Interest of Upper Digestive Endoscopy in the Monitoring of Biermer Disease: Experience of a Moroccan Unit
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Abstract: Biermer's disease is an autoimmune disease leading to chronic atrophic gastritis of the fundus. It is a precancerous condition that can lead to the development of carcinoid tumors and gastric adenocarcinoma. Indeed, stomach cancer is the second most common digestive cancer in Morocco. Its prognosis is poor with a survival at 5 years of about 15%, which requires regular endoscopic monitoring of Biermer disease. In this study, we report 239 cases of Biermer disease among 22531 esophagogastroduodenal endoscopies (EGDE) collected between January 2007 and December 2017 in the EFD-HGE department of the Ibn Sina Hospital in Rabat. Epidemiological, clinical, endoscopic and therapeutic aspects were analysed. The anatomo-pathological study determined the histological type of the polyps, its degree of dysplasia and the presence of Hp, intestinal metaplasia or gastric atrophy. All our patients with Biermer's disease had received an EGDE with antral and fundal biopsies every 3 years as part of their follow-up. In this work, the frequency of Biermer's disease was 1.06%. The average age of the patients was 40 years (20-81 years) with a slight male predominance (56.5%). The EGDE found congestive funditis with rarefaction of fundic folds in 162 patients (67.7%), small polypoid fundic lesions in 51 patients (21.3%), hyperplastic polyps in 10 patients (4.2%) with antral site in 9 patients and subcardial in one patient. EGDE was normal in 16 patients (6.7%). The anatomo-pathological study of biopsies concluded that there was chronic atrophic funditis with intestinal metaplasia without enterochromaffin-like (ECL) cell hyperplasia or dysplasia in 72 patients (32.3%), chronic atrophic funditis with intestinal and pyloric metaplasia and ECL cell hyperplasia without dysplasia in 90 patients (40.3%), a neuroendocrine tumor with ECL cell hyperplasia in 35 patients (15.7%), hyperplastic polyps in 20 patients (8.9%), a high-grade dysplasia tubular polyadenoma in six patients (2.7%). Hp infection was present in 75% of hyperplasic polyps, 50% of gastric adenomas and 50% of gastric neuroendocrine tumors (NETs). Biermer's disease is a precancerous pathology that can lead to fundic neuroendocrine tumours and gastric adenocarcinoma. In our study, 18.4% of patients had tumor degeneration, what requires a regular endoscopic and anatomo-pathological sollow-up.

Keywords: Biermer's, esophagogastroduodenal, Ibn Sina, unditis.

INTRODUCTION
Biermer's disease is the outcome of an autoimmune process, type A autoimmune fundic gastritis, an atrophy with its terminal phase achlorhydria and a reduction of intrinsic factor rates related to the disappearance of parietal cells and Vitamin B12 deficiency.

Diagnostic criteria remain discussed. It seems preferable to extend the definition to an entire autoimmune process irrespective of the stage of gastritis and to consider the diagnosis in case of chronic atrophic gastritis unrelated to Helicobacter pylori associated with signs of autoimmunity, either clinical, that is biological. About 20-27% of patients have iron deficiency that is sometimes the first sign of the disease. Vitamin B12 deficiency is late.

Biermer's disease is rarely complicated by fundal adenocarcinoma, but more often by fundamentally differentiated neuroendocrine tumors with enterochromaffin-like cells (EC-L tumors). They are tumors most often benign which require exceptionally a surgical act.

The aim of this work is to specify the epidemiological, clinical, endoscopic and histological characteristics of gastric polyps discovered during Biermer's disease and their therapeutic management.

MATERIALS AND METHODS

- This is a retrospective study carried out at the Department of Digestive Functional Explorations - Hepato-Gastroenterology (EFD-HGE) of the Ibn Sina Hospital in Rabat over a period of 10 years (2007-2017).
- All patients with Biermer's disease at diagnosis or during endoscopic follow-up have had a biopsy of the gastric lesion and also of the mucosa, i.e. 3 antral biopsies, 2 on each side of the pylorus and one on the angulus and 4 on the fundus.
- Two hundred and thirty-nine patients (n: 239) with Biermer disease were collected during the study period.
- All the data have been collected from upper gastrointestinal endoscopy registers.
- We have analysed epidemiological (Age and sex) and endoscopic characteristics: number, size and location, the appearance and morphology of polyps, also the appearance of the gastric mucosa.
- The descriptive endoscopic study focused only on the largest polyp when multiple lesions were involved.
- We have also analyzed Polyp’s (Histological nature, dysplasia, MI, AG, carcinoma) and Gastric mucosa Anatomopathology: Gastric atrophy, Intestinal metaplasia, dysplasia, Hp infection.

Finally we have talked about therapeutics:
- Endoscopic treatment: Removal biopsy, diathermic loop polypectomy, mucosectomy. Surgical treatment, Hp eradication treatment
- All patients had received either an excisional biopsy when the polyp was small or a simple biopsy followed by a polypectomy or mucosectomy during the first diagnostic endoscopy.

RESULTS

22531 upper digestive endoscopies were performed during the study period. 239 had Biermer's disease, a frequency of 1.06%.

The average age was 35 years (21-80 years) with a slight male prevalence of 56.5%. Among the gastric endoscopic lesions found at the EGDE, 2 types of atrophic mucosa were found in patients with Biermer's disease:

- Atrophic mucosa with polyps representing 18%.
- Atrophic mucosa without polyps representing 82%.

Among the polypoid lesions, we found: Neuroendocrine tumors (n: 35), hyperplastic polyps (n: 20) and gastric adenomas (n: 6)
In patients with NET, 23 patients had multiple polyps (66%) and 12 patients had single polyps (33%) (Figure 3). The endoscopic characteristics and biopsies had only focused on the largest polyp. The size of the polyps was less than or equal to 10 mm in 17 patients (50%), between 5 and 10 mm in 12 patients (33%) and less than 5 mm in 6 patients (17%).

The most frequent localization was fundus in 29 patients (83%) and antro-fundic junction in 6 patients (17%). The polyps were sessile in all patients. The removal of the polyp during the first endoscopy was performed in 16 patients (47%) by excisional biopsy and 12 patients (33%) underwent a polypectomy. 7 patients had received additional treatment (Mucosectomy) during a second endoscopy for therapeutic purposes. There were no immediate bleeding complications or secondary effects.

The histological nature of the polyps corresponded to grade 1 EC-L cell tumor type I in all our patients. 12 patients (50%) were Hp carriers. Intestinal metaplasia was present in half of the patients and ECL cell hyperplasia was also present (50.3%). If the neuroendocrine tumors (NET) were < 1cm and multiple, the follow up consisted of a EGDE with gastric biopsies every year.

8 patients (41%) had Hyperplasic polyps with a size less than 5 mm, 6 patients (33%) with a size between 5 and 10 mm and 4 patients (20%) with a size larger than 10 mm.

The most frequent localization was antral in 11 (58%) patients, sub cardiac in 4 patients (20%), fundic in 3 patients (13%) and antro-fundic in 2 patients (10%). Polyps were sessile in 13 patients (64%) and pedunculated in 6 patients (30%). (Figure 4)

The treatment of hyperplasic polyps was endoscopic by diathermic loop polypectomy in all our patients. There were no immediate bleeding complications or side effects. Hp infection was found in 75% of patients who had received eradication treatment.

Gastric adenoma (Figure 5) was unique in 5 patients (83%) and multiple in 1 patient (16.6%).

The descriptive endoscopic study focused only on the largest adenoma.

The size of the adenomas was larger than or equal to 10 mm in 4 cases (75%) and between 5 and 10 mm in 2 cases (25%). The most frequent location was the antrum in 3 patients (50%) and the fundus in 2 patients (33%). Antro-fundic localization was found in one patient (16%).

Sessile polyps were the most common in 4 patients (75%) and pedunculated in 2 (25%). Virtual coloring (NBI or FICE) was used in two cases to better characterize lesions.

All patients had received a first diagnostic EGDE with biopsy at the gastric polyp and gastric mucosa. A second therapeutic EGDE was performed in all our patients, allowing a polypectomy at the diathermic loop. The resection was complete with a hemostatic complement by clipping in 2 patients. No other complications were noted.
Fig-4: Endoscopic appearance of a hyperplastic gastric polyps

Thus, the histological study had focused on endoscopic resection and concluded that there was a low-grade dysplasia adenoma. Hp infection was present in 3 patients (50%).

Gastric adenoma of the antrum: Single sessile/plane lesion in the pre-pyloric region, seen in standard endoscopy and using FICE

Fig-5: Endoscopic appearance of a gastric adenoma

Table-1: Anatomopathological types of gastric polyps in Biermer's disease

<table>
<thead>
<tr>
<th></th>
<th>Our study (2016) n (%)</th>
<th>Study of Park (2010) n (%)</th>
<th>Study of Stockbrugger (1983) n (%)</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>223</td>
<td>461</td>
<td>80</td>
</tr>
<tr>
<td>Number of patients with polyps</td>
<td>61 (27)</td>
<td>143 (31)</td>
<td>34 (42,5)</td>
</tr>
<tr>
<td>Number of polyps</td>
<td>240</td>
<td></td>
<td></td>
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<tr>
<td>Hyperplasic</td>
<td>20 (32)</td>
<td>138 (57)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>NET</td>
<td>35 (57)</td>
<td>46 (19)</td>
<td>16 (47)</td>
</tr>
<tr>
<td>Adenoma</td>
<td>6 (9)</td>
<td>21 (8,75)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Pseudopolyp</td>
<td>0</td>
<td>20 (0,8)</td>
<td>0</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0</td>
<td>11 (4,5)</td>
<td>1 (2,9)</td>
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<tr>
<td>Lymphoma</td>
<td>0</td>
<td>3 (1,25)</td>
<td>0</td>
</tr>
<tr>
<td>GIST</td>
<td>0</td>
<td>1 (0,4)</td>
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DISCUSSION
Gastroenterologists are called upon to diagnose Biermer's disease in the following circumstances: Dyspeptic syndrome, anemia, whether microcytic, normocytic, macrocytic, iron-deprived or linked to vitamin B12 deficiency, hypergastrinemia, presence of parietal antibodies or intrinsic factor, context of other autoimmune diseases (Thyroiditis, type 1 diabetes, Vitiligo...) gastric polyps [4]. Other manifestations of Biermer's disease could be: various digestive disorders (Diarrhea, constipation), Hunter's glossitis related to mucosal atrophy, disorders of the dander, decreased fertility, rarer but more serious and often non-reversible neurological disorders.
These may be simple paresthesias, polyneuritis, severe combined sclerosis of the marrow or exceptional encephalic disorders combining visual disorders, dementia, mood and behavioural changes.

There is no correlation between the endoscopic aspect and the anatomo-pathological lesions, although the so-called “atrophy” aspect is suggestive. Polypoid lesions exist in 25% to 39% of cases [5, 6]. Most are hyperplastic polyps, less atrophic mucosa than non-polypoid mucosa ( pseudopolypes) and rarely adenoma or adenocarcinoma (Table 1). Pseudo polyoid gastritis is a particular aspect of Biermer's disease where the multiple small polypoid formations correspond to islands of fundic mucosa less atrophic than the non-polyloid mucosa. In the largest series of pseudopolypes of this type were present in 8% of the 240 subjects with Biermer's disease [6]. Diagnosis can only be made if biopsies are made on both polypoid formations and on the non-polypoid mucosa.

Fundic NETs represent less than 10% to 20% of polyps. In the absence of a specific study, the American recommendations (ASGE) do not indicate a minimum number of biopsies to be performed in fundus [7].

There are mainly 3 types of well differentiated fundic NETs, the first 2 types are constantly associated with hypergastrinemia, but not the third [8, 9]. Type 1 (70-80%) corresponds to NETs associated with fundic atrophic gastritis, mainly Biermer disease, type 2 (5-6%) corresponds to NETs associated with Zollinger-Ellison syndrome integrated with multiple endocrine neoplasia type 1 and type 3 NETs (14-25%) corresponds to NETs without promoting factors, called sporadics. Type 2 NET is never discovered before Zollinger-Ellison syndrome. The discovery of well-differentiated NETs from the fundus therefore essentially involves differentiating type 1 NETs (on Biermer’s disease) from type 3 NETs (sporadic). In type 1, there is hypergastrinemia, non-tumor fundal mucosal biopsies show fundal atrophic gastritis and hyperplasia of neuroendocrine cells, NETs are almost always multiple and measure less than 1 cm in more than 77% of cases, less than 2 cm in 99% of cases (Table 2) [10].

Anatomopathologically, type 1 NETs (associated with Biermer's disease) are almost always grade 1 (Ki 67 <2%, mitoses <2/10 large fields) while type 3 NETs are frequently grade 2 with high malignant and metastatic potential. Sporadic type 3 NETs are poor prognostic, malignant and are managed as gastric adenocarcinoma. In our study, all polyps were Grade 1 Type 1 NET TNEs.

The prevalence of NET associated with Biermer's disease ranges from 1.25 to 7.8% when Biermer's disease is discovered [5, 6]. In our study, this frequency is 1.06%. The incidence has recently been estimated at 0.9 per 100 patient-years in a series of 100 patients [11].

Surgical lumpectomy of tumours with metastatic risk possibly associated with antrectomy (suppressing hypergastrinemia and thus reducing the number of fundic tumours) is proposed in the following circumstances: size > 2 cm or invasion of the muscle. A total gastrectomy is indicated in case of adenopathy or lesion too high located, not resectable by a less invasive surgical procedure.

Several studies have shown that somatostatin analogues reduce the number of NETs associated with Biermer's disease [12]. These studies included only benign tumours less than 1 cm in size and showed recurrence upon discontinuation of treatment [12].

The risk of gastric cancer, much lower than that of NETs, was estimated in a recent meta-analysis at 0.27% per patient-year [13]. The relative risk of gastric cancer is 6.8 times higher than in the general population [13]. Risk factors include severity of atrophy, extension of intestinal metaplasia, age over 50 years and Hp infection [14].

Hyperplastic polyps are often located in the antrum, and often multiple in 15% of cases. They are generally sessile (sometimes pedunculated, 25%) or lobed, with a smooth surface that is more rarely ulcerated, and of small size (5 to 15 mm in diameter). In our series, the HPs were mainly located in the antrum and most often between 5 and 10 mm in size.

Histologically, they are made of crypts and elongated glands, more or less altered, with bifurcations and sometimes cystic dilations [1,2]. They develop on a mucosa in an uncontrolled regeneration phase with a chronic inflammatory stimulus (Biermer's disease, chronic antral gastritis).

<table>
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<th>Table-2: Characteristics of Type 1 Fundamental NETs</th>
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<tr>
<td><strong>Morphology</strong></td>
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<td><strong>Relative frequency</strong></td>
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<tr>
<td><strong>Seize</strong></td>
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<td><strong>Field</strong></td>
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<td><strong>Morphology</strong></td>
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Available online: http://saspublisher.com/sjams/
The risk of degeneration is between 0.5 and 7% [6.7]. This risk is greater when the polyp exceeds 10 mm [8]; this is further supported by a recent Korean retrospective study [9] involving 216 patients with 269 HP treated with endoscopic polypectomy or surgery of which 14 were neoplastic and the only predictive factor of a transformed polyp was a size > 10 mm (p=0.013). In our study, there were no cases of high-grade dysplasia or carcinoma even if the size is > 1 cm.

Gastric Adenomas are not the most common gastric polyps, but they are pre-cancerous lesions [1,2]. Their prevalence is assessed differently according to the series, but is estimated between 0.5 and 3.75% depending on the Western countries and between 9 and 27% in countries at high risk of gastric cancer such as China and Japan [1, 6]. They are most often sporadic, but can also be observed during familial adenomatous polyposis [2, 4].

In our study, these lesions were mainly localized in antrum (62.5%) with a size >10mm. Similar results are described in most studies [5]. Adenomas are pre-cancerous lesions and must be resected [3, 4]. In our study, all patients were resected by endoscopic resection (Polypectomy). The risk of malignancy is between 1 and 10%; this risk exceeds 40% in the case of polyp > 10mm and/or with a urban aspect 3.4. In our study, all adenomas were in low-grade dysplasia.

CONCLUSION

Biermer's disease is a precancerous pathology that can lead to fundic neuroendocrine tumours and gastric adenocarcinoma. In our series, 18% of patients had gastric polyps, hence the importance of regular endoscopic and anatomopathological monitoring.

It is essential, in the event of the discovery of a gastric polyp, to carry out biopsies at the level of the lesion but also on the gastric mucosa. The NETs have increased significantly in recent years, in our study they represented 14.6%. Any lesion larger than 10 mm should be investigated by EUS and CT scan for metastasis. Nevertheless, annual follow-up is required if the size is < 10 mm.

Hyperplastic polyps are common and sometimes associated with dysplasia if the size is > 1cm. They are resected endoscopically. As for gastric adenomas, they are rare lesions but are not considered as precursors of gastric cancer as is the case at the colonic level. But these are neoplastic polyps whose resection is mandatory regardless of their size. Concerning monitoring, it is 2 to 3 years if there are no polyps. Otherwise, monitoring must be annual.

Abbreviations

EGDE: Esogastroduodenal endoscopy
Hp: helicobacter Pylori
NTE: Neuroendocrin tumor
HP: Hyperplasic Polyp
FICE: Fuji Intelligent color Enhancement
NBI: Narrow Band Image

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