CLINICOPATHOLOGICAL STUDY OF AN IRAQI PATIENTS GROUP SUSPECTED TO HAVE COELIAC DIASEASE

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ABSTRACT

As the diagnosis of CD is more than expected among children and adults in Iraq, this study was carried out to describe the clinical features, histological and serological correlations in an Iraqi patients group consisted of adults and children suspected to have CD, to correlate the serological results with the intensity of mucosal damage. 314 patients (142 male, 172 female, mean age, 15 years, range, 1–72) were recruited in the study. All were suspected on clinical basis to have coeliac disease. Endoscopy and duodenal biopsy in addition to serological assessment were done. The duodenal biopsies interpreted histologically according to modified Marsh criteria and the sera were tested for antigliadin antibody (AGA), endomysium antibody (EMA) and anti tissue transglutaminase antibody (tTG ). It has been shown that histopathology still constitutes the golden standard test for ultimate diagnosis of CD according to Marsh criteria. Detection of the presence of EMA and tTG antibodies were diagnostic for the disease (PPV was 100%), while AGA is of less important since its sensitivity, was 77.6%. CD may be a prevalent life-long gastrointestinal diseases in Iraq. The study showed that the clinical features of coeliac disease have changed, symptoms are often minor and the disease can even be clinically silent. Histopathology was the golden standard test for diagnosis of the disease. Detecting the presence of serum antibodies was almost diagnostic for clinically suspected coeliac disease in children and adults especially EMA and tTG.

INTRODUCTION

Coeliac disease is a syndrome characterized by damage of the small intestinal mucosa caused by the gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamines) of barely, wheat and rye in genetically susceptible subjects. The presence of gluten in these subjects leads to self-continuous mucosal damage, whereas elimination of gluten results in full mucosal recovery. [1-3]

The clinical manifestations of coeliac disease are changeable in nature and vary markedly with the age of the patient, the duration and extent of disease, and the presence of extra-intestinal pathological conditions. In addition, to the classical gastrointestinal form, a variety of other clinical manifestations of the disease has been described, including atypical and asymptomatic forms. [4] Therefore, diagnosis of coeliac disease is extremely challenging and relies on a sensitive and specific algorithm that allows the identification of different manifestations of the disease. Serological tests developed in the last two decades provide a non-invasive tool to screen both individuals at risk for the disease and the general population. However, the current gold standard for the diagnosis of coeliac disease remains histological confirmation of the intestinal damage in serologically positive individuals. The keystone treatment of coeliac disease patients is a lifelong elimination diet in which food products containing gluten are avoided. [5-6] The disease should be detected as early as possible, because untreated CD is associated with many severe complications such as intestinal lymphoma or cancer and osteoporosis. [5,7]

For the case finding there are highly sensitive and specific autoantibody tests available; antigliadin antibodies, endomysial antibodies (EMA), and tissue transglutaminase autoantibodies (tTG) tests correlate well with the small bowel mucosal findings. [8-9] The population based screening studies worldwide have shown that the overall
prevalence of celiac disease ranged from 1:500 – 1:100. [7, 10] However, in clinical practice the disease often remains underdiagnosed. The major problem in diagnosing celiac disease is the multifaceted clinical picture of the condition. [9-10]

We know little about the situation of CD in Iraq because few studies have been conducted in Iraq yet [11-14]. These studies showed that diagnosis of CD is more than expected among children and adults in Iraq, meanwhile, large numbers of cases could be misdiagnosed due to limitation of serological antibodies usage in our laboratories except AGA. The present study was carried out to (1) describe the clinical features, histological and serological correlations in an Iraqi patients group consisted of adults and children suspected to have CD, (2) correlate the serological results with the intensity of mucosal damage in both ages.

PATIENTS, MATERIALS AND METHODS

This study was performed on 314 patients (142 male, 172 female, mean age, 15 years, range, 1–72) attending Teaching Gastrointestinal Hospital of Medical City in Baghdad. These patients were referred from different medical centers in Iraq, because they were suspected on clinical basis to have celiac disease. The project was approved by the Ethics Committee of College of Medicine, University of Baghdad, and local Ethics Committee of the GIT hospital and written informed consent was obtained from each adult or child’s parent individual participating in this study.

All patients were subjected to a personal interview using especially designed questionnaire format. The questionnaire gathered information included age, sex, complaint, duration of symptoms, type of diet, family history, oesophagastroduodenoscopy (OGD) findings, histopathological findings, CD serological tests findings, and the final diagnosis.

All patients underwent upper gastrointestinal endoscopy (OGD) with an Olympus endoscope (GIF-V 70, Olympus, Japan). During the procedure, 3-5 biopsy samples from distal duodenum were obtained for histological analysis. Formalin-fixed biopsy specimens stained with hematoxylin and eosin were studied with the use of light microscopy Biopsies were interpreted by two expert pathologists who were not informed about the clinical status of the patients and interpreted small intestinal histological features, according to the Marsh classification according to the modified Marsh criteria: [15-16] Marsh I consists of raised intraepithelial lymphocytes (IELs) with >40 lymphocytes per 100 enterocytes, Marsh II consists of raised intraepithelial lymphocytes and crypt hyperplasia, Marsh IIIa partial villous atrophy, Marsh IIIb subtotal villous atrophy, and Marsh IIIc total villous atrophy

Venous blood samples were obtained from each patient, and sera subjected to anti gliadin antibodies (AGA), endomysial antibodies (EMA) and anti- tissue transglutaminase antibodies IgA (tTG) tests. Serum IgA EMA was detected qualitatively by indirect immunofluorescent (IF) method using commercial slides of monkey esophagus (from Medic Company, Italy), with reticular staining of the muscularis mucosa at serum dilution of 1:3 reported as positive. However, AGA and tTG were performed by enzyme-linked immunosorbent assay (ELISA) in duplicate and according to the manufacturers’ instructions. Negative sera, for all antibodies in highly suspected celiac patients were subjected to the test with IgG monoclonal conjugate by IIF to exclude IgA deficiency disease associated with celiac disease.

Diagnosis of celiac disease was dependant on the presence of Marsh III only in histology examination. Any report, which did not include the features of Marsh III was considered as non-coeliac patient. Other diseases associated with chronic diarrhoea and abnormal mucosal morphology were excluded by careful clinical and laboratory assessment of each case, including careful examination of the stool to exclude parasitic or bacterial infection also by radiological and ultrasound investigations.

Statistics

Analysis comprised of summary statistics for gender and age. Data were analyzed using SPSS v10 for Windows and paired t-tests were used to compare the change in histopathology findings (Marsh grade). Data values were adjusted for age and initial values. Analyses where the P-value was <0.05 were considered to be statistically significant.

RESULTS

The results presented in this study were based on the analysis of data on a total of 314 patients in whom celiac disease was suspected on clinical grounds. Since children with CD differ from adults in certain aspects, many of the associations presented will be grouped into two categories; first, children (<18 years) second, adults (≥18 years).

1. Clinical profile

Among the 314 patients in whom celiac disease was suspected on clinical grounds, the diagnosis was documented in 226 patients only, the remaining 88 were labeled as non-coeliac patients.

The diagnosis of 26 (29.5%) of non-coeliac patients was duodenitis, while 18 (20.4%) of them were diagnosed as giardiasis, 3 (3.4%) had primary intestinal lymphoma and 2 patients (2.2%) had Crohn’s disease. The remaining 39 (44.3%) of non-coeliac group had a normal duodenal histology.

As shown in table 1, more females were affected by celiac disease among children. The female to male ratio among childhood celiac patients was 1.28: 1. Meanwhile, there was a slight male preponderance among the adult coeliac patients. The female to male ratio was 0.82 : 1.

| Table1: Frequency distribution of coeliac patients according to gender and age group. |
|-----------------------------------------------|-------------------|------------------|--------|
| Children                                      | Male | Female | Female/Male ratio | P-value |
| No.                                           | 68   | 87     | 1:2.81            | 0.122  |
| %                                             | 39.1 | 56.1   |                   |        |
| Adults                                        | 39   | 43.9   | 0.82:1            | 0.122  |
| No.                                           | 56   | 37     |                   |        |
| %                                             | 43.9 | 43.9   |                   |        |

The data in table 2, showed statistically significant higher proportion of celiac children had offensive diarrhoea (85.2%) as a complaint compared to (55.3%) among non-coeliac group. The same higher frequency of diarrhoea was noticed among adult coeliaics (42.3%, compared to 61.0% among non-coeliac group).

There was a statistically significant difference in the frequency of other complaints like weight loss, abdominal distension and recurrent mouth ulcers while there was a small and statistically insignificant difference in the frequency of other complaints like short stature, anemia, skin lesions, musculo-skeletal, between coeliac and non-coeliac group for both children and adults.

| Table2: Clinical profile of celiac and non-coeliac patients. |
|-------------------------------------------------------------|-------------------|------------------|--------|
| Children I had offensive diarrhoea                          | Male | Female | Female/Male ratio | P-value |
| No.                                           | 68   | 87     | 1:2.81            | 0.122  |
| %                                             | 39.1 | 56.1   |                   |        |
| Adults                                        | 39   | 43.9   | 0.82:1            | 0.122  |
| No.                                           | 56   | 37     |                   |        |
| %                                             | 43.9 | 43.9   |                   |        |
2. Histopathological profile

Table 3 shows the histological findings seen on examining the duodenal biopsy of coeliac patients. Duodenal biopsies revealed histopathological changes of coeliac disease (Marsh III) in 226 cases from 314 patients, 155 children and 71 adults.

Twenty six of 155 (16.8%) of coeliac children showed histopathological changes of Marsh IIla (partial villous atrophy), compared with 15 (21.1%) adult coeliac patients, while, 62 (40.0%) children and 25 (35.2%) adult patients showed Marsh IIib changes (subtotal villous atrophy), finally 67 (43.2%) children and 31 (43.7%) adult coeliac patients showed Marsh IIIc changes (total villous atrophy). Among non-coeliac patients, none of the children and adults had changes of Marsh III but 15 children (31.9%) and 14 adult (34.1%) showed Marsh I changes (infiltration of inflammatory cells), while 13 children (27.7%) and 9 adult (22.0%), showed Marsh II changes (Marsh I + crypt hyperplasia), table 3.

Table 3: Frequency distribution of coeliac and non-coeliac patients according to histopathological findings and age group.

<table>
<thead>
<tr>
<th>Children</th>
<th>Histopathology</th>
<th>Coeliac</th>
<th>Non-coeliac</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marsh I</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>31.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marsh II</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>27.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marsh IIla</td>
<td>26</td>
<td>16.8</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marsh IIlib</td>
<td>5.2</td>
<td>40.0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marsh IIIc</td>
<td>67</td>
<td>43.2</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>40.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>155</td>
<td>100</td>
<td>47</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4, 5 and 6 show serum antibodies positivity according to the disease status, age group and to the type and severity of histopathological findings.

4. SERUM ANTIBODIES

Tables 4, 5 and 6 show serum antibodies positivity according to the disease status, age group and to the type and severity of histopathological findings.

Table 4, shows high proportion of coeliac children showed positive serum antibodies. We found (89% AGA), (87.7% EMA), and (91.6% tTG) were positive, compared to (17% AGA) (2.1% EMA), and (2.1% tTG) for non-coeliac children and this difference is highly significant statistically. Meanwhile, adults CD showed (66.2% AGA) (100% EMA) and (100% tTG) compared with (12.2% AGA) (0% EMA) and (0% tTG). These associations between positivity rates and disease status, age group were statistically significant.

There was a statistically significant positive trend between serum positivity rate and the severity of histological changes in our coeliac patients. The AGA positivity rate increased from as low as 18.2% for patients with Marsh II changes to as high as 85.1% for those with Marsh III changes, while the rate of EMA positivity increased from (4.5%) for patients with Marsh II to (98%) for those with Marsh IIIic. The same applicable for tTG antibodies rate which increased from (4.5%) for patients with Marsh II to (100%) for those with Marsh IIIic changes (table 5).

As shown in table 6, the PPV of the serological tests in coeliac disease was high ranging from (92.4%) for AGA to (100%) for EMA and (99.6%) for tTG in patients with a clinical suspicion of coeliac disease. Given a positive test of any (3) antibodies one can be (92.4%) to (100%) confident that he is dealing with a real case of CD in clinically suspicious patients. On the other hand, according to NPV of the serological tests; given a negative test in a clinically suspicious situation excludes coeliac disease with confidence of (64.8%) in AGA, (85.6%) in EMA and (88.9%) in tTG.

The sensitivity was much lower (77.6% in AGA) than (95.8%) in tTG and (93.8%) in EMA. If these tests were to be used in screening for CD in general, one can expect to find true coeliac patients in (78%) if AGA was used, (94% if EMA or 96% tTG was used) of positive tested individuals.
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disease
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- al
confirmed
examination as the golden standard test for differentiating
[21
seen in apparently
that could raise the suspicion about small bowel disease. A
symptoms, most of the CD subjects showed some features
while severe offensive diarrhoea was the main presenting
stature, others had mil
subjects had no symptoms and presented only with short
present work was clinically heterogeneous (table 2). Some
usually more marked during the first years of life and then
are not fully understood. Symptoms of malabsorption a
occur at any time in life, from infancy to very old age,
expression of CD is so highly variable and why presentation
Gastrointestinal and extraintestinal manifestations and will
[3,
was
ible to the results reported
ible to the results reported
ible to the results reported
bility
PPV = positive predictive value, NPV = negative predictive value
The present work relied on the histopathological
examination as the golden standard test for differentiating
between coeliac and non-coeliac patients. CD diagnosis was
confirmed when there were infiltration of inflammatory
cells, mainly IELs, crypt hyperplasia and villous atrophy
(Marsh III). [23-27] However, in individuals who were on
normal diet and had normal small bowel villous architecture, they could still have gluten sensitivity. They
may be a cases of a latent coeliac disease and they might contracted small bowel villous atrophy and crypt
hyperplasia later in the disease process, other patients had villous atrophy, with no crypt hyperplasia; these changes
are not specific for coeliac disease, so they were not included in the group of coeliac patient. These facts were
accepted worldwide. [23-27]
In untreated coeliac disease, ingested gluten triggers
the production of IgA serum antibodies (AGA, EMA and
TG) in the serum and tissue. These antibodies seem to be
highly specific for CD. However, the AGA test is still the only
test in the diagnosis for children, adults,
and laboratory features
The histological sub classification of Marsh III (Marsh IIIa, Marsh IIIb, and Marsh IIIc) in this study, showed
the correlation between the severity of mucosal damage
and the appearance of autoantibodies. The question is how
many CD patients will be missed in screening programs
that rely too much on serology. The problem of negative
serology in untreated coeliac disease patients (19 cases
EMA and 13 tTG in this study) is underestimated, and data
about the subgroup with minor tissue damage are lacking
in the literatures. In the majority of studies, the sensitivity
of serological antibodies is evaluated in patients with
severe villous atrophy and an intestinal biopsy has been
suggested only in those cases showing at least one
abnormality on serology [20, 21]. Most likely a subgroup
of non-symptomatic coeliac patients negative for EMA or tTG
will be under diagnosed, especially those with partial
villous atrophy (Marsh IIIa). [29-30] At present, there is no
discussion in the literatures about serology negative coeliac
patients. It is important to avoid a self-fulfilling prophecy,
taking biopsies only from EMA or tTG-positive individuals.
Small bowel biopsy should be the first diagnostic
procedure when there is a clinical suspicion of coeliac
disease, in spite of positive or negative results of serology.
For small intestinal biopsy to be replaced by the serological
testing method as the diagnostic test of choice for coeliac
disease, a sensitivity and specificity approaching 100%
would be required. In order to reach this perfect rate,
combination of serology tests must be done to the patient
such as EMA with tTG. [32-33].

**Table 5: Serum antibodies positivity rates according to type and severity of histopathological findings**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Positive AGA</th>
<th>Positive EMA</th>
<th>Positive tTG</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.  %</td>
<td>No.  %</td>
<td>No.  %</td>
<td>No.</td>
<td></td>
</tr>
<tr>
<td>Marsh I</td>
<td>7  24.1%</td>
<td>0  0%</td>
<td>0  0%</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Marsh II</td>
<td>4  18.2%</td>
<td>1  4.5%</td>
<td>1  4.5%</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Marsh IIIa</td>
<td>33  80.5%</td>
<td>27  65.9%</td>
<td>31  75.6%</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Marsh IIIb</td>
<td>74  85.1%</td>
<td>84  96.6%</td>
<td>84  96.6%</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Marsh IIIc</td>
<td>78  78.6%</td>
<td>96  98%</td>
<td>98  100%</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Normal histology</td>
<td>2  5.4%</td>
<td>0  0%</td>
<td>0  0%</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>198  63.05%</td>
<td>208  66.24%</td>
<td>214  68.15%</td>
<td>314</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Table 6: Comparison between the performance characteristics of AGA test, EMA test, and tTG test in the diagnosis for children, adults, and total coeliac patients**

<table>
<thead>
<tr>
<th>Children</th>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>89.0%</td>
<td>82.9%</td>
<td>94.5%</td>
<td>69.6%</td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td>87.7%</td>
<td>100%</td>
<td>100%</td>
<td>71.2%</td>
<td></td>
</tr>
<tr>
<td>tTG</td>
<td>91.6%</td>
<td>97.8%</td>
<td>99.3%</td>
<td>77.9%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adults</th>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>66.2%</td>
<td>87.8%</td>
<td>90.3%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>tTG</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total patients</th>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>77.6%</td>
<td>85.3%</td>
<td>92.4%</td>
<td>64.8%</td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td>93.8%</td>
<td>100%</td>
<td>100%</td>
<td>85.6%</td>
<td></td>
</tr>
<tr>
<td>tTG</td>
<td>95.8%</td>
<td>98.9%</td>
<td>99.6%</td>
<td>88.9%</td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

This study demonstrates for the first time, to our
knowledge that among 314 patients in whom CD was
suspected on clinical grounds, the diagnosis was
documented in 226 patients only, meanwhile, the
remaining 88 were labeled as non-coeliac patients.

The sex distribution of coeliac patients showed a
slight female excess in the present study, but this was not
significant statistically for both children and adults. This
was compatible to the results reported in other countries
[3, 7, 17]
CD can present with a wide spectrum of
Gastrointestinal and extraintestinal manifestations and will
often be overlooked unless it is actively considered in
patients with unexplained clinical and laboratory features
or associated diseases [6]. The reasons why the clinical
expression of CD is so highly variable and why presentation
can occur at any time in life, from infancy to very old age,
among of CD subjects showed some features
that could raise the suspicion about small bowel disease. A
common feature of subclinical coeliac disease is the positive
clinical response to the gluten-free diet, which was
seen in apparently healthy subjects with minimal changes.

[21-22]

The present work relied on the histopathological
examination as the golden standard test for differentiating
between coeliac and non-coeliac patients. CD diagnosis was
confirmed when there were infiltration of inflammatory
cells, mainly IELs, crypt hyperplasia and villous atrophy
(Marsh III). [23-27] However, in individuals who were on
normal diet and had normal small bowel villous architecture, they could still have gluten sensitivity. They
may be a cases of a latent coeliac disease and they might contracted small bowel villous atrophy and crypt
hyperplasia later in the disease process, other patients had villous atrophy, with no crypt hyperplasia; these changes
are not specific for coeliac disease, so they were not included in the group of coeliac patient. These facts were
accepted worldwide. [23-27]

In untreated coeliac disease, ingested gluten triggers
the production of IgA serum antibodies (AGA, EMA and
tTG) in the serum and tissue. These antibodies seem to be
highly specific for CD. However, the AGA test is still the only
routine serological test using in Iraqi hospitals as an
indicator for CD. In the present study AGA, EMA, and tTG
were used as followed worldwide [28-30].

AGA appears specific to detect gluten sensitivity
rather than coeliac disease, since positive AGA was also
seen in other diseases and normal people. The test is of less
value in confirming a diagnosis of coeliac disease, if used as
a single test, but it is good for monitoring diet therapy in
established coeliac cases. [31] However, the higher
sensitivity and specificity of EMA and tTG in this study are
an important step and objective method in detecting CD
before endoscopy approach.

The histological sub classification of Marsh III (Marsh IIIa, Marsh IIIb, and Marsh IIIc) in this study, showed
the correlation between the severity of mucosal damage
and the appearance of autoantibodies. The question is how
many CD patients will be missed in screening programs
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combination of serology tests must be done to the patient
such as EMA with tTG. [32-33].

**PPV = positive predictive value, NPV = negative predictive value**
CONCLUSIONS
CD may be one of the most prevalent life-long gastrointestinal diseases in Iraq, since a fairly large number of coeliac patients were collected in a period of 20 months at one hospital in Baghdad; capital of Iraq. This study showed that the clinical features of coeliac disease have changed, symptoms are often minor and the disease can even be clinically silent. Histopathology was the golden standard test for diagnosis of the disease. Detecting the presence of serum antibodies was almost diagnostic for clinically suspected coeliac disease in children and adults especially EMA and tTG.

CONFLICT OF INTERESTS
The authors declare that there is no personal and funding conflict of interests associated with work

AUTHORS’ CONTRIBUTION
We declare that work was done by all the authors named in this article and all the liabilities pertaining to claims relating to the content of this article will be borne by the authors. Muhamed T Osman coordinated the study design and participated in the all laboratory work, data collection, analysis and drafted the manuscript. Sanaa A Al-Nasiry participated in the histopathology & serology work and data analysis. Makki H Fayadh participated in doing the patient’s endoscopy and clinical work. Balsam I Taha participated in the serological work. All the authors read the final manuscript.

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