Gastric Cancer in History

Subjects: Oncology

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Gastric adenocarcinoma is the fourth most common type of cancer and the second leading cause of cancer death in the world. Despite abundant traces of an ancient history, the comprehension of its pathogenic mechanisms is rather recent and continuously updated. We investigated about how the ancient civilizations tried to understand the exactly physiopathology of gastric cancer, from the time when they could not examine deeply the histological and pathophysiologic aspects of the disease, but they just based their knowledge on a visual analysis of the signs and consequences of such disease. We examined the historical evolving knowledge of the disease along the centuries on the gastroenterological, pharmacological, and surgical fields, defining how gastric cancer became an increasingly curable disease.

Keywords: Gastric cancer ; Helicobacter pylori ; Gastritis ; Atrophic gastritis ; Peptic ulcer disease (PUD) ; Gastric surgery ; Epidemiology ; History of medicine ; Famous patients ; Personalized medicine

1. Introduction

Gastric cancer is a well-known, life threatening condition affecting many people worldwide. Today, gastric cancer represents one of the leading causes of death worldwide, but very little is known about the antiquity, epidemiology and evolution of cancer in past human populations [1]. Currently, the incidence is decreasing thanks to early diagnosis, reduced incidence of *Helicobacter pylori* infection, diffusion of healthy lifestyles (including smoke cessation and good nutrition), but some geographical differences still remain in its incidence and mortality rate.

However, during the times gastric cancer accounted for a large number of deaths, mainly because of the lack of knowledge about its causes and of the absence of effective therapies. In fact, the first official surgical intervention for gastric cancer was performed in the late 19th century thanks to Prof, Theodor Billroth.

If the therapy of gastric cancer is recent, its history is very long, as reported in some documents from ancient civilizations. Starting from our own experience as surgeons and anesthesiologists, oral health professionals, pathologists, microbiologist and laboratory clinicians, we have focused the main steps of the evolution of the knowledge about gastric cancer, its etiology, and treatments through time.

2. Gastric Surgery and the Development of Endoscopy

The official history of gastric cancer surgery began 40 years later, when the French surgeon Jules Pean attempted the first gastric resection in 1879; the patient, unfortunately, died few days after. In 1880, Ludwig von Rydygier, professor of surgery at Krakow University, tried another gastric resection, but it was unsuccessful. The first successful gastric resection was attempted by Theodor Billroth, one year later, in the Allgemeine Krankenhaus Clinic in Wien. The patient was a 43-old woman who survived four postoperative months. The operatory technique used by Billroth maintained his name still today as Billroth I, which consists in a gastro-duodenal anastomosis directly connecting the gastric stump to the duodenal one. This intervention, technically more difficult, consists in reconstructing the alimentary tract similarly to the physiological one. Billroth, soon after, modified this operation for a more radical resection, known as Billroth II. These types of resections are currently used in the modern gastric surgery, but not for oncologic purposes [2].

In 1897, the Swiss surgeon Karl Schlatter performed the first total gastrectomy for a diffuse gastric cancer in Zurich, at the surgical department directed by Kronlein. He removed the whole stomach and made an esophagojejunostomy for reconstruction. The operation was successful, and she died for recurrent tumor after 14 months. Total gastrectomy was then practiced all over the world with different techniques, first by Charles B. Brigham in San Francisco and by Richardson in Boston [3].

The continuous development of research and new discoveries in the field of gastroenterology and gastric surgery continued in the 20th century.

During the last century many hypotheses have been proposed to explain the etiology and pathophysiology of gastric cancer. Based on the current knowledges of the time, environmental, and dietary causes were proposed, as well as the increased risk in persons having group A blood or menopausal women, etc. Such etiopathogenetic links were variously explained but, in most cases, never confirmed differing from the *Helicobacter pylori* infection that is currently confirmed as the main cause of gastric diseases, including cancer. Table 1 summarizes the main causes of gastric cancer proposed during the time.

Table 1. Summary of proposed causes of gastric cancer. During the 20th century gastric cancer was considered a consequence of preexisting or coexisting conditions (i.e., chronic atrophic gastritis), poor lifestyles, or paraphysiological conditions (i.e., diet poor in fibers, menopause, etc.), and to a genetic predisposition (gene mutations, group A blood, etc.). Most of these links were never confirmed, except the causative role of *H. pylori*.

Precursor Conditions	Enviromental Factors	Genetic Factors
• H. Pylori infection (CagA positive strains) • Pernicious anemia • Gastroesophageal reflux • Barrett's esophagus • Chronic atrophic gastritis and intestinal metaplasia • Ménétrier disease • Gastric adenomatous polyps • Previous gastric surgery (especially in partial gastrectomy: high risk of cancer of the gastric stump)	• Lifestyle (alcohol, tobacco smokers, obesity, low physical activity) • Low socioeconomic status • Dietary factors (diets rich in salt/sodium, rich in starch and poor in protein, smoked or poor preserved foods, low intake of fruit and vegetables) • Occupational exposures (workers processing rubber, asbestos and timber, or farming, mining, refining, as well as exposure to dusty and high temperature environments as in wood processing plant operators, cooks, food and related products machine) • Estrogens decrease with menopause • Viral infections (EBV, HBV?) • Radiations	• Family history of stomach cancer • Elderly (for degenerative changes and accumulated DNA damages) • Hereditary non-polyposis colon cancer • Li-Fraumeni syndrome • Downregulation of E-cadherin expression • Interleukin-1B gene mutation Hypo-gamma-globulinemia (primary immunodeficiency) • Group A blood

In 1915 a small amount of gastric juice was taken from a human stomach to study its characteristics by Jesse McClendon. Gastrointestinal endoscopy has passed through three principal changes in the forms of endoscopes used to examine the gastrointestinal tract: the "rigid endoscope" era (1805–1932); the "semi-flexible endoscope" or "Schindler" era (1932–1957); and the "fiber-optic" era (1957–present) [4].

Many important steps forward and progresses were made by scientists in the field of human nutrition and digestive system, researching about the chemical processes and the biochemical mechanism of physiological digestion, but also about the unknown etiopathogenetic agents that could cause the stomach cancer. In particular, based on previous demonstrations of close relationships of bacteria with cancers and tumor-like conditions, many pathologists and microbiologists were aiming to find one or more microorganisms related to gastric cancer [5][6][7].

Before the 1950s, there were many microbiological descriptions of bacteria in the stomach and in gastric acid secretions, lending credence to both the infective theory and the hyperacidity theory as being causes of peptic ulcer disease: from the theory of professor Francois de la Boe Sylvius, a Flemish scientist born in Hanau (currently a German city), who believed that acidic lymph fluid was the cause of cancers, to the theory of his contemporary, Nicolaes Tulp, who believed that cancer was a contagious poison that slowly spreads in the whole body. It was just in 1926 that Johanes Andreas Fibiger (1867–1928), professor of pathology in University of Copenhagen, received the Nobel Prize for discovering the etiopathogenetic agent causing the stomach cancer. He demonstrated that the roundworm which he called "*Spiroptera carcinoma*" could cause stomach cancer in rats and mice. He supposed this was the cause of gastric cancer because he

observed inflammatory and degenerative mucosal changes in the rats' stomach after feeding them with infected cockroaches. German scientists, such as Walter Krienitz, found spiral-shaped bacteria in the lining of the human stomach in 1875, but they were unable to culture them, and the results were eventually forgotten [6].

In 1915, Rosenow published his theory after he infected a large number of experiments animals with *streptococci*. In his paper [7], he demonstrated *streptococcus* as an etiologic factor in nine diseases, including gastric and duodenal ulcer, due to its affinity for the gastric mucosa.

3. The Discovery of the *Helicobacter pylori* and Its Relationship with Gastric Cancer

It was a significant turning point for the history of the gastric cancer when Barry J. Marshall and Robin Warren, two Australian researchers, discovered the bacterium *Helicobacter pylori* and deciphered its role in gastritis, peptic ulcer disease (PUD) and gastric tumors. For their great work they were awarded in 2005 the Nobel Prize in Physiology or Medicine [8]. Their studies revealed that gastritis, gastric and duodenal ulcerations and some type of gastric cancers were the result of infection with some curved, Gram-negative bacilli. The Gram negative curved bacillus *H. pylori* has become the prize bug of all times. Barry Marshall and Robin Warren the two discoverers of this organism have been awarded with this year's Nobel Prize. The Nobel committee at the Karolinska Institute of Sweden has selected this paradigm shift discovery of 1982 as the most impacting in medical sciences. This award has surprised many as the Nobel assembly has selected this 'Robert Koch styled medical detective work' for the prize as compared to many outstanding basic research stories on the waitlist. This editorial briefly touches the significant impact of *H. pylori* on gastroduodenal management and the path forward as the bug has become quite controversial in recent times. Bacteria colonizes the human stomach and periodontal pockets, causing a chronic active gastritis, which can complicate with peptic ulcer disease [9]. Before they announced their findings, a large number of physicians thought that stress and lifestyle factors were the major causes of these diseases. Warren and Marshall, at the first time, were regarded with skepticism and a lot of criticism but their major breakthroughs were soon widely accepted. To enforce their theory about the linkage between the *Helicobacter* and gastro-duodenal pathologies, Warren infected himself with the bacterium and developed the classical symptoms. This 'self-help' experiment was published in the Medical Journal of Australia [10]. In the 1994 the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) declared *H. pylori* a Group 1 carcinogen.

A Greek physician, Jonh Lykoudis (Ιωάννης Λυκούδης, 1910–1980), who was himself affected by gastritis and peptic ulcer, in 1968 developed a treatment which consisted of three types of antibiotics (2 quinolines, 5,7-diiodo-8-oxyquinoleine 0.125g; 5-iodo-7-chloro-8-oxyquinoleine 0.125g, and streptomycin sulfate 0.075g), with vitamin A 10,000 UI. He named these pills "*Elgaco*" (from the Greek term ἕλκος = ulcer, and the two words γαστρίτιδα = gastritis and κωλίτης = colitis). He used these pills as a therapy for gastritis and gastric ulcer, 6–8 times daily for 10 days, because he was convinced that the real cause of these diseases was infectious, but without knowing specifically what kind of infectious agent was involved. Vitamin A was included to increase the mucosal regeneration. He started treating thousands of patients (around 30,000) with great results and no toxicity. Despite this treatment being a successful one, he did not make a real clinical trial, so each treatment and outcome was not scientifically resumed. In 1966, Lykoudis attempted to publish his observations "Ulcer of Stomach and Duodenum" in the Journal of the American Medical Association, but it was rejected. Unfortunately, no copy of this text survived [11].

The actual "*Helicobacter pylori*" was originally named "*Campylobacter pyloridis*" and then "*Campylobacter pylori*" in 1987 (pylori is the circular opening leading from the stomach into the duodenum, from the Greek word "πυλωρός" = gatekeeper) [12][13]. His RNA analysis showed, in 1989, that the bacterium did not belong in the genus *Campylobacter*, so it was placed in the genus *Helicobacter* (from the Greek word *έλιξ* = spiral and *βακτήριον* = bacterium) [14][15].

In 1987, Thomas Borody, an Australian physician, proposed the first triple therapy for the treatment of duodenal ulcers [16]. In 1994, the National Institute of Health recommended antibiotics in the treatment of recurrent duodenal and gastric ulcers caused by *H. pylori*. Peptic ulcer disease associated with *Helicobacter* is currently treated with antibiotics to eradicate the infection and to allow the ulcer to heal. Previously, the only option was symptom control using antacids, H2-antagonists or proton pump inhibitors alone. Nowadays, he first-line therapy is the "triple therapy", based on the use of a combination of a proton-pump inhibitor and two antibiotics, clarithromycin and amoxicillin. In people who are allergic to penicillin, amoxicillin can be replaced with metronidazole. Other options are available in case of treatment failure for antibiotic-resistant bacteria: a "quadruple therapy", which adds a proton pump inhibitor, two antibiotics and a bismuth colloid, such as bismuth subsalicylate. In case of treatment failure for antibiotics resistance, which is an increasing problem in *H. pylori* infections, they can be replaced by the use of another antibiotic to which the bacteria is sensitive; for the treatment of clarithromycin-resistance, the use of levofloxacin has been suggested [17][18]. It has been demonstrated that gastric

mucosa-associated tissue lymphoma (MALT lymphoma, or MALToma), a rare mature B-cell neoplasm is associated with *H. pylori* infection. It is one of the rare and incredible cases of tumors curable by antibiotics therapy alone [19][20][21][22].

Table 2 summarizes the evolution of medical knowledge about gastric conditions from ancient Egypt to the discovery of *Helicobacter pylori* and its possible cure.

Table 2. Overview of the main steps of the knowledge about gastric cancer and its therapy.

2125 BC	**First researches in gastoenterological field during the 10th dynasty of the Pharaos by Irynathty, the court physician**
1600 BC	**First descriptions of cancer in the "Kahun (or Fayoum)", "Edwin Smith" and "Ebers" papyri**
1200 BC	**Earliest complete skeleton with multiple osteolytic metastatic bone lesions found in northern Sudan**
6th century BC	**Alcmaeon of Croton's studies on gastrointestinal mechanisms and digestive functions through animal's vivisection**
4th century BC	**First use of terms "καρκίνος" (karkìnos=cancer) and "καρκίνωμα" (karkìnoma= carcinoma) by Hippocrates**
3rd century BC	**Development of human anatomy's knowledge through dissections on cadavers made by Herophilus of Chalcedon and Erisistratus of Ceos**
1st century BC–1st century AC	**Use of drinks based on plant's extracts for gastrointestinal symptoms by Asclepiades and Dioscorides**
2nd century AC	**Introduction by Galen of the prefix "onco-" (*όγκο*-) and the suffix "-oma" (*-ομα*) to describe tumors in general, reserving the term "carcinoma" for the malignant ones**
3rd–6th century AC	**Classification of gastrointestinal diseases in the Oribasius Encyclopedia and in the Paul of Aegina's Compendium**
11th century AC	**Avicenna's Encyclopedia included all the Arabic medical knowledge of the time**
15–17th century AC	**"*Hôpital des cancers*" were created in France to isolate cancerous patients, considering cancer a contagious disease**
17th century AC	**Autopsy was allowed as a legal method for medical studies**
18th century AC	**Dr. Peyrile published his thesis about the cancer's origins, starting-point of the modern oncological era**
1805	**Rigid endoscope was first used to explore the gastrointestinal tract**
1881	**First successful gastric resection was attempted by Theodor Billroth**
1897	**First successful total gastrectomy was attempted by Karl Schlatter for a diffuse gastric cancer in Zurich**
1926	**J.A. Fibiger received the Nobel Prize for demonstrating the "Spiroptera carcinoma"**
1932–1957	**Semi-flexible endoscope first and then fiber-optic one were first used to explore the gastrointestinal tract**
1968	**J. Lykoudis developed a treatment (Elgaco) based on antibiotics and vitamin A to treat peptic ulcers**
1982	**B.J.Marshall and R.Warren recognized Helicobacter pylori as the cause of gastritis and peptic ulcers**
1987	**T.Bodory proposed a triple therapy for the treatment of duodenal ulcers**
1994	**WHO and IARC declared H.pylori a Group 1 carcinogen. NIH recommended antibiotics for the treatment of recurrent duodenal and gastric ulcers caused by this bacterium.**
2005	**B.J.Marshall and R.Warren received the Nobel Prize in Physiology or Medicine**

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