Dentistry 3000

Vol 5, No 1 (2017)
ISSN 2167-8677 (online)
DOI 10.5195/d3000.2017.66

Could recurrent aphthous stomatitis be linked to cancer development?

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Abstract

Background: Recurrent aphthous stomatitis is a common multifactorial oral mucosal disorder. Genetic and local factors causing RAS may contribute to the development of cancer. This study aims to explore this connection by examining a family with a history of RAS and ovarian cancer. **Case Description:** The family described in the case exhibits a history of minor recurrent aphthous stomatitis. The severity of this condition increases with each generation. One member of the family has no history of RAS but was diagnosed with ovarian cancer. Genetic testing for BRCA mutations was negative indicating a different genetic cause of the cancer. All affected members of the family indicate high levels of stress or difficulty responding to stressful situations. No treatment for RAS was performed due to its self-limiting nature. **Practical Implications:** Further research is needed before dentists begin to tell their patients with RAS they may be at higher risk of developing cancer. Diligent oral cancer screening and stress management counseling can decrease the risk to the patient.

Citation: Norton, E. (2017) Could recurrent aphthous stomatitis be linked to cancer development? Dentistry 3000. 1:a001 doi:10.5195/d3000.2017.66
Received: May 1, 2017
Accepted: May 2, 2017
Published: June 8, 2017

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Introduction

Recurrent aphthous stomatitis (RAS) is the most common oral mucosal lesion, affecting as much as 25% of the world population [1-3]. This condition is characterized by painful erosions or ulcers surrounded by an erythematous halo on the non-keratinized oral mucosa [2, 4]. The lesions may affect the day to day activities of the patients, especially eating, drinking and speaking [3]. Aphthae are identified as one of three types. The three types differ in size of ulcers, healing time and scarring upon healing. The first and most common type, which comprises 80-90% of all cases, is minor recurrent aphthous stomatitis [3]. In these cases, the lesions present are less than 1 cm in diameter, heal within seven to fourteen days and do not scar [3]. The second type is known as major recurrent aphthous stomatitis and is characterized by lesion greater than 1 cm in diameter that heal within 20-30 days with scarring [3]. The final type is known as herpetiform ulcers, which presents are multiple, clustered lesions 1-3 mm in diameter [3]. These lesions may coalesce to form larger lesions and usually heal within fifteen days [3].

Despite being an incredibly common condition, the etiology of recurrent aphthous stomatitis remains unclear. However, there is a general consensus that RAS is a multifactorial condition, with several factors implicated in its occurrence [1, 3, 5]. Many common local factors are thought to be involved such as viral and bacterial infections, allergic agents (such as food hypersensitivity), nutritional deficiencies and stress and anxiety [3-5]. In addition, there are also genetic factors that can predispose an individual to RAS. Certain HLA alleles have been found to be associated with patients with RAS as well as specific racial and ethnic segregations [2, 5]. RAS is associated with certain genetic syndromes such as Behcet's syndrome [5]. RAS is also known to accumulate in families, giving further strength to the theory of a genetic cause [5]. Early studies proposed an autosomal recessive or multigene mode of inheritance with environmental influences [4].

This paper aims to explore the possible connection between RAS and cancer development by examining a family with a history

of RAS as well as cancer. The practical implications of these findings in the dental clinic and possible ethical considerations will also be discussed.

Case Presentation

The family studied exhibits three generations of reported recurrent aphthous stomatitis with varying degrees of severity. One of the family members in the third generation is not affected by RAS, but she was diagnosed with ovarian cancer. Figure 1 is the family's pedigree, showing which individuals have been affected by RAS. Three consecutive generations have been affected, as seen in the pedigree. The family members in the fourth generation have not yet shown as signs of RAS, so their status is currently unknown. Each member's presentation of RAS and account of other risk factors will be discussed individually.

Family Member I:2

The initial presentation of RAS is seen in the first generation, in patient I:2. The family account of her condition is limited at this time. Her son, family member II:1, states he remembers his mother getting "canker sores a few times" when he was growing up. He could not remember any information about the size of the sores or the frequency of the episodes. No other signs that would indicate a systemic disease, such as Behcet's, were reported. Family member II:1 indicated that his mother was not under a high level of stress but did seem to be easily upset in some situations.

Family Member II:1

Family member II:1 indicated that he shared the same proclivity as his mother for "canker sores". He stated that he would get "attacks" about three or four times a year, lasting for about a week at a time. He said that the lesions were "mostly small" and based on this information and known prevalence of the different types of aphthae, it is safe to assume he was afflicted with minor RAS. Again, no indications of systemic disease were noted. When asked about his stress level, he indicated that his job was moderately stressful. He also mentioned that a few of his "attacks" coincided with times were his job stress was slightly higher.

Family Member III:2

Family member III:1 is the third member of this family to be affected by RAS. She stated she would have "frequent outbreaks of canker sores four to five times a year". She remembered her father being affected by canker sores "of similar size and duration" as those that she experienced. This indicates she also suffered from the minor type of RAS. She also mentioned that the "sores" affected her ability to eat, drink and carry on with some day to day activities. Still no indications of systemic disease were noted in this family member. Regarding daily stress, she stated that she did not have a stressful job, but admitted to "not always handling stressful situations well". She could not remember specifically if her outbreaks coincided with times of stress.

Family Member III:3

Family member III:3 stated that she "has never had an outbreak of canker sores" like her sister or father. However, she was diagnosed with Stage I ovarian cancer within the past two years. She was initially treated with six rounds of chemotherapy with minimal complications. During treatment, she was also tested for mutations of the BRCA genes, none of which were found. Within the last year, a CA125 test revealed elevated values and the family was concerned about a possible recurrence, although all scans were clear. Subsequent testing revealed no change in the values and the initial elevation was attributed to the presence of multiple hernias at the initial incision site, rather than recurrence. However, during the time between tests, the patient became so stressed that she was prescribed Xanax to help her relax. Based on this and observations from other family members, it has been concluded that family member III:3 should be characterized as a high stress individual.

Discussion

The goal of this study is to examine the possible relationship between recurrent aphthous stomatitis and cancer. In the family described, the link between RAS and ovarian cancer specifically will be discussed. The discussion will focus on the possible genetic factors making members of this family susceptible to these diseases as well as the local factor of stress. Also, the ethical concerns and possible implications of a familial

presentation such as the one describe in a dental practice will also be discussed.

Inheritance Pattern

Examining Figure 1, it is clear that this family has three consecutive generations affected by RAS and a fourth generation that could show signs of RAS but have not to date. Also both male and female family members have been affected. Using this information alone, it may be postulated that RAS is being inherited in an autosomal dominant fashion. This would be in direct contradiction to the initial proposal of autosomal recessive inheritance in 1965 [4]. However, this family is relatively small, making the sample size too small to reliably determine mode of inheritance from the pedigree alone. Also multiple members of the family are known to have high stress levels or difficulty properly dealing with stressful situations. This information supports the widely accepted theory of a multifactorial inheritance pattern.

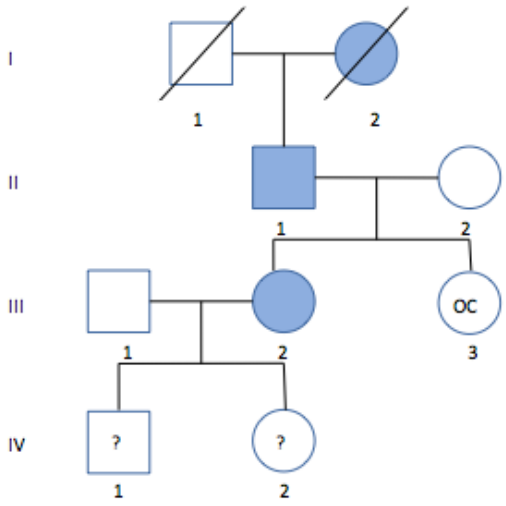

Figure 1. Family pedigree. Individuals with RAS are identified by the shaded figures. Member III:3 presented with ovarian cancer, marked OC. RAS presentation in members IV:1 and IV:2 has not yet been diagnosed, indicated by the "?".

Genetic Factors

Aphthous ulcers arise due to an abnormal immune interaction on the oral mucosal cells, categorizing it as an autoinflammatory disease [5]. It is thought that disruption in both the humoral and cellular immune systems contribute to the occurrence of RAS [4, 5]. Specifically, impaired activation of proinflammatory components such as tumor necrosis factors and interleukin-1 (IL-1) have been implicated [4, 5]. The IL-1 family are primary activators of the expression of endothelial cell adhesion molecules which facilitates the migration of leukocytes into tissues [4]. A member of the IL-1 family, IL-1β, is primarily released by monocytes and macrophages, as well as some nonimmune cells, such as fibroblasts and endothelial cells at sites of injury to stimulate increased migration of leukocytes [6]. The increased migration of leukocytes caused by increased release of IL-1β could account for the damage to mucosal cells that results in RAS [4]. Gene polymorphisms associated with IL-1β have been thought to correlate to a higher incidence of RAS, however studies of these polymorphisms have produced conflicting results [4]. Because research into specific IL-1 mutations has produced inconclusive results it is difficult to say if a mutation in IL-1β could be responsible for the presentation of RAS seen in this family. However, it has been previously concluded that multiple factors are involved in the presentation of RAS so a mutation of IL-1β could be contributing to the development of aphthous ulcers in this family. Genetic testing of this family may be helpful in determining if IL-1β is a major component of their RAS and could also reveal possible genes to focus on for future research. Given the history of cancer within this family it seems likely that tumor necrosis factor-α could have a large influence on the disease presentation seen.

Tumor necrosis factor-α (TNF-α) is another inflammatory cytokine involved with RAS. TNF-α has been implicated as a major contributor to the development of RAS. It is a major proinflammatory cytokine involved with the chemotaxis of immune components, such as neutrophils and major histocompatibility complexes (MHC) [5]. TNF-α is involved in cell signaling pathways, one of which is involved in apoptosis of cells [6]. Increased production of TNF-α could explain the destruction of mucosal cells in RAS through activation of the apoptotic pathway. It is also effective in the T cell-mediated immune response, which is responsible for a part of the immune-mediated pathogenesis of RAS [5]. It has been found that the number of CD4+ T cells is decreased and the number of CD8+ T cells is increased in pa-

tients with RAS [5]. TNF-α has many beneficial functions, in addition to its role in the immune response, including maintenance of homeostasis by regulating the body's circadian rhythm and promoting the remodeling of injured tissue [7]. However, prolonged existence of TNF-α in the body can produce negative effects. After remaining in the body for a long time, TNF-α loses its anti-tumor activity, which could result in the growth of various tumors throughout the body [7]. Development of RAS indicates an increase in TNF-α activity, which could lead to a decrease in the anti-tumor function of the cytokine. This would prevent TNF-α from destroying the developing cancer cells, allowing a tumor to form. As tests for other genetic mutations associated with ovarian cancer were negative, it is possible that increased TNF-α activity could be a contributing factor to the development of cancer in family member III:3.

Local Factors: Stress

Psychological stress has been implicated as a factor inducing RAS. All members of the family studied reported higher than normal levels of stress or decreased ability to handle stress. It has been found that patients with RAS had higher overall stress levels than patients without RAS [8]. Also many patients with RAS indicate that their outbreaks correlate to high stress times in their life [8]. As previously described, the pathogenesis of RAS involves increased immune activity leading to destruction of the oral mucosa [4, 5, 8]. Stress contributes to this activity by increasing the number of leukocytes at sites of inflammation [8]. In this family only one member, II:1, could recall a correlation between stress levels and appearance of aphthae. This discrepancy from the literature is probably due to the inaccuracy of the patient's memory, rather than a lack of association between stress and RAS. Also, stress is a complex factor which affects each person differently [8]. This could account for the different levels of severity described by family members II:1 and III:2.

Psychological stress has been found to have an effect on cancer development as well. It has been shown the increased stress levels could affect cellular processes, such as those involved in DNA repair [9]. This could lead to oncogenic mutations. It has also been found that stress may increase the rate of tumor growth [9]. Family member III:3 and her family indicated that she may not handle stressful situations well. The situation mentioned in this study (increased CA125 levels for a recovering cancer patient) would be an extremely stressful time for anyone and may not be the best indicator of this patient's response to stress. However, the family observed other situations in which the patient's response to stress was extreme, showing a pattern for this patient.

Practical Implications and Ethical Concerns

Due to the common nature of RAS, it is highly likely that a dentist will see and diagnose many patients with this condition throughout their career. The theory posed in this study raises the question: What should a dentist do considering their patient with RAS may be at higher risk of cancer? Another ethical question may be whether to tell the patient about this possible increased risk. At this point, there is not enough research to support this theory to warrant alarming a patient with simple RAS. However, the dentist may keep this theory in mind when examining a patient with a history of RAS. It may be prudent for the dentist to screen these patients for oral cancer more frequently in an attempt to discover any cancerous changes early. The dentist may also consider counseling their RAS patients regarding their stress level. This would both reduce their risk of RAS outbreaks and possibly the development of cancer. Regarding the family studied, the children in the fourth generation have not yet shown any signs of RAS. However, given the family history, it would be logical to monitor them closely for any signs of RAS or even cancer growth.

Conclusion

This study has examined the possible connection between recurrent aphthous stomatitis and the development of cancer by looking at a family with a history of both conditions. Both genetic and local factors contribute to the development of RAS as well as

cancer. In this family, it was suggested that increased TNF-α activity combined with high psychological stress contributed to the development of RAS in family members I:2, II:1 and III:2. These same factors, coupled with the lack of other genetic mutations, could have contributed to the development of ovarian cancer in family member III:3. As far as the practicing dentist is concerned, patients with RAS should be closely monitored, but at this point more harm than good would be done by telling these patients they could possibly develop cancer. More research needs to be done to solidify a connection between RAS and the development of cancer. This research could also elucidate new genes to study regarding the pathogenesis of RAS.

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