

Why does intestinal metaplasia develop early on gastric mucosa of mucosa-associated lymphoid tissue lymphoma patients?

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There is evidence suggesting that patients with mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach are at increased risk of developing gastric cancer. More specifically, it has been estimated that the risk of metachronous cancer is increased from 6- to 16-fold in these patients [1,2]. Such risk was putatively attributed to the persistence of lymphoma or to chemotherapy, but a role for the development of intestinal metaplasia (IM) on gastric mucosa following lymphoma remission could be pointed out. Indeed, IM is a precancerous lesion that significantly increases by 11.3-fold the probability of gastric cancer onset when the incomplete (colonic) IM type is present [3]. According to the Correa's cascade for gastric carcinogenesis, IM develops relentlessly following a long-lasting chronic active gastritis—mainly caused by *Helicobacter pylori* (*H. pylori*)—and atrophic gastritis, generally following years or decades [4]. The late onset of IM is further corroborated by the observation that it is distinctly more prevalent in the elderly than in young patients [4]. In contrast, some observations highlighted a very early (within few months) onset and progression of IM in both MALT lymphoma and diffuse large B-cell lymphoma patients following remission [5,6]. The reasons for this remain unclear. We would hypothesize that the lymphoepithelial lesions (LELs) on gastric mucosa of lymphoma patients may play a role.

Experimental data demonstrated a pivotal role for damage and loss of parietal cells in the development of IM. Apart from their role in gastric acid secretion and intrinsic factor production, parietal cells secrete a number of growth factors that influence the differentiation of other gastric lineages [7]. During a long-lasting *H. pylori* infection, the chronic inflammatory injury slowly leads a localized loss of parietal cells [8]. This represents a signal for cell regeneration from adjacent stem cells confined in the neck of gastric glands that differentiate into intestinal cells, leading to IM [8]. Most likely, this corresponds to a reparative/defensive process, when considering that *H. pylori* does not colonize IM areas on gastric mucosa [4]. Therefore, the chronic damage induces a scattered IM development in a single gland, or groups of glands, which progresses over a period of years.

A different scenario occurs when the injury on gastric mucosa is acute. An experimental observation showed that damage to parietal cells caused by toxic compound DMP-777 leads to the onset of spasmodic polypeptide expressing metaplasia, a precursor of IM [8], within just 1 day [7]. Therefore, an accelerated and complete disruption of parietal

cells would induce immediate regeneration by stem cells that differentiate into the IM phenotype and replace the original gland epithelium [7,8].

A similar process might occur in gastric mucosa of lymphoma patients. It is well-recognized that LEL represents the histological hallmark of gastric lymphoma [9]. Briefly, it consists in a histological lesion where monoclonal, neoplastic B-lymphocytes infiltrate the glandular epithelium and eventually destroy the gland (Fig. 1A-C). Therefore, the LEL induces an abrupt parietal cell loss, more similar to a toxic agent rather than chronic inflammation. When lymphoma regression is achieved, usually within 3-6 months following therapy [10], the loss of parietal cells is renewed by rising intestinal cells so that the original gastric glands are early replaced by IM glands (Fig. 1D), as occurs following acute damage [7]. Intriguingly, such a hypothesis is supported by the observation that IM starts to develop at the same gastric site as lymphoma [6]. Therefore, the co-localization between previous LELs and IM immediately after therapy suggests that LEL plays a direct role by acting through acute damage of gastric glands. Obviously, IM development following a chronic damage due to *H. pylori* infection, according to Correa's cascade, may also occur in these patients, and the two processes are not mutually exclusive. The presence of two pathways could explain the reason why IM is highly prevalent on gastric mucosa of lymphoma patients, with a high value 50-60% observed in some series [5]. Once developed, IM does not regress [4], but it tends to progress as far as metachronous gastric cancer in some lymphoma patients [11]. According to guidelines [12], follow up of lymphoma patients is advised every 6 months for 2 years and yearly for other 5 years. A long-term follow up could be suggested in those patients with gastric precancerous lesions following lymphoma remission.

In conclusion, the onset of IM on gastric mucosa early following lymphoma regression could be due to a rapid

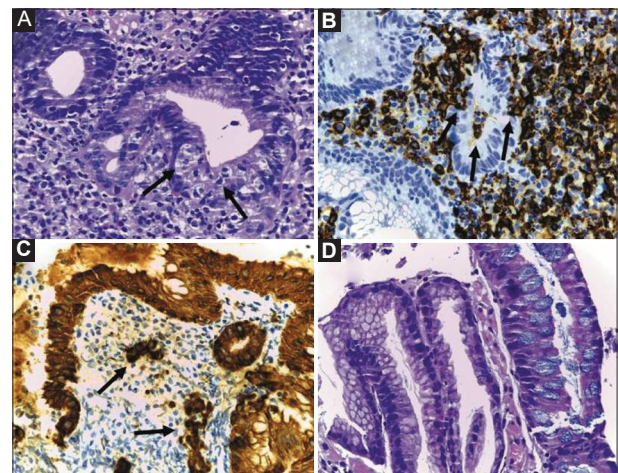


Figure 1 Aggregates of lymphomatous cells colonize gastric glands with distortion or destruction of the epithelium (lymphoepithelial lesion) (A, arrows, hematoxylin-eosin, original magnification 20×), as better appreciated with CD20 immunostain for B cells (B, arrows, original magnification 20×) and with cytokeratin (AE1/3) immunostain for epithelial cells (C, arrows, original magnification 20×). Intestinal metaplasia develops in gastric mucosa early after lymphoma regression (D, hematoxylin-eosin, original magnification 20×)

disruption of gastric glands by LELs with parietal cell loss, followed by an immediate repair with intestinalized cells.

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Conflict of Interest: None

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