# Clinical Case Report

## Pituitary carcinoid coexisting with systemic lupus erythematosus: A rare combination

ANUPAM BHAMBHANI, MANISH DUGAR, JYOTSNA RAO, RAVIKANTI PRASAD

**ABSTRACT**

**Gastrointestinal carcinoids have occasionally been reported in patients with autoimmune diseases. We report a middle-aged woman who presented with episodic hypertension and a skin rash. Initial evaluation led to the diagnosis of systemic lupus erythematosus for which the patient was treated. Further investigations revealed the presence of a carcinoid tumour in the pituitary. Although gastrointestinal carcinoids associated with autoimmune diseases have been seen occasionally, to our knowledge, extragastric carcinoid coexisting with an autoimmune disorder has never been reported before. A better understanding of how inflammation induces cytological changes leading to development of a carcinoid from a cellular and molecular perspective could provide potential therapeutic strategies for preventing these lesions.**

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### INTRODUCTION

Carcinoid tumour occurring as a primary tumour of the pituitary gland is rare and poses difficulties in diagnosis due to the physiological presence of somatostatin receptors at this site. We report a patient with pituitary carcinoid coexisting with systemic lupus erythematosus (SLE), presenting as paroxysms of difficult to control hypertension.

### THE CASE

A 46-year-old woman was referred for paroxysms of hypertension associated with recurrent urticaria, dyspnoea and swelling of the lips (angio-oedema) for 6 months. The common causes of anaphylaxis, namely food, drugs, hydatidosis, hyper-IgE, hereditary angio-oedema and hypereosinophilic syndrome, were excluded.

She also reported occurrence of another type of episodic rash, which was not associated with hypertension. Both the rashes occurred at different times (Figs 1a and b). When the latter rash recurred while she was hospitalized, it was diagnosed as a manifestation of leucocytoclastic vasculitis. There was a past history of arthralgia involving small and medium size joints since the age of 7 years. On examination, her blood pressure was 170/100 mmHg and she had non-tender, generalized lymphadenopathy. She was admitted with differential diagnoses of carcinoid syndrome, pheochromocytoma and/or collagen vascular disorder.

On investigation, her erythrocyte sedimentation rate (ESR) was raised (111 mm in the first hour, Westergren); there was macroalbuminuria and the serum creatinine and glomerular filtration rate (GFR) were 1.3 mg/dl and 66 ml/minute, respectively. Serum antinuclear and anti-ribonucleoprotein (RNP) antibody levels were raised while C3, C4 complement levels were depressed; C3 being 0.281 g/L and C4 0.0179 g/L (reference values 0.9–1.8 g/L and 0.1–0.4 g/L, respectively). Based on arthralgia, antibody profile, low complement levels, raised ESR, albuminuria, decreased GFR, and leucocytoclastic vasculitis, SLE was diagnosed and treatment started with corticosteroids. The lymphadenopathy resolved with corticosteroid treatment. Normal levels of 24-hour urine vanillyl mandelic acid (5.4 mg/day, reference value <13.6) and metanephrine (0.39 mg/day, reference value <0.90) ruled out pheochromocytoma.

Her plasma chromogranin A (CgA) was markedly raised (1200 ng/ml) but 24-hour urinary excretion of serotonin metabolite 5-hydroxy-indole acetic acid (5-HIAA) was normal. To confirm and locate the serotonin-secreting tumour, a somatostatin receptor scintigraphy (SRS) using radio-labelled gallium-68 analogue of somatostatin (Ga-68-DOTANOC) was performed in conjunction with positron emission tomography (PET). It revealed an asymmetric focus of increased isotope uptake in the left half of the pituitary gland (Fig. 2). A subsequent brain magnetic resonance imaging (MRI) showed a 3.7×3.5 mm adenoma in the left side of the pituitary gland corresponding to the site of increased DOTANOC uptake (Fig. 2). Gastrointestinal endoscopy and plasma gastrin were normal, ruling out gastric atrophy and neoplasia.

Addition of octreotide therapy to the already ongoing prednisolone (started for SLE earlier) resulted in dramatic disappearance of the systemic symptoms and rash.

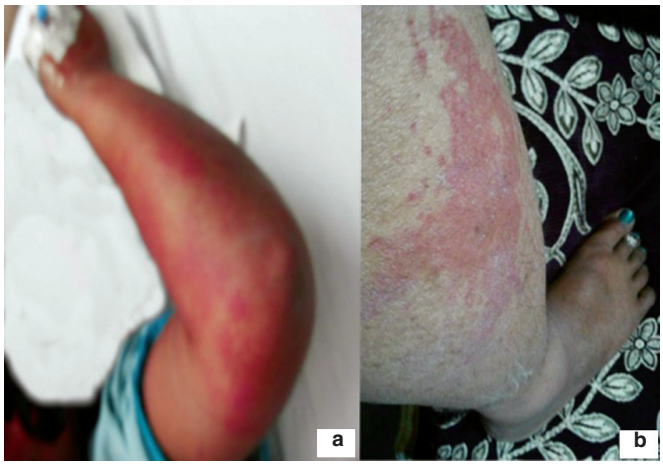


FIG 1. a: Urticarial rash; b: Leucocytoclastic vasculitis

Vydehi Institute of Medical Sciences and Research Center, Whitefield, Bengaluru 560066, Karnataka, India

ANUPAM BHAMBHANI Department of Cardiology

MANISH DUGAR Department of Rheumatology

JYOTSNA RAO Department of Nuclear Medicine

RAVIKANTI PRASAD Department of Radiodiagnosis

Correspondence to ANUPAM BHAMBHANI; *anupam.bhambhani@yahoo.in*

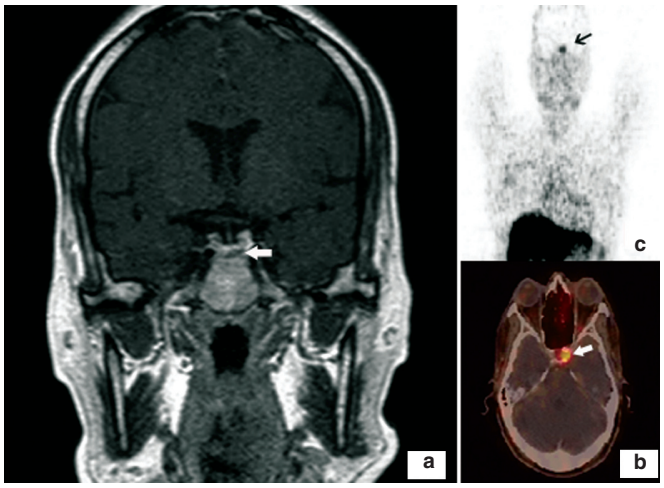


FIG 2. a: MRI brain showing left-sided pituitary micro-adenoma; b and c: Ga-68-DOTANOC scans showing increased radioisotope uptake in the area corresponding to the adenoma on MRI.

## DISCUSSION

Carcinoid syndrome is caused by neuroendocrine neoplasms, mostly originating in the gastrointestinal tract or tracheo-bronchial tree.[1,2] They may metastasize, but occur rarely as primary neoplasms of other organs. They usually present with urticaria, abdominal discomfort, diarrhoea, angio-oedema, bronchospasm, palpitation and fluctuating blood pressure.

We report a patient with paroxysmal systemic hypertension with recurrent anaphylactoid reaction, occurring in a 46-year-old woman who also had synovitis, leucocytoclastic vasculitis and serological features of autoimmune disease, later proved to be SLE.

Although gastrointestinal carcinoids associated with autoimmune diseases such as autoimmune hepatitis, atrophic-immune gastritis (AIG),[3] autoimmune thrombocytopenia[4] and SLE,[3] have been occasionally seen, extragastric carcinoid coexisting with autoimmune disorder has never been reported before.

Traditionally, the diagnosis of carcinoid is based on increased urinary excretion of serotonin metabolite 5-HIAA. This test was normal in our patient. The reported sensitivity and specificity of 5-HIAA for diagnosing carcinoid are 73% and 100%, respectively.[5–8] The low sensitivity is because 5-HIAA does not rise in atypical carcinoid,[8] a condition caused by tumours that produce 5-hydroxytryptophan (5-HTP) instead of 5-HIAA. Increased 5-HTP is related to the absence of the enzyme aromatic acid decarboxylase, which converts 5-HTP to serotonin. Symptoms in both typical and atypical carcinoid are the same.[6]

Our patient had very high plasma CgA, another useful biomarker for diagnosing neuroendocrine tumours, with sensitivity and specificity of 90% and 100%, respectively.[9] CgA is co-secreted with serotonin from carcinoids and is probably the most specific biomarker available. It is raised even in atypical carcinoids.[8]

In our patient, the nuclear and MRI imaging located the carcinoid neoplasm in the pituitary, a site that is rare for such primary tumours. Radio-labelled SRS with new generation somatostatin analogue 68-Ga-DOTANOC, has shown a high sensitivity for carcinoid tumours (90% in symptomatic patients).[10] This finding has to be interpreted keeping in mind that the pituitary gland physiologically has somatostatin receptors. However, in our patient, the isotope uptake was asymmetrical, being more on the left side, corresponding to the site of the adenoma seen in the MRI. These observations, along with clinical and biochemical findings, strongly support our diagnosis.

This patient is also important because the carcinoid coexisted with SLE. Several studies have reported increased risk of gastrointestinal carcinoids in individuals with autoimmune diseases such as AIG,[3,11] a relationship further supported by the fact that the prevalence of AIG is 2% in the general population, and is increased 3–5-fold in those with type 1 diabetes[12] and autoimmune thyroid disease.[13] The pathophysiology of the carcinoid–autoimmunity association has been hypothesized as: patients with AIG have chronic rise of serum gastrin due to gastric atrophy, which causes development of gastric carcinoid.[3] However, this hypothesis explains autoimmune mechanism for the gastric carcinoid only.

Carcinoids occur at younger ages when associated with autoimmune disorders.[4] This indicates the accelerating effect of autoimmunity on development of carcinoids.

Some investigators, using mice models, have demonstrated an association between autoimmunity, inflammation and development of gastric tumours via CD4+ T cells.[11] However, none of these studies included extragastric carcinoids. To our knowledge, this is the first report of pituitary carcinoid and SLE occurring together. This suggests that autoimmune disorders might facilitate the development of carcinoids through some mechanism other than the one described for gastric carcinoids.

### *Conclusion*

This case is important for multiple reasons. First, the patient presented with intermittent hypertension caused by carcinoid syndrome; second, primary carcinoid of the pituitary is rare; and third, this is the first reported case of pituitary carcinoid associated with SLE. This suggests a probable aetiopathological relationship between autoimmunity and carcinoid, which is different from the one so far hypothesized, i.e. AIG caused hypergastrinaemia inducing gastric carcinoid.

A better understanding of how inflammation induces cytological changes leading to development of carcinoid, from a cellular and molecular perspective, can provide potential therapeutic strategies for preventing these lesions. These mechanisms are grossly under-elucidated and need further research.

Prior knowledge of possible existence of such combinations and detailed investigation to explore the aetiopathogenesis of every observed symptom and sign in patients with difficult-to-treat hypertension helps in arriving at a proper diagnosis and treating such rare patients.

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