted as an acute decompensation of chronic heart failure with preserved ejection fraction in the setting of chronic kidney disease progression, probably as a result of the recent-onset nephrotic syndrome.

The patient was admitted and initiated on high dose diuretics (furosemide 80 mg/day continuous perfusion) which led to progressive improvement of congestion (remission of dyspnea and edema). During hospital stay, considering the procoagulant effect of the nephrotic syndrome, she also received prophylaxis of thromboembolic events with low molecular weight heparin. Stress ulcer prevention was employed using an antihistaminic agent – ranitidine, as proton pomp inhibitors interact with immunosuppressive therapy (mycophenolate mofetil). She was also left on her previous oral medication with metoprolol succinate 100 mg od and rilmenidine 1 mg bid.

Blood pressure values were high, with predominantly high systolic values. The 24 hours automatic monitoring revealed a non-dipper profile, with a mean

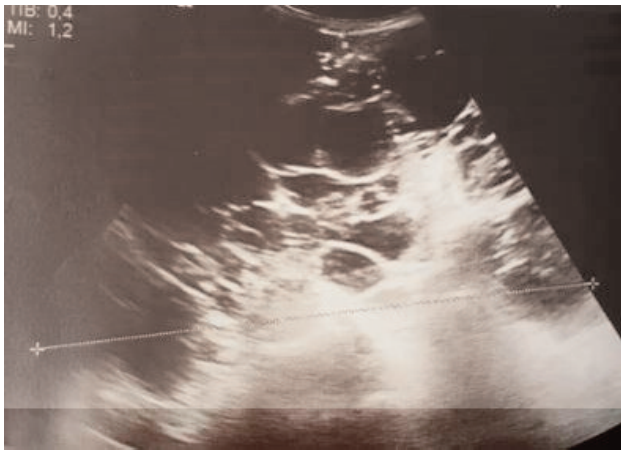

Figure 2. Abdominal ultrasound: Enlarged right native kidney (size>20 cm) with well-defined anechoic lesions which have thin walls, suggestive for polycystic kidney.

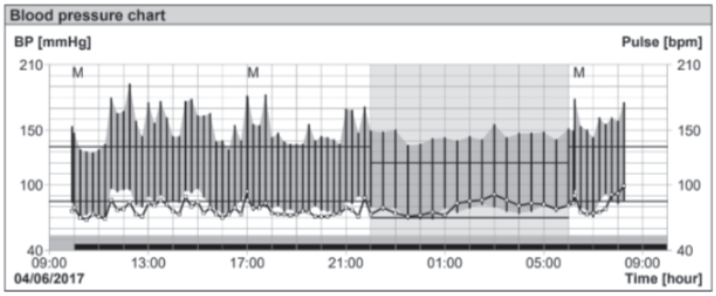

Figure 3. Automatic BP monitoring: High blood pressure, high day time systolic values

BP/24h of 150/80 mmHg, mean diurnal BP 154/82 mmHg, mean nocturnal BP 144/76 mmHg, a morning surge of 14 mmHg. Throughout the monitoring, multiple high readings were recorded, with a maximum BP of 192/129 mmHg (Figure 3). Control was hardly achieved with the addition of a calcium channel blocker (lercanidipine) and an alpha adrenergic antagonist (doxazosin), progressively increasing dosage (lercanidipine 10 mg bid, doxazosin 4 mg od) to finally reach BP values at the upper limit of normal.

On the third day of hospital stay, the patient described epigastric pain with a duration of 30 minutes. The electrocardiogram revealed new ST depression and negative T waves in the lateral derivations (Figure 4). The troponin I was negative, but troponin T was positive, difficult to interpret in the setting of renal failure and recently decompensated heart failure. There were no new motion abnormalities on echocardiography. Considering the high risk for renal patients to develop acute coronary syndromes, and a lack of consensus on diagnostic value of cardiac biomarkers in this patient population we chose a conservative management and thus administered clopidogrel 75 mg/day, atorvastatin 20 mg/day and 40 mg isosorbide mononitrate on top of previous medication. The patient was at very high risk for contrast-induced nephropathy requiring dialysis and thus coronary angiography was postponed. Chest pain did not recur. Electrocardiographic changes did not indicate the progression of ischemia (figure 5).

Clinically stable, with no dyspnea or chest pain, after the remission of congestion, the patient was referred to a nephrology unit. At this time proteinuria was persistent, but at lower levels compared to admission (3.4 g/24 h on discharge).

Discussion

Elevated BP and pulse pressure carry poor prognosis in transplanted patien.ts. High BP can decrease allograft survival and is also a risk factor for heart failure and death [1]. Receiving an allograft from a deceased donor, especially from a donor with a family history of hypertension, is a risk factor for developing hyperten-

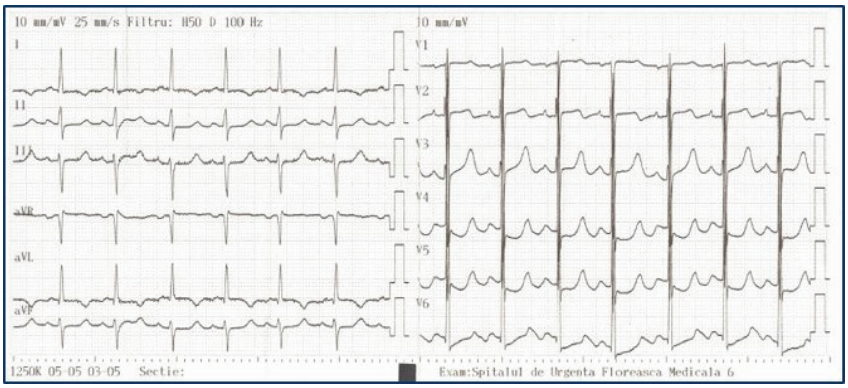

Figure 4 Electrocardiogram during chest pain: Sinus rhythm, 100 beats/minute, horizontal ST depression ~ 2 mm in V4-V6, negative symmetric T waves in D1 and aVL.

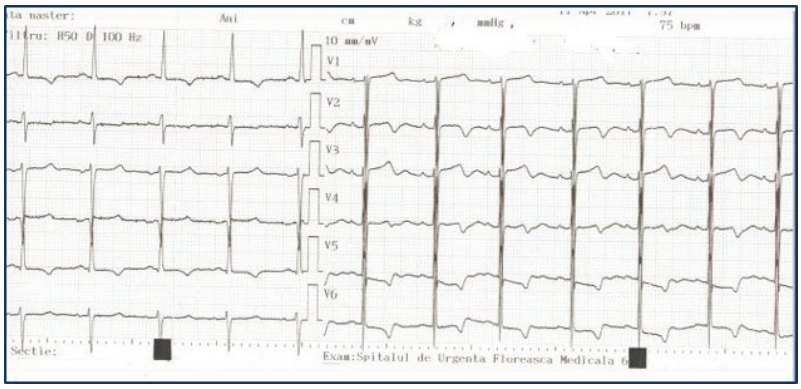

Figure 5 Electrocardiogram after remission of chest pain: Sinus Rhythm, 75 beats/minute, mild remission of ST depression, biphasic T waves V2-V6, persistent T wave inversion in D1 and aVL

sion. Transplantation of a kidney from a normotensive donor with a negative family history of hypertension is associated with longer normotensive periods in the recipients [2]. The mechanisms by which genetic factors influence renal function and predispose to the occurrence of hypertension are not well known.

After transplantation, hypertension is initially a result of volume overload, graft dysfunction or ischemia. But another important component in its development is the immunosuppressive treatment. Glucocorticoids do increase volume overload, but are not usually a major risk factor for chronic hypertension considering the rapid dose reduction. Calcineurin inhibitors, the corner stone of immunosuppressive therapy, lead to hypertension in almost all patients. They cause endothelial dysfunction, increase vascular tone and sodium retention via the renin-angiotensin-aldosterone system [1]. The impact of calcineurin inhibitors on blood pressure is milder than that of cyclosporine, which was used on a large scale before the appearance of calcineurin inhibitors. Cyclosporine acts by increasing both systemic and renal vascular resistance by releasing vasoconstrictors (endothelin). It is yet useful in the treatment of some patients with kidney transplantation [3].

Considering all these, hypertension is very frequent in transplanted patients. In one study, only 5% of kidney transplanted patients had BP below 130/80 mmHg [4].

In renal transplant recipients the goal BP is influenced by the presence or absence of proteinuria. According to recommendations from the Canadian Society of Nephrology, the goal BP in recipients who do not have proteinuria is below 140/90 mmHg. The Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes guidelines recommend BP target values below 130/80 mmHg. For patients with a spot urine total protein to creatinine ratio over 500-1000 mg/g, BP should be targeted at 130/80 mmHg. The European Best Practice Guidelines for renal transplantation recommend a BP less than 125/75 mmHg in patients with proteinuria [5,6]. The ESC/ESH guidelines on the diagnosis and management of hypertension have recommended in their most recent issue a target BP for general hypertensive patients below 140/90 mmHg, mentioning that if the treatment is well tolerated the BP should be lowered under 130/80 mmHg or more in most patients (Class I, Level of evidence A). In patients with chronic kidney disease, however, target systolic BP is recommended at 130-139 mmHg (Class I, Level of evidence A) [7].

In order to improve life expectancy, it is of utmost importance to properly treat hypertension. Several pharmacological key elements should be considered when administering antihypertensive drugs – a good level of cautiousness with medications eliminated through renal excretion, and attention to possible drug interactions with immunosuppressive therapy. There are some classes of medication that can be freely prescribed. Many physicians prefer a calcium channel blocker (CCBs) because it minimizes cyclosporine-induced renal vasoconstriction and is useful even in combination with other classes of immunosuppressive drugs, although the mechanism is not clearly understood. A systematic review of 29 studies with 2262 transplanted patients evaluated the administration of

CCBs versus placebo or no treatment. In 25 of these studies the CCBs were administered irrespective of BP values, from the first month after transplantation, in the other 4 studies the CCBs were administered in hypertensive recipients after the first month. There was no effect of CCBs on the risk of death at 12 months, but they had benefit effects on reducing the risk of graft loss at 12-month follow-up. Patients treated with CCBs had higher estimated or measured GFR [8]. The same review included 7 studies with 405 patients in which the administration of angiotensin-converting enzyme inhibitors (ACEi) versus CCBs were compared. Angiotensin-converting enzyme inhibitors were associated with a decrease in eGFR and an increase in the incidence of hyperkalemia.

Non-dihydropyridine CCBs, such as diltiazem and verapamil, are cytochrome CYP3A/4 inhibitors and lead to elevation of immunosuppressive drug levels (cyclosporine, tacrolimus, sirolimus and everolimus), and therefore to increased exposure and risk of adverse events. This usually takes place 48 to 72 hours after the initiation and cessation of CCB. Some clinicians preferentially use these agents to decrease the dosing requirement of immunosuppressive [9].

Dihydropyridine CCB, such as amlodpine and nifedipine, have a lower impact on cytochrome CYP3A/4 metabolism, therefore are preferred in such clinical scenarios [9]. Calcium channel blockers may have antiproteinuric effects, as in the case of verapamil and diltiazem, but not amlodipine. Unlike other dihydropyridine CCB, which determine dilatation of only the afferent artery, lercanidipine dilates both the afferent and the efferent glomerular arteries, therefore avoiding the increase of intraglomerular capillary pressure [10]. The REnal Disease: LErcanidipine Valuable Effect on urinary albumin Loses trial compared the effects of lercanidipine compound with enalapril versus the amlodipine plus enalapril combination. The results show a decrease in albuminuria values only in the lercanidipine group, but not in the amlodipine-treated patients [11].

In patients with chronic kidney disease and especially in the presence of congestion, diuretic agents are usually required to maintain volume balance. With the decrease in eGFR, loop diuretics become the only functional options. Torasemide is more potent and has a longer bioavailability than furosemide, becoming a better option especially in those who develop pseudo-resistance to diuretic therapy [5]. In transplanted patients, the use of ß-blockers may be associated with improved patient survival after major adverse cardiac events [12]. In this subtype of patients, major events were not predicted by any clinical or pharmacological variables, including age, gender, hypertension, diabetes mellitus, prior myocardial infarction, smoking, duration of dialysis or medical therapy. Major events, irrespective of type, were independently associated with higher mortality risk over a period up to 15 years, and this seemed to be blunted by ß-blocker therapy [12].

Another class of potent and highly used BP lowering therapy, especially in resistant renal hypertensives are adrenergic central agonists, which have minimal interaction with immunosuppressive treatment. The alpha blockers are eliminated predominantly trough bile, therefore can be used in patients with low eGFR [1].

If target BP cannot be achieved with the drug classes mentioned above, ACEi or angiotensin II receptors blockers (ARBs) can be added. Their role in transplanted patients is incompletely defined. Angiotensin converting enzyme inhibitors can induce anemia in transplanted recipients [13]. A recent study demonstrates that ACEi lower the hemoglobin only in renal transplanted recipients with initially higher levels [14]. They also can rise serum potassium levels, but are well known to decrease proteinuria [8]. In the first three months after renal transplantation ACEi/ARB are contraindicated because of their risk of rising serum creatinine levels, which may lead to difficult interpretation (possibly overlooking an acute allograft rejection) [15].

Hypertension is not always controlled by medical therapy. Occasionally high BP is a sign of post-transplant renal artery stenosis. This lesion usually becomes evident between three months to two years after transplant and occurs in almost 12% of hypertensive renal transplant recipients. There are several risk factors for its occurrence: difficulties in organ harvesting and operative technique, delayed allograft function, cytomegalovirus infection and atherosclerotic disease. A rise in serum creatinine levels after the initiation of ACEi/ARB may be a good indicator, but is not helpful in the actual diagnosis of renal artery stenosis in the donated kidney. The treatment of hypertension in these cases required angioplasty or surgery [16]. Percutaneous balloon angioplasty is useful in 80% of cases [17].

In patients with polycystic kidney disease nephrectomy of the native organ is associated with a decrease of BP values. In the research done by Shumate AM et al. BP control was studied in 118 transplanted patients with ADPKD. In one group the transplantation was done maintaining the native organ in place, while in the other concurrent or delayed nephrectomy of native organ was also performed. The number and dosages of antihypertensive drugs was recorded at the time of the transplantation and up to 36 months after. Concurrent ipsilateral native nephrectomy had an important role in decreasing the dosages of antihypertensive medications needed to control hypertension. Delayed contralateral native nephrectomy led to better BP control [18].

Many patients with chronic kidney disease are non-dippers. This is one of the strongest predictors of adverse cardiovascular outcomes and requires shifting the administration of at least one antihypertensive drug during the evening, in the attempt to normalize dipping pattern. In an open-label randomized trial that included 661 patients with eGFR below 60 ml/min/1.73 m^2 or an albumin-to-creatinine ratio over 30 mg/g the benefit of administration of one antihypertensive agent at bedtime was analyzed. The patients were randomly assigned to two groups – receiving all medication in the morning versus receiving one of the drugs in the evening. At baseline, the mean ambulatory BP was similar in both groups. After a mean follow-up period of 5.4 years those having taken one medication in the evening had a lower rate of major vascular events (myocardial infarction, stroke, or cardiovascular death, 2.7% versus 7.8%, p <0.001) [19].

Conclusions

Hypertension is present in almost all transplanted patients. It is a risk factor for cardiovascular disease and for decreasing allograft survival. It is important to treat high BP quickly and to achieve target BP values according to type of recipient – below 140/90 mmHg in non-proteinuric patients, below 140/80 mmHg in proteinuric patients. Both CCBs and diuretics are preferred in transplanted patients. Beta blockers and alpha-1 blockers can also be used. In the first 3 months after transplantation ACEi/ARB are contraindicated. In patients with chronic kidney disease it is recommended to administer at least one antihypertensive drug at bedtime, in order to normalize dipping pattern and improve cardiovascular outcomes. High BP values are sometimes a strong indicator of renal arterial stenosis but further investigations are required. Transplanted patients frequently associate multiple comorbidities and they are under immunosuppressive therapy, therefore they need special attention to drug interactions and side effects.

Conflict of interests

The authors have no conflicts of interests to declare.

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