

RESEARCH COMMUNICATION

Low Frequency of Human T-cell Lymphotropic Virus 1 Antibodies in Iranian Gastric Cancer Patients in Comparison to Controls

Seyed Mohammad Ebrahim Tahaei, Seyed Reza Mohebbi*, Seyed Reza Fatemi, Parvaneh Mohammadi, Fatemeh Nemati Malek, Pedram Azimzadeh, Shohreh Almasi, Dariush Mirsattari, Mohammad Reza Zali

Abstract

There is some evidence that human T-cell lymphotropic virus (HTLV-1) infection has a reverse association with gastric cancer (GC). Data about this association in the Iranian population are scarce. In this study we therefore assessed the frequency of anti-HTLV-1 antibody in GC patients and compare it to antibody presence in healthy individuals in Iranian population. This case control study was performed between 2008-2011 on 201 GC patients and 219 control subjects. HTLV-1 antibodies were assessed by ELISA and the positive results were confirmed by western blotting. Totals of 201 gastric cancer patients and 219 controls were enrolled in this study. The tumors in the majority of patients (45.3%) were in the distal (non-cardia) area. Mean age of patients at the time of diagnosis was 59.2 ± 12.5 and mean age of controls was 57.7 ± 11.3 . While only one GC patient (0.5%) was positive for HTLV-1 antibody, there were four individuals (1.89%) from the control group with antibodies. In addition, smoking had statistically significant relationship with cancer ($P=0.001$). Our study showed that the frequency of HTLV-1 antibody in patients was lower than in controls, similar to the results obtained in Japan. Further investigations with a larger sample size are needed in order to determine the association between GC and HTLV-1 infection in Iran.

Key words: Gastric cancer - HTLV-1 - Iran - seroepidemiology

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Introduction

Human T-lymphotropic virus 1 (HTLV-1) was the first known human retrovirus and was discovered in 1980 by Poiesz. This virus is the causative agent of adult T-cell lymphoma (ATL). This virus is also associated with a form of neurodegenerative illness which is called HTLV-1 associated myelopathy/ tropical spastic paraparesis (HAM/ TSP) (Poiesz et al., 1980).

The main transmission route of this virus is through blood, but there are some other forms of transmission like sexual contacts, sharing syringe between intravenous drug abuser and vertical transmission (Yoshida, et al., 1982). This virus is distributed globally, but it is more prevalent in Southwestern Japan, Caribbean basin, Southern America and some parts of Africa. Almost 22 million people are estimated to be infected with this virus (Proietti et al., 2005). In different studies in Iranian general population the prevalence rate of this virus

is reported to be between 0.5 percent and 0.7 percent (Abbaszadegan et al., 2003).

This virus has an oncogene in its genome called tax-1, which can immortalize cultured T-cells (Grassmann et al., 2005). In addition to this oncogene, virus makes other products which manipulate the cell cycle and hence make them cancerous (Boxus et al., 2009). The association of this virus with some forms of cancer other than ATL has been investigated recently. Most of these studies have been performed in Southwestern Japan, where the prevalence of this virus is high. In different studies they showed that this virus is not associated with increasing risk of colorectal, lung, biliary tract and liver cancer (Arisawa et al., 2003; Hirata et al., 2007). In some of these studies, investigators have shown that the prevalence of HTLV-1 infection between GC patients is lower in comparison to healthy individuals (Hirata et al., 2007; Matsumoto et al., 2008).

Gastric cancer is the 4th most common cancer in the world and the second reason of mortality from cancer

Research Center for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran *For correspondence: srmohebbi@gmail.com

globally; the first position belongs to lung cancer (Krejs, 2010). According to the national cancer registration report of Iran Ministry of Health and Medical Education (2007), this cancer is the second and fourth most common cancer in Iranian men and women, respectively.

There has been no study so far apropos of this association in Iranian population. This study was designed to investigate the frequency of anti-HTLV-1 antibodies in GC patients referred to gastroenterology ward of Taleghani hospital in comparison to control group.

Materials and Methods

This case control study was performed between Aug. 2008 and April 2011. During this time all of 201 GC patients- who were referred to Taleghani hospital, Tehran, Iran, were enrolled in this study. The control group was comprised of 219 individuals that were selected from healthy individuals who had been admitted to the Endoscopy ward of Taleghani hospital for various reasons like heartburn, anemia and weight loss and as a part of their diagnostic procedure went through endoscopy and had not shown any sign of malignancy. The study was approved by the Institutional Medical Ethics Committees of Research Center for Gastroenterology and Liver Disease, Shahid Beheshti University of Medical Sciences. All participants signed a written informed consent and anonymity was warranted. One blood sample was collected from each participant. In addition, subjects were interviewed by a trained personnel and a questionnaire containing demographic data was completed for each subject. All cases had histological confirmation of their tumor diagnosis. Sera separated from each blood sample, were kept in -20 degree Celsius until the time of serologic tests. Enzyme-linked immunosorbent assay (ELISA) technique (Diapro, Italy) was used for assessing the presence of anti-HTLV-1 antibody in subjects. The positive results were confirmed with western blotting.

All statistic analysis was carried out by SPSS Program. Pearson's chi square was performed to test for independence of discrete variables. Student's t-test was used to compare means of some continuous variable between two independent groups. For calculation of odds ratio we use the binary logistic regression. Continuous variables are represented here as mean±Standard Deviation and other parameters as frequency and percentage. A P value of 0.05 or less was considered statistically significant and all reported P values were two sided.

Results

Two hundred and one confirmed GC patients-confirmation was done through biopsy and pathology results- were enrolled in this study. Mean age of patients at the time of diagnosis was 59.0±12.8 and they were

between 22 and 85 years old. Of these, 155 (77.11%) were male and 56 (22.89%) were female. 219 individuals were enrolled in this study as control subjects. The control group consisted of 92 (42.01%) men and 127 (58.99%) women. The mean age of control group was 57.67±11.29. In regards to gender distribution, number of male was significantly higher than females in GC patients (p-value= 0.001 OR= 3.65 CI= 2.32- 5.74). The mean age of men and women in case group was 60.64±12.68 and 55.00±12.16, respectively and there was no significant difference between them (P=0.55). The mean age of male and female subjects in control group was 55.51±16.33 and 59.45±16.42, respectively. In regards to smoking, we saw a significant relationship between GC patients and control subjects (p=0.001 OR 4.73 CI= 2.64-8.47). Forty (19.9%) cancer patients had tumor in Cardia, twelve (5.97%) in Fundus, eighteen (8.95) in Body, forty six (22.88%) in Entrum, thirty six (17.91%) in higher curvature, seven (3.48%) in Pylor, two (0.99) in lower curvature and forty (19.89%) were Not Otherwise Specified (NOS). Based upon regional classification, 70 (34.82%) had GC in cardia (proximal) section of stomach and 91 (45.26%) patients had cancer in non-cardia region and 39 (19.4%) of patients were undiagnosed. The mean age of Cardia and non-Cardia patients was 60.94±11.64 and 57.96±12.51, respectively. No significant difference was observed between these two groups according to their age (P=0.23). 25 percent of Cardia patients were female and 28.8 percent of non-Cardia patients were female. There was no significant difference between two sexes in the position of cancer (P=0.679).

One GC patient (0.49%) and four subjects (1.89%) from control group had anti-HTLV-1 antibodies. Rate of HTLV-1 infection in control group was higher than case group. Three out of four seropositive subjects in control group were female. The only seropositive GC patient was a male subject.

Discussion

Gastric cancer is one of the most common cancers worldwide. This cancer is the second cause of mortality related to cancer. Although the incidence of this type of cancer has been reducing during past decades, this rate is high in countries like Japan and Korea (Ahn et al., 1991; Yamamoto, 2001). In Iran this type of cancer is abundant in Northwestern part, especially in Ardebil (Sadjadi et al., 2003). Although *H. pylori* infection is one of the main causes of GC, in recent years the role of another infectious agent, HTLV-1, has been highlighted. In contrary to other kinds of infection which have stimulatory role in cancer, it seems that this virus has prohibitive effects in GC (Arisawa et al., 2003; Hirata et al., 2007; Matsumoto et al., 2008).

Epidemiologic studies have shown that HTLV-1 is endemic in Khorasan province. In a study in Mashhad- the capital of Khorasan province- researchers reported that the prevalence rate of this virus among blood

donors was 0.77% (Abbaszadegan et al., 2003). In another study which was performed on Iranian organ donors, investigators showed that prevalence of this virus was 1.7% (Arjmand et al., 2009). Prevalence of this virus is higher among those individuals who receive blood or blood products. In several studies in different provinces of Iran, researcher reported 2.18% in Boushehr (Poorkarim, 2005), 6.2% in Tehran (Anaraki, 2005) and 1.6 percent in zahedan (Moradi, 2002) among thalassemic patients.

In this study we found out that the rate of HTLV-1 infection between GC patients is lower than healthy individuals. This finding is in accord with the previous studies performed in Japan. In Hirata's study, researchers found out that the risk of GC incidence was lower in infected persons in comparison to controls (p-value=0.01, adjusted OR=0.46). Hirata and colleagues (2003) also evaluated the association between other forms of cancer like biliary tract, lung, esophagus, liver and colon and rectum with HTLV-1 infection. They did not find any correlation between these types of cancer and HTLV-1 (Hirata et al., 2007). Arisawa and colleagues were also unable to find any association between incidence of other forms of cancer excluding ATL and GC and infection with HTLV-1. They reported a decrease risk of GC incidence (Rate Ratio= 0.42). Matsumotu and his colleagues (2008) reached the same results. They discovered in their cohort study, that 2.7 percent of persons with HTLV-1 infection developed GC cancer, while in negative patients the rate was seven percent. This association was statistically significant (p-value=0.002, OR=0.38).

In our study, non-cardia (distal) GC was more frequent. Various studies in different parts of the world have shown that the prevalence of non-Cardia GC is rising in developing countries, while the opposite trend is happening in the developed world. The incidence of cardia GC is increasing in those countries (Blot et al., 1991; Brown et al., 2002). This finding is in contradiction with the report of Derakhshan and his colleagues. They reported that the prevalence of cardia is several times higher than most of western countries (Derakhshan et al., 2004). The reason for this contradiction lays in this fact that Derakshan study was focused on patients from one Province, while in our study we enrolled patients from all over the country.

Hundred and fifty five out of two hundred and one (77%) studied GC patients were male. In different studies, it has been observed that men are more prone to GC compared to women (El-Serag et al., 2002 ; Krejs, 2010). In the case of non-Cardia GC the ratio is 2 male to 1 female, in Cardia the ratio is 3-5 male to 1 female. In Derakhshan and his colleagues' study (2004), this rate was reported to be 2.2:1.

In addition, we saw that rate of smoking was higher in gastric cancer patients. It has been shown previously in Northwestern parts of Iran that smoking is a risk factor in both types of cardia and non-cardia GC (Derakhshan

et al., 2008). Studies in other parts of the world have also demonstrated relationship between smoking and gastric cancer risk (González et al., 2003; Koizumi et al., 2004). In these studies, researchers ascertained that the effect of smoking was stronger for non-Cardia type of gastric cancer (Chao et al., 2002).

In conclusion, even though we were not able to analyze the causal relationship between infection with HTLV-1 and reduced risk of GC, we found out that prevalence of HTLV-1 infection is lower in GC patients compare to control subjects. Further investigation with larger sample size should be performed on Iranian GC patients to shed light on the features of relationship between HTLV-1 infection and gastric cancer.

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