

CASE REPORT

The Occurrence of Oral Allergic Reaction in Patients with Illness-Anxiety Disorder: An Imaginary Illness Turns into a Real Lesion

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ABSTRACT

Background Allergic reaction affects up to 30% of the world's population, with underlying pathophysiology involving immunoregulatory dysfunctions and the most common oral symptom is ulceration. **Case Description** A 33-year-old male patient did doctor shopping of Oral Medicine Specialists in Jakarta with the fear of having oral cancer and was diagnosed of hypochondriasis by psychiatrist. The patient noticed a small irregular red macule on the palate that grew wider every day. There was no pain, bleeding or migration of lesion reported. Hematology profile showed an increased level of Immunoglobulin E (IgE). The red macule completely resolved after administration of Loratadine 10 mg once daily for a month. The patient was educated for routine oral check-up and psychiatry consultation. **Conclusion** Hypochondriasis may cause immunoregulatory imbalance by modulating Th2 cytokines system that is responsible in IgE level and may produce the unspecific oral manifestation which gave positive response with antihistamine drug.

Key words: illness-anxiety disorder, hypochondriasis, allergy, oral manifestation

INTRODUCTION

Anxiety is one of the most common mental health problems and commonly affect young age, but is behind depression in term of research and clinical screening.^{1,2} Anxiety is hardly screened in primary health care although it can impair one's function and productivity.¹ Studies found that only 15% to 36% of all anxiety cases can be recognized in primary health care.¹ Anxiety mostly described as a worry feeling and considered as a normal thing. However, when it comes to severe condition which impair one's function and productivity, it becomes a physical disease.² Anxiety also has been associated with alcohol abuse, smoking habit, low socio-economic, history of psychotherapy and psychology problems, history of addiction, chronic diseases, physical activity, obesity, being unmarried, and unemployed.³⁻⁵

The prevalence of anxiety is quite high, with around 272.2 million cases globally with predominantly affect female.⁶ The prevalence is found to be high in countries that are in conflict, high income, and Latin America.⁶ Another study from World Health Organization World Mental Health Survey Initiative found that among 85,052 respondents from 17 countries, the lifetime prevalence of anxiety disorder was 14.3% and the 12-months prevalence was 8.3%.⁷ The prevalence of anxiety disorder was found the lowest in China (lifetime: 4.8%; 12-month: 3%), and the highest in the United States (lifetime: 31%; 12-month: 19%).⁷ Based on the first national survey done by the University of Gajah Mada and other collaborators in 2022 published on the University website, in Indonesia, 3.7% of teenagers suffer from anxiety disorders (a combination of social phobia and generalized anxiety disorder), followed by major depressive disorder (1.0%), conduct disorder (0.9%), Post Trauma Stress Disorder (PTSD) (0.5%), and Attention Deficit Hyperactivity Disorder (ADHD) (0.5%). Illness anxiety disorder (IAD), previously known as hypochondriasis, is a condition characterized by preoccupation with having serious undiagnosed medical problems and caused the subjects to have excessive health-related behaviors.^{8,9} According to Marcus et al (2007), hypochondriasis subjects tends to misinterpret their body sensation as a serious sign of an illness, which lead to a high level of anxiety and overestimation of the outcome of the illness.¹⁰ Some studies presented strong evidence of the close association of anxiety to medically unexplained symptoms and increased use of healthcare facilities.¹¹⁻¹⁴ It is also strongly suggested that anxiety disorders may cause chronic medical illness, low health-related quality of life and physical disability.^{1,15-18}

There are some studies which link anxiety and allergy, and this is thought to be an anxiety-immune-nervous systems linkage or now known as psychoneuroimmunology (PNI).^{19,20} According to Lennart Seizer (2022), there are three possibly related oral manifestations due to PNI: periodontitis, herpes labialis, and oral lichen planus.²¹ In a study by Gregory, et al (2009), although there was an increased self-reported allergy among individuals with anxiety, however the total Immunoglobulin (Ig) E level was not increased.¹⁹ Immunoglobulin E was measured as it plays important role in allergies and its level usually increases in those with atopy.¹⁹

Here, we discuss a patient with an increasing symptom of IAD due to anti depression drug withdrawal which led to the increased IgE level and occurrence of oral allergic reaction. The oral allergic reaction increased the IAD symptoms and caused the patient to do doctor shopping to seek help from several Oral Medicine specialists.

CASE REPORT

A 33-year-old male patient came to Oral Medicine (OM) Clinic Cipto Mangunkusumo General Hospital, Jakarta with the fear of having oral cancer. The patient works as a financial staff, married with two children. He had no medical history of any systemic disease, routine dental check-up and absence of bad habits (smoking and alcohol drinking). However, the patient admitted that he was currently under psychiatric treatment due to hypochondriasis. The patient was reluctant to take the medication regularly. The hypochondriasis had been diagnosed several months after his mother's death due to lung cancer. He routinely checked up on his mouth condition several times every day. Any minor findings which he considered unusual would raise his anxiety and make him seek Oral Medicine specialists. In times when his anxiety rose, he experienced the occurrence of redness on his face several times, and the redness subsided after topical application of steroid ointment, given by the Internist (Allergy Immunology consultant). The patient also experienced erosions, candidiasis, and chemical burn on the palate due to the application of some drugs prescribed by other specialists to overcome his symptoms (such as high doses of systemic steroids and nitrite solution). The internist (Allergy Immunology consultant) instructed a laboratory test, and the laboratory result showed a slightly increased IgE level (199.6 IU/ml, reference value <150 IU/ml), but a normal value for anti-double-stranded DNA (anti-ds-DNA) and anti-nuclear antibody (ANA). The Internist then referred him to Psychosomatic consultant, but he refused.

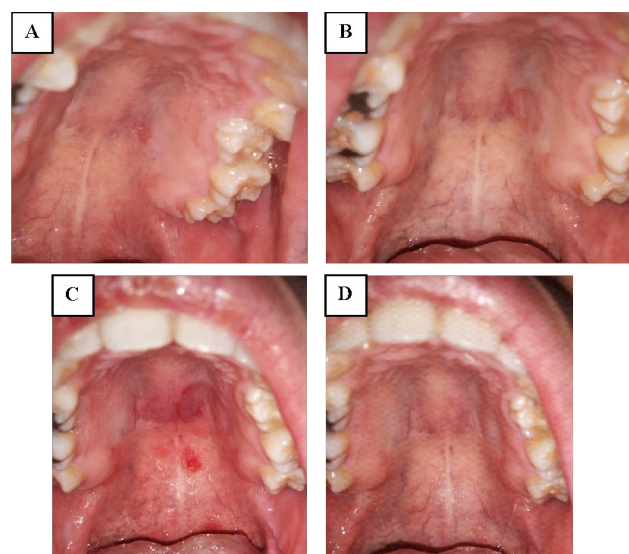


Figure 1. The initial appearance of painless red spot on left hard palate (A). The red spot became more apparent a week after first found (B). The red spot became wider, and another red spot appear three weeks after first found (C). The red spot started to diminish after continuation of psychiatric medication and commencement of antihistamine drug (D).

Previously, he only visited the Oral Medicine specialist every two or three months, to have a routine full mouth check-up for an oral cancer screening, as his psychiatrist suggested him to do so. The last couple of months, his hypochondriasis symptoms rose as he discontinued the psychiatric medication and refused to have another psychiatric counseling session. He noticed a spot of redness on his hard palate, which was getting wider, without any other symptoms arising. He checked on his palate more frequent than usual, he woke up in the middle of the night just to check up the redness on his palate, he skipped meals to avoid the redness from becoming wider, he was unwilling to go to work or do any household activities, he frequently mentioned about death to his wife, and he isolated himself from his daughters. The intraoral examination showed a painless spot of non-elevated redness (macule) on his left hard palate, without any breach of mucosa (Figures A and B). His laboratory result showed a two-fold increased IgE level (241.7 IU/ml, reference value <100 IU/ml), while other tests were within the normal range. The patient had been prescribed Cetirizine 10 mg once daily by the Oral Medicine specialist which he was reluctant to take due to dizziness. The patient also refused to have a psychiatric counseling session with the thought of having a psychiatric counseling session only when the redness on his palate subsided. During those weeks without any treatment taken, the redness became wider which worsened his anxiety (picture C). The patient visited an Oral Medicine specialist in private practice to check his oral condition for the same complaints. A working diagnosis as oral manifestations of allergy background was made. The patient was prescribed Loratadine tablets of 10 mg once daily for one month while finding out the other possible triggered factor. Fortunately, the redness was gradually fading and then fully subsided (picture D). The follow-up visit was planned one month after the antihistamine treatment commencement. At the follow-up visit, one month after the antihistamine treatment commencement, there were not symptoms and intraoral lesions found.

DISCUSSION

The hypochondriasis patient was diagnosed to have an oral manifestation of allergy. The allergy background was correlated with psychoneuroimmunology. Human has an ability to response against a hostile environment or stress condition with “fight or flight” response as first suggested by Walter Cannon in 1929, with its main function is to keep the human in a balanced condition or maintain body homeostasis.²² The stressful condition can be either a positive or negative event, for example job promotion, losing job, daily hassle, or family member death.²⁰

During this process, hypothalamus stimulates medulla of adrenal gland to secrete adrenaline and noradrenaline, while hypothalamus also produces corticotrophin releasing hormone (CRH) which travel through the hypothalamic pituitary adrenal (HPA) axis.²² The CRH stimulates the release of adrenocorticotrophic hormone (ACTH) to circulation, which then target the cortical cells to release glucocorticoid (GC) into the blood.²² The negative feedback mechanism controls the GC and eventually ends the release of CRH.²² GC is an important mediator in inflammatory response and the low GC and cortisol level which led to increase Th2 response is thought to be an important pathogenic mechanism in chronic allergic disease.²³

Being worry about health condition and alert toward symptoms or body’s changes are considered as a normal expression and can be a useful as an early sign to seek medical evaluation and/or treatment.²⁴ When the worry turns into preoccupation, continuous distress, and interferes daily life, then it falls into an anxiety disorder.²⁴ Anxiety is described as worry feeling and considered as a normal thing, but when it comes to severe condition which impair one’s function and productivity, it becomes a disease.² The prevalence of anxiety is quite high, around 272.2 million cases globally with predominantly affect female,⁶ but only 15% to 36% of all anxiety cases can be recognized in primary care.¹

Hypochondriasis is an anxiety disorder which define as preoccupation with bodily symptoms and fear of having serious illness and life-threatening illness.²⁴ Hypochondriasis can be primary or as secondary symptoms of other mental disorders (e.g: depression).²⁴ The diagnostic criteria for hypochondriasis is somehow considered too narrow and give some challenge in clinical practice.²⁵ According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by American Psychiatric Association 2013, hypochondriatic disorder is changed into illness anxiety disorder (IAD) and somatic symptoms disorder (SSD).²⁴ With the two new categorizations, it is

estimated that 25% of previously diagnosed as hypochondriasis is now met the criteria of IAD, and the other 75% is met the criteria of SSD.²⁵

Illness anxiety disorder (IAD) is a condition which characterized as preoccupation with having serious undiagnosed medical problems and caused the subjects having excessive health-related behaviours.^{8,9} This condition usually lasts more than six months and caused the subjects to routinely and frequently checking up the body for signs and symptoms of a disease with high level of anxiety.⁸ Illness anxiety disorder is considered as a chronic and relapsing condition with an onset frequently in early to middle adulthood.⁹ According to Marcus et al (2007), the hypochondriatic subjects tend to misinterpret their body sensation as a serious sign of an illness, which lead to high level of anxiety and overestimate the outcome of the illness.¹⁰ They believe that healthy body has no physical symptoms and they have no power in preventing an illness to arise or recur.¹⁰ Interestingly, a cohort study showed that with the development of serious medical illness, the anxiety decreased in hypochondriasis patients.²⁶

On previous visits, our patient came with the fear of oral cancer due to his observation of the presence of tongue papillae or reddish blood vessel on soft palate or varicose on ventral of tongue. He was routinely and frequently checking up his oral cavity to find even the smallest pathology sign, and any unusual finding in his oral cavity according to him would lead to worsen anxiety and even thought of dying frequently. He was already educated not to routinely and frequently check-up his oral cavity, but he failed to obey it due to his high level of anxiety.

The criteria diagnostic of IAD according to DSM-5 are: 1) Preoccupation with having or acquiring serious illness, 2) Somatic symptoms are not present or are mild in intensity, 3) High level of anxiety about health or patient easily alarmed about personal health status, 4) Excessive health-related behaviors or maladaptive avoidance of medical settings, 5) Illness worry present for at least six months, and 6) Illness worry not better explained by another psychiatric conditions.^{9,24,26} The DSM-5 categorized IAD into two types, the care seeker and care avoidant.^{9,26} The care seeker type will make the subjects seek many professional help to request diagnostic testing and seek reassurance of the feared illness, and they tend to keep on dissatisfying of their medical care, while the care avoidant will avoid physicians due to their fear of confirmation of their feared illness.^{8,9,26} The care seeker type of IAD patients become a burden to health system due to high health cost. The increased level of anxiety in the care seeker type of IAD patients is related to the increased total outpatient cost, laboratory and radiology cost, procedure cost, frequent visit to specialist, frequent hospitalization and presentation to emergency department.²⁶ Our patient is considered as the care seeker type, as he also did "doctor shopping" to several Oral Medicine specialists in order to ensure him that he does not have oral cancer or other fatal oral diseases, and he also visited internist (Allergy Immunology consultant) to ensure that he does not have any autoimmune diseases.

The IAD subjects choose specific organ as focus of their obsession based on four factors according to Griffith (1984): (1) the organ which originally weak, (2) the family of origin may have modeled its use, (3) the organ may have specific symbolic value to the individual, (4) its use may be fashionable.⁹ As of our patient, the reason why he got obsessed with his oral cavity is unknown, since the focus organ is different than his late mother's disease. His hypochondriasis onset was several months after his mother's death due to lung cancer more than a year ago.

Mental disorders can significantly cause role impairment, work loss and work cut-back.^{27,28} Some studies presented strong evidence of the close association of anxiety to medically unexplained symptoms and increased use of healthcare facilities.¹¹⁻¹⁴ It is also strongly suggested that anxiety disorders may cause chronic medical illness, low health-related quality of life and physical disability.^{1,15-18} In one survey, it is suggested that anxiety disorders had association with hypertension, arthritis, asthma and ulcers.²⁷ The worsen anxiety in our patient led to his unwillingness to engage with his family or any household activities, and to go to work. This influenced his relationship with his family members.

Studies found that psychological stress can escalate clinical symptoms of immune-mediated in patients with allergy.²⁹ One study in patients with allergic rhinitis confirmed the role of anxiety on allergen-induced histamine release.²⁹ Anxious atopy patients have higher incidence of positive skin prick test compare to non-anxious atopy patients.²⁹ It is postulated that in anxious atopy patients, mast cells are activated in response to stress.²⁹ There are some studies which link the anxiety and allergy, and this is thought to be an anxiety-immune-nervous systems link or now known as psychoneuroimmunology (PNI).^{19,20} Allergy can be stimulated by psychological stressor, and based on

the duration, the psychological stressor can be categorized as acute (minute to hours), subacute (less than a month) and chronic (months to years).²⁰ One study even showed an enhancement of allergic inflammatory response due to natural stress exposure.³⁰ In this case, the patient was suffered from chronic psychological stressor.

In a study by Gregory, et al (2009), although there was an increased self-reported allergy among individuals with anxiety, however the total Immunoglobulin (Ig) E level was not increased.¹⁹ Immunoglobulin E was measured as it plays important role in allergies and its level usually increase in those with atopy.¹⁹ Allergy is an immune reaction as a result of the induction IgE that binds to mast cells via high affinity FcεR1 receptors.²⁰ The re-exposure of allergen will cause a cross-linking of mast cells-bound IgE which activate and release of mast cells content (histamine, leukotrienes, tryptase, chymase, kininogenase, heparin), and lead to vasodilatation and vascular leak.²⁰ Afferent nerve fibers express receptors for those mast cell contents.³¹ The activation of C-fiber's nociceptive receptors will cause physiologic changes, including the occurrence of wheal-and-flare reaction.³¹ This nerve-mediated mast cell activation can even be induced by auditory tone as an allergen.³¹ During the relapse of anxiety, our patient experienced wheal-and-flare reaction on his face several times prior the occurrence of a painless spot of non-elevated redness (macule) on his left hard palate, accompanied by the elevation of IgE level.

The late phase allergic reaction occurs after the recruitment and migration of inflammatory cells (eosinophils, basophils, neutrophils, T lymphocytes, and macrophage) to the target tissues.²⁰ The Th2 cytokines play important role in this ongoing inflammation.²⁰ This pathway supports the appearance of oral manifestations as the only flat redness of the oral mucosa due to inflammation result from allergic reaction. The production of IgE itself is under Th2 cytokines control.³² IL-4 and IL-13 are responsible for isotype switch from IgM to IgE, IL-4 is also mast cell growth factor, and IL-5 is a chemotactic, growth and activation factor for eosinophil.³² Allergy can be considered as an immunoregulatory imbalance as Th2 predominate the immune system.²⁰ Some studies suggest that a chronic psychosocial stress is associated with Th2 predominance.²⁰ Thus, it can be concluded that the psychological stress may induce or exacerbate allergy.²⁰ This above allergy-immune pathogenesis is well-suited to the background of this patient, as the oral manifestations can be close related to IAD mechanism and long term anti-histamine may be as one of solution for this case.

CONCLUSION

Illness anxiety disorder (IAD) or hypochondriasis may increase the mechanism of allergy and may produce unspecific oral manifestation. Immunoregulatory imbalance in patient with IAD play important role in the eruption of allergic lesion-like which also related to increased IgE and show positive response with antihistamine drugs.

CONFLICT OF INTEREST

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

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