

Complete Response to Systemic Combination Therapy in a Gastric Cancer Patient in Inoperable Condition: A Case Report

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Abstract

Background: Gastric cancer is a leading cause of death worldwide and the average survival rate of patients within a year of diagnosis remains low. Currently, surgical resection is the major treatment strategy, and the effectiveness of chemotherapy remains debatable. Infections involving *Helicobacter pylori* (*H. pylori*) and the Epstein-Barr virus have been implicated in gastric cancer pathogenesis. In addition, extensive immunosuppression in patients caused by latent infections and chemotherapy limits their response to existing therapies.

Case presentation: A 73-year-old man presented with stage IV gastric cancer (T2N0MII stage, cell group II). The tumor was inoperable due to concomitant multiorgan dysfunction and consequently, the patient was treated with a combinatorial therapy consisting of immunocorrective and antimicrobial therapy, as well as chemotherapy. The medications used for treatment include interferon- α , interleukin-2, statins, fenofibrate, macrolides, proton pumps, and antiviral drugs. Following treatment, tumor cells redifferentiated into normal glandular epithelial cells. A 2-year follow-up study of the patient after treatment revealed a complete remission from cancer.

Conclusion: This case report demonstrates the possibility of using a systemic approach to treat inoperable gastric cancer. In addition, the observations made in this study should aid the design of novel treatment strategies for gastric cancer.

Keywords: Gastric cancer; Combinatorial therapy; Immunosuppression; Immunocorrective therapy; Antimicrobial therapy

Background

Gastric cancer is the fourth most prevalent cancer and the second most common cancer-related mortality worldwide. Currently, the average 5-year survival rate is only 20% to 25% [1,2]. In 2008, there were 988,000 new cases of Gastric Cancer (GC), and 736,000 fatalities from GC worldwide [3].

Resection of the tumor remains the standard treatment for gastric cancer; however, treatment outcomes remain unsatisfactory due to a high rate of post-surgical tumor relapse [2,4]. There is still no widely accepted chemotherapy regimen for GC. Pre-operative chemotherapy is usually preferred in Europe, whereas postoperative chemotherapy is commonly used in the United States. In East Asia, adjuvant fluoropyrimidine chemotherapy is the preferred course of treatment [4]. However, based on the results of most clinical trials, the therapeutic efficacy of various chemotherapy schemes and methods is very low, and the average survival rate remains below 1 year in most of these studies [5]. The peak incidence of GC occurs between ages 50 and 70 years [6]. Multiple somatic pathologies are found in older patients, often restricting choices in treatment and excluding the possibility of any targeted or aggressive treatment of the cancer.

In the last 10 years, there has been a growing list of publications on the role of viral and bacterial infections in gastric cancerogenesis [7,8]. To date, at least two infectious agents are known to be carcinogenic – *Helicobacter pylori* (*H. Pylori*) and the Epstein-Barr virus (EBV).

According to the International Agency for Research on Cancer, the EBV is classified as a Group 1 carcinogen [9]. The presence of EBV has been detected in the neoplastic cells of some GCs, and such tumors are identified as EBV-associated gastric cancers (EBVaGCs). It is estimated that 10% of total GCs are EBVaGCs, and more than 90000 patients are diagnosed annually with these tumors [8].

There is little doubt on the role of *H. pylori* in gastric cancerogenesis.

In fact, *H. pylori* infections have been found in more than 60% of GC cases [10,11].

A major challenge in cancer treatment is that patients are already in an immunosuppressive state before commencing treatment. The paradox lays in the fact that most methods of cancer treatment are themselves potent immunosuppressants. Thus, during chemotherapy, the immunosuppression that results from surgical trauma following tumor resection may be an insurmountable obstacle, leading to the deterioration of treatment results [12,13].

The onset of immunosuppression during chemotherapy occurs via two main possible mechanisms. The first mechanism involves the inhibition of the immune system and bone marrow hematopoiesis caused by anticancer cytotoxic agents, which leads to a decrease in the number and functional viability of white blood cells, red blood cells and platelets. Another mechanism of immunosuppression is the activation of latent infections. Up to 85% of chemotherapy complications result from the activation of pathogenic properties of normal gut microbiota (including mouth microbiota) and skin microbes [14]. Frequently, clinical manifestations of immunosuppression are caused by outbreaks involving *Herpesviridae* family infections, including herpes simplex, herpes zoster, or other members of the *Herpesviridae* family [15]. These findings are noteworthy given that the EBV is also a member of the *Herpesviridae* family. Ironically, the occurrence of such infections following chemotherapy may in fact promote tumor growth. In

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fact, the development of secondary neoplasms following a course of chemotherapy has been previously shown [16]. Hence, chemotherapy, which should have theoretically “killed” tumor cells in the patient, instead becomes a promoter of tumor growth.

The above findings suggest that well-known GC treatment methods have reached the limits of their potential, and there has been little progress made in the field in recent years. Ironically, well-studied and commonly used cancer therapeutic agents, which have a proven carcinogenic nature in GC, have not been targeted for systemic therapy. In addition, the dual states of primary immunosuppression resulting from carcinogenesis, and immunosuppression caused by chemotherapy have not been used as the subject of systemic immune therapy.

In the present report, we present a case of inoperable gastric cancer with a background of *H. pylori* and EBV infections, as well as severe immunosuppression. As described below, the admitted patient presented with severe gastric adenocarcinoma and would not have survived surgical intervention. Hence, we decided to apply a different approach based on pathogenic inhibition and systemic correction of the biological, immunological and metabolic effects of carcinogenesis.

Case Presentation

A 73-year-old male patient with stomach cancer (T2N0MII stage, cell group II) was admitted to our hospital in a deteriorating condition and a state of confusion. The patient was found to be incapable of walking and caring for himself. His previous medical records revealed that he had kidney cancer (T2N0M0) and a right-sided nephrectomy 10 years earlier and myocardial infarction 8 years earlier, followed by post-infarction cardiosclerosis. He also had a coronary artery bypass surgery 3 years previously.

Upon physical examination, his skin was found to be earthy gray, dry, with reduced turgor and signs of acrocyanosis, or a persistent blue discoloration of the extremities. The mucous membranes of his mouth and tongue were dry. His abdomen was found to be swollen and tense, and his liver was palpable 4-5 cm below the costal margin where the smooth edge is felt. When an auscultation of the abdomen was performed, peristalsis was not clearly audible, bowel sounds were sporadic, and stools were absent for 14 days.

Further examination revealed that the patient experienced painful breathing and difficulty breathing in (inspiratory dyspnoea). The examination also revealed intercostal retraction, or inward movement of muscles between the ribs, resulting from reduced pressure in the chest cavity on inspiration. The frequency of respiratory movements was 23-28 movements per minute and there was no breathing detected in the lower parts of both lungs. Upon percussion of the abdomen, percussion sounds were dull below ribs VII-VIII on both sides of the mid-scapular line, suggesting an underlying abdominal mass. No pulse was detected at the radial and posterior tibial arteries, and the carotid arteries were poorly perfused and stressed. Upon further examination, an occasional deficit in the pulse (18-23 beats per minute) was detected, and the heart rate was abnormally slow.

Given the patient's history of cardiovascular disease, we next examined his cardiac status at admission. The patient was previously diagnosed with coronary artery disease and a permanent form of atrial fibrillation. Upon examination, a left ventricular coronary impairment and three-vessel coronary injury disease, as well as arterial hypertension (third degree, with risk of fourth degree hypertension) were found. After undergoing a 6-minute walk test, the patient was diagnosed with

class III angina, based on the New York Heart Association (NYHA) functional classification system. The patient's cardiac history showed that he had chronic congestive heart failure (NYHA class II). He also had arterial vertebro-basilar basin ischemia with weakness on the left side of the body (hemiparesis), third degree dyscirculatory encephalopathy, stenosis of the right internal carotid artery (57%), third-degree chronic cerebral vascular insufficiency, atherosclerosis of the arteries of the lower limbs, a distal form of injury, and stage II lower limb ischemia. In addition, the patient was diagnosed with metabolic syndrome, including moderate subcompensated diabetes mellitus type 2 and diabetic polyneuropathy.

Moreover, the patient had concomitant diseases that included chronic obstructive pulmonary disease, chronic congestive medium-heavy bronchitis in an exacerbated stage, bilateral pleural effusion, and third-degree respiratory failure. Further examination revealed that the patient suffered chronic prostatitis (infection of the prostate gland), bilateral hydrocele, latent cholelithiasis (gallstones), postoperative ventral hernia, chronic pyelonephritis of a single kidney, third-degree chronic left renal failure, and paresis (weakness) of the intestine. The patient's state at admission was rated at 10% based on the Karnofsky Performance Scale Index and he had an Eastern Cooperative Oncology Group performance status of grade 4.

Laboratory investigation of the patient's blood revealed elevated levels of T-cytotoxic (CD3+CD8+) cells (44.29; normal range 18-25) and immunoglobulin E (IgE; 348 U/mL; normal range 0-100 U/mL). Serologic testing of the patient showed positive results for *Helicobacter* IgG (64.6 U/ml), EBV capsid antigen IgG (78.3 U/ml), EBV nuclear antigen IgG (166 U/ml), *Chlamydia* IgG (trachomatis, pneumonia, psittaci; 1.1 S/CO), Cytomegalovirus IgG (4.62 U/ml), and Herpes simplex virus type I IgG. Results of testing on the total bilirubin (20.7; normal range 3.4-20.5 μ mol/L), direct bilirubin (11.8; normal range 1.8-8.6 μ mol/L), high-density lipoprotein (HDL)-cholesterol (0.78; normal range >1.0 μ mol/L) revealed deviations out of the normal range.

Given the abnormalities revealed by his blood tests, the patient was prescribed a combinatorial therapy that included antiviral treatment (including treatment with interferon and interleukin) and anti-*H. Pylori* therapy. The treatment regimen also included hypoglycemic and lipid metabolism-regulating drugs, as well as antimetabolite chemotherapeutic drugs. The patient received 10 courses of therapy. Each course of treatment lasted 28-30 days.

Changes in tumor size and tumor differentiation were observed during the course of treatment as shown in Figure 1. The size of the tumor was defined as a product of the minimum size of the tumor multiplied by its maximum size during the treatment. It should be noted that the highest size of the tumor was observed during the fifth and sixth courses of treatment. At the same time, tumor cytogenesis reversed from a poorly differentiated to a well-differentiated phenotype. Following treatment, the tumor regressed and tumor cells were replaced by the normal mucosal lining of the stomach (Figures 2-4).

In keeping with a systemic approach to the patient's treatment, changes in the levels of triglycerides, cholesterol and lipoproteins were also observed. Notably, the levels of triglycerides, total cholesterol, and high and low-density lipoproteins gradually decreased during the course of the treatment. A sharp increase of high and low-density lipoproteins was previously observed during active growth of the tumor.

Triglyceride and HDL-cholesterol levels were then used to calculate the Atherogenic Index (AI) of plasma. The AI reflects the balance

between the atherogenic and protective lipoproteins and is known to predict cardiovascular risk. The AI was highest before treatment, when the patient was in a deteriorated state, and during active progression of the tumor. Interestingly, during this period, levels of triglycerides, total cholesterol, and high and low-density lipoproteins were decreasing, whereas the AI was increasing. This observed decrease of cholesterol could be explained by two mechanisms. The first is a potential loss of the structural precursor of steroids and androgens. A second mechanism could involve a reduction of corticosteroid activity, which compensates for the possible secretion of endogenous interferon. Biologically, this could serve as a compensatory mechanism for the lack of cytokines, involving a reduction in the levels of cytokine antagonists, rather than an increase in cytokine production. Such mechanisms may serve to maintain the production of antitumor cytokines. In this case, the increase in AI observed could be explained not by an increase in one of the cholesterol fractions, but by an imbalance of all its components.

Following treatment, the patient's health condition was determined

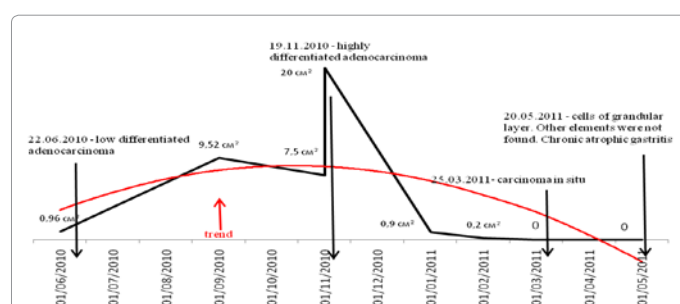


Figure 1: Changes in tumor size (cm²) in the stomach wall with time, and cytogenesis during treatment examined with esophagogastroduodenoscopy.



Figure 2: Gastric mucosa after treatment. Histological analysis reveals poorly proliferative, mostly "light" epithelium in the gastric mucosa. Sclerosis in the stroma, plethora, stasis, focal lympho-histiocytic infiltration, hemorrhages, and fibrin deposition with decaying leukocytes are also observed.

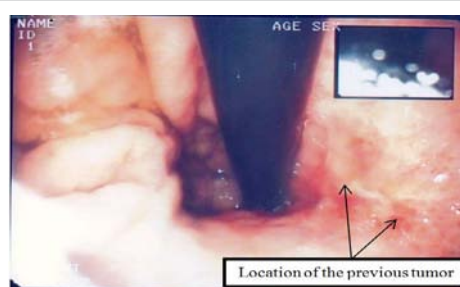


Figure 3: Gastric mucosa after 1 month of treatment. Histological analysis reveal thickening of the mucosal layer with randomly arranged glands, proliferating cylindrical cells, and goblet-shaped epithelial cells. Sclerosis is observed in the stroma, along with diffused lympho-histiocytic infiltration, stasis, and thrombosis.

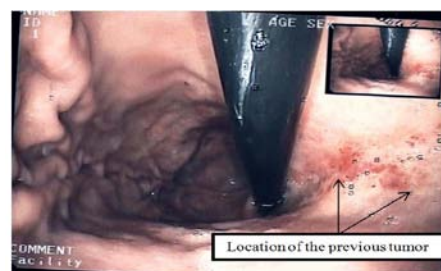


Figure 4: The patient's gastric mucosa after treatment. Longitudinal focus of mucosa with hyperemia. No fibrin is observed. Based on histological analysis only cells of the glandular epithelium are observed.

to be physically and psychologically stable. To date, the patient is free of cancer and in a normal state of aging.

Conclusions

Surgical invasion remains the main treatment option for patients with gastric cancer. However, neither surgery nor chemotherapy provides systemic control of tumor growth. This manuscript represents a clinical case where the patient could not be treated by conventional therapies.

Our treatment approach used was based on immunocorrective and chronic infection therapy (targeting *H. pylori* and EBV), and treatment of the metabolic syndrome. Following 5-6 courses of combinatorial therapy, cytotoxic therapy with capecitabine was performed in standard doses. According to the recent Maastricht IV/Florence Consensus report, *H. pylori* infection is the most consistent risk factor for gastric cancer, and the eradication of *H. pylori* was suggested to significantly reduce the rate of the disease [17]. Since the presence of chronic viral infections, such as EBV and CMV typically indicate low-grade inflammation, we used immunocorrective and antiviral therapy.

One of the specific features of the treatment approach was the duration of drug application: the antiviral therapy was applied continuously for 10 months. Prolonged use of a complex of metformin, statin, and fenofibrate allowed correction of dyslipidemia and hyperglycemia in the patient, as well as monitoring of the stability of metabolic parameters.

It is important to note that no fixed treatment regimen is suggested using this approach. Rather, the therapy in this case was highly personalized and developed based on the results of laboratory tests and analyses. Using this treatment approach, the priority was not to merely localize the tumor, but to treat the deteriorating patient as a whole. The treatment strategy described in this study resulted in the gradual reversal of poorly differentiated adenocarcinoma cells to normal epithelial cells. The results of our study suggest that the process of drug-driven re-differentiation is possible.

Our observations suggest that the use of antimicrobials for cancer treatment should become a systemic and routine practice. To date, the role of infections in cancer etiology is not well understood and is likely highly underestimated. In addition, chronic infections in patients should be considered, along with the patient's immune profile and the presence of metabolic disorders. Hence, changes in treatment strategy in favor of a more complex approach may be highly beneficial for cancer patients.

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