Chronic venulectasias secondary to persistent flushing in the setting of a metastatic well-differentiated neuroendocrine tumor

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Key words: carcinoid syndrome; dermatology; flushing; neuroendocrine; oncology; venulectasias.

INTRODUCTION

Neuroendocrine tumors (NETs) arise from enterochromaffin cells and commonly originate in the gastrointestinal tract, constituting 35% to 42% of small bowel tumors.[1] Functional tumors secrete serotonin, substance P, histamine, catecholamines, and prostaglandins.[2] In advanced disease, hepatic metastases bypass liver metabolism of serotonin, leading to carcinoid syndrome (CS).[1] CS affects 10% of patients with NETs[2] and is reserved to describe a constellation of symptoms related to excess serotonin: flushing, diarrhea, bronchospasm, and cardiac lesions.[1] Cutaneous flushing remains the hallmark of CS[2] and can be episodic or persistent,[1] the latter indicating long-standing and/or advanced disease. Chronic flushing can lead to the development of venulectasias and bluish facial discoloration. Specifically, long-standing midgut tumors produce a characteristic fixed cyanotic flush.[1,2] Initial diagnostic testing for CS is measurement of 24-hour urinary 5-hydroxyindolacetic acid. For patients with an established diagnosis, serum chromogranin A[2] is an appropriate tumor biomarker. Treatment for CS is aimed at symptoms. Treatment for NETs can include surgical resection, chemotherapy, cytoreductive therapy, somatostatin analogs (SSAs), radiolabeled SSAs, everolimus for SSA-refractory cases,[1] and a novel tryptophan hydroxylase-1 inhibitor.[3] Avoidance of activities and agents that induce episodic flushing may be used. To our knowledge, no cases of chronic venulectasias in the setting of metastatic NETs have been reported.

Abbreviations used:

CS: carcinoid syndrome
NET: neuroendocrine tumor
SSA: somatostatin analog

CASE REPORT

This is a case of a 67-year-old male with a 5-year history of stage IV neuroendocrine cancer originating in the ileum who presented to clinic with blue discoloration of the face. He was diagnosed by computed tomography/octreotide scan 5 years prior; his symptoms at that time included several months of diarrhea, fatigue, and progressively worsening flushing. He was started on octreotide 20 mg monthly with dramatic symptom improvement. A year later due to disease progression, the octreotide was increased to 40 mg monthly. A chemotherapy regimen was added for 1 year thereafter and discontinued during the COVID-19 pandemic. His most recent positron emission tomography/computed tomography scan revealed hypermetabolic disease of the distal small bowel with mesenteric nodules and 30 liver metastases. A liver biopsy done 1 month before his visit confirmed well-differentiated World Health Organization Grade 1 NET. His chromogranin A levels had been stable since his diagnosis but had recently risen to 24,390 ng/mL (normal 0-103 ng/mL). His current treatment regimen included lanreotide 120 mg monthly; he was scheduled for peptide receptor radionucleotide therapy. He reported daily episodes

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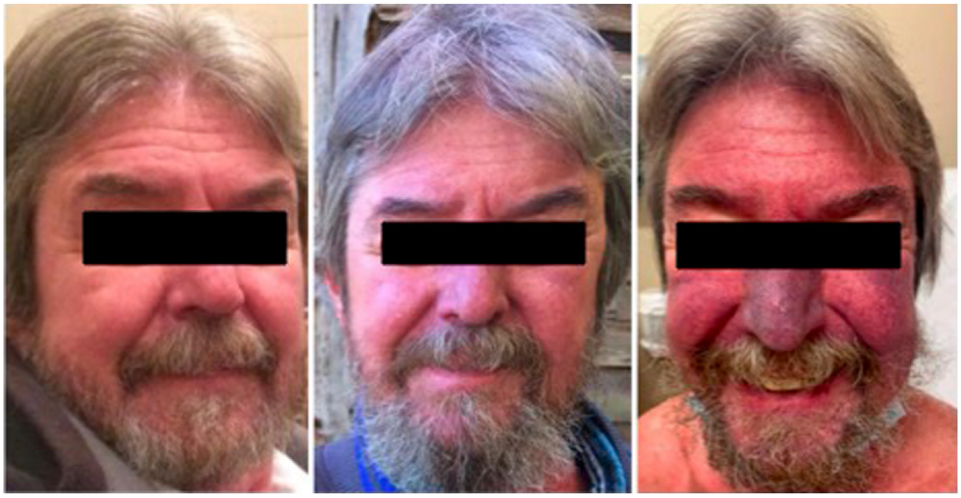

Fig 1. Progression of persistent flushing and development of chronic venulectasias in a patient with stage IV neuroendocrine tumor; (L-R: February 2016, October 2019, January 2022).

of diarrhea with nausea, anorexia, abdominal discomfort, and fatigue; he had remained functional, but with poor quality of life. His skin had been diffusely erythematous but stable since starting treatment; his episodic facial flushing had reportedly diminished over the last year. He had previously been prescribed metronidazole gel and doxycycline, without relief. The new blue discoloration had come on gradually over the preceding months. On presentation, the patient had confluent purple vascular papules on the nose and cheeks (Fig 1), with red vascular patches on the chest and hands. Clinically, chronic venulectasias secondary to persistent flushing in the setting of CS and progressive NET was suspected. Laser treatment was recommended if desired.

DISCUSSION

This case illuminates a rare sequela of persistent flushing, chronic venulectasias, in the setting of CS secondary to somatostatin-refractory NET. NET uniquely requires treatment for the tumor and associated hormone-excess state. While curative resection would treat both problems, metastatic disease is often present and dual treatment is required. CS symptoms are difficult to control as serotonin antagonists have a little effect on flushing.[3] CS is associated with higher tumor grade, advanced stage disease, a midgut primary site, and a significant reduction in overall survival.[4] Most patients report a significantly negative effect on quality of life. This case highlights the importance of recognizing the complications of CS secondary to longstanding NET and the complexity of treatment.

Conflicts of interest

None disclosed.

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