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Risks of Lymphoma and Digestive Cancers in Patients with Celiac Disease: Cohort Study

A M. Mahmoudi*, I. Benelbarhdadi, C. Berhili, N. Lagdali, M. Borahma, FZ. Ajana

Department of Hepato-gastroenterology of medicine C University Hospital Ibn Sina, University Mohamed V, Rabat, Morocco
*Corresponding author: manalmahmoudi1991@gmail.com

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Abstract BACKGROUND: The association between celiac disease (CD) and the development of various malignant tumors, in particular gastrointestinal cancers, has been reported by several studies. However, the close relative risks (Odds Ratio) of these complications compared to the population are still insufficiently known and estimates of the risk factors for the development of these complications in patients followed for CD remain controversial. Objective: To estimate the close relative risks of malignant complications in a cohort of patients with celiac disease compared to the Moroccan population and to determine the risk factors for the development of these complications. Methods: Our work is a retrospective, descriptive and analytical study, carried out within the Department of Medicine C of the CHU IBN SINA Mohammed V University of Rabat, over a period of 23 years - between 1995 and 2018 -, and on a basis of 284 cases of celiac disease, from which we have extracted a series of 16 cases of celiac disease with at least one malignant gastrointestinal complication. Using a case-control study, we were able to determine the risk of these complications compared to the general Moroccan population. Results: We gathered a population of 16 celiac patients with one or more malignant gastrointestinal complications, out of a total of 284 cases of CD, the prevalence was 5.6%. We found a significant increase in the risk of developing digestive malignancies during CD with an Odds Ratio (OR) of 46 (95% confidence interval [CI] 34–63) and p value <0.0001). This risk was higher during the period of per diagnosis, we also objectified a significant increase in risk of all types of cancers found in our series compared to those of control cases. The two risk factors for malignant complications found in our study are non-compliance with the gluten-free diet and delayed diagnosis. Conclusions: There is a significant increase in the risk of malignancy in patients diagnosed with CD. Particularly during the period of per diagnosis. This risk according to this cohort can be reduced by the good observance of the gluten-free diet and an early diagnosis in the face of the most severe symptoms of this pathology.

Keywords: *celiac disease, lymphoma, digestive cancer*

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1. Introduction

Celiac disease (CD) is an autoimmune inflammatory enteropathy secondary to gluten ingestion occurring in genetically predisposed patients (HLA-DQ2 / DQ8). The prevalence of the disease is estimated at about 1/100 in Western countries [1], and is characterized by a small inflammation of the intestinal mucosa and villous atrophy [2]. Currently, the only treatment for CD is the gluten-free diet (RSG) [3].

The association between MC and the development of various malignant tumors, in particular gastrointestinal cancers, has been reported by several studies [4]. However, the close relative risks (Odds Ratio) of these complications are still insufficiently known and estimates of the risk factors and protective factors for the development of these complications in patients followed for CD remain controversial.

The aim of our work is to estimate the close relative risks of these malignant complications in a cohort of patients with celiac disease compared to the Moroccan population and to determine the risk factors and protective factors for the development of these complications.

2. Patients and Methods

This is a retrospective descriptive and analytical study on a cohort of 284 Moroccan adults suffering from celiac disease, followed in our department of medicine C at the Ibn Sina university hospital center, Mohammed V university, Souissi, Rabat, between June 1995 and June 2018.

The collection of epidemiological, clinico-biological, endoscopic, histological and evolutionary data was carried out from medical records using a pre-established operating sheet. All our patients benefited from an initial consultation and/or hospitalization specializing in hepato-gastroenterology, a complete clinical examination, a biological assessment

of malabsorption, a serological assessment, an abdominal ultrasound, a Esogastroduodenal fibroscopy with duodenal biopsies.

The diagnosis of Celiac Disease was based on clinical, biological, histological, serological arguments, and on the basis of the evolution of patients on treatment with a gluten-free diet (RSG).

Data entry and analysis was carried out using SPSS Statistics 22.0 software.

To estimate the close relative risks (Odds Ratio) of developing gastrointestinal carcinomas and different types of malignant lymphomas in our patients, we performed a population-based case-control study based on the city's cancer registry Rabat established by the directorate of epidemiology and fight against diseases of the Ministry of Health in Morocco.

3. Results

We gathered a population of 16 celiac patients with one or more malignant gastrointestinal complications, out of a total of 284 cases of CD, with a prevalence in CD of 5.6%.

The average age of our patients at the time of Mc's diagnosis was 39.54 years with a standard deviation of 12.92 years (39.54 ± 12.92), while The average age of our patients at the time Digestive cancer diagnosis was 35.8 years with a standard deviation of 10.92 years (35.8 ± 10.92). We noted a female predominance in our patients with 11 women (69%) and a sex ratio M / F of 0.45.

They were 7 cases of lymphoma (including 5 cases of non-Hodgkin's malignant lymphomas of the small intestine; one case of refractory type 2 sprue which progressed to intestinal epithelial lymphoma type T and one non-Hodgkin's lymphoma case lymph node); 4 cases of gastric adenocarcinomas; 2 cases of small adenocarcinomas and 1 case of neuroendocrine carcinoma of the jejunum; one case of pancreatic adenocarcinoma and one case of hepatocellular carcinoma.

In our series, 4 patients had a notable family history, for the rest of the patients there was nothing to report: two patients had cases of CD in their family and two cases had cases of cancer in their family.

The time taken to diagnose cancer compared to the diagnosis of CD, could be determined in all our patients. This period varied from 0 months to 25 years, with an average of 5.4 years. It was: - Greater than 5 years in 12.50% (n = 2) of the patients; Less than 2 years old in 12.50% (n = 2) of patients; Between 2 and 5 years in 18.75% (n = 3) whereas it was contemporaneous with the diagnosis of CD in 9 patients (56.25%). So at the time of diagnosis of digestive cancers the RSG was not yet established in 56.25% of cases because the diagnosis of CD was contemporaneous with the diagnosis of digestive cancer; RSG was well followed in 3 patients while poor adherence to RSG was observed in 4 patients (25%).

Clinically, all of our patients were symptomatic when diagnosed with cancer. The time between the onset of symptoms and the diagnosis of CD varied from 3 years to 20 years, with an average of 7.4 years. The digestive symptomatology was dominated by diarrhea, while the extradigestive symptomatology was dominated by weight loss and anemic syndrome. The clinical examination objectified a fold of malnutrition in 5 patients, a painful impasto in peri-umbilical region in 2 patients and an edemato-ascitic syndrome in only one patient. The body mass index (BMI) could be calculated in all our patients, we found in our series: - 37.5% (n = 6) of patients with normal weight. - 43.7% (n = 7) of lean patients and 18.8 (n = 3) of pre-obesity patients.

All our patients had a biological malabsorption syndrome, The serology was based on Anti Endomysium Antibodies and Anti Transglutaminase Antibodies: 15 patients were seropositive (94%), the endoscopic aspect was a cracked, scaly and sawtooth appearance in 37.5% (n = 6) of cases; a nodular appearance in 6.2% (n = 1) of the cases. Fold thinning was noted in 37.5% (n = 6) of the patients. Whereas the mucosa was normal in 18.8% (n = 3) of the cases.

To analyze our results, we first estimated the close relative risks (Odds Ratio) of developing gastrointestinal carcinomas and different types of malignant lymphomas in our patients thanks to a population-based case-control study based on the cancer registry of the city of Rabat established by the directorate of epidemiology and fight against diseases of the Ministry of Health Morocco. Then we determined the main risk factors for the development of gastrointestinal malignancies in our patients.

After adjusting the age and sex of our patients with the series of control cases. We found a significant increase in the risk of developing digestive malignancies during CD with an Odds Ratio (OR) of 46 (95% confidence interval [CI] 34–63) and p value <0.0001). This risk was higher during the per diagnosis period with an Odds Ratio (OR) of 52 (95% confidence interval [CI] 39–68) against an Odds Ratio (OR) of 36 (95% confidence interval [CI]] 24–53) in the post-diagnosis period, we also objectified a significant increase in the risk of all types of cancer found in our series compared to those in the control case with Odds Ratio (OR) lymphoma of 411 (95% confidence interval [CI] 350–600); gastric adenocarcinoma Odds Ratio (OR) of 234 (95% confidence interval [CI] 148–370); small adenocarcinoma Odds Ratio (OR) of 10536 (95% confidence interval [CI] 596–18697); Odds Ratio (OR) pancreatic adenocarcinoma of 90 (95% confidence interval [CI] 50–109) and Odds Ratio (OR) hepatocellular carcinoma of 117 (95% confidence interval [CI] 42–320) SEE Table 1).

Table 1. Close risks of malignant tumors observed in our cohort compared to the general population

	OR	IC 95%	P
Totale des tumeurs	46	34-63	0.001
Lymphomes	411	350-600	0.001
Gastric adenocarcinoma	234	148-370	0,005
Small adenocarcinoma	10536	596-18697	0,0001
Pancreatic adenocarcinoma	90	50-109	0.005
Hepatocellular carcinoma	117	42-320	0.003

Table 2. Determination of the predictive factors of the malignant complication during CD

	univariate analysis			Multivariate analysis		
	OR	IC (95%)	P	OR	IC (95%)	p
gluten-free diet deviation	1,9	1,75-2,57	0,010	2,025	1,65-4,57	0,001
Diagnostic delay of coeliac disease	1,6	1,54-2,54	0,001	2,58	1,85-4,58	0,0001
Young age to diagnosis	1,03	0,723 – 1,463	0,8			
Sex.	1,5	0,967 – 7,109	0,500			
Family Antecedent of neoplasia	1,45	0,009 – 0,075	0,231			
Family Antecedent of CD	1,148	1,052 – 3,422	0,157			

At the end of this detailed descriptive study of our series, we can now answer the questions of our objective to determine the predictive factors of gastrointestinal malignant complications during celiac disease, and to do this, we used the statistical method binary logistic regression by including the following variables in the univariate regression model: age; the patient's gender; non-compliance with the RSG; the notion of family history of CD; family history of cancer and delayed diagnosis of CD. In a multivariate model and after adjusting the different confounding parameters, the two parameters that stand out associated with the occurrence of gastrointestinal malignant complications are non-compliance with the gluten-free diet with an Odds Ratio (OR) of 2.02 (95% confidence interval [CI] 1.75–4.57), delayed diagnosis of CD with an Odds Ratio (OR) of 2.58 (95% confidence interval [CI] 1.58 4.58). It is recalled that the significance threshold (p) has been limited to values less than 0.05 (SEE Table 2).

4. Discussion

In this prospective study, we did find a significant overall increase in the risk of malignancy in people with celiac disease compared to the general population. This association has been shown for a long time [5,6]. Several studies have also shown this increase, a large meta-analysis carried out in 2015 which included 50,504 patients followed for CD and these results indicated that CD increased the risks of all malignant tumors as well as gastrointestinal malignancies [4]. Another recent study published in 2018 which used a case-control study to determine the relative risk with cases (lymphoma or gastrointestinal carcinoma) and controls (melanoma or basal cell carcinoma) diagnosed from 1994 to 2014 this study concluded also that newly diagnosed CD patients have an increased risk of lymphoma and digestive cancers [7].

In our series we found that the diagnosis of CD was contemporaneous with the diagnosis of cancer in 9 patients (56.25%) and therefore the risk was higher during the period of per diagnosis with an Odds Ratio (OR) of 52 (95% confidence interval [CI] 39-68) against an Odds Ratio (OR) of 36 (95% confidence interval [CI] 24-53) in the post-diagnosis period this has also been demonstrated in others studies [4]. This variation in risk can be explained over time by the fact that there are latent forms of CD diagnosed via the initial symptomatology of abdominal cancers which are sometimes similar to the symptoms of CD. This observation can also be explained by the delayed diagnosis of latent or mono symptomatic forms which were sometimes treated in the long term by symptomatic treatments which probably caused a more rapid evolution towards malignant complications.

In our study we found two risk factors for progression to malignant complications during CD which were: non-adherence to the gluten-free diet with an Odds Ratio (OR) of 2.02 (95% confidence interval [CI] 1.75-4.57), delayed diagnosis of CD with an Odds Ratio (OR) of 2.58 (95% confidence interval [CI] 1.58-4.58). The role of RSG has been the subject of several studies which have also confirmed the protective role of RSG [8]. This protective role of RSG may also explain the decrease in the risk of malignancy over time as has been shown in other studies [9].

Our study has certain limitations. First of all, we were able to include the results of a single medical service for hepato gastroenterology. Then the patients were initially assessed in a celiac referral service. The presence of a gastrointestinal malignancy may have led to symptoms that led to the diagnosis of celiac disease. Finally, our study is based on the population thanks to the use of national cancer registration data to estimate the malignancy rate in the general population this is common in studies of this type but which, as we all know, has several limits.

In conclusion, in this prospective population-based cohort study, we showed a significant increase in the risk of malignancy in CD. Particularly before during the diagnostic period. This risk according to this cohort can be reduced by the good observance of the gluten-free diet and an early diagnosis in the face of the most severe symptoms of this pathology.

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