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Familial Bilateral Pheochromocytoma Complicated by Acute Ischemia of the Lower Limbs

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Abstract **Case Report**

Introduction: Few authors have ever reported acute ischemia of the lower limbs (AILL) as a presentation of pheochromocytoma. ***Case Report:*** We present a case of familial bilaterla pheochromocytoma complicated by AILL. ***Discussion and Conclusion***: we aim to illustrate the pathophysiological, clinical and therapeutic features of this rare case of pheochromocytoma and describe this complication (AILL), wich mainly linked to the catecholaminergic effects on the cardiovascular system, may jeopardise the functional prognosis of the locomotor system, thus affecting the quality of life of these patients.

Keywords: Pheochromocytoma, Familial, Cluster, Acute Ischaemia, Lower Limbs, Surgery.

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INTRODUCTION

Pheochromocytoma is a rare neuroendocrine tumor that arises from the chromaffines cells of the adrenal medulla. The incidence of PPGL represents 2 and 8 per million, with a prevalence that ranges between 1/2500 and 1/6500 [1]. Four to eight % of adrenal incidentalomas are PCCs [2].

Pheochromocytomas develop frequently on a sporadic basis [3, 4]. However, about a quarter of pheochromocytomas that are suspected to be sporadic are associated with a germline mutation [5, 6].

Patients presente severe hypertension and/or symptoms of catecholamine excess, including paroxysmal headache, sweating, and palpitations, but the clinical picture can sometimes be non-specific, making diagnosis more difficult in rare instances.

Pheochromocytomas have been associated with AILL, but there are very few cases reported in the literature.

CASE REPORT

A 42-year-old male patient, diabetic since 1 year, with familial history of pheochromocytoma, admitted to the ER for dyspnea, bilateral hypochondrial pain and acrocyanosis.

On examination a BloodPressure (BP) of 170/100 mmhg, Heart Rate (HR) 127 bpm, Respiratory Rate (RR) 32 cpm, bilateral pleurisy and ascites of great abundance, purpuric lesions with cyanosis of toes, tip of nose and left ear, branched livedo of thighs, legs and hands **(Figure 1)**. Biology: Blood count: hyperleukocytosis 10016/mm3, microcytic hypochromic anemia 11.2 g/dl, thrombocytosis: 790000/mm3. Echocardiography: global hypokinesia, moderate left ventricular dysfunction at 35%. Arterial and venous echodoppler of the lower limbs came back without anomalies.

Abdominal CT (Computed Tomography) scan showed a right adrenal mass of 115*90*100 mm, heterogene with irregular contours, central necrosis, a tissue density, & another left of 32*25*54 mm, isodense and heterogene spontaneous density at 40 HU with cystic areas, diffuse infiltration of mesenteric fat, pulmonary nodules and right iliac bone lesions **(Figure 2**). On biological examination, 24 h urinary methoxylates derivatives (UMD) were largely elevated between 4 and 44 times normal **(Table 1).** The diagnosis of pheochromocytoma was made, patient was placed on alpha blocker, diuretics, ACE inhibitors, low-molecular-weight heparins (curative dose) and antialdosteronics.

Assessement of MEN2 (multiple endocrine neoplasia type 2) returned to normal. Suddenly we noted a rapid worsening of the patient's clinical condition, with hemodynamic instability, leading to an urgent referral to operating room for rescue adrenalectomy. Surgery resulted in the removal of a mass measuring approximately 12 cm **(Figure 3)**. Perioperatively, the patient presented a cardiac arrest which was recuperated, followed by multivisceral failure, for which he was maintained under intubation, assisted ventilation and vasoactive drugs for 5 days before being extubated. Echocardiography was reworked objectifying an intraventricular thrombus and patient has been put under antithrombotic drugs.

During surgery, a granular appearance was noted on the peritoneum, prompting the urological surgeons to take biopsies for histological comparison, the result being in favor of an epitheliogigantocellular granuloma with necrosis. The diagnosis of associated tuberculosis was evoked, but the biological work-up (bronchial and pleural Genxpert, adenosine deaminase from ascites fluid were negative).

Pathological examination of adrenal mass was in favor of a pheochromocytoma, with a PASS score of 9 with expression of anti-chromogranin A, anti-synaptophysin and anti-PS 100 Ac.

The evolution was marked by a worsening of the foot lesions with the development of necrosis (Figure 4). A lisfranc amputation was performed 40 days after the right adrenalectomy.

After 2 months, the patient was taken back for a 2nd left adrenalectomy, performed laparoscopically. Histology was in favor of a pheochromocytoma with a PASS score of 5.

The onset of chills, night sweats and febrile spells prompted a repeat Genxpert test, which this time came back positive, and our patient was started on antibacillaries.

Post-operative follow-up was marked by the disappearance of ecchymosis and cyanosis of the nose, arms and thighs **(Figure 5),** a good, disappearance of signs of TBK impregnation and good healing of the stumps obtained after 3 months of amputation. Removable prostheses were made for our patient, enabling him to resume standing with independent walking.

One year after the 2 nd adrenalectomy, the patient began to present again Menard's triad with right lumbago, the DMU came back high at, and the adrenal CT scan showed a mass in the right adrenal lodge encompassing the right renal vein, of 39*23*44 mm in favor of recidive for which the patient was surgically recovered.

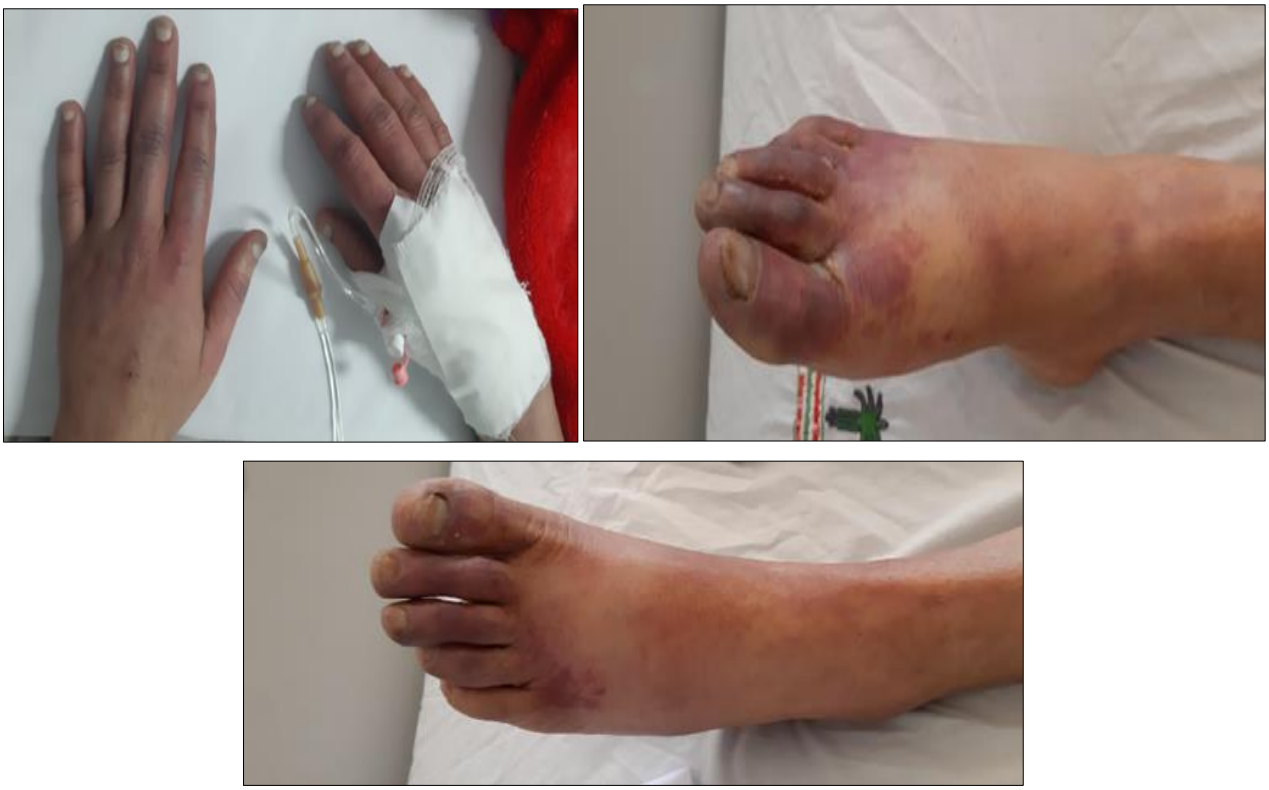

Figure 1: Purpura, livedo, cyanosis of toes and hands.

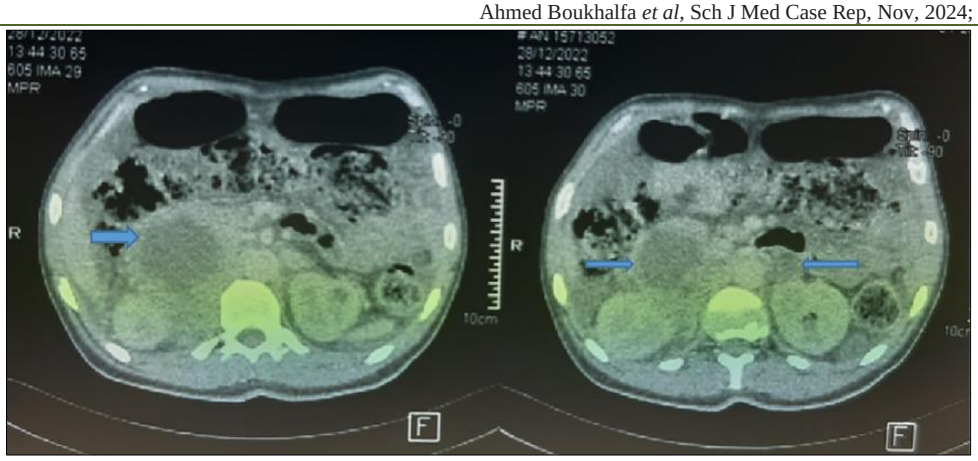

Figure 2: Adrenal CT-Scan: bilateral adrenal masses (blue arrow).

Table 1: Patient's urinary methoxylated derivatives values.

Twenty-four hours Urinary Methoxylated Derivatives	Results (mg/24h)	Normal values mg/24h)
Metanephrine	1,08	0,04-0,27
Normetanephrine	20,15	0,07-0,46
Dopamine	25	<0,46

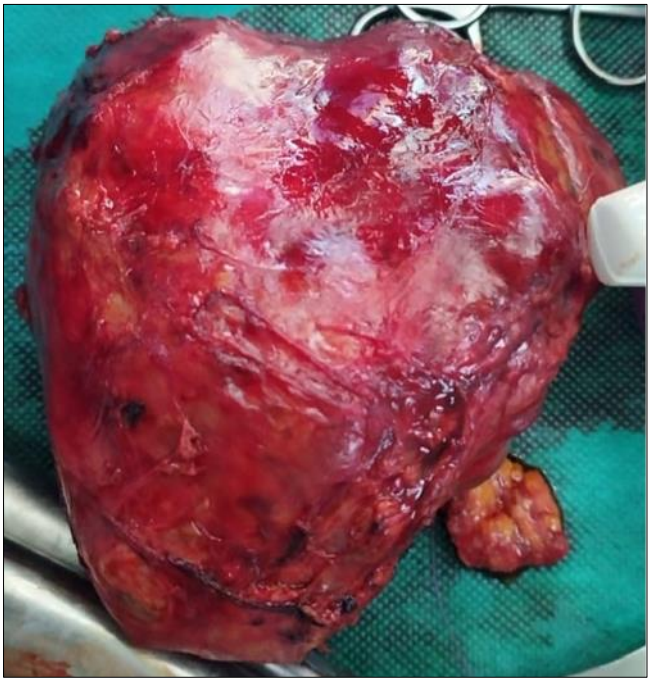

Figure 3: Right adrenal mass: intraoperative macroscopic appearance

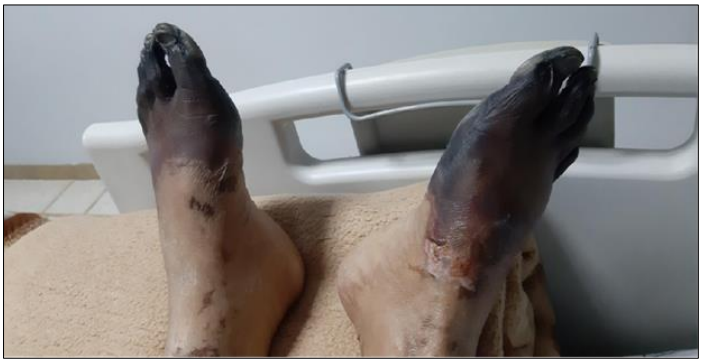

Figure 4: necrosis of the two forefeet.

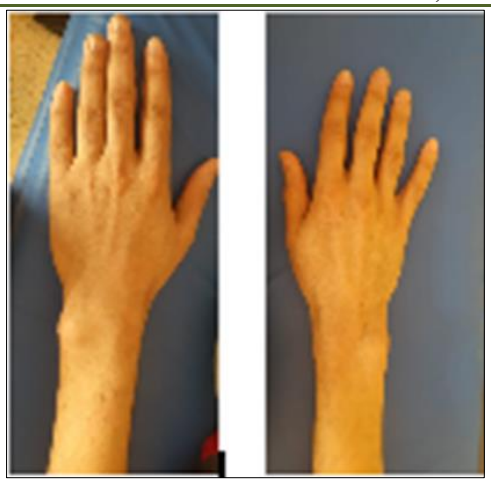

Figure 5: Disappearance of ecchymosis and cyanosis of hands.

DISCUSSION

This case demonstrates two particularities; the familial nature of the patient's pheochromocytoma and a rare mode of presentation: acute ischemia of the lower limbs.

Between 30 and 40% of cases of pheochromocytoma have a genetic origin due to germline mutations. These are solid tumors characterized by the highest genetic predisposition. For this reason, it is recommended that all patients undergo genetic screening [7-8]. The genetic trait can be either isolated or syndromic. The first pheochromocytoma associated syndrom to be discribed was neurofibromatosis type 1 syndrome (NF1) reported by Suzuki *et al*., in 1910 [9], while multiple endocrine neoplasia type 2 (MEN2) and Von Hippel Lindau disease (VHL) are the most frequent syndromic associations [10].

Genetic mutations in pheochromocytomas are divided into 3 groups or molecular clusters: pseudohypoxia cluster 1 (1A and 1B, Mutations: SDHA[AF2]/B/C/D, FH, MDH2, IDH, GOT2, SLC25A11 and DLST), kinase-signaling cluster 2 (Mutations : the rearranged-during-transfection :(RET) proto-oncogene, (NF1),(HRAS), transmembrane protein 127 (TMEM127), Myc-associated factor X (MAX :) and fibroblast growth factor receptor 1 (FGFR1), and Wnt signaling cluster 3. Belonging to a specific group gives pheochromocytoma specific clinical, biochimic and prognostic features (11). SDHx mutations in pheochromocytoma and paraganglioma (PPGL) result in the accumulation of succinate, increased levels of methionine, glutamine, and myoinositol, as well as decreased levels of fumarate, glutamate, citrate, isocitrate, and several other metabolites [12, 13]. A high succinate-to fumarate ratio helps discriminate between PPGLs with and without SDHx mutations. Moreover, simultaneous measurement of all mentioned metabolites discriminates SDHx from non-SDHx tumors, with a 100% sensitivity and specificity. This is important for patients with SDHx-related tumors who present with low catecholamine secretion or biochemically silent disease. SDHx tumors (particularly SDHB) display more aggressive behavior and have a high metastatic potential [14].

In our context, the sequencing of the RET gene is the only one available and it is underway in our patient Clinical presentation is highly variable, ranging from the specific Menard triad (palpitations, headaches and profuse sweating) to sometimes atypical clinical pictures such as acute limb ischemia (ALI).

Despite rarity, pheochromocytoma can result in peripheral ischemia and vasculopathy that results in necrosis or gangrene, these complications can be explained by diffuse peripheral arterial constriction, by activation of vascular α1-adrenoceptors, secondary to cathecolamine hypersecretion, arterial occlusion of cardiac thrombus embolism in patients with catecholamine-induced arrhythmias [15].

Despite their severity, these thromboembolisms of the lower limbs are rarely described. Approximately 30 cases of thrombus related to pheochromocytoma have been reported in the literature [16, 17], and 80% of thromboses secondary to pheochromocytoma are of cardiac origin, they represente the leading cause of ALI and is usually secondary to cathecolaminergic cardiomyopathy [18]. Chronic peripheral ischemia induced by elevated catecholamines can mimic peripheral artery disease, presenting with claudication and limb pallor and pain [19].

In our patient the echocardiographic examination noted hyperechoic apical ventricular formation in favor of thrombus.

In the case of pheochromocytoma induced acute limb ischemia (ALI), treatment of choice includes an open surgical or using catheter direct thrombectomy (CDT). Early trials show successful CDT in 70% of cases [20].

Our patient's severe clinical condition and hemodynamic instability precluded initial opensurgery or CDT. The initial suvetage adrenalectomy ensured our patient's survival, but lesions in the lower limbs progressed to necrosis, necessitating 2-stage amputation.

Amputation may sometimes be unavoidable; in a work published by a Spanish team in 2018 [21], they reviewed the literature of 12 cases, noting ischemic involvement Upper and lower limbs in 3 cases, lower in 5 cases, amputation was performed in 3 cases.

CONCLUSION

we have reported a rare mode of revelation of pheochromocytoma; acute ischaemia of the lower limbs in an equally rare context represented by the heredity of this type of adrenal tumour.

The diagnostic hypothesis of pheochromocytoma should therefore be borne in mind in the event of any acute ischaemia, especially in the context of hypertension in young people.

the hereditary genetic profile of this type of tumour should be considered in the presence of a family history, as was the case with our patient, emphasising the importance of genetic family screening.

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