Brief communication

Diarrheic syndrome as a clinical sign of intestinal infiltration in progressive B-cell chronic lymphocytic leukemia

E. Abella a,*,1, T. Gimeneza,1, J. Gimeno b, M. Cervera a, C. Pedro a, E. Gimeno a, A. Alvarez a, A. Salar a, B. Bellosillo b, S. Serrano b, C. Besses a

a Department of Clinical Hematology, Spain
b Department of Pathology, Hospital del Mar, Paseo Marítimo 25-29, 08003 Barcelona, Spain

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Abstract

Gastrointestinal involvement is a rare event in patients with B-cell chronic lymphocytic leukemia (B-CLL) and is usually associated to lymphomatous transformation. However, in autopsy studies the reported incidence of microscopic infiltration can reach up to 50% of cases. Seven B-CLL patients in advanced stage/progressive disease were evaluated by colonoscopy because of continuous diarrhea. Five out of seven patients (71%) presented histological evidence of colonic infiltration. Persistent diarrhea in patients with progressive/advanced B-CLL can be a clinical sign of intestinal infiltration and justifies endoscopic examinations.

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1. Introduction

B-cell chronic lymphocytic leukemia (B-CLL) is the most prevalent form of leukemia in adults in western countries. It is characterised by a progressive accumulation of mature and immunoincompetent lymphocytes in bone marrow and lymphoid organs and its clinical course is heterogeneous. Median survival ranges from 5 to 10 years and patients usually die because of progressive disease and/or secondary complications such as infections, transformation to large cell lymphoma and others.

Extranodal involvement has been usually reported in lung, pleura, skin, central nervous system and kidney. In this setting, patients are generally in progressive disease, have received several lines of treatment and their prognosis is ominous.

The incidence of gastrointestinal (GI) tract involvement in B-CLL is low, even in post-mortem studies [1] and the majority of cases are often reported in the context of transformation to an aggressive lymphoma (Richter syndrome). Clinical symptoms are variable; some patients complain of abdominal pain, ischemic colitis, or persistent diarrhea [2], although others do not present clinical signs suggestive of intestinal infiltration.

We describe five B-CLL patients with progressive disease and advanced Binet’s stage in which the only clinical sign of GI involvement was diarrhea non-responsive to medical therapy. Endoscopic examinations allowed us to demonstrate involvement of the lower GI tract by B-CLL.

2. Material and methods

Between 1997 and 2006, 130 patients (73 males and 57 females) were diagnosed of B-CLL in our institution according to NCIWG criteria [3]. During this period, 34 gastrointestinal endoscopic procedures were done in 27 patients (gastroscopy (n = 15) and colonoscopy (n = 19)). The reasons to perform a gastroscopy were as follows: anemia (n = 5), suspicion of neoplasia (n = 3), abdominal pain (n = 2), melena (n = 2), diarrhea (n = 2) and esophagitis (n = 1). Colonoscopy was carried out by the following reasons: persistent
diarrhea ($n = 7$), changes in bowel habits ($n = 4$), active intestinal bleeding ($n = 4$), colonic neoplasia follow-up ($n = 2$) and microcytic anemia ($n = 2$).

Six out of seven patients with diarrhea were in advanced stage and/or progressive disease. Gastric and/or bowel biopsies were performed in all cases even if no macroscopical mucosal changes were present. When microscopic lymphocytic infiltration was observed, immunohistochemistry techniques were applied in order to confirm B-CLL immunophenotype. When it was feasible, IgH rearrangement studies were done.

### 3. Results and discussion

Clinical and histological characteristics of patients with persistent diarrhea are shown in Table 1.

Gastroscopy did not show macroscopical evidence of B-CLL infiltration in any patient. In one patient with human immunodeficiency virus (HIV) infection, candidiasis in esophagus was detected. In this patient histology demonstrated chronic gastritis and atrophic mucosa. However, when immunohistochemistry was applied, a small gastric lymphoid infiltrate was detected expressing positivity for CD79a, CD23 (weak), CD5 (weak) and CD43. Such findings were compatible with silent B-CLL infiltration. In a second patient who underwent a gastroscopy because of epigastric pain, microscopic study showed focal and minimal atypical lymphoid infiltration at the antrum, but IgH rearrangement was negative. In two additional patients gastroscopy allowed the diagnosis of gastric adenocarcinoma and pancreatic carcinoma.

Seven patients with persistent diarrhea non-responsive to conventional medical therapy were examined by colonoscopy. Only in two cases macroscopic lesions were observed: an ulcer in ascending colon and a sigmoid diverticile. Five out of seven patients (71%) presented infiltration by lymphocytes in the intestinal mucosa: four in the colonic mucosa and one case in the ileum (Fig. 1). In one of them, simultaneous involvement of sigmoid and colonic mucosa was observed. Rectum infiltration was not noticed in any case.

Focal and diffuse infiltration by characteristic B-CLL lymphocytes were seen in four and one cases, respectively. Immunohistochemistry was performed in 3 out of 5 cases, showing lymphocytes positivity to CD5, CD19, and CD23 (Fig. 2). Cyclin D1 was negative in all five cases, excluding mantle cell lymphoma.

In 4 out of 5 cases a molecular study was done. Clonality pattern in intestinal mucosa infiltrates was demonstrated by IgH rearrangement in 2 out of 4 cases. The same clonal

<table>
<thead>
<tr>
<th>Binet’s stage</th>
<th>Localization/macroscopic appearance</th>
<th>Microscopic findings</th>
<th>Molecular study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C Ascendant and transverse colon and sigma/normal</td>
<td>Focal infiltration</td>
<td>Positive</td>
</tr>
<tr>
<td>2$^a$</td>
<td>C Ascendant colon/ulcer</td>
<td>Diffuse infiltration</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>C Descendent colon/normal</td>
<td>Focal infiltration</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>C Terminal ileum/ Sigmoid diverticile</td>
<td>Focal infiltration</td>
<td>Negative</td>
</tr>
<tr>
<td>5$^b$</td>
<td>B Colon/normal</td>
<td>Focal infiltration</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>C Normal</td>
<td>Normal</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>A Normal</td>
<td>Normal</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not determined.

$^a$ Case 2: IgH clonal rearrangement was identical in colonic biopsy and peripheral blood lymphocytes.

$^b$ Case 5: focal lymphoid infiltration was observed in antral curvature and in colonic mucosa despite normal macroscopic appearance.
peak was identified in peripheral blood in 1 out of 2 cases.

All patients with intestinal involvement were in refractory and progressive disease except one case who was in stage B and had initiated treatment with polychemotherapy. This patient had microscopical antral infiltration, too. Richter transformation was not demonstrated in any case.

B-CLL remains an incurable disease despite new treatment strategies including chemotherapy-monoclonal antibodies combinations and hematopoietic stem cell transplantation. Patients finally die because of infectious complications, progressive disease or transformation to an aggressive lymphoma.

The GI involvement in B-CLL have been historically reported to be uncommon (5–13%) [1,4], and when present, is often associated in the majority of cases to Richter transformation. Any localization of GI tract can be affected. Macroscopically, the type of involvement is variable, with presence of masses, ulcers, or even no detectable lesions. Patients with GI involvement can be asymptomatic or present as described by Gonçalves et al. [2] with GI hemorrhage [6], chronic colitis, abdominal pain, or persistent diarrhea [2]. However, even in cases without clinical manifestations, microscopic infiltration can be present in more than 50% of autopsy studies [5].

Prolla and Kirsner [5], in a study over 148 autopsies of patients with leukemia, reported necropsic findings in 18 cases of B-CLL. Lesions affected esophagus, stomach, small intestine and large bowel. Macroscopically, GI mucosa was normal or presented two types of lesions: hemorrhagic or infiltrative (focal or diffuse). Esophageal mucosa was affected by B-CLL infiltrates in 22% of cases. Macroscopic and/or microscopic gastric involvement was observed in 72% of cases. In small intestine no lesions were detected in duodenum, jejunum and ileum and no evidence of microscopic involvement was seen. Colonic lesions were detected only in seven cases (hemorrhagic mucosa (n = 4) and leukemic infiltrates (n = 3)). In conclusion, they reported an incidence of leukemic infiltrates of the GI tract in 12 cases (66%) with B-CLL or chronic lymphoproliferative syndrome (three gross leukemic infiltrates and microscopic lesions in nine cases). In this series, no case reported persistent diarrhea in the clinical history.

Gonçalves et al. [2] reported a patient in advanced stage with diarrhea in which invasion of upper and lower GI tract was demonstrated in the absence of Richter syndrome. Kuse and Lueb [7], described five cases of infiltrative lesions in upper and/or lower GI tract but clinical symptoms were not reported.

In our series, we observed microscopic involvement of the lower GI tract in 5 out of 27 patients with B-CLL in which GI endoscopies were performed. All but one patient were in advanced C stage, had received chemotherapy because of progressive disease and manifested chronic diarrhea as the clinical symptom of GI involvement. This type of involvement in B-CLL is infrequent during the clinical course of the disease and is usually observed in advanced stages. The majority of the reported cases did not show suggestive clinical signs and usually had a normal macroscopic appearance by endoscopy.

In conclusion and according to our experience, the associated clinical sign pointing to GI infiltration was persistent diarrhea. In this setting, a gastrointestinal examination with biopsy, immunohistochemistry and molecular studies is recommended in order to exclude GI lymphocytic infiltration.

Conflict of interest statement

The authors reported no potential conflict of interest.

Contributions

EA, TG and CB designed the study and were responsible for the final interpretation of the data and the final draft of the manuscript.

JG, MC, CP, EG, AA, AS, BB and SS all made substantial contribution to the analysis or interpretation of the data or revising it critically for important intellectual content; all authors approved the final version to be published.

Acknowledgement

The content of the manuscript has not been previously published and it is not being considered for publication elsewhere in whole or part in any language.

References