

PARAGANGLIOMA E ANGIOEDEMA

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RESUMO – Paragangliomas ou Feocromocitomas extra-suprarrenais são tumores raros derivados do tecido cromafim que tendem a ocorrer esporadicamente ou no contexto de doenças genéticas complexas. São tumores com apresentação clínica variada, dependente do seu perfil secretório ou do efeito de massa determinado pela neoplasia. Sintomas dermatológicos são raros, tendo sido classificados como agudos/paroxísticos ou crónicos. É apresentado caso de uma Eurocaucasiana de 40 anos de idade que referia, nos últimos 2 anos, episódios auto-limitados de angioedema, diarreia, toracalgia, hiper ou hipotensão arterial, dispneia e ansiedade. Estudos laboratoriais e, posteriormente, avaliação imagiológica e exame patológico permitiram identificar um paraganglioma drenante para a veia renal esquerda, o qual foi extirpado com sucesso. Durante a cirurgia, a manipulação do tumor desencadeou uma nova crise grave, a qual exigiu, com carácter de emergência, a instituição de medidas de suporte avançado de vida. A recuperação decorreu sem incidentes, tendo-se verificado uma rápida regularização dos valores laboratoriais a par de uma remissão clínica completa, sem novos episódios verificados durante 17 anos.

PALAVRAS-CHAVE – Paraganglioma; Feocromocitoma; Angioedema; Manifestações cutâneas.

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ABSTRACT – Paragangliomas or extra-adrenal pheochromocytomas are rare tumors that arise from chromaffin tissues and tend to occur either sporadically or in the context of complex genetic disorders. They are clinically heterogeneous in nature - symptoms deriving either from the secretory profile of the tumor or from the mass effect of the neoplasm. Dermatologic symptoms are quite seldom described in the literature and have been classified in acute or chronic. The case of a 40 YO Caucasian female that had been enduring for the last 2 years recurring self-limited episodes of angioedema, diarrhoea, chest pain, hypertension or hypotension, dyspnoea and anxiety is reported. Biochemical studies and further imagiologic work up and, later on, pathologic exam allowed to identify a paraganglioma that drained to the left renal artery. Upon surgery, during tumor manipulation, the patient developed an additional systemic crisis that required active life support. Recovery was regular, with a quick and sustained normalization of lab results as well as on the clinical side, with no further episode for the last 17 years.

KEY-WORDS – Paraganglioma; Pheochromocytoma; Angioedema; Skin manifestations.

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INTRODUCTION

Pheochromocytomas are catecholamine-producing neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. Tumours developed from extra-adrenal chromaffin tissue are reported to as paragangliomas or extra-adrenal pheochromocytomas¹. Nearly 85% of these tumours originate in the adrenal medulla, the remaining 15% developing from extra-adrenal chromaffin tissue².

Overall, pheochromocytomas are rare, usually benign tumours that occur with equal frequency in both genders in adulthood, with a peak incidence in the 3rd-4th decades. They represent a most rare, yet curable cause of hypertension, accounting for about 0.1%-0,6% of patients with standard diastolic hypertension^{3,4}.

In over 95% of cases, they occur sporadically, most often as an isolated tumour in individuals aged 40-50 years; familial/hereditary forms are usually diagnosed earlier, in children and in adults before 40 years⁵, where they tend to be multiple, bilateral, extra-adrenal and to occur in the context of genetic disorders such as Neurofibromatosis type I, Multiple Endocrine Neoplasia Syndrome (Sipple`s or Mucosal Neuroma Syndrome), von Hippel-Lindau Hemangiomas and the Familial Paragangliomas^{1,6,7}.

Often referred to as the "great mimicker"(1), clinical presentation is quite variable and, consequently, diagnosis is often difficult as clinical manifestations are protean, subtle and erratic, function of the variable secretory profile of several compounds, namely catecholamines, neuropeptides and other vasoactive amines⁸⁻¹⁰.

CASE REPORT

A 40 YO female presented to the Dermatology Outpatient Clinic for recurrent angioedema episodes affecting her neck (Fig. 1), upper trunk and limbs, oral mucosae and face. Having started 2 Y before, these 1-4 hour lasting episodes, were occurring more and more frequently (every 2 weeks in the last 2 months) with several accompanying symptoms such as "flushing",

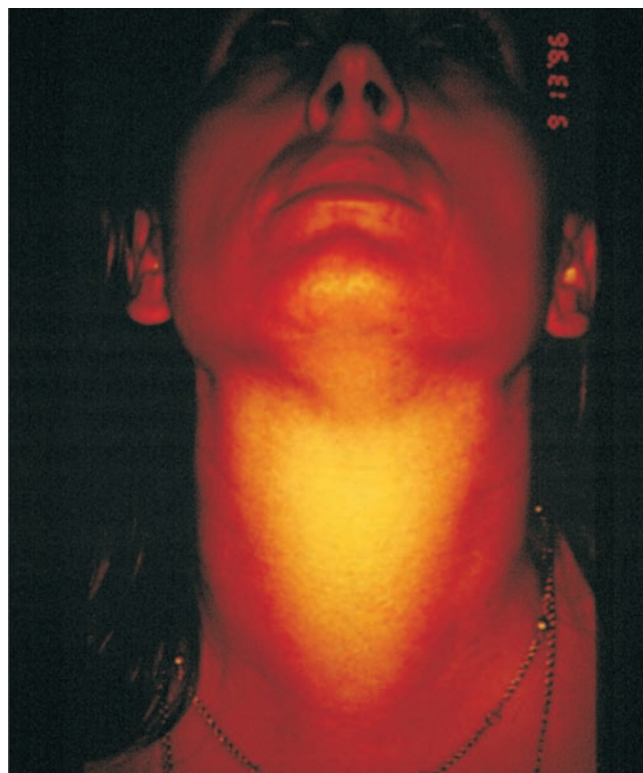


Fig. 1 - Angioedema of the neck area.

anxiety, dyspnoea, wheezing, hoarseness, chest pain and aqueous diarrhoea. Less frequently reported were complaints of pallor on the extremities followed by transient flushing on the arms, neck and décolleté areas. During these episodes her blood pressure would be normal, high or low and no "triggering cause" could ever be found. Her past medical history was otherwise unremarkable, except for bronchial asthma she endured until she was 13 years of age.

Previously viewed as "allergic" in nature, she had been subjected to thorough allergological investigations which gave inconclusive results. She accordingly had been for long periods on antihistamines such as loratadine, cetirizine, astemizol and ketotifen. Such approaches proved unsuccessful as far as the number, duration and severity of the recurring attacks. These, which had led to multiple ER referrals, had

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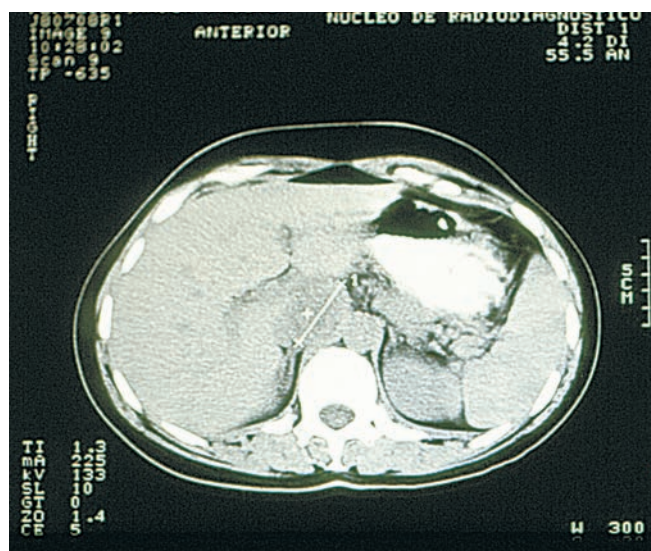


Fig 2 - CT-scan of the adrenal glands. A 4.2cm diameter paravertebral round homogeneous mass.

been interpreted either as psychoneurotic or as allergic, having been treated with combinations of antihistamines, systemic corticosteroids and anxiolytics and sedatives.

Laboratory work up including C2,C3,C4,CH100, C1Inh,T3,T4,Tsh,blood cortisol ,urinary 5-hydroxy indolacetic acid, blood electrolyte and calcium levels were either normal or negative. Urinary 24h. metanephrines were elevated (3234ng/24h urinary volume of 1200ml/24h) (N<1000 ng/24h). Blood and urine samples were eventually collected (intercritical period) for PTH, Calcitonin, VIP, PP, Gastrin, Glucagon, Somatostatin and Neurotensin. These were normal. Ophthalmologic examination was normal.

Topographic work up with a CT-Scan (Fig. 2) and MIBG Scintigraphy (Metaiodine-131-iodobenzylguanidine) (Fig. 3) was followed by the surgical excision of a 4.2cm diameter paraganglioma draining to the left renal vein.

During surgery, the manipulation of the tumour elicited, in spite of previous pharmacological adrenergic blockade with labetalol, a severe episode of angioedema, tachycardia and hypertension that required active vital support. Pathologic examination confirmed the diagnosis of Paraganglioma. Immunohistochemistry for VIP was negative. Post surgical recovery was normal; the patient has been well, with a follow up that included urinary metanephrines, VMA, catecholamines and imagiological studies. She has endured no further crises for the last 17 years.

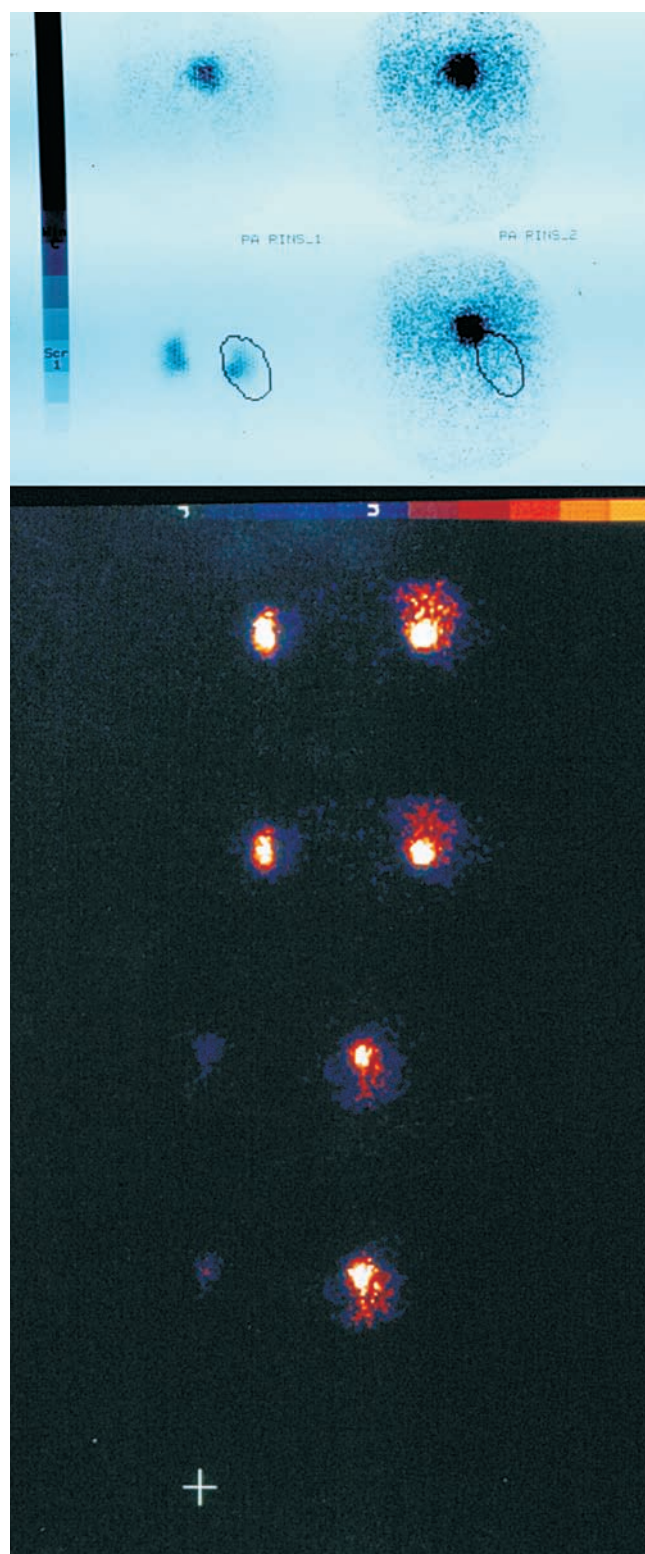


Fig 3 - MIBG Scintigraphy (48h): Intense focal fixation in the right adrenal gland. Rest of the body unremarkable.

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DISCUSSION

Pheochromocytomas are tumours seldom referred to in the dermatological literature. Cutaneous manifestations have however been reported, having been classified as acute/paroxysmic or chronic¹¹ (Table 1).

Table 1 - Pheochromocytoma. Dermatologic manifestations.

1. Acute, paroxysmic
• Pallor of the face and extremities ¹²
• Flushing (face and upper trunk) ¹²
• Hyperthermia ¹³
• Hyperhidrosis ¹³
• Acrocyanosis ¹¹
2. Chronic
• Acrocyanosis, erythrocyanosis
• Erythematous violaceous papules ¹⁴
• Raynaud's phenomenon
• Hypochromic macules ¹⁵
• Necrotizing vasculitis ¹¹
• Violaceous macules on the feet
• Palmar plantar keratoderma ¹⁶
• Addison-like hypermelanosis ¹⁷
• Granulosis Rubra Nasi ¹⁸
• Leukocytoclastic vasculitis ¹⁹
• Chronic urticaria ²⁰

These manifestations are due to the direct pharmacological effects of the catecholamines on sweat glands and cutaneous vasculature (hyperhidrosis, acrocyanosis, hyperthermia, flushing or pallor...); to incompletely clarified mechanisms that include the biological effects of several neuropeptides and vasoactive amines on the skin (Table 2), or still unknown tumour-mediated trophic stimuli on the skin (Addison-like hypermelanosis, palmar plantar keratoderma...).

In our particular case, it is noteworthy:

1. The direct chronological concordance between systemic crises and the angioedema episodes;
2. The intra-surgical angioedema episode elicited by the manipulation of the tumour and;
3. The long lasting episode-free remission period (17 years now) after surgery.

Also worthy of mention were the negative results of several neuropeptides in the urine, blood and in the

Table 2 - Pheochromocytoma. Secretion products.

1. Catecholamines (AD, NA, Dopamine)	
2. Peptides	
• Somatostatin (SOM)	• VIP
• Substance P	• IL-6
• CGRP	• PTH
• Adrenocorticotropin	• NPY
• Beta endorphin	• Serotonin
• Lipotropin	• Gastrin
• Neurotensin	• Galanin
• Adrenomodullin	• Pancreastatin
• Calcitonin	• Met enkephalin

tumour itself (Immunohistochemistry for VIP). These results were disappointing in face of several previous reports of VIP-secreting pheochromocytomas that were clinically associated with diarrhoea²¹. They can however be explained bearing in mind both the extremely short biological half life of those neuropeptides and the facts that neither the samples were collected during an episode of angioedema nor peptides like Substance P or CGRP namely, were titrated.

Also deserving a comment is the well-recognized fact that both anaesthesia and tumour manipulation are frequently reported to elicit a catecholaminergic crisis in these patients which, of course, has to be taken into account when surgical procedures are performed¹. That was indeed our patient's case, who endured an important intra-surgical crisis that required active life support.

In sum, we report on an extremely unusual case of a patient with an extra-adrenal pheochromocytoma (paraganglioma), in whom angioedema episodes were synchronous with paroxysmic systemic crises and that experienced no further crises, ever since surgical removal of the tumour was undertaken, 17 years ago.

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