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CASE REPORT

Atypical Histiocytic Infiltration Simulating Diffuse-type Carcinoma in a Gastric Ulcer due to Non-Steroidal Anti-Inflammatory Drugs

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A 83-year old man treated with naproxen during two years was admitted because of hypovolemia and peritoneal irritation. A panendoscopic study was performed and an ulcer localized at the large curvature of the stomach was disclosed. In the gastrectomy specimen the ulcer showed necrosis, edema, fibrosis, chronic inflammatory infiltrate with lymphocytes and plasma cells. Additionally, atypical cells with irregular and hyperchromatic nuclei or vacuolated cytoplasm were seen in the lamina propia and infiltrating the muscular layers; isolated signet-ring-like cells were also seen. Histochemical study with periodic acid-Schiff, mucicarmin, and colloidal stains revealed mucosubstances in these cells. A poorly differentiated carcinoma was initially diagnosed. However, the immunohistochemical study were positive for histiocytic markers (CD-68, S-100 protein) and negative for epithelial markers (cytokeratin; and epithelial membrane antigen). The positivity of mucus stains in the histiocytes could be explained in this case by phagocytosis of mucous substances released from broken hyperplastic glands in the vicinity of the ulcer. To our knowledge, atypical histiocytic infiltration in gastric ulcers has not been previously described; thus, it should be included in the group of gastric carcinoma mimicks. (Pathology Oncology Research Vol 8, No 4, 272–274)

Keywords: atypical, histiocytic, gastric, ulcer, NSAID

Introduction

Most diffuse-type gastric carcinomas can be easily recognized in endoscopic biopsies and in gastrectomy specimens. There are, however, other pathologic conditions that could simulate diffuse-type carcinoma with or without signet-ring cells. These include the following: gastric xanthomas;[1,2] high grade gastric lymphomas;[3] carcinoma-like signet-ring-cells in gastric mucosa-associated lymphoid tissue lymphoma,[4] and artifactual signet-ring-like cells of gastric lymphomas.[5] On the other hand, chronic peptic ulcer usually does not represent a problem in the differential diagnosis, although some cases may display atypical regenerative changes of the gastric mucosa that may resemble intestinal adenocarcinoma. Here, we describe a case of a gastric ulcer secondary to administration of non-steroidal anti-inflammatory drugs (NSAID), which showed atypical histiocytic infiltration closely resembling diffuse-type gastric carcinoma as in the sections conventionally stained with hematoxylin and eosin, as in the special stains for mucins.

Case report

A 83-year old man complained of two week history of asthenia, adinamia, epigastralgia, abdominal distension, and melena. He had precedents of naproxen ingestion over the past two years due to chronic articular disease. He was admitted showing disorientation, hypotension (90/50), and hypovolemia. The laboratory tests revealed hemoglobin of 9.4 g/dL and hematocrit of 28. The computerized axial tomography was irrelevant. A panendoscopy was performed and a 3.5 cm-gastric ulcer was found at the large curvature of the stomach. The gastric biopsies showed ulceration and necrosis in some of the tissue fragments, as well as acute and chronic inflammatory infiltrate. Groups of atypical cells were seen in the lamina propia and interpreted as a poorly differentiated carcino-

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ma. The patient developed peritoneal irritation and a laparotomy with total gastrectomy was perfomed. A segment of the transverse colon that was firmly attached to the gastric wall was also extirpated. On gross examination, the gastrectomy specimen showed at the antrum a 3.8 x 3.2 cm ulcer with smooth and regular borders perforated and sealed with the transverse colon. Histopathologically, the ulcer showed necrosis, edema and fibrosis; there were gastric glands with foveolar hyperplasia in the vicinity of the ulcer, some of which were dilated and contained abundant mucus (***Figure 1***). A chronic inflammatory infiltrate, consisting of lymphocytes and plasma cells was observed. In several histologic fields, atypical histiocytes with irregular and hyperchromatic nuclei or vacuolated cytoplasm were seen (***Figure 2***); additionally, isolated signet-ring-like cells were observed (***Figure 3***). There were also scanty multinucleated giant cells of foreign body-type. Atypical histiocytes were seen in the ulcer, the lamina propia and infiltrating the muscular layers. The histochemical study (periodic acid-Schiff, mucicarmin, and colloidal stains) revealed mucosubstances in atypical cells (***Figure 4***). Immunohistochemical study was performed using the following antibodies: CD-68; pan-keratin, (VMS, Tucson, USA); S-100 protein; epithelial membrane antigen (Dako Corp, Denmark), and high- and low molecular weight keratin (Dako Corp, Carpinteria, Calif, USA). The atypical cells were positive for CD68 and S-100 protein (***Figure 4***) and negative for cytokeratins (high- and low-weight and pan- keratin) and epithelial membrane antigen. Helicobacter pylori was not observed in the endoscopic biopsy, nor in the gastrectomy specimen. Finally, a perforated and sealed gastric ulcer due to NSAID was diagnosed. The patient was discharged from the hospital in good condition; however, he suffered from angina pectoris and died three weeks later. Post-mortem study was not performed.

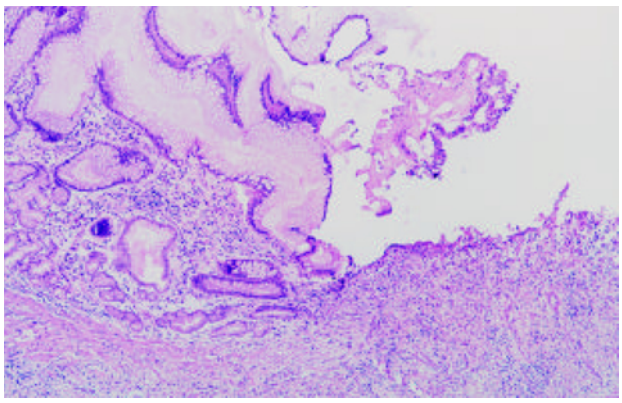

Figure 1. *Gastric ulcer in gastrectomy specimen. Hyperplastic glands are shown in the vicinity of gastric ulcer (HE, x16)*

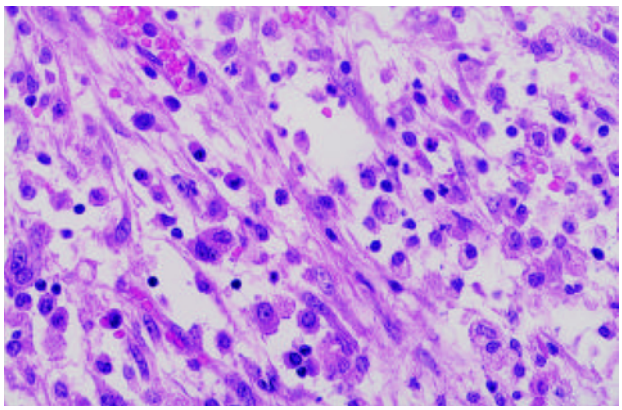

Figure 2. *Detail of the gastric ulcer. There is edema and atypical histiocytes with irregular and hyperchromatic nuclei; some of them show vacuolated cytoplasm (HE, X66)*

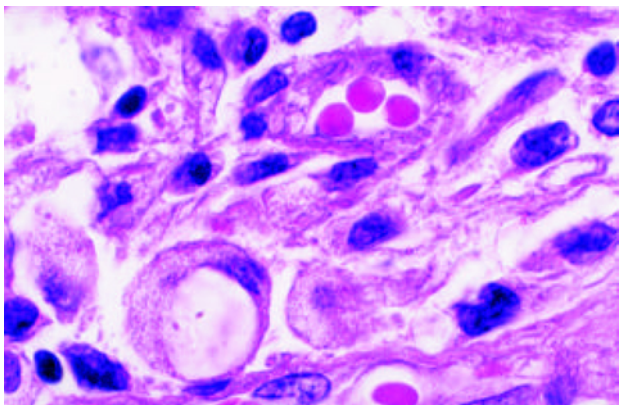

Figure 3. Signet-ring-like cell and atypical histiocytes in gastric ulcer (HE, X250)

Discussion

In the absence of Helicobacter pylori infection, the most likely etiology for the patient's gastric ulcer is the chronic administration of naproxen. The tissue damage in peptic ulcers due to NSAID is characterized by paucity of inflammatory cells, edema, telangiectasia, foveolar hyperplasia, and an increased number of smooth muscle fibers in the lamina propia resembling those of biliary reflux gastritis.[6-9] Some authors have found that foveolar hyperplasia is the single most important feature of NSAID-induced gastric mucosal injury.[8] However, other authors have not confirmed any histologic change as characteristic of gastritis due to these such drugs.[10]

The case described here is exceptional because of the large quantity of histiocytes with atypical aspect resembling diffuse-type gastric carcinoma. Although the positive result of the mucous stains in the atypical cells strongly suggested this diagnosis, the benign nature of the lesion was established by immunohistochemical studies. The positivity of mucous stains in atypical histiocytes could be explained as due to of phagocytosis of abundant mucosubstances released from the hyperplastic foveolar cells.

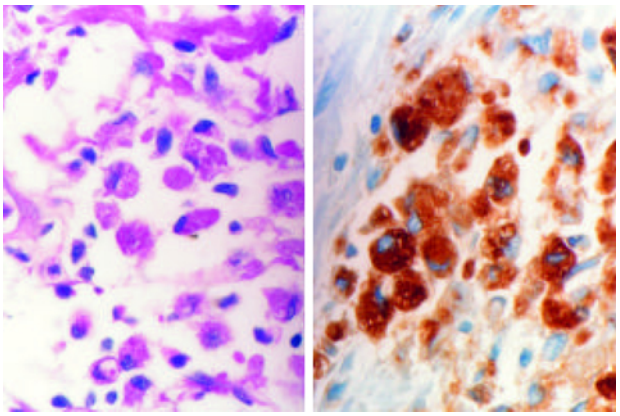

Figure 4. *Histochemical study. The periodic acid-Schiff with diastase is positive in atypical histiocytes (left) (X160). In the immunohistochemical study, the histiocytes show strong reactivity with CD68 (right) (X160)*

Ball and James[11] observed that a common feature of stomachs harboring an ulcer is mucous loss from the surface epithelium. This feature was found in this case and it was more prominent near the ulcer. To our knowledge, reactive histiocytosis has been reported only in one malignant ulcer. Ogawa et al[12] described a peculiar form of reactive, non-granulomatous proliferation of CD68 positive histiocytes in a case of early gastric adenocarcinoma. In their case, the histiocytes were found in the submucosal layer just beneath the gastric carcinoma; showed plump eosinophilic and foamy cytoplasm, eccentric small nuclei, and apparent nucleoli.

Although the atypical histiocytic response in gastric ulcer seems to be exceptional, it should be included in the group of simulators of diffuse-type carcinoma of the stomach. This case illustrates that atypical histiocytes in a gastric ulcer may resemble neoplastic cells not only in sections conventionally stained with hematoxylin and eosin, but also in those with mucous stains. Recognizing atypical histiocytes in a gastric ulcer would prevent a source of erroneous diagnosis of carcinoma, which may result in extensive surgery and unnecessary treatment with radiation and/or chemotherapy.

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