

Role of Autoimmune Gastritis in Gastric Cancer

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It has been known for 70 years that gastric cancer occurs mainly in a stomach with gastritis. Gastritis was previously so prevalent that it was regarded as an aging phenomenon. Since the description of *Helicobacter pylori* (Hp) as the main cause of gastritis and peptic ulcer disease (1), Hp was soon accepted as the most important gastric carcinogen (2). The mechanism by which Hp induces gastric cancer has not been found despite intensive research for 30 years. However, a major breakthrough was achieved when Uemura et al. (3) described that Hp predisposes to gastric cancer only when having induced atrophy of the oxyntic mucosa. This led us to propose that hypergastrinemia due to reduced acid secretion leading to gastric hypoacidity was the pathogenic factor in Hp-associated gastric cancer (4). Autoimmune gastritis (AI) has been accepted as a separate type of gastritis having a much lower prevalence than Hp gastritis. Hp and AI gastritis have special traits (Table 1), but no test that can definitively discriminate between the 2 types.

Therefore, there have been discussion whether also AI gastritis could be initiated by Hp. The fact that any signs of previous Hp infection cannot be found at late phases of AI gastritis does not preclude a Hp infection at earlier phases. Thus, Hp cannot live in a stomach without acid production and accordingly not after total loss of oxyntic glands as is the case in long-standing AI gastritis. After death of Hp, Hp antibodies will dwindle and finally disappear leading to negative serology. Whatever the initial role

Table 1. Features of the 2 types of chronic atrophic gastritis in the oxyntic mucosa

	<i>Helicobacter pylori</i> induced	"Autoimmune" type
Antral affection	+++	+
Parietal cell antibodies	+	+++
Degree of oxyntic atrophy	++	+++
Acid secretion	+	0
Gastrin	+	+++
Pepsinogen I (PG I)		
Lack of intrinsic factor	?	+++
<i>Helicobacter pylori</i> serology	+++	+

+, mild; ++, moderate; +++, severe; 0, no acid; ?, uncertainty/variability.

of Hp in AI gastritis, Hp is not present in the late phase without gastric acidity.

AI gastritis has for long been known to predispose to gastric carcinoma as well as gastric neuroendocrine tumors (NETs) originating from the target cell of gastrin, the enterochromaffin-like (ECL) cell. The prevalence of ECL cell NETs in AI gastritis is much higher than that of Hp gastritis, although such tumors also have been described in Hp gastritis. This discrepancy made Graham and Zou (5) to publish a table where AI gastritis caused only NETs and Hp gastritis only adenocarcinoma, and thus discarding decades of accumulated reports of gastric cancer in patients with pernicious anemia. The higher frequency of ECL cell NETs in AI gastritis compared with Hp gastritis may be explained by higher gastrin values due to a more complete oxyntic atrophy combined with a normal antral mucosa. Hp antral gastritis reduces the G cell density and thus lowers gastrin in blood. On the other hand, Hp

gastritis starts earlier in life than AI gastritis. Therefore, individuals with Hp gastritis have a longer time with a moderate hypergastrinemia that by stimulation of proliferation increases the risk of mutations. Accumulation of mutations finally leads to gastric cancer. In AI gastritis, on the other hand, the more marked hypergastrinemia leads to more pronounced stimulation of the ECL cell leading to ECL cell NETs as well as carcinomas (Table 2) (6).

The role of the ECL cell in human gastric carcinogenesis has been greatly neglected. In fact, it may be the cell of origin for an important part of gastric carcinomas (6). We will also add that it is well established that oxyntic atrophy is the common mechanism for gastric cancer. This could incriminate not only gastrin but also secondary gastric infections in the carcinogenesis. However, since Hp gastritis is not involved in the carcinogenesis of the cardia, this possibility seems less likely. If microbiologic contamination

Table 2. Type of gastritis and the risk of gastric neoplasia

Types of chronic atrophic oxyntic gastritis	Degree of atrophy	Degree of hypergastrinemia	Duration of hypergastrinemia	ECL cell NETs	Patients risk of carcinoma ^a
<i>Helicobacter pylori</i> induced	++	++	+++	+	++
Autoimmune	+++	+++	++	+++	++

+, mild; ++, moderate; +++, severe; ECL, enterochromaffin-like; NET, neuroendocrine tumor.
^a*Helicobacter pylori* infection is much more prevalent than "autoimmune" gastritis and thus more important cause of gastric cancer, but in the individual patient the risk may be similar.

should be the mechanism, one would expect uniform increase in gastric cancer throughout the stomach.

To conclude, the etiology of AI gastritis is still unsettled, but AI gastritis predisposes not only to gastric NETs, but also to gastric cancer. Whether the cancer risk is so high that these patients should be followed by upper endoscopic surveillance has been discussed.

CONFLICTS OF INTEREST

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