Muhammed Waheeb Al.Obaidy et al /J. Pharm. Sci. & Res. Vol. 10(5), 2018, 1306-1309

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Helicobacter Pylori infection related to Lung Cancer Histopathologically

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Abstract

Background:
Helicobacter pylori is one of the most common bacterial Infections of humans affecting approximately 50% of the world's population, And leads to many gastrointestinal and respiratory diseases. One of the Respiratory diseases is lung cancer.
Objectives: to show relationship between H Pylori infection and lung cancer histopathologically
Methods:
Sixty patients with lung cancer (34 patients with adenocarcinoma and 26 with squamous cell carcinoma) have been included to this study. All enrolled subjects underwent a15 minute, lateral flow immunoassay for the qualitative detection of IgG antibodies anti-H. Pylori in human serum (CTK Biotech, Inc USA) and a lateral immunochromatographic assay for the qualitative detection of H. Pylori antigen in human fecal specimen (CTK Biotech,Inc USA) , A p value of <0.05 was considered as significant. The statistical data analysis was performed with SPSS 22.
Results:
60 lung cancer patients:(41)(68.4%) persons had H pylori Ab positive and (19)(31.6%) persons had Ab negative, while only(22)(36.6%) persons had H pylori Ag positive and(38)(63.4%) persons had Ag negative. From (34) adenocarcinoma patients there are (26)(76.4%) patients had H pylori Ab positive and only (8) (23.6%)had Ab negative . From (26) squamous cell carcinoma patients there are (15) (57.7%) had Ab positive and (11) (42.3%) had Ab negative. From (34) adenocarcinoma patients there are (15) (44.2%) adenocarcinoma patients had H pylori Ag positive and (19) (55.8%) had Ag negative. From (26) squamous cell carcinoma patients there are (7) (27%) of squamous cell carcinoma had Hpylori Ag positive and (19) (73%) had Ag negative.
Conclusion:
The results of this study shows that the patients with H. pylori seropositivity antibody was significantly higher than negativity in adenocarcinoma patients, while in squamous cell carcinoma H. pylori seropositivity antibody was slightly higher. And stool antigen negative patients higher than positive in both type of cancer.

Key words: lung cancer, H pylori infection

INTRODUCTION:-

The lung cancer is a main health problem with a generally badPrognosis, during the last 50 years; its incidence is dramatically increasing,not only in men but also in women. It is one of the most common causes of mortality in the world (1,2), Lung cancer is the second most common cancer in both men and women. Most recent estimates of American Cancer
Society reflect 160340 deaths due to lung cancer (87,750 in men and 72,590 in women), accounting for about 28% of all cancer deaths in United States (3). The overall incidence of lung cancer has been strongly associated to cigarette smoking. It also occurs in association with occupational and environmental exposure to carcinogenic agents (Radon,Asbestos, Pesticides, Heavy metals, Air pollutants, and etc.…).
There are some other factors related to the development of lung cancer such as familial predisposition, genetic alteration, and more recently *H. pylori* infection (4-6).
Lung cancer histopathologically divided into two groups, which influence management and treatment decisions:
Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancers, there are subtypes of NSCLC, which start from different types of lung cells. But they are grouped together as NSCLC because the approach to treatment and prognosis (outlook) are often similar.
Adenocarcinoma: About 40% of lung cancers are adenocarcinomas.These cancers start in early versions of the cells that would normally secrete substances such as mucus. This type of lung cancer occurs mainly in current or former smokers, but it is also the most common type of lung cancer seen in non-smokers. It is more common in women than in men, and it is more likely to occur in younger people than other types of lung cancer. Adenocarcinoma is usually found in outer parts of the lung; though it tends to grow slower than other types of lung cancer and is more likely to be found before it has spread, this varies from patient to patient. There are many types and subtypes of adenocarcinoma (pre-invasive lesions,
Minimally invasive adenocarcinoma, Invasive adenocarcinoma, and Variants of invasive adenocarcinoma). People with a subtype of adenocarcinoma called *adenocarcinoma in situ* (previously called *bronchioloalveolar carcinoma*) tend to have a better outlook than
Those with other types of lung cancer.
Squamous cell (epidermoid) carcinoma: About 25% to 30% of all lung cancers are squamous cell carcinomas. These cancers start in early versions of squamous cells, which are flat cells that line the inside of the airways in the lungs. They are often linked to a history of smoking and tend to be found in the central part of the lungs, near a main airway (bronchus).
Large cell (undifferentiated) carcinoma: This type accounts for about 10% to 15% of lung cancers. It can appear in any part of the lung. It tends to grow and spread quickly, which can make it harder to treat. A subtype of large cell carcinoma, known as *large cell neuroendocrine carcinoma*, is a fast-growing cancer that is very similar to small cell lung cancer.
Other subtypes: A few other subtypes of NSCLC, such as adenosquamous carcinoma and sarcomatoid carcinoma, are much less common. (7)
Small cell lung cancer (SCLC): accounts for 15% of all lung cancers, most aggressive of lung cancer subtypes. it was believed originated from neuroectoderm but actually may developed from common pulmonary stem cell, small cell carcinoma express many neurohormones may act locally or may have systemic effect, approximately about 80% of it are central in

location and found mainly in submucosal area. It characterized by rapid clinical growth and may spread quickly into mediastinal lymph node without
respiratory tract involving.

***Helicobacter pylori* (H. pylori)** is one of the most common bacterial infections of humans affecting approximately 50% of the world's population, H. pylori (Hp) is Gram-negative, spiral, and has multiple flagella at one end, which make it motile, allowing it to burrow and live beneath the mucus layer adherent to the epithelial surface. H. pylori use an adhesin molecule (BabA) to bind to the Lewis b antigen on epithelial cells. Here the surface
pH is close to neutral and any acidity is buffered by the organism's production of the enzyme urease. H. pylori synthesis ammonia from urea and elevate the pH around the bacterium and between its two cell membrane layers. H. pylori mainly colonises gastric-type epithelium and exclusively found in the duodenum in association with patches of gastric metaplasia. H. pylori cause chronic gastritis by producing a local inflammatory response in the underlying epithelium (9).

The pathogenesis of H. pylori majorly relays on the producing of several bacterial agents to the host, including cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), type IV secretion system (T4SS), outer inflammatory protein A and adherence factors (10). Cytotoxins and carcinogenesis-associated proteins of H pylori. The cytotoxin-associated protein (CagA) and the vacuolating cytotoxin (VacA) are important virulence determinants of H pylori and may elaborate complex cellular responses of epithelial cells in Hp pathogenesis and carcinogenesis (11).

Based on the phenotypic analyses of clinical isolates of Hp, more of the strains can be classified into two broad groups—those expressing both VacA and CagA (type I) and those producing neither (type II). The remaining Hp strains have an intermediate phenotype (type III), expressing CagA independently of VacA (CagA+VacA−) or vice versa (CagA−VacA+)
(12).

The CagA gene is located within the Cag pathogenicity island region on the bacterial chromosome, which encodes proteins important for structure and function of T4SS (13). Approximately, 60–70% of Western Hp strains and all of East Asian strains express CagA (14). Many studies described that CagA+ strains are closely connected with the development
Of acute gastritis and pre-malignant and malignant lesions (15).

The relationship between CagA and malignancy were demonstrated in animal
Models (16), supporting strong evidence for the role of CagA as a bacteriumderived
oncoprotein VacA, the second most extensively studied Hp factor, enhances Hp virulence though its pleiotropic functions in vivo. The gene encoding VacA is present in almost all Hp strains (17).

There is relationship between VacA and gastroduodenal diseases (e.g. peptic ulcer, atrophic
gastritis and gastric cancer) (18). The differences in the VacA structure at the signal region (s1 and s2) and the middle region (m1 and m2) lead to variations in the vacuolating activity (19). Many studies in Western countries showed that individuals infected with VacA s1 or m1 strains have an increased risk of peptic ulcer or gastric cancer compared with those with
VacA s2 or m2 strains (20, 21).

Extra gastric manifestations:

There are strong association between H pylori and many abnormal conditions, e.g. cardiovascular (22–24), hematologic (25-27), eye and skin (28–30) and hepatobiliary diseases (31-33); diabetes mellitus (34–36) and neurological disorders (37–39). And also H pylori infection has been associated to be involved in autoimmune pancreatitis and pancreatic cancer (40), and can increase the risk of transforming growth factor-β1-mediated tumorigenesis by disturbing the balance between apoptosis and proliferation of hepatocytes (31). There is also relationship between H pylori infection and colorectal, laryngeal–hypo pharyngeal malignancy (41, 42).

Diagnosis:

Helicobacter pylori tests are used to detect a Helicobacter pylori (H. pylori) infection in the stomach and upper part of the small intestine (duodenum). Four tests are used to detect H. pylori:

***Urea breathe test.** A urea breath test checks to see if you have H. pylori bacteria in your stomach. This test can show if you have an H. pyloriinfection. It can also be used to see if treatment has worked to get rid of H. pylori.

***Stomach biopsy**. A small sample (biopsy) is taken from the lining of your stomach and small intestine during an endoscopy. Several different tests may be done on the biopsy sample.

* **Blood antibody test.** A blood test checks to see whether patient's body has made antibodies to H. pylori bacteria. If he has antibodies to H. pylori in his blood, it means he either is currently infected or has been infected in the past. In this test we don't need to do any think before we have test, sensitivity and specificity of this test is more than 90%

***Stool antigen test.** A stool antigen test checks to see if substances that trigger the immune system to fight an *H. pylori* infection (*H. pylori* antigens) are present in patient's feces (stool).If it's positive that mean patient has active Hpylori infection. So stool antigen testing may be done to help support a diagnosis of *H. pylori* infection or to find out whether treatment for an *H. pylori* infection has been successful. In this test medicines may change the result of test, so patient must be stop taking some medicine like antibiotic, bismuth containing drug and proton pump inhibitor. The test has 98% specificity and 94% sensitivity. (34)

MATERIAL AND METHOD:-

This study was conducted at the Department of Pulmonary Medicine, at Baghdad teaching hospital, 60 consecutive patients with histopathologically verified primary lung cancer were enrolled in the study. Lung carcinoma diagnosis was confirmed by fiber optic bronchoscopy and/or transthoracic needle aspiration, tru cut biopsy. We differentiated it by expert
Histopatholgsit in and outside the hospital.

Inclusion criteria

Patient at 18 years old and above with primary lung cancer and don't have any H pylori eradication therapy.

Exclusion criteria

Previous H pylori eradication therapy, a history of surgery on the upper gastrointestinal tract.

All patients underwent a15- minute, lateral flow immunoassay for thequalitative detection of IgG antibodies anti-H. Pylori in human serum (CTK Biotech, Inc USA) and a lateral immunochromatographic assay for the qualitative detection of H. Pylori antigen in human fecal specimen (CTK Biotech, Inc USA).

Statistical analysis:-

The relation between lung cancer and H. pylori infection was assessed by paired *t* test. All results were compared among two groups by percentage and frequency table sand charts. A p value of <0.05 was considered as significant. The statistical data analysis was performed with SPSS 22.

RESULTS:-

This study was carried out in Baghdad teaching hospital a (60) histologically verified lung carcinoma patients (34) (56.6%) presented with adenocarcinoma and (26) (43.4%) with squamous cell carcinoma. figure. 1 (38)(63.3%) of patient with cigarette smoking and (22) (36.7%) without smoking. (42)(70%) of patient are men and (18) (30%) are women.

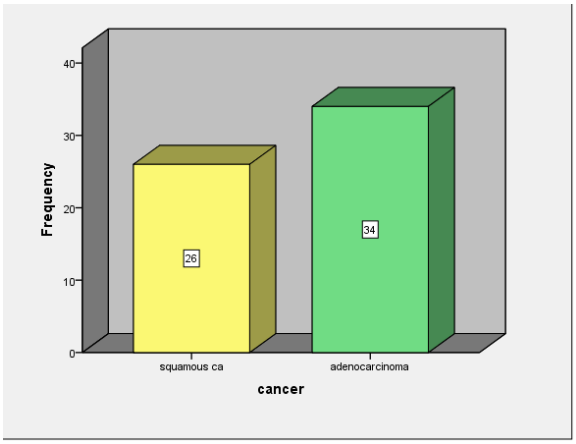

Figure 1 Histopathologically type

The median age of patients about (57.8±11.4) years.
We are found from (60) lung cancer patients :(41)(68.4%) persons had H pylori Antibody positive and (19)(31.6%) persons had Antibody negative, figure.2 While only (22) (36.6%) persons had H pylori Antigen positive and (38) (63.4%) persons had A negative. figure.3

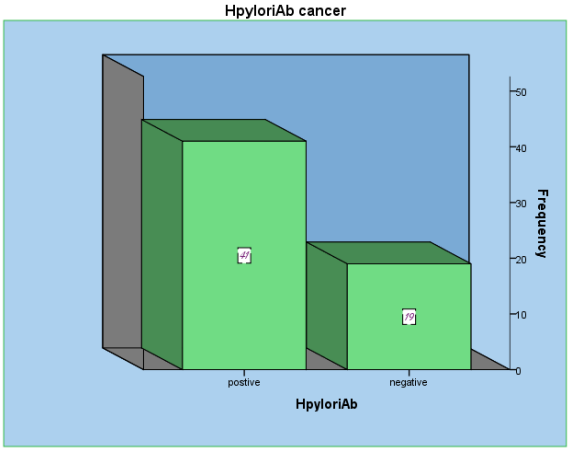

Figure 2: Lung Cancer related H pylori Antibody.

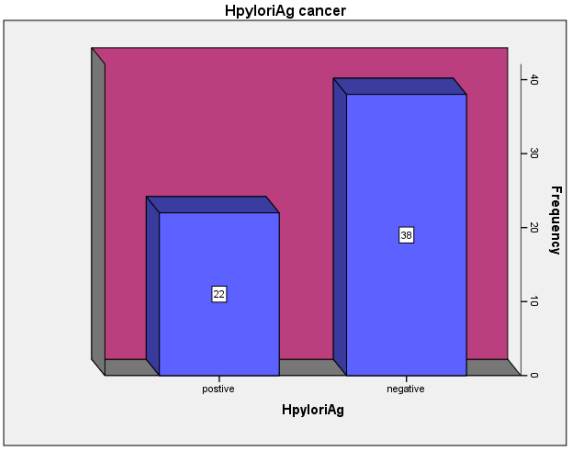

Figure 3:Lung Cancer related to H pylori Antigen

From (34) adenocarcinoma patients there are (26) (76.4%) patients had H pylori Antibody positive and only (8) (23.6%) had Antibody negative. figure. 4.

From (26) squamous cell carcinoma patients there are (15) (57.7%) had Antibody positive and (11) (42.3%) had Antibody negative. figure.4

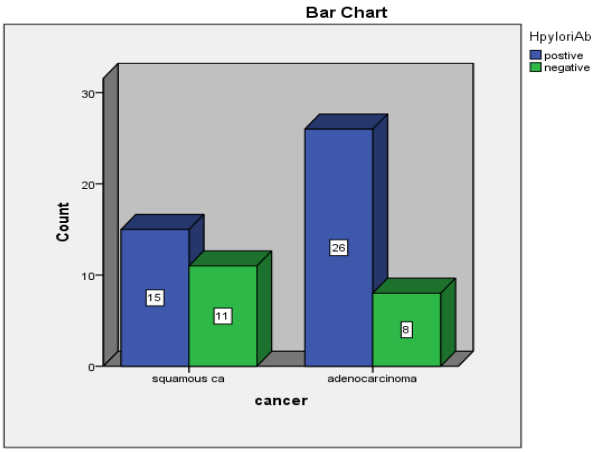

Figure. 4 (Hpylori Ab related to squamous & adenocarcinoma)

From (34) adenocarcinoma patients there are (15) (44.2%) adenocarcinoma patients had H pylori Antigen positive and (19) (55.8%) had Antigen negative. figure.5
From (26) squamous cell carcinoma patients there are (7) (27%) of squamous cell carcinoma had H pylori Antigen positive and (19) (73%) had Antigen negative. figure.5

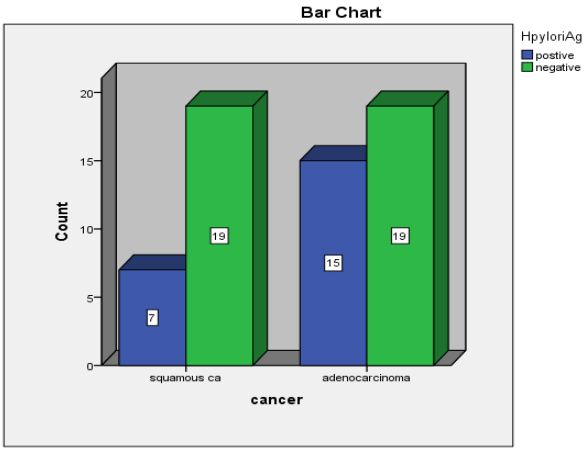

Figure 5 (H pylori Antigen related to Squamous & Adenocarcinoma)

DISCUSSION:-

In this study; we found, H. pylori seropositivity antibody was significantly higher than negativity in adenocarcinoma patients, while in squamous cell carcinoma H. pylori seropositivity antibody was slightly higher. And stool antigen negative patients higher than positive in both type of cancer, that's mean, the H pylori infection as cause of lung cancer related to adenocarcinoma lung cancer more than to squamous cell carcinoma.
In this sample we take it all the 60 lung cancer patients presented with only squamous and adenocarcinoma there is no other type of lung cancer we found.
Previous studies investigated the association between H. pylori andlung cancer , Ece et al (2005)Turkey found 43 non-small cell lung cancer cases, all current smokers:22 squamous cell (SCC)(21 males,1 females);21 adenocarcinoma (AC);(14 males,7 females), in this study we found there is no difference between the adenocarcinoma and squamous

lung cancer as related to H pylori infection. Gocyk *et al* (2000) Poland found 50 histologically confirmed cases of lung carcinoma, histologic type 80% squamous cell carcinoma, 20%adenocarcinoma. In this study the H pylori related to squamous cell carcinoma more than adenocarcinoma. Reason for the increased risk of lung cancer in *H. pylori* infected patients can be explained in several ways. (i) *Hpylori* is a Gram-negative bacteria with lipopolysaccharides the major component of the cell wall. Lipopolysaccharide stimulates the production of pro inflammatory cytokines including interleukins and tumor necrosis factor-alpha. This leads to chronic inflammation and immune stimulation, which may contribute to carcinogenesis. (ii) The lungs arise embryological from the same endoderm cells that form the lining of the gastrointestinal tract and possess similar neuroendocrine and paracrine cells releasing various hormonal peptides and their receptors including gastrin releasing peptide and gastrin. It is a well-known fact that *H. pylori* infection in the stomach markedly enhances and prolongs the release of gastrin. Gocyk et al. showed that gastric *H. pylori* infection in lung cancer patients is accompanied by a significant increase in gastrin plasma and bronchial lavage levels as well as by increased mRNA expression for gastrin and its receptors, as well as for Cyclooxygenase-1 (COX-1) and COX-2 in the tumor tissue [14].Gastrin could contribute to lung cancer by inducing higher mucosal cell proliferation of bronchial epithelium to atrophy and induction of COX-2

CONCLUSION

From this study, we found the patient present with H pylori infection more susceptible to had adenocarcinoma lung cancer than had squamous cell carcinoma.

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