Italian Journal of Medicine

Malignant hypertension and hyperreninemia: primary or secondary hypertension? A case report

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Key words: Malignant hypertension; hyperreninemia; multi-organ damage; primary and secondary hypertension.

Acknowledgments: the authors would like to thank Mrs. Ann Pilkington, for her support in reviewing the English text.

Contributions: all authors followed the patient during hospitalization. AB followed up on the patient during hospitalization and day service; the author made substantial contributions to the interpretation of clinical data and wrote the scientific work. SP followed up the patient during day service and collected the patient's data. VO and PP reviewed the work. MC and AC worked out the tables and the figure. MC revised the use of English.

Conflict of interests: the authors declare no potential conflict of interests.

Patient consent: the authors certify that they have obtained patient consent form. In the form the patient has given her consent for clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity.

Abstract

Malignant hypertension is a rare condition characterized by severe hypertension and multi-organ ischemic damage. Marked activation of renin-angiotensin system is observed in many patients, but its persistence over time is not known. We report a case of 42-year-old woman presented with severe hypertension and multi-organ damage. Initial evaluation showed elevated value of direct renin concentration with normal plasma aldosterone concentration, and a nodular lesion in the left adrenal gland. The differential diagnosis between primary and secondary form of hypertension had to be questioned. Consequently the patient was followed up for 20 months. Repeated checks showed a significant increase in renin levels with a normal aldosterone concentration and regression of organ damage. After 20 months renin values returned within normal limits. Hyperreninemia persisting over a long period of time has not been fully explained. Long term follow-up allowed us to attribute malignant hypertension to de novo essential hypertension.

Introduction

Malignant hypertension is a rare and severe form of hypertension characterized by a rapid and significant increase in blood pressure and multi-organ ischemic damage with a poor prognosis. The most recent definition emphasizes multi-organ damage with particular reference to retinopathy, acute renal failure, encephalopathy and thrombotic microangiopathy.[1,2] The renin-angiotensin system is believed to play a crucial role in the pathogenesis of organ damage. However, the extent of renin-angiotensin activation and its persistence over time is not known.

We report a case of malignant hypertension associated with multi-organ damage and onset of hypertensive encephalopathy, in which a pronounced elevation in plasma renin levels was observed over a long term follow up.

Case Report

A woman of 42-year-old with no prior history of hypertension was admitted to the emergency department of our hospital with headache, nausea, neck pain and disorders of the visus. She was affected from multiple sclerosis treated with interferon beta 1a. On admission, her blood pressure was 220/150 mmHg, pulse 110 beats per minute and temperature was 36.5°C. Suddenly the patient had a generalized tonic-clonic seizure with loss of consciousness. The blood pressure increased to 260/150 mmHg. The patient was immediately transferred to Intensive Care Unit and submitted to oro-tracheal intubation and mechanical ventilation. The hypertensive emergency was managed with nitroglycerin infusion and urapidil bolus ev. Brain computed tomography (CT) and then magnetic resonance imaging (MRI) were performed on the same day. CT showed a widespread area of edema affecting the cerebellar hemispheres, the trunk and the posterior parieto-occipital regions bilaterally. MRI revealed extensive hyperintensity in the same regions and affecting mostly the occipital and parietal lobes on T2-weighted. These findings were suggestive of posterior reversible encephalopathy syndrome (PRES).[3] In the first days of hospitalization, the patient's blood tests showed a rapid change as shown in Table 1. On admission to the emergency room, the biochemical parameters were within normal limits. On the second and third day an increased level of creatinine, mild hypokaliemia, anemia and thrombocytopenia were observed. Anemia associated with presence of schistocytes on peripheral smear and an increased LDH suggested ongoing hemolysis. Fibrin degradation products and CRP were also elevated. Renal failure was associated with a proteinuria of 1404 mg over 24 h and related hypoalbuminemia. After 3 days the patient was transferred to our internal medicine department. On admission she was alert, conscious, apiretic with a pressure of 150/110 mmHg, heart rate of 105 beats per minute and respiratory rate of 18 acts per minute. Echocardiography showed left ventricular hypertrophy and reduced left ventricular ejection fraction (EF 48%). On fundal examination there were retinal hemorrhages and exudates (grade IV hypertensive retinopathy).

These findings were to be refer to malignant hypertension associated with multi-organ damage.

Adequate blood pressure control was achieved using different antihypertensive drugs, such as calcium channel blocker, diuretic, beta-blocker and angiotensin II receptor antagonist. Interferon-beta was stopped. Given the severity of clinical manifestations, several diagnostic tests were performed to rule out secondary causes of hypertension. Laboratory tests showed a normal plasma aldosterone concentration (PAC) and elevated value of direct renin concentration (DRC) as shown in Table 2. 24-h urinary excretion of catecholamines and total metanephrines were within the normal range.

Hyperreninemia could be due to the presence of a renovascular disease, a renin-secreting tumor, chronic parenchymal renal disease or a scleroderma renal crisis. The latter hypothesis was excluded by the absence of circulating autoantibodies. Ultrasonography revealed normal symmetrical kidneys. There was no evidence of renal artery stenosis on Doppler ultrasound. The abdominal and pelvic CT scan showed a hypodense nodular lesion in the left adrenal gland, suggestive of adenoma. The finding was confirmed by MRI. Adrenal adenoma was considered an incidentaloma not being compatible with hyperreninemia. Alternatively the adrenal adenoma could be preferable to a rare form of primary hyperaldosteronism in which the plasma renin activity is initially elevated and subsequently suppressed.[4,5] On the other hand, an extrarenal renin-producing tumor is extremely rare.[6]

During hospitalization progressive reduction in blood pressure values was obtained up to normal level. The second brain MRI showed complete resolution of vasogenic edema in the brain and medulla. Laboratory tests were within normal limits at the time of hospital discharge, although proteinuria persisted. The patient was discharged on the twelfth day in good clinical condition and with indication to continue the follow-up at our arterial hypertension clinic. Antihypertensive therapy prescribed at discharge included carvedilol 12.5 mg twice a day, amlodipine 10 mg/day and olmesartan hydrochlorothiazide 20/12.5 mg/day.

The follow-up of the patient lasted 20 months. Every 4 months blood, urine and instrumental tests were performed. Laboratory tests showed a significant increase in DRC, up to 3834.0 mU/L, with

normal values of blood pressure. After 20 months from the acute event, renin levels returned within normal limits. Table 2 shows the values of DRC and PAC in the follow-up period; the same table records the values relating to the sodium and potassium status for each hormonal sample. Many elements can affect the renin such as posture, time of day the sample is taken, age, sodium intake and various antihypertensive drugs. Before each test, olmesartan hydrochlorothiazide was suspended for two weeks and replaced by doxazosin in order to maintain control of hypertension. As recommended by the guidelines, the blood sample was obtained in the morning, after 60 min sitting rest.[7] During the follow-up period antihypertensive drug therapy was gradually reduced in relation to reduction and normalization of blood pressure values, as shown in Figure 1. Compliance with antihypertensive therapy was complete as the patient believed in the need of medications and as she had a close follow-up.

Eight months after the acute episode, the fundus exam showed stage 2 hypertensive retinopathy while echocardiogram highlighted left ventricular hypertrophy regression with normalized ejection fraction and the 24- hour urine collection showed no proteinuria.

Discussion and Conclusions

Malignant hypertension is the most severe form of hypertension characterized by rapid and significant increase over baseline blood pressure associated with multiple organ damage,[1,2] including bilateral retinal hemorrhages and/or exudates and papilledema, encephalopathy, acute heart failure and acute deterioration in renal function. Sometimes it is associated with microangiopathic hemolytic anemia.[8] Clinical manifestations and presentation can be variables in relation to the system mainly involved for each patient. In the majority of cases, malignant hypertension is due to essential hypertension, particularly when untreated or inadequately treated. However any form of secondary hypertension may progress to malignant hypertension. The secondary causes have been reported in younger patients and include renovascular diseases, renal parenchymal disease, endocrine dysfunction such as pheocromocytoma, primary

hyperaldosteronism, renin-secreting tumor.[2] Differential diagnosis between essential and secondary hypertension is often a challenge especially during the acute phase of the pathology.

The reported case had all clinical features of malignant hypertension. The onset symptoms were expression of brain damage as demonstrated by bilateral, T2-hyperintense MRI lesions, due to vasogenic edema. The lesions resolved completely with blood pressure reduction.[3] In the acute phase of the pathology, the patient presented severe fundus lesions, renal failure including proteinuria, impaired systolic function with left ventricular hypertrophy and intravascular hemolysis with fragmented red blood cells and consumptions of platelets. The characteristics of anemia associated with coagulations alterations, were compatible with microangiopathic hemolytic anemia.[8] In this context, the increase in CRP observed in our patient in the malignant phase might be explained by the simultaneous activation of coagulation and inflammation.[9]

Malignant hypertension is considered a renin-dependent form of hypertension, but the extent and persistence of renin-angiotensin system activation are greatly variable and not fully known. In addition, cases without elevated reninemia have been reported.[8] The activation of the renin-angiotensin system is believed to be due to renovascular ischemia as a result of severe hypertension and of renal arterioles damage.[8,10] Activation of the renin-angiotensin system can trigger a vicious circle, as described by Laragh, causing further vascular damage and further increase in blood pressure.[11]

The finding of hyperreninemia and its persistence over time were the characterizing elements of the clinical case. High renin malignant hypertension could be related to renovascular disease, chronic parenchymal renal disease, scleroderma renal crisis, renin-secreting tumor, blunt trauma to the kidney;[2,12,13] alternately, activation of the renin-angiotensin axis could represent the expression of vascular damage induced by a significant elevation of the blood pressure in the transition from benign to malignant hypertension.[8,10]

Given the seriousness of the case, the differential diagnosis between essential form and curable causes of hypertension was crucial. For this purpose the patient underwent renal duplex ultrasound

exam with no evidence of renal artery stenosis. Abdomen and pelvis CT and MRI showed the presence of a nodular lesion in the left adrenal gland. At the beginning the lesion was interpreted as an incidentaloma, as the values of aldosterone and urinary catecholamines were normal. However, in order to confirm this hypothesis and to exclude rare forms of hyperaldosteronism with increased renin levels in the malignant phase as previously described by other authors,[4,5] were repeated the hormonal dosages in the following months. Repeated laboratory tests at intervals of 4 months showed a significant increase in DRC dissociated from plasma aldosterone values (Table 2) and from pressure values (Figure 1). The value of DRC was normal at the 20th month.

Several antihypertensive drugs can give rise to hyperreninemia, including diuretics, ACE-inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine calcium channel blockers and aldosterone antagonists.[14] The patient was on ARBs therapy which, associated with the other drugs, was effective in lowering blood pressure. It is not known whether the ARBs long-term effects may have contributed to the persistence of such elevated renin levels, as observed in our patient.

In the months preceding the last dosage of DRC, the ongoing antihypertensive therapy was stopped and alpha methyldopa was started, at the request of the patient who wanted to face a pregnancy and avoid potentially harmful drugs. Alfa methyldopa is known to decrease renin level,[15,16] but we don't believe this could explain the sudden changes in renin level observed in our patient. The DRC was not measured in balance on sodium diet, but the value of sodiemia and sodiuria were always within the limits of the norm (Table 2). As shown by the values included in the table, the renin levels are independent of sodium and potassium status.

The lack of DRC suppression over a long period of time in the post-malignant phase has not been fully explained. In addition, in our patient we observed organ damage recovery in the first months of follow-up . Several authors have shown a correlation between renal microvascular damage and renin hypersecretion in patients with malignant hypertension.[8,17,18] Our patient did not undergo kidney biopsy due to the rapid improvement in renal function, therefore it was not possible to correlate renin levels with renal microvascular injury.

On the basis of clinical and laboratory findings and after long-term follow-up, we conclude that our patient had de novo primary hypertension complicated by a malignant phase. The long follow-up was in order to insure that the DRC and PAC discrepancy in the post-malignant phase was not due to secondary forms of hypertension. In any case, clinical and laboratory monitoring of the patient is persisted.

In conclusion, this case highlights the role of renin-angiotensin system activation as key factor to malignant hypertension pathogenesis and the difficulty in differentiating between primary and secondary hypertension in the malignant phase. Furthermore, this case stresses the role of adequate follow-up of all patients in the post-critical phase, in order to exclude secondary form of hypertension, evaluate the regression of organ damage and monitor renin and aldosterone levels.

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Table 1. Laboratory data of our patient during hospitalization.

	Day 1	Day 3	Day 12
Hb (g/dL)	13.6	8.3	10.4
Schistocytes	No	Yes	No
Platelets (x10^3/uL)	76	69	320
Creatinine (mg/dL)	0.73	1.32	0.75
eGFR (mL/min)	102	50	99
Na+	135	142	145
K+	3.4	3.1	4.2
Total bilirubin (mg/dL)	0.2	1.32	0.29
ASAT (U/L)	61	49	35
ALAT (U/L)	124	88	78
Albuminemia g/dL	2.3	2	2.6
LDH (U/L)	358	466	285
Troponin I (ng/mL)	0.202	0.182	0.048
NT-proBNP (pg/mL)	1258	13.617	514
D-Dimer	2023	2756	534
Fibrinogen (mg/dL)	251	547	234
PCR	2.9	186	4
Proteinuria mg/24 h	1404	1827	1035
Albuminuria mg/24 h	764	1078	600

Table 2. Values of direct renin concentration (DRC), plasma aldosterone concentration (PAC) and of sodium and potassium status during hospitalization and post-critical phase.

	Hospitalization	4th month	8th month	12th month	16th month	20th month
DRC (mU/L)	407	56.1	3834	2138	1135	41.6
PAC (ng/dL)	9.1	12.4	12.2	10.2	8.3	6.6
Na (mEq/L)	138	139	137	139	140	138
K (mEq/L)	3.1	4.3	4.6	4.4	4.0	4.1
24h UNaV (mEq/24 h)	224	160	128	180	250	179
24 h UKV (mEq/24 h)	49	40	45	48	72	46

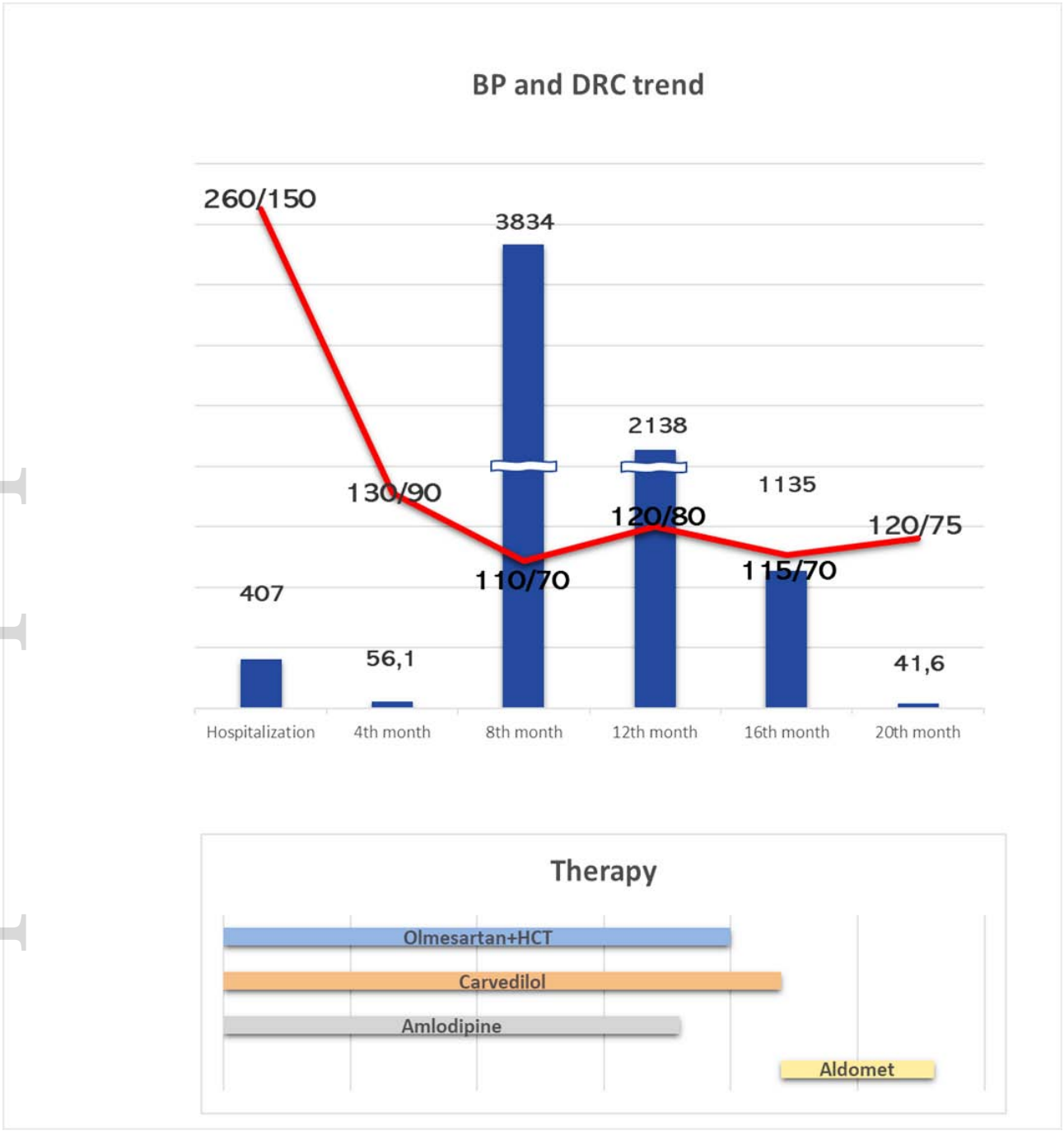

Figure 1. Clinical course: mean arterial pressure (red line), direct renin concentration (blue columns) and antihypertensive therapy over the 20-months follow-up.