Infection with Hydatid Cyst can Predispose to Liver and Lung Cancers

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Abstract

Background: Infections are major causes of malignancies. Several parasitic agents are well documented in their association with different cancers. However, the causative relationship of many other parasitic agents with cancers are still a debate issue.
Aim: The current study aimed to investigate the possible role of hydatid cyst (HC) in liver and lung cancers.
Subject and Methods: A case /control study which involved 42 patients with HC, 35 patients with liver or lung cancer and 25 healthy control was conducted. Serum levels anti-Ehinococcus IgG antiboies, Carbohydrate antigen (CA19-9), caspase-8 and gamma glutamyltransferase (GGT) were determined by enzyme linked immunosorbent technique (ELISA) using commercial kits.
Results: Eleven patients with liver or lung cancer (32.42%) gave positive result for anti-Echinococcus antibodies compared to one case (4%) among control (OR= 8.3, 95%CI=0.978-70.55). Hydatid cyst and cancer groups showed significantly higher serum levels of CA19-9 and GGT than control group, while caspase-8 levels declined in cancer group compared with that of HC and control group.
Conclusion: These data suggest a possible role for HC as a carcinogenesis in liver and lung cancers.

Keywords: hydatid cyst, liver and lung cancers, CA19-9, caspase-8, GGT

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Introduction

Cancer is a leading cause of death worldwide. It is caused by heterogenous and overlapped factors. Infectious agents are estimated to be responsible for 17.8% of all cancer cases (Parkin, 2006). All cancer-associated infectious agents share in common their ability to induce chronic infection or establish latency (Oluwasola, and Adeoye, 2007). Although the major cases of infection-caused malignancies are attributed to viral infection (), parasitic agents, especially helminthes do involve. International Agency for Research on Cancer

(IARC) classified *Schistosoma haematobium*, *Clonorchis sinesis* and *Opistorchis viverrini* in group I (infectious agents definitely carcinogenic for human), while *Schistosoma japonicum* in group 2B (agents probably carcinogenic for human) (Benamrouz et al., 2012). The association of many other parasites with cancer is a debate issue. For instance, *Trichomonas vaginalis* and *Cryptosporidium parvum* are frequently accused for their role in prostate cancer and colorectal cancer respectively (Al-Mayah *et al*, 2013, Certad et al., 2010) but there were no decisive evidences that supporting these claims. Even more controversial is the role of some cestodal infections whether they have carcinogenic or anticancer role. Infection with hydatid cyst lies within this category. Hydatidosis is an infection with the larval stage of *Ehinococcus granulosus*. It is quite common in many developing countries including Iraq (Sajjadi, 2005). Akgul *et al.* (2003) in a large retrospective study reported a significantly lower prevalence of cancer in patients with hydtidosis. Berriel et al. (2013) used human HC fluid to immunize mice against experimentally-induced colon cancer, and found some degree of protection against tumor challenge. However, many vital changes accompanying HC infection like oxidative stress and immune suppression suggest a carcinogenesis rather than anticancer effect of this parasite. Thus, the present study aimed to investigate the association of hydatidosis with liver and lung cancers.

Subjects and Methods

Study Population

A case/control study was conducting during the period from Septemper 2014 to February 2015 to demonstrate the potential role of HC in cancer development. The study involved three groups: the first one (HC group) involved 42 patients who were attending Baaquba Hospital (11 males and 31 females, age range 28 to 71 years, average 44.21 years) with confirmed HC (either in the liver or lung or both) infection by X-ray and ultrasound examination. The second (cancer group) involved 35 patients (23 males and 12 females, age range 28 to 80 years, average 55.22 years) who were attending Al-Amal National Hospital for Cancers and Medical City/ Baghdad, with histopathologically confirmed liver (12 patients) or lung (23 patients) cancers. Other 25 apparently healthy individuals (13 males and 12 females, age range 30 to 69 years, average 48.16) were recruited to represent control group. A consent form was obtained from each participant which included age, gender, smoking status, residence, occupation and educational level.

Blood Samples

Five ml of venous blood was drown from each subject, from which the serum was obtained and kept at -20 C until be used.

Laboratory Assays

Commercial kits were utilized for estimation of serum levels of anti-echinococcus IgG antibodies (GmbH/ Germany), CA19-9 (Human/ Germany), caspase-8 (MyBiosource/ USA)

and GGT (Human/ Germany) using ELISA technique. The instruction protocols were followed in each of these kits.

Statistical Analysis

Data were expressed as a mean± standard deviation. The Statistical Package for the Social sciences (SPSS, version 14) was used for statistical analysis. Risk association between the different factors and the development of liver or lung cancers in HC patients by the calculation of adjusted odd ratio and 95% confidence intervals using multivariate logistic regression. Analysis of variance and t-test were used to compare means of different variables between three or two groups respectively. A *p*-value < 0.05was considered statistically significant.

Results

Anti-Echinococcus IgG Seropositivity

All patients with HC were positive for Anti-Echinococcus IgG. Out of 35 patients with liver or lung cancers, 11 patients (32.42%) had positive result for Anti-Echinococcus IgG antibodies compared with only one case from 25 control (4%) with significant difference (OR= 8.3, 95%CI=0.978-70.55).

Serum Levels of CA19-9, Caspase-8 and GGT

Mean serum levels of CA19-9 in HC, cancer and control groups were 76.16± 58.26 U/ml, 110.77±96.47 U/ml and 10.81±9.12 U/ml respectively, with both HC and cancer groups differed significantly from control. Cancer group showed relatively low levels of caspase-8 (60.86± 41.20 pmol/L) which was less significantly than that of control (92.3±41.2 ..) and insignificantly than that of HC group (72.2± 54.72 pmol/L). Finally, both HC and cancer group had significantly higher levels of GGT (95.06± 66.73 U/L and 105±41.42 U/L respectively) than control (17.21±6.87 U/L).

Table (1): Serum levels of CA19-9, caspase-8 and GGT in HC, cancer and control groups

Variable	HC	Cancer	Control
CA19-9 (U/ml)	76.16± 58.26[a]	110.77±96.47[a]	10.81±9.12[b]
Caspase-8 (pmol/L)	72.2± 54.72[ab]	60.86± 41.20[a]	92.3±41.2[b]
GGT (U/L)	95.06± 66.73[a]	105±41.42[a]	17.21±6.87[b]

Different small letters indicate significant differences

Risk factors

The study revealed a significant effect of each of age, gender, smoking, residency and occupation on the development of liver or lung cancer in HC patients. Mean age of HC patients was 42.98±14.46 years compared with 55.23±13.26 years for cancer patients ($P \leq 0.001$). Females infected with HC showed less tendency to develop liver or lung cancer than males (OR=0.29, 95%CI=0.113-0.74). Cancer develops in smoker HC patients by 6.982-fold than those who are non-smokers (OR=6.982, 95%CI= 2.551-19.1, while HC rural residents expose liver or lung cancers by 5.48-fold compared with urban residents (OR= 5.48, 95%CI=2.007-14.98). Finally, some occupations (other than farmers and butchers) expose their HC careers to liver or lung cancers by 10.26-fold compared with house-keeping women (OR= 10.26, 95%CI=2.95-35.69). On the other hand, level of education does not seem to have an effect on predisposing HC patients to cancer (Table 2).

Table 2: Risk factors that predispose hydatid cyst patients to liver or lung cancers

Risk factors	**HC patients (42)**	**Cancer Patients (35)**	***P*-value**	**OR(95%CI)**
Age Mean±SD	42.98± 14.46	55.23±13.26	0.001	
Gender			0.012	
Male	11 (26.19%)	23 (65.71%)		1.0
Female	31 (73.81%)	12 (34.28%)		0.29(0.113-0.74)
Smoking			0.001	
Non-smokers	31 (73.81%)	10 (28.57%)		1.0
Smokers	11 (26.19%)	25 (71.42%)		6.982(2.551-19.1)
Residency			0.017	
Urban	16 (38.09%)	27 (77.14%)		1.0
Rural	26 (61.91%)	8 (22.85%)		5.48(2.007-14.98)
Occupation			0.001	
House-keeping	21 (50%)	11 (31.42%)		1.0
Farmers	9 (21.42%)	3 (8.57%)		0.46(0.08-2.57)
Butchers	7 (16.67%)	2 (5.71%)		0.77(0.13-4.61)
Others	5 (11.9%)	19 (54.28%)		10.26(2.95-35.69)
Educational level			0.152	
Illiterate	3 (7.14%)	2 (5.71%)		1.0
Primary	26 (61.9%)	14 (40%)		3.75(0.33-42.46)
Secondary	12 (28.57%)	12 (34.28%)		5.0(0.85-29.08)
Higher education	1 (2.38%)	6 (17.14%)		1.923(0.3-12.05)

Discussion

Cancers are multifactorial diseases which are initiated and progressed by different and interacting causes. Few parasites are well documented to be associated with certain cancers. The current study revealed a strong association between previous infection with HC (as indicated by seropositivity for anti-echinococcus IgG) and liver and lung cancers, HC patients have 8.3-fold chance to develop liver or lung cancer compared to un-infected individuals. These results do not agree with previous works by Akgul et al. (2003) who reported a significantly lower prevalence of cancer in patients with hydtidosis.

To further support the hypothesis, we have estimated the serum levels of some factors which are supposed to be associated with tumors. The carbohydrate antigen sialyl Lewis-a, most commonly known a CA19-9 is a protein that is found in small quantities as glycolipid and as an O-linked glycoprotein on cancer cells, although trace amount of this antigen can be found on certain types of normal cells (Ballehaninna and Chamberlain, 2012). Normal cells produce disialyl Lewis-a which is expressed on the cell surface and acts as a ligand for some immune cells to achieve immunosurveillance. In many cancer cells, there is an epigenetic silencing of the gene responsible for sialyl transfer which results in the accumulation of sialyl Lewis-a on the surface of the these cells (Kannagi, 2007). Some quantities of CA19-9 detaches and found its way to the blood where it can be estimated by different assays. In this study, CA19-9 was found to be elevated significantly in HC and cancer group compared with the control. While it is usual to find such elevation in patients with liver or lung cancer, high levels of CA19-9 in HC patients is unusual finding. Of course it cannot be attributed to gene silencing because there is no evidence for that in the available literatures. Rather, the most reasonable explanation is that there may be an activity for cancer cells in somewhere in the host especially that CA19-9 is mostly expressed during early stages of cancerous process (Ballehaninna and Chamberlain, 2012). This elevation in HC group provide an evidence for the association of HC with cancer.

Apoptosis (programmed cell death) is a vital process that regulates the delicate balance between cell division and death (Evan and Vousden, 2001). In mammals, apoptosis is initiated through three pathways, of which the extrinsic pathway involves caspase-8. This pathway is triggered by ligation of death ligands (e.g FasL, TNF-α, TRAIL) to their death receptors and then the activation of caspase-8 which plays a central role in the transmission of death signals during apoptosis (Liu et al., 2011). Reduced caspase-8 expression or dysfunction of this protein will affect the apoptosis and fosters the carcinogenesis (Fulda, 2008). In fact, Evasion of apoptosis, a hallmark of human cancers, can be caused by the inactivation of caspase-8 through different mechanisms, such as genetic alterations, epigenetic modifications, alternative splicing or posttranslational changes (Fluda, 2010). Although the study revealed insignificant difference in the serum levels between HC group and control, the HC group did not differ significantly from cancer group in this regard. Thus, there is a shortage in caspase-8 expression in HC group. Again, it cannot accuse the HC to cause genetic or epigenetic alteration, but some events related to cancer should be take place in host resulted in this shortage.

Gamma-glutamyltransferase is an enzyme involved in the metabolism of glutathione, and as such it is considered as a component of the cell protection system against oxidative stress (Whitfield, 2001). In a recent study, Mok et al. (2015) showed that serum levels of GGT≥ 60 IU/L is associated with high hazard ratios for all cancers, especially liver cancers, in both men and women in Korean population. GGT levels increase in response to the oxidative stress which arises due to disturbed equilibrium between pro-oxidant/antioxidant homeostasis that further takes part in generation of reactive oxygen species (Uttara et al., 2009). The oxidative stress is known for its harmful effect on DNA and subsequent initiation of cancer (Barzilai and Yamamoto, 2004). Thus the oxidative stress induces cancer but not the reverse. Bak et al. (2012) and Kurkuoglu et al. (2012) reported significantly increased total oxidant and oxidative stress in patient with HC compared with healthy control. Accordingly, it is reasonable to assume that infection with HC is involved in carcinogenesis thorough increase the oxidative stress in the host.

Beside the oxidative stress, there may be other more important factors by which HC indirectly influence the host susceptibility to cancer. These factors usually affect the immune status of the host. (Zhang et al., 2008) found that the hallmark of chronic HC infection is the presence of high level of interleukin-10 (IL-10). Although this cytokine has a diverse effect, there are several lines of evidence that IL-10 overexpression in different malignancies might contribute to tumor development, in particular, by suppressing the antitumor immune response (Matsuda et al., 1994). Moreover, IL-10 might even be a tumor cell growth factor in certain tumors (Asadullah et al., 2003). On the other hand, protoscolices of HCs have many immunomodulatory molecules, the most important of which is the antigen B (AgB). This antigen can directly suppress the host immune cells such polymorphonuclear cells and their chemotaxis and alter the cytokine balance (Rigano, 2001).

Collectively, these data suggest a role of HC with cancer in liver and lung. To the best of our knowledge, this is the first report to link liver or lung cancer with HC. However further studies are needed to draw a solid conclusion.

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