Digestive and Liver Disease 46 (2014) 400–404

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Enteroscopy for the early detection of small bowel tumours in at-risk celiac patients

Carolina Tomba[a,*], Luca Elli[a], Maria Teresa Bardella[a], Marco Soncini[b], Paolo Contiero[c], Leda Roncoroni[a], Martina Locatelli[a], Dario Conte[a]

[a] Center for the Prevention and Diagnosis of Celiac Disease and Gastroenterology Unit II, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and Università degli Studi di Milano, via F. Sforza 35, 20122 Milan, Italy
[b] Gastroenterology Unit, Azienda Ospedaliera Ospedale San Carlo Borromeo, via Pio II 3, 20153 Milan, Italy
[c] SC Registro Tumori ed Epidemiologia Ambientale, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian 1, 20133 Milan, Italy

ARTICLE INFO

Article history:
Received 14 August 2013
Accepted 8 December 2013
Available online 15 January 2014

Keywords:
Celiac disease
Enteroscopy
Small bowel
Malignancies

ABSTRACT

Background: A subset of celiac patients shows a high risk for small bowel malignancies.
Aims: To select celiac patients considered at risk and evaluate the diagnostic yield of enteroscopy in this context.
Methods: Celiac patients were enrolled from a tertiary referral centre during the period June 2011–June 2013, based on the following criteria: (i) patients diagnosed when aged 50+ and with poor response to gluten-free dieting; (ii) low dietary compliance; (iii) alarm symptoms. The patients underwent small bowel capsule endoscopy and/or double-balloon enteroscopy. Control populations were represented by the 165 non-celiac patients undergoing capsule endoscopy for obscure gastrointestinal bleeding, and the 815,362-strong population of the Italian province of Varese as a registered cohort.
Results: Fifty-three patients (19% males, mean age 43.6 ± 17.4 years) were evaluated. Two jejunal adenocarcinomas and one ileal neuro-endocrine tumour were diagnosed by enteroscopy (the diagnostic yield for malignancies in the selected population being 5.7%). In the non-celiac controls the detection rate of small bowel tumours by capsule endoscopy was 0.6% ($P = 0.04$). When compared to the registered population, the relative risk for intestinal malignancy was 1282 (95% CI, 407–4033; $P < 0.0001$).
Conclusions: Capsule endoscopy and double-balloon enteroscopy can be considered for early disease management of a subset of celiac patients.

1. Introduction

Celiac disease (CD) is the most common chronic autoimmune enteropathy in western countries, and has an estimated prevalence ranging from 1:100 to 1:200 [1]. It is usually characterized by a benign course with both clinical and histological remission, provided that a strict gluten-free diet is followed. Less frequently, CD is characterized by a complicated course, for example [2] when dealing with a refractory disease (RCD) or with malignancies of the gastrointestinal tract, namely lymphoma and adenocarcinoma of the small bowel (SB). Different studies estimated a relative risk for neoplastic intestinal complications in CD ranging from 2 to 40 [3–5] for primary gut lymphoma, and from 10 to 60 [3,6,7] for adenocarcinoma. However, the results from recent studies carried out in the north-Italian and Finnish populations and investigating the potential effect of hidden (undiagnosed) CD on the incidence of gastrointestinal tract malignancies, failed to prove any impact of CD on the overall frequency of these tumours [8,9].

Although uncommon, the discussed malignancies are characterized by poor prognosis, as indicated by an overall survival rate at 30 months of 58% and 45% in patients with adenocarcinoma and lymphoma, respectively, reflecting the high prevalence of late diagnosis [10].

Age at CD diagnosis reportedly plays a relevant prognostic role, as an increased incidence rate of cancer has been reported when CD was diagnosed during adulthood and in the elderly [3,11,12].

Poor mucosal healing despite an ongoing gluten-free regimen has been reported in up to 73% of CD patients with malignant SB complications [10]. The lack of histological improvement may be due to both inadequate compliance and unresponsiveness to gluten-free diet, thus representing an intermediate step of lymphoma development, as occurs in type-II RCD.

The effect of compliance to gluten-free diet on the incidence of lymphoma has often been investigated, with contradictory results: a few studies supported the protective role of a strict gluten-free

* Corresponding author. Tel.: +39 02 55033384; fax: +39 02 55033325.
E-mail addresses: tomba.carolina@gmail.com, carolina.tomba@alice.it (C. Tomba).

1590-8658/$36.00
http://dx.doi.org/10.1016/j.dld.2013.12.009

diet [3,10,13], while other studies [2,5,14] reported a persistent risk of lymphoma in spite of gluten withdrawal.

Altogether the above data have led to the following considerations: (i) the risk of gastrointestinal malignancy in CD is not homogenously distributed; (ii) attention should be especially paid to those CD patients with demographic and clinical features that identify them at a presumably higher risk of having a neoplastic complication; (iii) for such a subset of CD patients an early diagnostic strategy of SB tumours is yet to be evaluated.

The difficulty in SB exploration used to be the major problem for the early diagnosis of intestinal tumours. The introduction of small bowel capsule endoscopy (SBCE) and device-assisted enteroscopy facilitated the study of the SB mucosa. The enteroscopic techniques have been applied to both the diagnosis and management of patients with complicated CD, even if the data currently available are mainly obtained from retrospective investigations.

Based on the aforementioned considerations, the present study aimed at prospectively evaluating the selection criteria, including the suspected risk factors for SB malignancies in CD and the diagnostic yield of SBCE and double-balloon enteroscopy (DBE), in the early detection of intestinal malignancies for this CD cohort.

2. Methods

From June 1, 2011 to June 30, 2013, all consecutive CD patients attending the Centre for the Prevention and Diagnosis of Celiac Disease – Gastroenterology 2 Unit at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy) were prospectively evaluated. According to the international guidelines [15,16] CD diagnosis was based on the histological evidence of duodenal atrophy (a type 3 lesion according to the Marsh–Oberhuber classification). The presentation type was categorized as classic (diarrhoea, weight loss, longitudinal growth retardation), mono/paucisymptomatic (i.e. dyspepsia, anaemia, hypertransaminasemia, osteopenia) or associated with the presence of dermatitis herpetiformis (DH).

The patients were enrolled according to the following inclusion criteria:

(i) The CD diagnosis occurred when patients were aged over 50 years, with persistence/recurrence of gastrointestinal symptoms after 6 months on gluten-free diet.
(ii) Lack of compliance to gluten-free diet (defined as the conscious and regular gluten ingestion for at least two years).
(iii) Presence of alarm symptoms/signs, either at diagnosis or during the follow-up.

The study was approved by the local Ethical Committee and was carried out in accordance with the Declaration of Helsinki. Patients fulfilling the inclusion criteria gave their written informed consent to be enrolled in the study and then underwent the following work-up: routine blood tests (i.e. full blood count, ferritin, transaminases, alkaline phosphatase, gamma-GT, glycaemia, cholesterol, triglycerides, TSH); anti-endomisium and anti-transglutaminase antibodies; endoscopy of the upper gastrointestinal tract with at least four oriented duodenal biopsies; determination of histologic grading (Marsh–Oberhuber's classification) and CD3/CD8 immunohistochemistry; SBCE; DBE in case of positive findings at SBCE or when SBCE was contraindicated. Further investigations were carried out when clinically indicated. In details: TCR rearrangement analysis in case of suspected RCD or intestinal lymphoma; HLA typing to determine a genetic CD susceptibility; colonoscopy with multiple mucosal biopsies when suspecting colonic tumours, inflammatory bowel disease or microscopic colitis; CT or MRI-enterography for tumour staging or in case of intestinal obstruction. SBCE (Pillcam SB2.4, Given Imaging, Yoqneam, Israel) was performed after intestinal cleaning with a 3-litre polyethylene-glycol (PEG)-based solution (to be assumed the day before the examination) and overnight fasting. Patients with a cardiac pacemaker underwent examination under continuous cardiac monitoring. The Given Imaging recording system was positioned according to the manufacturer's instructions; data were downloaded on a dedicated computer workstation and analyzed by a dedicated software (Given Imaging, Yoqneam, Israel). In those patients who had undergone major abdominal surgery or presented symptoms consistent with possible intestinal obstruction, SBCE was preceded by the evaluation of the intestinal canalization by patency capsule (Agile, Given Imaging, Yoqneam, Israel). As from Given Imaging specifications, the examination time with Pillcam SB2.4 was of at least 9 h. All the registrations were conducted till battery exhaustion. The SBCE imaging results were defined as "good" if at least 90% of the mucosal surface was visualized, "sufficient" if at least 80% of mucosa was observed, and "poor" in case of worse intestinal cleaning.

The same physicians performed SBCE and DBE, and were in charge of CD management. In case of positive SBCE findings, DBE (Fujinon, Saitama, Japan) was then carried out. The following endoscopic features were considered for histological evaluation: mass lesions, ulcers, nodules or nodular mucosal patterns, extensive (beyond 30% of SB transit time) or patchy distribution of atrophic features (mosaicism, scalloping, fissures). The route of insertion was planned according to the estimated site of the lesion as of SBCE (cutoff at 70% capsule progression). Histological and immunohistochemical evaluations (CD3, CD8) were performed on the samples obtained from both the lesion and the adjacent mucosa.

One-hundred and sixty-five non-celiac patients, matched for gender and age, and undergoing SBCE for obscure gastrointestinal bleeding (overt or occult), were included as a control group for the SBCE diagnostic yield evaluation. The incidence of the tumour types diagnosed in the CD cohort was compared to that of a registered population (from the Lombardy Regional Cancer Database) of the Varese province (815,362 inhabitants), assumed as an index of incidence in the general population. Subjects with CD were excluded from the abovementioned database. The tumour sites and histological types according to the ICDO3 classification (International Classification of Disease for Oncology, WHO, 2000) are reported in the Database with a level of completeness and diagnostic accuracy of 98.7% [17].

2.1. Statistical analysis

Statistical analyses were performed using SPSS ver. 18. A *P*-value of <0.05 was considered statistically significant (significance level for the tests: 5%, two tails). The sample size was calculated assuming a 5% prevalence of malignancies in the CD cohort. The normal distribution of the sample was verified through the Kolmogorov–Smirnov test. Continuous variables were analyzed with the ANOVA Oneway variance test or with the non-parametric Kruskal–Wallis test. The significance level was further verified by multiple comparison analysis (Tukey or Mann–Whitney's test). Categorical variables were compared with the X^2 or Fisher's exact test.

3. Results

3.1. Patients' profile

Fifty-three consecutive patients were enrolled, of whom 10 were males (19%); mean BMI was $21.5 \pm 3.8\ kg/cm^2$, mean age at diagnosis was 43.6 ± 17.4 years, and was 49 ± 4.6 years at enrolment. When first diagnosed, 36 patients (68%) showed a classic clinical presentation, 16 (30%) were mono/paucisymptomatic and one (2%) had DH. Eight cases (15%) tested negative at serology for