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CASE 1

Clinical history

74 yrs old man. Recent anorexia and weight loss, with upper abdominal pain. Moderate arterial hypertension, no other past medical history. Under NSAIDs for vague rheumatismal pain. On upper digestive endoscopy, large eroded folds in the gastric body. Two slides of gastric biopsies are submitted: (1) body; (2) antrum.

Histological lesions

Gastric biopsies were performed in the antrum and in the fundus. They show typical features of lymphocytic gastritis. The fundic mucosa (1) shows diffuse inflammatory changes, present on all 4 specimens. There is an increased number of intraepithelial lymphocytes (IELs) in the surface and crypt epithelium, that is confirmed by immunohistochemistry. IEL number is higher than 30 per 100 epithelial cells, and IELs express CD3 and CD8. The lamina propria shows an increase in inflammatory cells, mostly lymphocytes and plasma cells. There is also focal surface erosion, with fibrin deposit and neutrophils. There is no glandular atrophy nor intestinal metaplasia.

In the antrum (2), the lesions are similar, with increased IELs, but there is no erosion. There is no *Helicobacter pylori* (*H. pylori*) infection. Biopsies taken from the small intestine are normal.

Diagnosis

Lymphocytic gastritis

Discussion

Lymphocytic gastritis was described initially by Haot et al in 1985 (1, 3, 5). It is an uncommon form of chronic gastritis with a distinctive histological picture but still a poorly understood pathophysiology (4).

Histological and immunohistological features

Diagnostic feature

The diagnostic feature of lymphocytic gastritis is a marked intraepithelial lymphocytosis. The count has to be made on the surface epithelium, on 400 to 500 epithelial cells. A number of 25 IELs per 100 epithelial cells is considered as a threshold for the diagnosis of lymphocytic gastritis. However, this number is much higher in most cases, with a mean number about 50 IEL for 100 epithelial cells in most series, i.e., 10 times higher as in other types of chronic gastritis and 20 times higher as in normal mucosa. In typical cases, the surface epithelium is crowded with dark nuclei surrounded by a clear halo,

typical of normal IEL. This increased number of IEL is only present in the surface and foveolar epithelium with no involvement of the glandular layer.

Topography

Lymphocytic gastritis can be present in the antrum and/or the body, depending upon the associated conditions and endoscopic features (see infra).

Immunophenotype of IELs (8)

In typical cases of lymphocytic gastritis, immunostaining is not necessary to make the diagnosis. IELs in lymphocytic gastritis have the phenotype of normal IELs: a vast majority are CD3+ T lymphocytes, and 70-80% express CD8 in the cell surface. Most of these IELs are activated cytotoxic T-lymphocytes, as shown by their expression of TIA-1, a cytotoxic granule-associated protein. B lymphocytes are absent from the epithelium in lymphocytic gastritis.

Associated lesions

The typical increased IELs are usually associated with a chronic inflammatory infiltrate in the lamina propria, of variable intensity, and composed of lymphocytes and plasma cells. The foveolar pits may be tortuous and elongated. In a number of cases, erosions are present. Eroded areas contain fibrin deposits and active inflammation with neutrophils, that may obscure the IEL infiltrate.

Clinical and endoscopic features

Lymphocytic gastritis has a frequency of 1.5% to 4% of chronic gastritis (2), and is found in about 1% of dyspeptic patients undergoing upper GI endoscopy. Although most cases have been reported in Europe and United States, lymphocytic gastritis has also been described in other parts of the world. It is seen in most cases in adults, although there have been also case reports in children. A slight female predominance is present.

Associated conditions will be discussed later. They include celiac disease, *Helicobacter pylori* (*H. pylori*) infection, and to a lesser extent Crohn's disease, HIV infection, gastric lymphoma, and esophageal carcinoma.

Clinical features are highly variable, from dyspepsia to the rapid development of an alarming symptomatology suggestive of a gastric neoplasm, with abdominal pain, anorexia, severe weight loss. In a small subset of patients there may be protein-losing gastroenteropathy with peripheral oedema.

Endoscopic features are also variable, ranging from a normal aspect to the highly suggestive aspect of varioliform gastritis, showing enlarged gastric folds with nodules that contain central erosion. The correlation between endoscopic varioliform gastritis and lymphocytic gastritis is high in cases with diffuse and corporeal endoscopic lesions (53 of 55 cases diagnosed by endoscopy corresponding to lymphocytic gastritis in a series by Haot et al) (4) but is much weaker in antral varioliform gastritis (1 of 11 cases in the same series). On the other hand, 20 to 50% of cases of lymphocytic gastritis do not present as varioliform gastritis on endoscopy.

Associated conditions

Frontier cases with Ménétrier's disease

Some cases presenting clinically (low acid secretion and protein loss) and endoscopically (giant gastric folds) as Ménétrier's disease show histologically lymphocytic gastritis in

addition to the classical features of Ménétrier's disease. On the other hand, many authors have reported an association between lymphocytic gastritis and protein-losing gastropathy. It appears therefore that there is an overlap between lymphocytic gastritis and Ménétrier's disease, with a spectrum of lesions ranging from pure lymphocytic gastritis to classical Ménétrier's disease, through intermediate lesions of "hypertrophic" lymphocytic gastritis.

Collagenous gastritis

Collagenous gastritis is a very uncommon form of chronic gastritis with about 20 cases reported in the literature to date. Its aetiology is unknown, and it is defined histologically by the presence on gastric biopsies of a thickened subepithelial collagen band in association with an increased number of inflammatory cells in the lamina propria. In view of the relationship between the two types of microscopic colitides, i.e. lymphocytic colitis and collagenous colitis, there is a possibility that collagenous and lymphocytic gastritis are linked in some way. In a series of 6 cases we have reported, an increased number of IELs was present in the stomach in 2 cases (6).

Lymphocytic gastritis and celiac disease

Celiac disease is an important cause of lymphocytic gastritis. Approximately half of the patients with celiac disease and a flat duodenal mucosa meet the criteria of lymphocytic gastritis. Conversely, significantly higher IEL counts are found in the duodenal mucosa of patients with lymphocytic gastritis and half of them have evidence of abnormal small intestinal permeability. These data indicate that in some cases lymphocytic gastritis represents a reaction of the gastric mucosa to gluten ingestion.

Links with *H. pylori* infection

In most published series, *H. pylori* infection is present in a minority of cases (20 to 40%) of lymphocytic gastritis. Moreover, in *H. pylori*-positive cases with lymphocytic gastritis, *H. pylori* colonization is often minimal or focally localized mainly in the corpus. Conversely, the majority of adult patients with lymphocytic gastritis will have positive levels of serum anti-*H. pylori* antibodies. This may be due to the cytotoxic effects of activated T lymphocytes on *H. pylori* leading to reduction or even complete elimination of the bacteria.

Differential diagnosis

The histological picture of lymphocytic gastritis is distinctive, and once the pathologist is aware of this entity, the diagnosis is easily made in most cases. Diagnostic difficulties may occur in cases with multiple erosions, due to non specific inflammatory changes (necrosis, polymorphs etc.) that may obscure the increase in IELs. Celiac disease and Ménétrier's disease are not differential diagnoses but associated or linked conditions in most cases.

In gastric MALT lymphomas there is epithelial destruction by the lymphoid infiltrate, which does not occur in lymphocytic gastritis, and the neoplastic lymphoid cells are CD20 positive and CD3 negative.

In chronic active *H. pylori* gastritis, the surface and crypt epithelium may be infiltrated by neutrophils, but the number of IEL is usually less than 5 per 100 epithelial cells.

Evolution and treatment

Spontaneous resolution of the disease is possible, but in most cases, lymphocytic gastritis follows a protracted course and must be considered a chronic disease. Patients with ulcers and/or erosions are treated with proton pump inhibitors (PPI). But in cases associated with other conditions, the main part of the treatment is directed against those conditions: gluten-free diet in celiac disease, and antibiotics with PPI in *H. pylori* gastritis. Very interestingly, it has been reported in the only randomized-controlled anti-*H. pylori* trial of lymphocytic gastritis that the healing rate was comparable high irrespective of the *H. pylori* status at baseline (7).

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CASE 2

Clinical history

48 yrs old woman. No remarkable past medical history. For 5 years, several attacks of right upper abdominal pain with transient and mild increase in gamma-glutamyltransferase. Normal abdominal US and CT scan, with normal intra- and extrahepatic biliary tract. On repeated upper digestive endoscopies, polypoid lesion of the major papilla, increasing in size on the last examination (from 15 to 20 mm). Two series of biopsies show reactive and inflammatory changes, with no evidence of neoplasia. On echoendoscopy, the nodule measures 26mm in its greater dimension and is limited to the ampulla of Vater. Due to strong clinical suspicion of an ampulloma, duodenopancreatectomy is performed. The slide that is submitted is from the major papilla.

Morphological lesions

On macroscopy, the surgical specimen shows a nodular polypoid lesion (30 x 20 mm) of the major papilla, covered by a normal duodenal mucosa. There is a moderate dilatation of the Wirsung duct and common bile duct. The head of the pancreas is macroscopically normal.

The entire lesion of the papilla and ampulla of Vater was sampled for histological examination, and the lesions were similar on all slides, including the slide that was submitted in the seminar.

The lesion consists of multiple lobules of glands, mainly located in the muscle layers of the Vaterian system and major papilla. The abnormally located glands are covered by a single-layer epithelium that shows no atypia and no mitotic figures. The lobular formations consist of small glands sometimes disposed around a larger gland and surrounded by a myofibroblastic and fibroblastic proliferation. There are also mild non specific inflammatory changes. The duodenal wall and the pancreas are normal at distance from the papilla.

Diagnosis

Adenomyoma of the ampulla of Vater.

Discussion

Adenomyoma is a rare benign lesion of the hepatobiliary and gastrointestinal tract, with most cases described in the gallbladder. A few cases have been reported elsewhere in the gastrointestinal tract, including the stomach, small bowel, bile ducts and the ampullary region. Adenomyoma of the Vaterian system is an exceptional benign lesion. In the WHO classification it is defined as a tumor-like lesion of extrahepatic bile ducts (1,2). The neoplastic or malformative origin of this lesion is still subject to controversy. Despite its benign nature, adenomyoma is responsible for biliary obstruction and can be misdiagnosed as carcinoma or adenoma. Therefore it is treated frequently by extensive surgery. We have reported recently a series of 13 cases, with detailed histological and immunohistochemical features (3).

Morphological features

Macroscopy

The diagnosis of adenomyoma was made in our series and in most single case reports on histological examination of surgically resected specimens. On macroscopic examination, the ampulla of Vater and/or the terminal portion of the common bile duct exhibit a firm, grossly nodular lesion measuring 10 to 30 mm in diameter, that extend to the major papilla in most cases.

The overlying mucosa is normal, without ulceration. In some of our cases there were associated pancreatic abnormalities: annular pancreas in one case and pancreas divisum in 2 cases.

Histological features

The histological aspect of adenomyoma is characterized by multiple lobules of glands, mainly located in the muscle layers of the Vaterian system resulting in a hypertrophy of the sphincter of Oddi (which also explains the stenosis of the terminal common bile duct). Involvement of the major papilla can be present. The abnormally located glands are covered by a single-layer epithelium that shows no atypia and no mitotic figures and are surrounded by a myofibroblastic and fibroblastic proliferation. This component may contain also sparse capillaries, inflammatory cells, and muscle fibers. Nonspecific inflammatory changes may be present, and they could be secondary to sphincterotomy or migration of gallstones.

Pancreatic heterotopia of the duodenal wall is present in some cases, with transition zones between heterotopic tissue and adenomyoma showing progressive loss of acinar structures and endocrine islets and an increase of ductular-glandular structures.

Immunohistochemical features

Proliferative activity, as estimated by immunohistochemical staining with Ki67 antibody, is absent in the myofibroblastic component of the lesion, and very low in the epithelial component, similar to that observed in the normal pancreatic ducts. Glandular epithelial cells, similarly to the normal epithelial cells of the pancreatic and biliary duct system, express cytokeratin 7, and do not express cytokeratin 20. The myofibroblastic phenotype of most spindle cells is confirmed by a strong cytoplasmic expression of smooth muscle actin.

Clinical and imaging features

In our series of 13 cases, adenomyoma was diagnosed only in adult patients (mean age: 63 years, range: 38-78 years), with no male or female predominance. Clinical complaints initially suggested long term biliary tract obstruction, and relapsed after sphincterotomy. In 3 cases several episodes of increase of serum aminotransferase level were noted. In 3 cases the lesion was discovered incidentally in patients presenting unrelated conditions. Preoperative imaging procedures suggested a diagnosis of Vaterian system tumor. Most lesions were of small size, with a benign or malignant nature that was not established before surgery. On endoscopy, the major papilla showed a nodular pattern without ulceration. Endosonography showed intra-ampullary heterogenous lesions (measuring between 10 and 21 mm) stenosing the terminal part of the common bile duct. The proximal common bile duct and/or the pancreatic duct were dilated in most cases with bicanalar dilation in 4 cases.

Endoscopic papilla biopsies (performed in 9/13 cases) showed epithelial cell atypias that were considered as highly suggestive for dysplasia in 6 of the cases. This was interpreted retrospectively as rather secondary to a regenerative post-sphincterotomy process and/or to the reactive changes related to migration of gallstones.

Treatment and evolution

In our series of 13 cases, pancreaticoduodenectomy was performed in all cases, due to either severe and/or recurrent symptoms after sphincterotomy. On follow-up (1 to 73 months), there was no evidence of recurrence in any of the patients.

There is no established treatment for Vaterian system adenomyoma in the literature. Endoscopic sphincterotomy should be required in order to restore adequate biliary drainage. When a surgical treatment is decided, intra-operative frozen section could be of help leading to a limited resection instead of extensive surgery like pancreaticoduodenectomy. Some authors suggest a careful follow-up in such cases, with repeated endoscopic retrograde cholangiographies to ensure the benign diagnosis. It appears retrospectively that in our series, ampullectomy could have been the treatment in eight cases.

Histogenesis

The histogenesis of adenomyoma is still a subject of controversy. The most widely accepted hypothesis is that adenomyoma represents a form of incomplete heterotopic pancreas. The presence of hyperplastic smooth muscle tissue can be explained by secondary muscle proliferation due to some stimulus emanating from misplaced epithelium, or by muscle misarrangement, or by an aberrant growth invading and distorting normal muscle. The possibility of a complex form of heterotopia, of enteropancreatic type, could explain the presence within the same lesion of different glandular epithelial patterns such as Brunner's glands and intestinal glands. However, pancreatic heterotopic tissue was present in only 3 of our cases.

Conclusion

Vaterian system adenomyoma is a rare lesion of clinical importance. In the majority of cases, although it is an entirely benign lesion, this is because of its clinical and endosonographic similarities with ampullary tumors like adenoma, or carcinoma. The clinicopathological features of ampullary adenomyoma are consistent with a heterotopic nature, but other mechanisms (hyperplasia of intramural glands of the common bile duct, reactive changes due to the inflammatory response to migration of gallstones) are probably involved in the genesis of this lesion.

Immunohistochemical criteria like cytokeratin 7 expression and a low proliferative index (Ki67) in the epithelial cells (without cytokeratin 20 expression) should be considered in the analysis of ampullary biopsy specimens in order to differentiate adenomyoma from adenomatous or carcinomatous ampullary tumors, and thus considered as well in the decision to perform a limited surgical resection.

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