

## CASE REPORT

# The Role of The Immune and Endocrine Function in Burning Mouth Syndrome Patient with Moderate Depressive Episode Accompanied by Gastro-Esophageal Reflux Disease

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## ABSTRACT

**Background:** Burning mouth syndrome (BMS) is a chronic disease characterized by taste change and burning feeling of clinically normal oral mucosa. This case report was to discuss the role of immune and endocrine function in BMS. Patient had moderate depressive episode and her general health was worsening by Gastro-Esophageal Reflux Disease (GERD). **Case:** A 19-year-old female complained about burning feeling in her entire mouth shortly after had chili sauce. She already felt the burning sensation episodes for four months. She also complained about the same burning feeling in her chest especially when eating spicy and sour food. She also had another complaint of anxiety and stress. After a thorough history, physical and supportive examinations and followed by filling out Depression Anxiety Stress Scale 42 (DASS 42), patient was referred to ENT, internist and psychiatrist. The diagnosis was concluded as BMS in moderate depressive episode patient with GERD. To reduce the oral symptoms, patient was advised to avoid spicy and sour food. She was also prescribed with chlorine dioxide oral mouthwash and sterile soda bicarbonate water. At the same time, the internist prescribed lansoprazole and braxidin, while the psychiatrist prescribed sertraline and clobazam. **Conclusion:** The etiology of BMS in this case is not fully understood, but it is thought to be multifactorial with local, systemic and psychological factors. A thorough work-ups and follow-ups were important to build patient's trust and contribute to the successful of the treatment plan. In the management of BMS, recognition and elimination of GERD as triggering factors in this case were crucial, which eventually reduce intensity, recurrence and frequency of the burning sensation.

**Key words:** *Burning mouth syndrome, GERD, depressive episode*

## INTRODUCTION

Emotional factors have potential influence physically and could manifest in all of our bodies, including pathological changes or subjective symptoms in gastrointestinal tract.<sup>1</sup> In the stomach, psychological disorder may induce the development of Gastro-Esophageal Reflux Disease (GERD), while in the oral mucosa one of the manifestation is burning mouth syndrome (BMS).<sup>1</sup>

BMS is defined as burning sensation in the absence of any apparent findings in the mouth and blood test.<sup>2</sup> This syndrome affected mostly female rather than male with ratio of 3:1.<sup>3</sup> BMS was subclassified into primary and secondary.<sup>2</sup> Primary BMS stands for the condition which neuropathological cause is likely to be the cause and cannot be attributed to any other systemic or local cause.<sup>2</sup> Secondary BMS resulting from local or systemic pathological conditions.<sup>4</sup>

Various etiologies can lead to BMS and may be contributed by more than one factor, which makes patient visit different medical specialists. Psychological disorders are common conditions that play important roles in the occurrence of BMS either directly or indirectly.<sup>1</sup>

A moderate depressive episode (MDE) is an affective disorder, which is characterized by the presence of at least one of the five main symptoms and had present for at least two weeks.<sup>3</sup> The symptoms involved in this condition are depressed mood, decreased interest and pleasure, guilt or worthlessness, loss of appetite or weight, and suicidal.<sup>5</sup> Common somatic symptoms are often found in patients with MDE, including fatigue, lack of energy and painful physical symptoms.<sup>6</sup> Moderate depressive episode can induce GERD and subsequently lead to BMS or directly induces BMS.<sup>7,8</sup>

GERD is a condition with multifactorial etiologies characterized by the reflux of stomach content into the esophagus, which causes several symptoms such as heartburn radiating upward to the oral mucosa.<sup>9</sup> GERD is categorized into two subtypes based on endoscopic findings: erosive reflux disease (ERD) and non-erosive reflux disease (NERD).<sup>4</sup> Many studies have investigated the relationship between functional gastrointestinal disorder and psychological factors. Relationship has been established between the brain and the gastrointestinal tract.<sup>10</sup>

The aim of this paper is to report on the management of BMS associated with moderate depressive episode with GERD in a 19-year-old female patient.

## CASE REPORT

A 19-year-old female patient came to The University of Airlangga Dental Hospital, Surabaya with a chief complaint of burning sensation in her entire mouth. This sensation had started shortly after consumption of chili sauce a month before. The complaint was followed by a sore throat, fever, and pain on the palate and buccal mucosa. Patient had previously visited a doctor at a primary health centre and had been prescribed with dexamethasone 0.5 mg, cefadroxil 500 mg and povidone iodine 1% mouthwash. Intraoral examination revealed no abnormality (**Figure 1A**) except hyperemic mucosa on the tonsils and oropharynx (**Figure 1B**). Body mass index was normal with temperature 36.4°C.



Figure 1A. The intraoral mucosa showed no abnormality on the first visit

The working diagnosis in the initial visit was chronic tonsillopharyngitis with a differential diagnosis COVID-19-related symptoms and BMS. Povidone iodine 1% mouthwash was given as antiseptic mouthwash. Treatment plan for the second visit were sialometric examination, and referral for SARS-COV-2 PCR test, blood test. The patient was also referred to Ear, Nose, and Throat (ENT) specialist.



Figure 1B. Hyperemic mucosa on the tonsils and oropharynx on the first visit

On the follow up meeting through teledentistry eight days since the first visit, patient still experienced burning sensation on her buccal mucosa and followed by a sore throat. At this teledentistry session, a further anamnesis revealed that patient had been diagnosed with tuberculosis and on anti-tuberculosis therapy for six months. During this visit, the patient expressed her anxiety and stress related to her serious disease due to independently browsing the internet about the disease. According to this finding, the questionnaire Depression Anxiety Stress Scale 42 (DASS 42) was introduced and filled out. The DASS 42 questionnaire results showed depression score 17 (moderate), anxiety score 19 (severe), stress score 27 (severe). On intraoral examination, there was no mucosal change except hyperemia and keratosis in the tonsil and oropharynx mucosa. Patient had been tested negative for SARS-COV-2 antigen test, thus COVID-19 was excluded. The working diagnosis of this case was changed to BMS with psychological stress, while chronic tonsillopharyngitis was considered as differential diagnosis. Previous symptomatic therapy was halted and changed to chlorine dioxide mouthwash and neutropin vitamin. Patient was referred to ENT clinic to exclude differential diagnosis and to psychiatry clinic to ascertain risk factors.

Patient came back to Dental Hospital of University of Airlangga on the 14th day since the first appointment. She still experienced burning sensation in her mouth, especially after eating spicy and sour food. The sore throat was followed by heartburn. Sialometric examination was performed with normal unstimulated salivary rate (0.5 ml/minutes). Blood tests were performed to monitor the patient's general health status and to confirm the presence of nutritional deficiencies as risk factors (**Table 1**) However, blood examination showed normal results in all panels. On this visit, patient revealed that she had psychological trauma from her adoptive mother's death due to illness. The patient was anxious that she might also experience similar disease as well. The diagnosis and supportive intraoral therapy remained the same. In ENT clinic, she was diagnosed chronic tonsillitis and treated with amoxicillin trihydrate 500 mg, diclofenac sodium 50 mg and dexamethasone 0.5 mg. The sore throat persisted even after she took all the prescribed medications. Intraoral examination at the next visit showed hyperemia on the tonsils and oropharynx. The patient was informed that she will be referred to an internist to examine her heartburn complaint and also to psychiatrist based on mental complaints and the DASS 42 score.

Fifty-one days since the first visit, patient had a follow-up appointment via teledentistry. Her complaints of burning sensation in the mouth and heartburn were getting worst. Patient admitted that she was hospitalized for GERD and was currently under observation by an internist. She was on medication consisted of lansoprazole and braxidin. The whole abdomen ultrasound examination showed no abnormality. Endoscopy and biopsy of the gaster by gastroenterologist revealed hyperemic on the antrum and without any erosion, ulcer nor inflammation in the gaster, esophagus and duodenum. Based on the classification of GERD, this finding was classified into a non-erosive reflux disease (NERD). On histopathology examination of the antrum mucosal tissue, infiltration of polymorphonuclear neutrophils was found without any sign of malignancy. The presence of *Helicobacter pylori* was negative. Clinically, there was atrophy of papilla on the posterior dorsum of the tongue, unilocular, with the size of 4x5 cm, clearly delineated and irregular border lesion which was tender on palpation (**Figure. 2**). At this stage, the working diagnosis was changed to BMS with GERD associated to psychological stress. Previous symptomatic therapy was ceased and changed to a new prescription instructions for gargling with  $\frac{1}{4}$  tsp baking soda +  $\frac{1}{8}$  tsp salt + warm water gargle three times a day. The patient was then planned to be referred to psychiatrist.

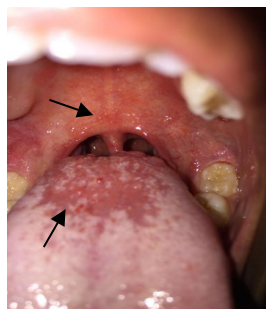


Figure. 2 Atrophy papilla on the posterior dorsum of the tongue, unilocular size 4 X 5 cm with irregular border.

One hundred and six days since first visited, patient still complained of burning sensation in her mouth, heartburn and cough. Mouthwashing with baking soda was regularly done by the patient three times a day. On intra-oral examination, there were no mucosal abnormality related to burning sensation except erythema of the oropharynx (**Figure 3**). During this visit, the patient admitted that she was reluctant to see a psychiatrist because she was worried that she would be put in “pasung” (the extinct traditional practice to treat mental illness patients by seclusion or restrain) if she was treated by the psychiatrist. Eventually, she was willing to do counseling with a psychiatrist and get the treatment after receiving some persuasion. Patient was diagnosed by psychiatrist of moderate depressive episode (MDE) with somatic symptoms according to ICD X diagnosis criteria. Patient was prescribed with sertraline 50 mg and clobazam 10 mg.

On objective examination, seven days after the psychiatric session and after taking the drug, the patient felt more relaxed. She reported burning sensation in her mouth and heartburn were getting better gradually. She was then advised for routine follow-up visit to psychiatry clinic and continued taking medication.



Figure 3. Normal appearance of oral mucosa. Arrow showed the hyperemia of the oropharynx and tonsils mucosa.

Table 1. The Blood Analysis

Parameter	Value	Normal range
Hemoglobin (g/dl)	18.0	12.0-17.4
Leukocyte ( $10^3/\mu\text{l}$ )	7.92	5-10
Eritrocyte ( $10^3/\mu\text{l}$ )	5.06	4.0-5.2
Hematocrit (%)	36,85	36-52
Trombocyte ( $\mu\text{l}$ )*	226,000	150,000-450,000
MCV (fl)*	67	76-96
MCH (pg)*	21.7	27-32
MCHC (g/dl)	32.4	30.0-35.0
RDW (%)	12.8	11.5-14.5
MPV (fl)	9.8	6.8-10
Limphocyte (%)	19.9	25-70
Monocyte (%)	4.5	3-7
Granulocyte (%)	77.6	50-75
Basophil (%)	1	0-1
Segmented neutrophil (%)	67	50-70
ESR (mm/hours)	20	0-25
Procalcitonin (%)*	0.29 %	<0.05 %

\*Abnormal value

**Table 2.** Treatment Management Steps

Treatment Step	Diagnosis	Symptoms	Management Treatment	Oral and Systemic Treatment	Result	Differential Diagnosis	Possible Predisposition Factor
<b>1<sup>st</sup> Step</b>	Susp. Chronic tonsillopharyngitis	<ul style="list-style-type: none"> <li>Burning mouth sensation</li> <li>Sore throat</li> <li>Fever</li> <li>Sore in palatum and buccal mucosa</li> </ul>	<ul style="list-style-type: none"> <li>CBC Test</li> <li>Sialometri</li> <li>Swab antigen/PCR SARS CoV 2</li> </ul>	<ul style="list-style-type: none"> <li>Povidone iodine 1 % mouthwash</li> <li>Neurotropic Vitamin</li> </ul>	<ul style="list-style-type: none"> <li>CBC test → normal</li> <li>Sialometri → Normal (0,5 ml/minute)</li> <li>Antigen swab → negative</li> </ul>	<ul style="list-style-type: none"> <li>Burning Mouth Syndrome</li> <li>Covid-19</li> </ul>	Nutritional Deficiency
<b>2<sup>nd</sup> Step</b>	Susp. Burning Mouth Syndrome	<ul style="list-style-type: none"> <li>Burning Mouth sensation</li> <li>Sore Throat</li> <li>Anxiety</li> </ul>	<ul style="list-style-type: none"> <li>Visited ENT specialist</li> <li>DASS-42 examination</li> </ul>	<ul style="list-style-type: none"> <li>Chlorine dioxide mouthwash</li> <li>treatment form ENT (Amoxicilin trihydrate, dexamethasone, natrium diclofenac)</li> </ul>	<ul style="list-style-type: none"> <li>ENT → Not responding treatment</li> <li>DASS → D (17) moderate A (19) Severe S (27) severe</li> </ul>	Chronic Tonsillitis	Psychological Factor
<b>3<sup>rd</sup> Step</b>	Susp. Burning Mouth Syndrome Associated GERD	<ul style="list-style-type: none"> <li>Burning mouth sensation</li> <li>Sore throat</li> <li>Heartburn</li> <li>cough</li> </ul>	<ul style="list-style-type: none"> <li>Patient being hospitalized and under supervision internist</li> </ul>	<ul style="list-style-type: none"> <li>Chlorine dioxide mouthwash</li> <li>treatment form Internist (Lansoprazole, Brazidin)</li> </ul>	<ul style="list-style-type: none"> <li>USG → normal</li> <li>Endoscopy → hyperemia in antrum; erosion (-), Ulcus (-), inflammasi (-) in gaster, esophagus, duodenum</li> <li>Biopsy gaster → no malignancy, proliferation PMN, H.Pylori (-) <ul style="list-style-type: none"> <li>Internist Diagnosis → GERD</li> </ul> </li> </ul>		Psychological Factor
<b>4<sup>th</sup> Step</b>	Burning Mouth Syndrome in Moderate Depressive Episode with somatic syndrome in patient with GERD	<ul style="list-style-type: none"> <li>Burning mouth sensation</li> <li>Sore throat</li> <li>Heartburn</li> <li>Cough</li> <li>Atrophy papilla on the tongue</li> </ul>	<ul style="list-style-type: none"> <li>Consultation session with psychiatry</li> </ul>	<ul style="list-style-type: none"> <li>gargling with baking soda 1/4 tsp + 1/8 tsp salt + warm water</li> <li>Treatment from Psychiatry (Sentriline 50 mg, clobazam 10 mg)</li> </ul>	<ul style="list-style-type: none"> <li>Psychiatri diagnosis → Moderate Depressive Episode with somatic syndrome in</li> </ul>		

## DISCUSSION

Burning mouth syndrome remains a challenging disorder for health care providers and is probably of multifactorial origin with uncertain aetiopathogenesis. Patients experienced burning sensation especially on the tongue and buccal mucosa, tender, tingling and numbness of the oral mucosa. The etiology of BMS remain unclear, but psychiatric disorder and GERD can induce BMS, either directly or sequentially.<sup>11</sup>

Psychological assessment was performed using the Depression Anxiety and Stress Scale-42 (DASS-42). The DASS-42 has excellent psychometric qualities and has been found to be valid and reliable across studied populations.<sup>12</sup>

In this case report, a 19-year-old female complained burning sensation in all over her mouth which then followed by heartburn. She was grieving and had lost her loved one when she was 16 years old due to untimely diagnosed illness. Her adoptive mother was considered as the source of affection for her. After her adoptive mother passed away, the patient was raised by her biological mother, who was considered unwise and being criticized for her inconsistent parenting. It was known that loss of love object event was one of the cause of stressors in anxiety patients. This has been recorded in a study that somatic symptoms may be caused by depressive and anxiety. Further explanation stated that the combination of etiological factors (e.g. interaction with family, trauma event, loss of love object) independently cause the onset of depressive disorders as well as the somatic symptoms.<sup>13</sup>

Somatization was closely related to gastrointestinal sensorimotor processes, including gastric sensitivity through bidirectional signaling mechanisms between the gastrointestinal tract and the central nervous system (brain-gut axis).<sup>5</sup> This process involved into modulation of visceral afferent signals and the influence of efferent output of central stress and emotional, arousal circuits on motor and immune functions of the gastrointestinal tract.<sup>14</sup>

Another mechanism is that persistent anxiety problems lead to hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, a contributing factor to MDE.<sup>6</sup> This hyperactivity may be caused by a malfunction of the glucocorticoid receptor, and impairs the negative feedback circuit of the HPA axis.<sup>6</sup> Damage to glucocorticoid receptors can cause depression through impaired neurogenesis and decreased hippocampus volume, include serotonin, thereby increasing cortisol levels and causing altering in the immune system.<sup>15</sup>

Decreasing the production of serotonin and increasing the production of tryptophan catabolites that are toxic for the brain and increased levels of the pro-inflammatory cytokine interleukin (IL-2) and acute phase C-reactive protein and tumor necrosis alpha.<sup>7</sup> IL-2 stimulates secretion of proinflammatory cytokines such as IL-1, TNF- $\alpha$  and TNF- $\beta$ , inducing infiltration and activation of immune cells that result in recruitment of greater numbers of macrophages, mast cell and T-lymphocytes, creating a vicious cycle that makes the inflammatory state constant and chronic.<sup>7</sup> Proinflammatory cytokines are associated with nociceptive signaling and are usually increased in neuropathic pain disorder include BMS.<sup>7</sup> This cytokine also induce inflammation on the gastrointestinal tract, include gaster and oral mucosa.<sup>15,16</sup>

Both of these mechanisms can explain changes in the gastrointestinal system. In this case report, somatic symptoms were found in the form of BMS and NERD. The two complaints can be directly or sequentially act as a manifestation of MDE. Based on the psychopathology above, it is the reason for the MDE with somatic symptoms.

GERD is a condition characterized by the reflux of stomach content into the esophagus, which causes several symptoms such as heartburn radiating toward the mouth.<sup>8</sup> This disease results from an imbalance between harmful properties of refluxed stomach content, mechanism of esophageal clearance and esophageal mucosal resistance.<sup>8</sup> Common risk factors for GERD include the absence of a hiatus hernia, a low BMI, presence of *H. pylori*, and also psychological factors including anxiety and depression. Among the two of GERD subtypes based on endoscopic findings (Erosive and Non-Erosive Reflux Disease), NERD is closely related to MDE.<sup>10</sup> This patient was diagnosed with BMS as a result of the underlying psychological condition, which was MDE with somatic symptoms and worsened by GERD.

Therapy given to the patient was a chlorine dioxide agent with the brand name Oxyfresh® lemon mint, which contain peppermint oil and sodium citrate. Sodium citrate was known to induce saliva production while stabilized chlorine dioxide functioned as the disinfectant and sanitizing agent,

and also aloe vera which functioned as an anti-inflammation.<sup>9</sup> Other ingredients such as zinc, folic acid, aloe vera and chamomile help accelerate wound healing and reduce the sensation of pain.<sup>10</sup>

The topical intraoral therapy was replaced in the follow up visit into gargling with baking soda or sodium bicarbonate (NaHCO<sub>3</sub>) and warm salt water right after the patient was diagnosed with NERD type. This gargle helped neutralizing the acidity in the mouth.<sup>11</sup> The acid-based balance acting as a buffer can help neutralize acids caused by NERD.<sup>12</sup> It also could prevent further hyperemic and burn sensation caused by acidic reflux in the oropharynx and intraoral areas.<sup>17,18</sup> Some clinical findings in this patient that suggest acid involvement in the oral cavity were the depapillation at the base of the tongue and erosive palate. These are typical findings of oral manifestation of gastric acid that rises to the oropharynx and intraoral.

In addition, the patient was prescribed sertraline 50 mg and clobazam 10 mg by psychiatrist. Sertraline is a selective serotonin reuptake inhibitor (SSRI) selective and potent inhibitor of serotonin reuptake, also known as inhibitor of serotonin transporter.<sup>3</sup> Sertraline is commonly used for depression, obsessive compulsive disorder (OCD), bulimia, and panic attacks.<sup>3</sup> Clobazam is a medication for seizure and anxiety disorder. Clobazam works by balancing the flow of electricity in the brain and relaxing the muscles that tense up during a seizure.<sup>5,12</sup> However both drugs are also reported would cause xerostomia and also dysgeusia, these were anticipated for the next patient follow ups.

## CONCLUSION

Treatment of MDE patients requires extra care with psychosocial intervention. Long-term care is required to the management of BMS in these patients. A thorough work ups and follow ups were important to build patient's trust and contribute to the successful of the treatment plan. Close communication among health professionals (dentists, psychiatrists and internists) was needed. In the management of BMS, recognition and elimination of NERD as a triggering factor in this case report were crucial and eventually reduce intensity, recurrence and frequency of the burning sensation.

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## CONFLICT OF INTEREST

The authors declare that there were no conflicts of interest related to this case report.

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