RECURRENT MISCARRIAGE AND CELIAC DISEASE, A RARE ASSOCIATION? – CASE REPORT

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PURPOSE: *TO REPORT THE CASE OF A YOUNG WOMAN WITH RECURRENT MISCARRIAGES THAT HAS BEEN DIAGNOSED WITH CELIAC DISEASE IN THE GASTROENTEROLOGY AND HEPATOLOGY DEPARTMENT OF FUNDENI CLINICAL INSTITUTE. AFTER 12 MONTH OF GLUTEN-FREE DIET SHE HAS MANAGED TO GIVE BIRTH TO A HEALTHY BABY.*
DESIGN: *CASE REPORT*
PATIENT: *29 YEARS OLD WOMAN WITH 3 RECURRENT MISCARRIAGES*
TREATMENT: *GLUTEN-FREE DIET*
EXPECTED OUTCOME: *THE BIRTH OF A HEALTHY BABY*
DIAGNOSIS: *UPON ADMISSION THE PATIENT DIDN'T HAVE ANEMIA AND SHE TESTED POSITIVE FOR ANTI TTG ANTIBODIES AND ANTI GLIADIN ANTIBODIES. DUODENAL BIOPSY WAS TAKEN DURING ENDOSCOPY AND THE HISTOPATHOLOGY EXAMINATION IDENTIFIED CHANGES CHARACTERISTIC FOR CELIAC DISEASE. AFTER 12 MONTHS OF GLUTEN-FREE DIET THE PATIENT GAVE BIRTH TO A HEALTHY BABY.*
CONCLUSION: *ALTHOUGH THERE ARE NO PRECISE GUIDELINES FOR THE SCREENING OF CERTAIN FEMALE PATIENTS WITH INFERTILITY, THE CAREFUL IDENTIFICATION OF SOME POTENTIAL CASES IS FOLLOWED UP BY A QUICK SUCCESS QUANTIFIED AS THE SUCCESSFUL PREGNANCY AND CHILDBIRTH.*

KEYWORDS: CELIAC DISEASE, GASTROENTEROLOGY, HEPATOLOGY, ENDOSCOPY, MISCARRIAGES

CONTEXT: Celiac disease is an autoimmune disease with many systemic manifestations and no specific symptoms. Failure to recognize these symptoms may lead to a delay in the diagnosis, a late disease onset and major long term complications.

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Once upon a time considered to be a rare disease, the celiac disease is now present in 1/100 persons[5]. Despite the high prevalence, more than 95% of the affected individuals remain undiagnosed probably because approximately 38% of them have asymptomatic disease and the doctors associate their symptoms with other diseases.

'Classic' celiac disease involves the existence of gastrointestinal symptoms or consequences due to malabsorption. It is the most documented form of the disease. Patients have nausea, bloating, tympanites, discomfort, abdominal pain, abnormal stool, usually diarrhea, light tan or grayish, foaming, malodorous. Classical symptoms include also weight loss despite a normal appetite, more frequent in the children, which have failure to thrive. Fatigability and weakness are the result of the low absorption of nutrients in the small intestine and also because of the iron deficiency anemia.

'Atypical' celiac disease is characterized by the absence of gastrointestinal manifestations or poor gastrointestinal symptoms. The extra intestinal symptoms like iron deficiency anemia, failure to thrive, osteoporosis or infertility are to the fore. Paradoxically, this form of celiac disease is more common than the 'classic' form but because of the absence of gastrointestinal symptoms is often underdiagnosed.

It is well known the association between celiac disease and infertility or other conception disorders. The incidence of celiac disease is greater in females because they address to the healthcare providers more often than males. The sex ratio for celiac disease is 2.5:1 for females[6].

The celiac disease can associate with many other conditions like osteoporosis, autoimmune diseases, malignancy, neurological disorders, but the most devastating for women are infertility, recurrent miscarriage and perinatal complications. Although there are many articles and clinical trials about this topic, there are no precise guidelines to define the risk groups for which screening should be mandatory. That's why the association between these two conditions is often known as the 'neglected clinical association[7].

CASE REPORT

We will present you the case of a 29 years old female, married for 5 years, that didn't use any methods of contraception during all this time. The patient addressed our clinic for the emission of 4-5 soft stools per day since the last 6 months associated with significant weight loss, about 10 kilograms. She reported the absence of periods for about 3 months.

Upon admission the patient had a poor general condition, she was dehydrated, had diffuse abdominal pains, bloating, nausea and vomiting. She denied smoking, alcohol use or drugs. She had a weight of 46 Kg (101 lb) and a height of 163 cm (5.34 ft) with a BMI of 17.3 Kg/m^2 (she was underweighted). Prior to this episode she had a weight of 56 Kg (123 lb) with a BMI of 21.1 Kg/m^2.

From her medical history we found that she was diagnosed with gluten intolerance at the age of 1 year and 4 months. She followed a gluten-free diet for 2 years and then returned to a normal diet. Her first period was at the age of 13 years and 6 months. Her periods have always been irregular and she had amenorrhea for the last 3 months. Her family medical history was negative for celiac disease or inflammatory bowel disease.

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[5] Celiac disease: epidemiology, pathogenesis, diagnosis, and nutritional management. Schuppan D[1], Dennis MD, Kelly CP. Nutr Clin Care. 2005 Apr-Jun;8(2):54-69.

[6] Characteristics of adult celiac disease in the USA: results of a national survey.
Green PHR, Stavropoulos SN, Panagi SG, Goldstein SL, Mcmahon DJ, Absan H, Neugut AI Am J Gastroenterol. 2001 Jan; 96(1):126-31.

[7] Coeliac disease.Review. Green PH, Jabri B Lancet. 2003 Aug 2; 362(9381):383-91

Her blood panel showed a mild hypochromic microcytic anemia (Hb: 10.1 g/dl, MCV: 77 fl, MCHC: 30g/dl), serum ferritin 44 ng/dl, transferrin saturation 20%. Beside an elevated ASAT (125 U/L) and ALAT (100U/L), the rest of the chemistry panel was within normal values. She tested negative for hepatitis B and C. Her stool analysis was negative for bacteria and parasites. Anti tTG antibodies were positive (98.62 U/ml) and anti gliadin antibodies were positive too.

The endoscopic examination of the second part of the duodenum revealed flattened folds and a nodular pattern of the mucosa. Six biopsies were taken each with only one passage of the biopsy forceps and they were examined by the histopathology experts from our clinic.

Figure 1. Endoscopic view: flattend folds and nodular mucosa

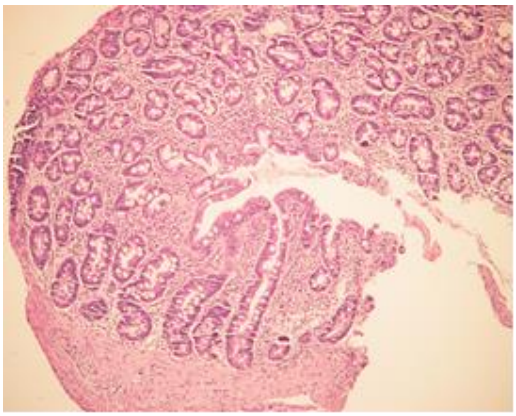

Figure 2. Duodenal mucosa with moderate inflamation in chorion and subtotal villous atrophy – few shortened, marginal, remaining villi, HE, 100x

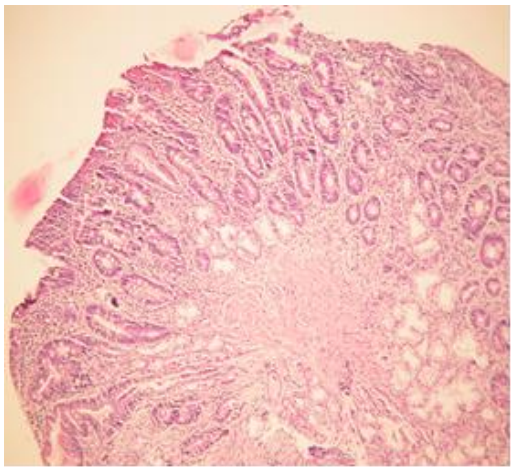

Figure 3. Duodenal mucosa fragment with extended total villous atrophy and crypt hyperplasia, HE, 100x

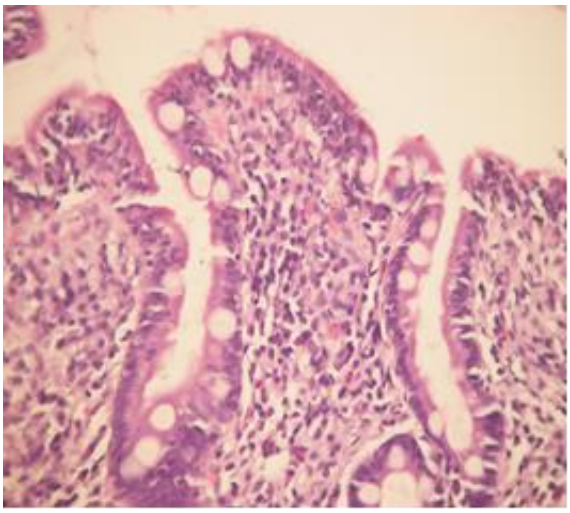

Figure 4. Detail of the section with few remaining villi showing lymphoplasmacytic infiltration and multiple intraepithelial lymphocytes, HE, 400x

The patient was diagnosed with celiac disease and started a gluten-free diet. Her symptoms faded spectacularly by the first weeks of treatment. After 12 months she managed to give birth to a healthy male baby (2950 gr.) after 39 weeks of gestation.

DISCUSSION

There are many published clinical trials that suggest a link between celiac disease and infertility or perinatal complications. There are also some clinical trials that deny any connection between these two conditions. This happens because there are no precise guidelines to establish the risk groups where screening for celiac disease should be recommended.

More and more data suggest that women with celiac disease have a decreased fertility span due to late menarche and early menopause[8]. The number of babies given birth by a woman with celiac disease appears to be lower than in general population and this difference fades away after the start of a gluten-free diet[9]. Few clinical trials report that the mother's age when the first baby is born is higher than in a control group[10].

The pathophysiology of these disorders associated with celiac disease is not clearly understood. While the pathophysiology of most of the complications of celiac disease is not completely understood, there are many data that support a direct link between nutritional imbalance and inflammatory response on one hand and the onset of fertility disorders on the other hand. Despite all these data, the nutritional imbalance is frequently hard to be identified. That's why malabsorption is less likely to be the only mechanism involved. There are many theories to explain the mechanisms involved. One of these theories suggests that placental tTG binds directly to maternal autoantibodies which cause disturbances to the placental functions and nutrients exchange[11]. Another hypothesis claims that maternal immune system fails to sense the fetus immune system due to altered phagocytosis and the release of fetal antibodies in the blood stream. This new theory remains to be confirmed but it could explain most of the perinatal complications associated with celiac disease[12].

This case report supports once again that the gluten-free diet is mandatory all life. When this diet is neglected or avoided long term complications of celiac disease arise.

One of the most fearsome complications of this disease that affects mainly the women is infertility of unknown origin. Exactly as stated in literature, the embrace of a gluten-free diet is quickly followed up by a normalization of the fertility potential. It is very important to recognize this association because most of the cases have very few clinical symptoms or only extra intestinal manifestations. Because there are no precise guidelines for the screening of women with celiac disease, the attention must be channeled on the identification of every potential case.

What's so particular about this case is that the patient had increased aminotransferase levels, a finding in 20% of cases[13].

This patient has many risk factors that could recomand screening for celiac disease

1. recurrent miscarriage
2. the late appearance of the first menstrual cycle

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[8] Celiac disease and its effect on human reproduction: a review. Soni S[1], Badaw J Reprod Med. 2010 Jan-Feb;55(1-2):3-8.y SZ.
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[9] Cosmin CIORA , Mircea DICULESCU. Fertility disorders associated to coeliac disease-retrospective study. Research and Science Today 2(8)/2014 , 231-238.

[10] Reproductive life disorders in Italian celiac women. A case-control study
Domenico Martinelli, Francesca Fortunato, Silvio Tafuri, Cinzia A Germinario,
BMC Gastroenterol 2010; 10:89.

[11] Anti-tissue transglutaminase antibodies from celiac patients are responsible for trophoblast damage via apoptosis in vitro.Di Simone N, Silano M, Castellani R, Di Nicuolo F, D'Alessio MC, Franceschi F, Tritarelli A, Leone AM, Tersigni C, Gasbarrini G, Silveri NG, Caruso A
Am J Gastroenterol. 2010 Oct; 105(10):2254-61.

[12] Maternal celiac disease autoantibodies bind directly to syncytiotrophoblast and inhibit placental tissue transglutaminase activity.Anjum N, Baker PN, Robinson NJ, Aplin JD
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[13] Prevalence and causes of abnormal liver function in patients with coeliac disease.
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Liver Int. 2013 Aug;33(7):1128-31. doi: 10.1111/liv.12178. Epub 2013 Apr 21.

3. amenorrhea
4. unexplained iron deficiency anemia
5. persistent elevations of serum transaminases.

However until the occurrence of specific clinical manifestations of celiac disease (dehydration, abdominal pain on palpation spontaneous and diffuse, sensation of bloating, nausea and vomiting) it has not been investigated for this pathology. Increasingly more cases of celiac disease are silent forms. Index of suspicion against a potential case must therefore be very high. The mass screening in patient populations is not yet recommended by any medical practice guide. It places great emphasis on identifying punctual each case. This can only be done by educating health professionals involved in the evaluation of women with fertility disorders whether we are talking here of family physicians or gynecologists.

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