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REVIEW ARTICLE

Using of *Nigella Sativa* Oil as an Immunodulator in Management of Extraintestinal Features of Refractory Coeliac Disease

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ABSTRACT

This paper describes the journey of a 34-year-old man with coeliac disease who presented with three extraintestinal features; chronic urticaria, stomatitis and iron deficiency anemia in addition to gastrointestinal complaints. Diagnosis of coeliac disease was established by intestinal biopsy and coeliac serological evidences. He was put on gluten-free diet for one year. After follow-up period, his extraintestinal features didn't resolve with persisting partial villous atrophy (Marsh IIIa) despite strict gluten free diet and he was considered to have refractory coeliac disease. Treatment by Nigella sativa oil was suggested to him for 3 months in addition to continuation of gluten free diet. After these 3 months his extraintestinal features were completely resolved and his gastrointestinal symptoms were disappeared with complete histological remission and disappearance of serum antibodies.

Kewwords: Coeliac disease, Coeliac antibodies, gluten free diet, Nigella sativa.

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INTRODUCTION

Coeliac disease (CD) is an autoimmune chronic intestinal disease caused by a hypersensitivity to gluten in genetically predisposed individuals that result in malabsorption. CD very often presents with atypical features (extraintestinal) rather than the expected gastrointestinal problems. Chronic urticaria, iron deficiency anemia (IDA) and stomatitis are some of these extraintestinal features which usually would not alert the clinicians to order serological coeliac antibodies tests and then refer the patient to gastrointestinal clinic. Gluten-free diet is (GFD) strongly recommended in all CD cases with atypical symptoms and is able to cure the extraintestinal disorders. Persistent symptoms and ongoing mucosal pathology, observed in few cases of CD patients, are usually considered to have refractory CD.

Immunomodulators are becoming a viable adjunct to established modalities offering a novel approach for the treatment of immunological diseases in the coming decades of 21st century. Among these natural immunomodulators is Nigella sativa (black seed) which belongs to the *Ranunculaceae* plant family and have an extensive history of medicinal use that dates back thousands of years. [1]

CASE PRESENTATION

A 34 year old male was seen initially at Dr. Muhamed Osman Private Clinic in Baghdad, Iraq, with two years history of complaints of loose bowel movements, generalized weakness, and intermittent hives. He was referred to our clinic for further investigations and management to exclude gastrointestinal causes of his chronic urticaria since he had received various medications without any significant improvement. Additional history revealed weight loss of 7 kg in the last two years and occasional episodes of diarrhea, nausea, cramps, flatulence, abdominal distension, colic, difficulty with falling asleep, lack of appetite. Stools were large volume, without mucus or blood with a frequency of 4 – 5 per 24 hours. The patient also described a six month history of appearance of intermittent hives started as a raised itchy eruption around his wrists. This would last 24-48 hours and subside however the eruption would last longer and spread to his feet. He also experienced lesions at mouth. The lesions had a mean duration of a month and occurred in any region of the oral mucosa, particularly on the tongue. They were large or small symptomatic ulcerations. Patient was very athletic and in most respects would be considered extremely healthy and past medical and surgical history was unremarkable. He had not travelled or never experienced similar symptoms, and had no personal or family history of gastrointestinal or skin diseases. He was referred to a dermatologist who confirmed that his skin condition was chronic urticaria. He was not found to be allergic to dust mites, pollens and moulds by skin prick testing. He was nonsmoker and non alcoholic. The dermatologist did not offer treatment of urticaria except antihistamines and refer him to our center.

Physical examination revealed pallor with thin built. There were no other significant physical findings. However, at the time of his assessment in our clinic he has stomatitis with

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swollen tongue but did not have any urticarial lesions. Initial laboratory investigation, showed hemoglobin of 10.2g/dl MCV 70, serum iron, TIBC and folate levels were all low with normal eosinophil counts. Stool for occult blood was negative on two occasions and stool was negative for parasites. Screening test for Hepatitis B & C were negative. His thyroid hormone concentrations were normal. Anti-gliadin antibodies (AGA), endomyseal antibodies (EMA), and anti- tissue transglutaminase antibodies (tTG) were all positive (table 1). Upper gastrointestinal endoscopy was normal and biopsies were taken from distal part of duodenum. Histopathological examination showed subtotal villous atrophy, crypt hyperplasia with marked infiltration of intraepithelial lymphocytes (Marsh IIIb). PAS positive macrophages or granuloma were not seen. Based on the above findings, the diagnosis of coeliac disease was strongly established with three associated extraintestinal features of stomatitis, iron deficiency anemia and chronic urticaria. He was advised gluten free diet and given topical treatment for the oral lesions by a dentist as the oral lesions disappeared 7 days after treatment began. On follow up visit 12 months later, he showed clinical improvement but not complete. Stools were normal volume, without mucus or blood with a frequency of 1 – 2 per 24 hours. Haematological findings of IDA positive response but still need treatment. He has experienced few episodes of urticaria in addition to few light oral lesions during the last 12 months. Coeliac anti-gliadin antibodies, endomyseal antibodies were negative, however, anti- tissue transglutaminase antibodies were still positive. Repeat endoscopy and biopsy from the distal duodenum showed partial villous atrophy, crypt hyperplasia with slightly increase intraepithelial lymphocytes (Marsh IIIa). Diagnosis of refractory CD was established and he was advised to keep continue on strict gluten free diet in addition to oral Nigella sativa oil (NS) capsules (one capsule with a dose of 450mg, twice a day), as dietary supplement for a period of 3 months. On follow up 2nd visit 3 months later (15 months after initial diagnosis), he showed excellent clinical improvement. Normal bowel movement and he has not experienced any further episodes of urticaria with complete remission of oral lesions. He had also gained weight. Normal complete blood counts, anti-gliadin antibodies, endomyseal antibodies, and anti- tissue transglutaminase antibodies were all negative. Repeat endoscopy and biopsy from the distal duodenum revealed normal villi, decreased cellular infiltration and crypts appeared normal. (table1)

Table1: Patient's main laboratory findings before treatment, after 12 months of treatment, and after 15 months of treatment.

	Before treatment	After 12 months of treatment	After 15 months of treatment
Hb g/dl	10.2	12.8	14.9
MCV fl	70	85	89
MHC pg	24	28	29
MCHC g/dl	27	32	33
s.Ferritin	8	30	32
AGA	Positive	Negative	Negative
EMA	Positive	Negative	Negative
tTG	Positive	Positive	Negative
Histology	Marsh IIIb	Marsh IIIa	Marsh 0 (normal)

DISCUSSION

The pathogenesis of CD remains incompletely understood. We know that gliadins and other proteins from cereal grains can cause CD in susceptible people. These proteins are degraded into negatively charged peptides that cross the mucosa of the small intestine by some unclear mechanism. In genetically susceptible people, these peptides are then taken up by DQ2 or DQ8 antigen presenting cells and presented to CD4+ T cells. The activation of these DQ2 and DQ8 restricted CD4+ T cells results in a Th1 inflammatory response that leads to tissue damage [2].

CD has a very wide clinical spectrum and includes symptomatic cases with either classical CD with intestinal features (for example, chronic diarrhea, weight loss) or non-classical extraintestinal features (for example, anemia, osteoporosis, urticaria and oral… etc). Due to extraintestinal features, many CD cases currently escape diagnosis and are exposed to the risk of long-term complications, for example, infertility and lymphoma, even if it is now appreciated that the prevalence of these complications is lower than previously reported. [3]

Treatment of CD is based on strict, lifelong adherence to a GFD. Majority of CD patients respond well to GFD with resolution of both intestinal and extraintestinal symptoms and an improvement in histology and serology; however a significant minority of patients will continue to be symptomatic. These patients can present a difficult diagnostic and therapeutic challenge. Refractory CD is a rare condition defined as persistent malabsorptive symptoms and villous atrophy despite strict adherence to a GFD with negative serology for anti-tTG or EMA [4]. The cause and exact incidence of refractory CD is unknown, however it is an important diagnosis to make as it can carry such a poor prognosis [5]. Refractory CD treatment strategies have focused on immunosuppression as glucocorticoids in addition to GFD. Evidence for patients with refractory CD is encouraging with most patients achieving clinical remission and mucosal healing with steroids or a combination of steroids and azathioprine [4-5]

In our case NS was used as an immunonodulator for the treatment of three extraintestinal features with refractory CD in one patient depending on the promising results of NS in treatment of some immunological diseases [6-11]. It has been proven that NS extract has prophylactic effect in asthmatic patients [6], NS plays a role in cell-mediated immunity and, thus, it is useful in ameliorating inflammatory and immune conditions [7]. NS seeds were found to produce an increase in the ratio of helper to suppressor T cells and to enhance natural killer cell activity in normal volunteers (8). NS improves the specific immunotherapy in allergic rhinitis patients [9] and in addition has an effect on rheumatoid arthritic rats [10]. However NS has therapeutic effect in treatment of chronic urticaria. [11]

Our CD study group has studied before the potential benefits of NS oil administration when used with GFD as an adjunct treatment modality in the treatment of coeliac disease in general [12]. We noted that NS oil, if added to GFD has significant effect on histological recovery profiles of 16 subjects with CD more than the effect of using GFD alone. We demonstrated in other study that administration of NS oil with GFD in treatment of IDA associated with refractory CD can lead to increase all hematological indices in addition to complete histological recovery with complete absence of CD antibodies [13]. However, the

actual mechanism by which NS oil exerts its anti-coeliac disease effects needs to be further investigated. According to our previous results and this case presentation, we propose using of NS oil in clinical management of CD, however further studies need to be done to conceptualize the exact role of NS on autoimmunity not only in CD but other autoimmune diseases as well.

CONCLUSION

Administration of Nigella sativa oil with GFD in treatment of extraintestinal symptoms caused by refractory CD can lead to complete remission.

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