

DISCUSSION

In the last three decades, the appreciation of the role of infections in cancer etiology has greatly expanded. Among the 13 million new cancer cases that occurred worldwide in 2008, around 2 million (16%) were attributable to infections. Concurrently, the approach to prevention of infection-related cancers is shifting from cancer control to infection control, for example, vaccination and the detection of infected individuals.⁽²⁰²⁾

Recently, bacteria have been linked to cancer. *H. pylori* is the first bacterium to be termed a definite cause of cancer in humans and to be considered as a Group 1 carcinogen, by the International Agency for Research on Cancer.⁽²⁰³⁾ *H. pylori* accounts for 46% of infection-associated cancers in more developed areas.⁽²⁰⁴⁾

H. pylori colonizes the gastric mucosa causing chronic gastritis, gastric ulcers, gastric cancer and lymphoma of mucosa associated lymphoid tissue (MALT)⁽²⁰⁴⁾. The clinical outcome related with this infection has been associated with host, genetic factors, and environmental factors. Many of pathogen virulence factors have been studied⁽²⁰⁵⁾ like surface exposed or surface secreted antigens such as the cytotoxin associated protein [CagA], the vacuolating cytotoxin protein [Vac A], Urease subunits [UreA&UreB], heat shock protein HSPA HSP B flagellin subunits catalase, lipopolysaccharides and several undefined antigens.⁽²⁰⁶⁾ After *H. pylori* adheres to the surface of the epithelium the bacterium secretes the virulence factor that allows colonization of the mucosa. The *cagA* gene is a key marker in the Cag pathogenicity Island [CagPAI]. CagA is injected into the host cell through type IV secretion system which triggers the activation of several signaling pathways and generate cellular changes and induction of inflammatory interleukins⁽²⁰⁷⁾. The presence of *cag A* gene in *H. pylori* strains is associated with the development of peptic ulcer and gastric cancer in humans⁽²⁰⁸⁾.

Another important virulence factor of *H. pylori* is the vacuolating cytotoxin gene A [VacA]. It is encoded by the gene *vac A*. This gene has four regions: a signal sequence consisting of the allele S1, with its three subtypes SLA SLB SLC and s2, an intermediate sequence, a deletion sequence and a middle sequence that may have the m1 or m2 alleles. The combination of S and M alleles determine the toxin vacuolating activity responsible for major damages of the epithelial cells.^(209,210) In the current study, we aimed to study the association of *H. pylori* and Hepatitis C virus antibody in leukemia and malignant lymphoma patients and to correlate them with the serological response to the six *H. pylori* antigens [CagA, VacA, UreA p25, p19 and p30]. (Chen *R et al* 2004)

Samples were withdrawn from 100 patients presented with malaise, severe anemia, fatigue and weight loss. Serum samples were assayed for the *H. pylori* antigens [CagA, VacA, UreA, P25, p19 and p30]. The frequency of *H. pylori* infection in the present study was found to be more than or equal to 90% of our patients. This showed that some studies indicate that seropositivity to some *H. pylori* antigens could be used as a serological marker for bacterial virulence⁽²¹¹⁾. At times has been made to

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find serological markers of *H.pylori* virulence which could be correlated with the severity of *H. pylori* associated diseases. (Jakic-Razumovic et al 2000) .One of the serological tests the immunoblot assay which has the advantage also of being useful to investigate possible relationships between disease presentation and the presence of specific *H.pylori* antigens. Previous studies have demonstrated that immunoblots techniques can reveal multiple major antigens. Although the serum antibody response to *H. pylori* depends on both the characteristics of this strain and the host response it can provide clues in predicting the severity of *H. pylori* associated diseases.⁽²¹²⁾

In this study, we use helico-line immunoassay strips to examine the immunoreactive antigen that can be simultaneously detected on the strips and use the immunoreactive band for determining any correlation with clinical outcomes. We revealed that certain types of leukemia and malignant lymphomas might be associated with different serological responses to certain *H. pylori* antigens⁽²¹³⁾. CagA and VacA appear to play a major role in pathogenicity. The associations between the CagA and VacA antibodies and clinical outcomes have been reported⁽²¹⁴⁾. Infection with *H. pylori* evokes both local and systemic antibody responses. CagA is the important pathologic marker with a high immunogenic response⁽²¹⁵⁾. In Europe CagA positive *H. pylori* has been reported to account for 60 to 70 percent of *H. pylori* strains⁽²¹²⁾. (Schumann C et al 2006) while reports from East Asian countries have shown that more than 90% of *H. pylori* strains are CagA positive irrespective of the disease presentation.⁽²¹³⁾ (Tajana FK, et al 2009)

Convincing evidence have linked *H. pylori* in both gastric cancer and mucosa associated lymphoid tissue [MALT] lymphoma. MALT lymphomas originating in the stomach are causatively linked to *H. pylori* infection.

Seventy-five percent of gastric MALT lymphomas regress after the eradication of *H. pylori* with antibiotics, and those that do not respond are typically at an advanced stage or carry a specific t(11;18) (q21;q21) translocation.

More recently researchers reported that the Helicobacter spp were identified in the liver tissue resected from patients with hepatocellular carcinoma, as this study has shown that more than or equal to 90% of the cases have had *H. pylori* and HCV antibodies. This have been supported with the Cammorta et al 2002, that as a co-risk factor, a high prevalence of *H. pylori* and Hepatitis C virus [HCV] in the stomach of patients with HCV infection, In these subjects, the presence of both HCV & *H. pylori* in the gastric mucosa was significantly associated with marked or moderate inflammatory infiltration. Oligoclonal immunoglobulin H gene rearrangements were detected in patients who harbored both *H. pylori* and HCV in their stomach. It is suggested that HCV and *H.pylori* cooperate to induce lymphocytic inflammation. Some researchers have found a high seropositivty of antibodies to *H. pylori* in patients with HCV positive liver diseases. A study done by El-Masry et al showed *H. pylori* positivity in 55.6% of HCV infected patients compared to 39.4% in their healthy controls (p=0.03). They found also a remarkable increase in *H. pylori* prevalence with advancing hepatic lesions.⁽²¹⁶⁾

Discussion

The role played by *H. pylori* and *HCV* in development of hematological malignancies [Leukemia and Malignant Lymphoma] remains controversial. Many conflicting reports have been published to date. Finally we can conclude that many tested bacterial virulence antigens are highly immunogenic and can induce antibody response in almost all patients such as CagA and VacA which may be useful for differentiating clinical outcome among the patients, also we can conclude that p120 {CagA} and p30 {OMP} seropositivity more often present in patients with acute leukemias and malignant lymphomas, but the Vac A remains controversial whether it plays a role in the cancer process or not as 50% of cases had VacA antibody.⁽²¹⁷⁾

SUMMARY

The highest prevalence of *Hepatitis C virus* (HCV) and *Helicobacter pylori* has been reported in Egypt but few researches among Leukemic and malignant Lymphoma cases. So The present study was designed to screen acute Leukemia and Malignant Lymphoma patients for *H. pylori* antibodies to six virulent antigens by a new line immunoassay and correlate the clinical status to epidemiological markers of bacterial virulence factors as well as screening the same cases to *HCV* antibodies as a risk cofactor and correlate between both. Cases of the present study were selected from Hematology unit (Internal Medicine) of Alexandria Main University Hospital from June 2012 till September 2013.

One hundred Leukemia/ Malignant Lymphoma cases who were fully investigated by clinical and laboratory tests were the candidate of our screening serological study. Acute leukemia cases were early diagnosed by CBC and bone marrow examination. Malignant lymphoma were also early diagnosed by lymph node biopsy. Screening for *H. pylori* antibodies to six virulent antigens were performed by line immunoassay following the manufacturer's instructions.

It was LINE test kit for the quantitative detection of *H. pylori* specific IgG antibodies in human serum (Verotec-Genzyme, USA). Screening for *HCV* antibodies were done by rapid commercial test following the manufacturer's instructions .

Our results revealed that antibodies to Cytotoxin associated gene(Cag A) were predominant among cases and a significant association ($p < 0.05$) between antibodies to vacuolating (Vac A) antigens of *H.pylori* and *HCV* antibodies among our Leukemic and Malignant Lymphoma cases .We can conclude that rapid noninvasive methods by line immunoassays could easily screen hematogenous malignancies to these carcinogenic pathogens (*HCV and H.pylori*).

CONCLUSION

From our study, we can conclude the following:

- Egypt might be one of the highest prevalence rates of HCV infection in the world , with high incidence of hepatic morbidity and mortality from the late complications of HCV infection , such as chronic hepatitis , cirrhosis and hepatocellular carcinoma
- Seropositivity to *H.pylori* specific antigens maybe useful as indirect markers in the screening of *H.pylori* infected patients
- The high association of Cag A with the malignant cases is quite remarkable and can be used as a powerful marker for *H .pylori* .
- The quite remarkable association of HCV infection with the malignant cases might be evident
- The VacA and P30 antigens were associated with 50 and 80 percent of cases respectively, especially p30 was associated with HCV .

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