Burning mouth syndrome and mast cell activation disorder

Lawrence B. Afrin, MD, Charleston, South Carolina
DIVISION OF HEMATOLOGY/ONCOLOGY, MEDICAL UNIVERSITY OF SOUTH CAROLINA

Burning mouth syndrome (BMS), a chronic diffuse oral pain syndrome affecting ~1% of the general population, is diagnosed when explanatory oral pathology and other identifiable causes are absent. BMS has been recognized for decades, but its etiology remains unknown and has not previously been attributed to mast cell disease. Three cases of BMS are reported in which evidence of an underlying mast cell activation disorder (MCAD) was found; all 3 patients’ oral pain responded well to MCAD-directed therapy. Mediators released from mast cells have a wide range of local and remote effects and potentially may cause the neuropathic changes and/or inflammation thought to lead to the symptoms of BMS. Mast cell disease either in oral tissue or at sites remote from the mouth should be considered in the differential diagnosis of BMS. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:465-472)

Burning Mouth Syndrome (BMS), also termed Burning Mouth Disorder, is a distinct pain disorder classically consisting of chronic diffuse oral mucosal pain (often relieved by eating or drinking), dysgeusia, and xerostomia in the absence of lesions or other detectable changes in the oral mucosa which can explain the pain, though oligosymptomatic presentations (i.e., pain with or without dysgeusia or xerostomia) are more commonly seen. Epidemiologic studies in the Americas, Europe, and South Africa suggest that BMS affects 0.7%-15% of the general population, much more often women (7:1 vs. men) in their middle and later years. Spontaneous remission is rare, although one-half to two-thirds of patients may experience improvement within 6-7 years of onset. BMS typically significantly adversely affects quality of life, and BMS patients commonly are chronic high consumers of health care resources. Many conditions have been noted to cause BMS symptoms, such as infections, allergic reactions, gingivitis, dental treatment, nutritional deficiencies, pemphigus, oral cancer, Sjögren syndrome, and other endogenous and iatrogenic salivary gland dysfunction. Associations of variable strength between BMS and many other conditions (e.g., menopause, diabetes) have been noted as well. The term BMS is often applied initially to patients presenting with symptoms and without immediately identifiable oral lesions to which the pain can be reasonably attributed. However, chronic diagnosis of BMS is typically reserved for cases which remain idiopathic after thorough evaluation.

Studies have shown trigeminal-facial sensory anomalies, increased pain thresholds, and mucosal neurovascular microcirculatory system disturbances in BMS patients. Presently it is thought that changes in the peripheral and/or central nervous system may cause the symptoms in BMS, but the specific natures of these changes and their true etiologies remain elusive. The most specific pathway to BMS symptoms yet suggested has identified, via positron-emission tomographic scanning, nigrostriatal dopaminergic inhibition putatively affecting trigeminal nociception through loss of sensory inhibition, but evidence remains inconclusive. There is no definitive cure for BMS. A large variety of treatments have been proposed, but overall response to therapy is generally poor. Antidepressants, anxiolytics, capsaicin, alpha-lipoic acid, pyridostigmine, and cognitive/behavioral therapy, among other agents and therapies, have benefited some patients, but responses have not been predictable or reliable. As such, identification of a specific underlying cause, presumably permitting specific therapy (more likely than empiric therapy) to yield symptom relief, is the imperative in each BMS patient.

BMS has not previously been attributed to mast cell disease (MCD). Of hematopoietic origin but largely confined (in sparse distributions) to solid tissues in all systems throughout the body, MCs normally react to local chemical and physical stimuli by producing and releasing a wealth of potent mediators which help maintain homeostasis in both local and remote tissues. More than 200 MC mediators directly and indirectly affect processes in virtually all cells with resulting tissue/organ and clinical consequences. Specific consequences in the individual patient with aberrantly functioning MCs depend on the specific pattern of mediator release, which can differ substantially from one patient to the next, making clinical recognition of any variant
of MCD challenging. Given the range of molecular and cellular effects of MC mediators, symptoms and findings in MCD span the gamut of human symptomatology and clinicopathology. Aberrant MC function has been found to underlie a growing spectrum of previously idiopathic (and often inflammatory) illnesses, including some neuropathic conditions, raising the possibility of a link with BMS.

Historically, MCD has been thought to be rare and largely has been divided between childhood dermatologic presentations of urticaria pigmentosa (UP) and even rarer adult presentations of systemic mastocytosis (SM), whose most striking symptom is unprovoked anaphylaxis. Although specific genetic anomalies have only rarely been found in UP, it has become clear that SM (as defined by World Health Organization consensus diagnostic criteria)11 is primarily a disease whose cellular and clinical behaviors result specifically from the D816V mutation of the MC transmembrane KIT stem cell factor receptor. KIT is expressed more heavily by far on the membrane of the MC than on any other cell and directly or indirectly governs the majority of MC functions. More recently, though, there has been developing recognition of a much larger spectrum of previously idiopathic (and often inflammatory) illnesses,9,10 including some neuropathic conditions, raising the possibility of a link with BMS.

Presented here are 3 patients who presented with BMS, were found to harbor MCAD, and experienced good relief of BMS symptoms with MCAD-directed therapy.

CASE 1

A 58-year-old woman with a past medical history (PMH) of hypertension, osteoporosis, and diverticulosis presented acutely in mid-2004 with mild fatigue and severe, disabling, burning pain, dysgeusia, and xerostomia throughout the oral mucosa (pain was consistently 10 on a 0-10 scale). Vague mild discomfort was also present throughout the entire remainder of the gastrointestinal tract, but she denied any sense of acid reflux. She reported anorexia due to her oral symptoms but was not losing weight. She also reported coincident onset of episodes of other varying symptoms at varying times, including flushing, malaise, insomnia, irritated eyes, mild proximal dysphagia, nonbloody diarrhea, and migratory edema. She endorsed subtle dyspnea but denied wheezing or chest pain. By early 2005, episodic flushing had largely abated, but a migratory abdominal wall cellulitis developed. No infectant could be found, and the cellulitis proved to be refractory to multiple antibiotics before resolving spontaneously 3 months later. Initial extensive investigations by specialists in internal medicine, dermatology, endocrinology, rheumatology, infectious disease, dentistry, otolaryngology, oral surgery, gastroenterology, and pain management were unrevealing, including normal oral examinations and oral biopsies and consistently normal routine blood counts and serum chemistries. She was thought by her oral physicians and pain management specialists to have BMS, but her endocrinologist thought a neuroendocrine disorder or systemic mastocytosis was more likely. Serum serotonin was found mildly elevated at 272 ng/mL (normal range 50-220 ng/mL). Plasma free catecholamines showed elevated norepinephrine (738 pg/mL, normal range 80-520 pg/mL) and dopamine (32 pg/mL, normal range 0-20 pg/mL). Urinary metanephrines, vanillylmandelic acid (VMA), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) were repeatedly normal. Other biochemical and radiographic searches for thyroid dysfunction, pheochromocytoma, carcinoid, other adrenal tumors, and medulary thyroid carcinoma were unrevealing. Serum tryptase and 24-hour urinary N-methylhistamine (uNMH) and prostaglandin D2 (uPGD2) were tested to also evaluate for systemic mastocytosis, but results were normal. Upper and lower endoscopies with an extensive set of random mucosal biopsies looking for major gastrointestinal tract inflammatory disorders showed only mild chronic gastritis and reflux esophagitis. In mid-2005, serum chromogranin A was found by a gastroenterologist (looking for a gastrointestinal neuroendocrine disorder) to be mildly elevated at 91 ng/mL (normal range 0-50 ng/mL). Repeated testing 4 months later found a level of 8,617 ng/mL (without use at either time of proton pump inhibitors or any finding of renal or cardiac failure).

She was suspected of having a neuroendocrine malignancy and was referred for oncologic evaluation. Her oral symptoms remained her worst symptoms by far. Physical examination remained essentially unremarkable; only mild dermatographism was seen. An extensive search for neuroendocrine malignancy (urinary 5-HIAA/metanephrines/VMA/HVA, computerized tomography (CT), magnetic resonance imaging, positron-emission tomography/CT scanning, octreotide scanning, and methyliodobenzguanine scanning) was unrevealing; serial serum chromogranin A determinations showed continued marked fluctuations (93-1,100 ng/mL). Bone marrow aspiration and biopsy (looking for metastatic neuroendocrine malignancy or systemic mastocytosis) were normal. Symptoms continued, and repeated upper and lower endoscopies with biopsies in mid-2006 (again looking for a focus of neuroendocrine malignancy as the putative source of the elevated chromogranin and, presumably, the symptoms) again showed chronic gastritis and reflux esophagitis.

Repeated esophagogastroduodenoscopy in mid-2007 was again grossly normal; a set of random mucosal biopsies now showed increased eosinophils in a gastric polyp and eosinophilic esophagitis in the gastroesophageal junction, of uncertain clinical significance at the time. Repeated upper and lower endoscopies with biopsies in mid-2008 found reflux esophagitis and chronic duodenitis but not increased eosino-
phils. Repeated bone marrow aspiration and biopsy were again normal.

Throughout these investigations, symptoms proved to be refractory to multiple empiric therapies, including assorted narcotics, benzodiazepines, antidepressants, gabapentin, pilocarpine, proton pump inhibitors, antibiotics, and estrogen and multivitamin supplementation. In early 2009, owing to increasing suspicion of MCD as the only possible unifying diagnosis for her full assortment of problems, immunohistochemical reexamination of the mid-2008 duodenal biopsy found gross overexpression of CD117 (55 cells per high power field; Fig. 1) and CD2 (145 cells per high power field), but not CD25. KIT D816V mutation analysis was negative. Plasma histamine was found to be mildly elevated (9 nmol/L, normal range 0-6 nmol/L). Repeated serum tryptase and uNMH were normal. MCAD was diagnosed.

Initiation of antihistamines (loratadine 10 mg, famotidine 40 mg) and nonsteroidal antiinflammatory drugs (celecoxib 200 mg), all twice daily, immediately decreased her oral and other gastrointestinal pain to 1/10. Other symptoms moderately improved, too. Examination showed resolution of malaise. Improvement had been sustained 20 months so far at the time of writing, although during a 4-month period of loss to follow-up in which she also stopped celecoxib and loratadine, burning mouth pain flared to 5/10, immediately returning to 1/10 upon starting aspirin 650 mg twice daily.

CASE 2

A 60-year-old woman with a PMH of well controlled mild diabetes mellitus type 2 and mild hypercholesterolemia developed buccal ulcers with white pseudomembranes and severe diffuse burning mouth and throat pain (persistently 10 on a 0-10 scale). Lichen planus was clinically diagnosed, but multiple treatments proved to be unhelpful. All of the oral lesions grossly resolved spontaneously after 6 months, but 10/10 pain persisted. After another 6 months, a random oral mucosa biopsy by her oral surgeon (while the oral mucosa continued to grossly appear normal) revealed superficial lichenoid changes and a perivascular lymphocytic infiltrate in the deeper connective tissue. A specific cause for her severe symptoms and the clinical significance of the histologic findings were uncertain. Evaluations by her internist and another oral surgeon also were unrevealing for a specific cause. Routine blood counts and serum chemistries were normal. No medications potentially causative of her symptoms (e.g., angiotensin-converting enzyme inhibitors) had been prescribed. Her pain was refractory to multiple empiric therapies, including assorted narcotics, benzodiazepines, antidepressants, proton pump inhibitors, antibiotics, and multivitamin supplementation. She was diagnosed with BMS by all of her physicians at the time.

Three years after symptom onset, further evaluation discovered additional chronic symptoms, including migraine headaches, irritable bowel syndrome, osteoarthritis, episodic migratory pruritus, and unpredictable flushing. Physical examination showed a tired woman but was otherwise unremarkable, including in the oral cavity. No dermatographism was noted. Laboratory studies, however, showed mildly elevated plasma histamine (8 nmol/L) and highly elevated plasma histamine (9 nmol/L).
uPGD$_2$ (733 ng/24 h, normal range 100-280 ng/24 h). Serum tryptase, serum chromogranin A, and uNMH were normal. However, plasma factor VIII, chromogranin A, plasma histamine, and 24-hour urinary histamine for her full assortment of symptoms. Serum tryptase and urinary histamine remained unremarkable, she frequently placed her fingertips to her face about her mouth as if trying to massage away the pain. MCAD was thought to be the best explanation for her oral pain and dysgeusia, she denied neuropathy; she also denied episodes of marked hypertension, wheezing, or diarrhea. There were no suspect medications; she reported an allergy to hydrocodone. On examination, marked malaise, fatigue, fatigue, and happy. Cognitive dysfunction appeared resolved, and she no longer placed her hands to her mouth. Dermatoglyphism persisted unchanged. Improvement had been sustained 5 months so far at the time of writing, except for a 4-day period of abstinence from aspirin before a procedure, during which time her burning oral pain returned within 2 days to 9/10 but remitted again to 3/10 shortly after resuming aspirin.

CASE 3
A 64-year-old woman acutely developed persistent 10/10 burning mouth pain, xerostomia, and dysgeusia. No cause was immediately evident. PMH included frequent upper respiratory infections in childhood, episodes of shingles at ages 35 and 63 years, and stage II breast cancer at age 59 years treated only with surgery and 5 years of tamoxifen. She appeared depressed. Oral examination was repeatedly normal. Evaluations by 2 internists, a dentist, 2 otolaryngologists, infectious disease and rheumatology specialists, and 2 oral surgeons were unrevealing, including routine hematologic and chemistry laboratory evaluation, 2 oral mucosa biopsies, and a minor salivary gland biopsy. All of her oral physicians thought that she met criteria for BMS, and her other physicians had no other suggestions. Her pain and other symptoms were refractory to multiple empiric medical therapies, including propoxyphene/acetaminophen, venlafaxine, and multiple courses of antibiotics.

Further evaluation 8 months after symptom onset found coincident development of anorexia (but no weight loss), cold intolerance, night sweats, throat irritation, mild proximal dysphagia, palpitations, nausea, treatment-refractory culture-negative urethritis, migratory edema, fluctuating cognitive dysfunction, and presyncope 2-3 times per week. Other than her oral pain and dysgeusia, she denied neuropathy; she also denied episodes of marked hypertension, wheezing, or diarrhea. There were no suspect medications; she reported an allergy to hydrocodone. On examination, marked malaise, mild word-finding and memory dysfunction, and moderate dermatoglyphism were additionally noted. Although oral examination remained unremarkable, she frequently placed her fingertips to her face about her mouth as if trying to massage away the pain. MCAD was thought to be the best explanation for her full assortment of symptoms. Serum tryptase and chromogranin A, plasma histamine, and 24-hour urinary NMH and PGD$_2$ were normal. However, plasma factor VIII level was markedly elevated (287%, normal range 50%-150%) and plasma free catecholamines showed elevated norepinephrine (690 pg/mL, normal range 80-520 pg/mL) and dopamine (28 pg/mL, normal range 0-20 pg/mL). Blind biopsies were taken throughout the gastrointestinal tract on bidirectional endoscopy but were normal on hematoxylin and eosin (H&E) staining and CD117 immunohistochemical staining. Flow cytometry was not available, and the patient declined to undergo marrow examination.

She experienced no improvement after 2 weeks of twice-daily loratadine 10 mg and famotidine 40 mg, but within 2 days of starting twice-daily aspirin, she began realizing significant improvement in all symptoms, improving further as the dose was increased. At an aspirin dose of 650 mg twice daily, her oral pain was “tremendously” improved at 6/10, and at 975 mg twice daily it was 3/10. She appeared energetic and happy. Cognitive dysfunction appeared resolved, and she no longer placed her hands to her mouth. Dermatoglyphism persisted unchanged. Improvement had been sustained 5 months so far at the time of writing, except for a 4-day period of abstinence from aspirin before a procedure, during which time her burning oral pain returned within 2 days to 9/10 but remitted again to 3/10 shortly after resuming aspirin.

DISCUSSION
The etiology of BMS has long been unclear. Known causes of diffuse oral mucosal pain include infection (most commonly candidal), erosive inflammatory disorders, oral cancer, allergy, Sjögren disease, and medication side effects. However, the essence of primary/idiopathic BMS is chronic oral mucosal pain with no clear provocation and no detectable explanatory oral pathology. Although the true nature of their relationship to BMS remains unclear, many comorbidities and abnormalities have been recognized in BMS patients, including stress, fatigue, psychiatric illness (especially anxiety and depression), inflammatory syndromes, nutritional deficiencies, type 2 diabetes, dysfunctional uterine bleeding, menopause, pruritus, tinnitus, contact or systemic allergy, autoimmune, anemia, and central and peripheral neural dysfunction. Given the etiologic uncertainty and associative menagerie in BMS, treatment unsurprisingly remains unsatisfactory. Symptoms persist for most BMS patients, engendering much consultation and testing, often to little avail.

The mast cell and associated disease were first recognized more than a century ago. In 1869, Netterton and Tay described a rare urticarial skin disease, a symmetric distribution of pigmented maculopapular lesions later termed UP. In 1877, Ehrlich described a granule-laden connective tissue cell with unique metachromatic staining properties, which he termed a mastelle, or well nourished cell. In 1887, Unna associated MCs with UP, and in 1949 Ellis associated MCs with internal disease, initially defining SM. In 1987, Schwartz identified tryptase as a marker of SM, and in 1995 Furitsu et al. identified the D816V activating mutation of the KIT transmembrane receptor tyrosine kinase (CD117), which later was proved to be present in most adult SM. In 1998, Escribano et al. showed some SM MCs, unlike any known normal cells, coexpress CD117/CD25 or CD117/CD2. Many features of SM, such as mast cell aggregation, spindle morphol-
ogy, and CD25 expression, are now understood to be specifically driven by the \( KIT \) D816V mutation.\(^{16} \)

MCs are of hematopoietic origin but circulate only briefly early in their development and complete maturation in a wide distribution of tissues. Although overall much more sparsely distributed than most other types of cells, MCs are relatively abundant beneath environmentally exposed epithelial surfaces and adjacent to blood and lymphatic vessels, permitting sentinel function.\(^{25} \) MC recruitment, development, and survival are governed principally by interactions between \( KIT \) and its ligand (stem cell factor). Although other rare forms exist, the spectrum of MCD is principally divided into cutaneous mastocytosis (CM), SM, and MCAD. Both CM (usually diagnosed in childhood) and the 10-fold less prevalent SM (most common in middle-aged adults) are rare proliferative diseases of equal gender distribution. Prevalence estimates for SM and CM are in the range of 0.001\% to 0.01\%.\(^{6,8,14,26-28} \) The various forms of CM (UP is most common) are limited to skin involvement. SM usually involves the skin, too, but extracutaneous involvement is additionally present. SM is generally subdivided (per current World Health Organization diagnostic criteria\(^{11} \)) into indolent SM (by far the most common form), SM with associated clonal hematologic non-MC lineage disorder, aggressive SM (involving organ dysfunction due to MC infiltration), and the very rare MC leukemia.

In contrast to SM and CM, MCAD is a more recently recognized entity\(^{8} \) and appears to be relatively nonproliferative and significantly more prevalent, although epidemiologic investigations have not been performed and would be inherently challenging owing to the disorder’s marked genetic and thus clinical heterogeneity. A European consensus in 2007\(^{14} \) proposed diagnostic criteria for MCAD consisting of clinical and laboratory evidence of aberrant MC mediator release and, ideally, pathologic demonstration of abnormal MCs, all in the absence of meeting formal criteria for proliferative bone marrow.\(^{30} \) Therefore, elaboration of different sets of mediators in different MCAD patients results in different symptoms (in multiple body systems, synchronously or dis-synchronously, and often subtle or slow to develop) and different objective findings and secondary illnesses. The symptoms in MCAD often are traceable to childhood or adolescence and typically are intermittent and/or fluctuant over years to decades. Frequent health provider consultations (often to little avail) and substantially delayed diagnosis are the norm. Before diagnosis, MCAD patients typically are seen as inexplicably chronically ill and learn to live with their symptoms, many of which come to be attributed by default to aging or circumstantial events. Contrary to the typical paradigm in which specific symptom A + specific examination finding B + specific laboratory result C leads to suspicion of diagnosis D, an underlying MCAD can be reasonably suspected in the patient who suffers any assortment of chronic idiopathic ailments potentially explicable by aberrant MC mediator release, as well as in the patient in whom a definitively diagnosed major illness is insufficient to explain some aspects of the presentation (e.g., frequent syncope in an early-stage lymphoma patient).

Although some of the laboratory and pathologic consequences specifically resulting from the \( KIT \) D816V mutation in SM are now known,\(^{16} \) research to identify the specific consequences of the other mutations found in MCAD is just beginning. The causes of the mutations in MCD are unknown; hypotheses include genetic or epigenetic inheritance and infections by DNA-transforming viruses. The mutagenic capacity of some viruses has been well established, and the ability of some viruses to infect MCs has also been established,\(^{31} \) though no MC-infecting mutagenic virus has yet been identified.

MCs elaborate scores of mediators, but few (e.g., tryptase, histamine, PGD\(_2\)) are relatively specific to MCs,\(^{32-34} \) increasing the importance of clinical assessment in diagnosis of MCAD. In SM, tryptase (comprising \(~25\% \) of the MC’s total protein load\(^{35} \)) is commonly elevated in the serum and reflects the extent of the proliferating MC population. In contrast, in MCAD serum tryptase is usually normal\(^{16} \) and one or more surveys of other MC mediators (e.g., histamine, PGD\(_2\), heparin, carboxypeptidase A, serotonin,\(^{36} \) chromogranin A,\(^{36} \) catecholamines,\(^{37} \) factor VIII,\(^{38} \) etc.) may be required to identify, or at least suggest, aberrant MC activity. No standard screen has been defined based on evidence, but in practice an assessment of serum tryptase, plasma histamine and PGD\(_2\), and uNMH and uPGD2 (preferably while off NSAIDs) constitutes a reasonable initial screen, possibly repeated (and/or fol-
lowed by assessment of other mediators, such as noted above) if the initial screen is negative but clinical suspicion persists. Although the mediators aberrantly expressed in any given variant of MCAD may be most increased when the patient is most symptomatic, increases above normal nevertheless can usually be found in one or more mediators (even between, or without, frank “attacks”) and may warrant subsequent search for histologic evidence. Identifying elevated MC mediators is challenging for many reasons, including unpredictable durations and periodicities of mediator release, brief half-lives, and heat lability. Twenty-four-hour chilled urine samples can be difficult to collect and transport properly but provide a better understanding of average mediator levels unless spot urine or blood samples can be collected within a few hours of a frank anaphylactic episode.

Detection of aberrant MCs is desirable (but not required) as diagnostic confirmation before treatment. In SM, MC aggregates are commonly found in marrow, nodes, gastrointestinal and respiratory tracts, and skin. However, in MCAD, aggregates of MCs are rarely found and quantitative and/or qualitative MC aberrancy is usually shown via molecular techniques, such as immunohistochemistry and multicolor flow cytometry. The sparse and patchy distributions of MCs in MCAD also may inhibit detection of their increased numbers via random biopsies (as in the present case 3), and KIT mutation analysis is constrained by lack of commercial assays for most of the non-D816V mutations found to date in MCAD. Diagnosis is further complicated by the pleomorphism of MCs, which can masquerade as lymphocytes (as in the present case 1), plasma cells, macrophages, histiocytes, or spindle cells. Therefore, even when H&E staining of biopsies shows no increase in MCs of classic appearance, advanced pathologic analysis for MCD (e.g., tryptase, giemsa, toluidine blue, and/or CD117 stains; flow cytometry for coexpression of CD117/CD25 or CD117/CD2, etc.) is warranted when clinical findings are suggestive of MCD. The cases here and in other reports suggest that a gastrointestinal tract survey with random biopsies evaluated specifically for MCD may be more productive in an evaluation for MCAD than marrow examination, but this point has not been specifically studied.

Treatment of MCAD is almost as challenging as diagnosis. Standard therapy remains undefined, and it is not presently possible to predict which one or more of the several therapies available will prove to be optimal for the individual patient. Therapeutic approaches include inhibiting mediator production (e.g., NSAIDs, such as aspirin, often requiring high doses), blocking released mediators (e.g., histamine H1 and H2 receptor blockers, leukotriene inhibitors), and/or stabilizing activated mast cells (e.g., cromolyn, pentosan, interferon, or tyrosine kinase inhibitors, such as imatinib). Standard dosing of any of these agents for the purpose of controlling MC disease is not established. In practice, selection and optimal dosing of these agents remain largely empiric and vary substantially among patients. For example, celecoxib was prescribed as 200 mg twice daily in case 1 versus 100 mg once daily in case 2 because patient 1’s pain objectively appeared much worse than patient 2’s. Financial issues sometimes affect treatment selection and dosing as well. An effective regimen is identifiable in most patients, but patience often is required while progressing through multiple therapeutic trials. Cytotoxic chemotherapy typically provides little benefit, and cellular therapy (i.e., allogeneic stem cell transplantation, usually performed for refractory hematologic malignancies which develop secondarily to MCD) almost never eradicates MCD.

Although criteria for SM were not met in the present 3 cases, MCAD was supported by consistent clinical histories and investigations as well as by responses to MCAD-directed therapy. Although the therapeutic responses of BMS symptoms to MCAD-directed therapy suggest that MC mediators may have directly or indirectly caused these symptoms, the identities of the specific mediator(s) and pathway(s) responsible for BMS symptoms remain unknown. Therefore, the relationship of MCAD to BMS remains one of association, not causation. The differential findings of mediator expression in the patients reported here suggest that yet other mediators not examined may have been the culprits either in activating oral tissue nociceptors or more proximal neural pathways or in otherwise causing neurotoxicity in the oral nociceptive pathways.

Of note, the mélange of clinical problems often found in association with BMS mirrors the marked clinical heterogeneity of MCAD. Thus, one potential unifying explanation for the wealth of diseases, syndromes, and findings inexplicably associated with idiopathic BMS is that assorted variants of MCAD may underlie at least some portion of the heterogeneity of associated findings in some BMS patients. Given that many MC mediators have inflammatory and neuropsychiatric effects, this hypothesis is not inconsistent with current thinking regarding a neuropathic origin to BMS. MCAD perhaps can even explain some of the oddest associations with BMS, such as the rare idiopathic Cronkhite-Canada Syndrome (CCS) involving nonadenomatous gastrointestinal tract polyps and, in different CCS subtypes, varying incidences of burning mouth, dysgeusia, xerostomia, diarrhea, abdominal discomfort, alopecia, hyperpigmentation, and nail dys-
trophy. Gastrointestinal histologic observations and therapeutic response similar to those found in case 1 have also been described in a CCS patient.45

Although the true nature of the relationship between MCAD and BMS remains unclear, the findings in the present report suggest that MCAD should be considered in the differential diagnosis of primary/idiopathic BMS in patients who also have other findings (e.g., episodic presyncope) for which the complex (but not especially enigmatic) biologic behavior of MCAD provides a potentially unifying explanation. Evaluation for MCAD may even be warranted in carefully assessed patients whose sole symptoms are BMS symptoms but who are not found to harbor any of the other diseases traditionally associated with BMS. Comprehensive history and physical examination remain the clinician’s best tool for initially directing the evaluation of BMS symptoms. Given the morbidity and prevalence of BMS, further research into the potential relationship between MCAD and BMS, and the utility of MCAD-directed therapy for BMS, may be warranted.

The author thanks David Lewin, MD (Department of Pathology, Medical University of South Carolina) for providing the photomicrographs in Fig. 1.

REFERENCES


Reprint requests:
Lawrence B. Afrin, MD
Division of Hematology/Oncology
CSB903, MSC635
Medical University of South Carolina
96 Jonathan Lucas St.
Charleston, SC 29425-6350
afrinl@musc.edu