Esophagitis may not be a Major Precursor Lesion for Esophageal Squamous Cell Carcinoma in a High Incidence Area in North-Eastern Iran

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ABSTRACT

BACKGROUND

Esophageal squamous cell carcinoma (ESCC) is usually detected in advanced stages resulting in a very poor prognosis. Early diagnosis needs identification of clinically relevant precancerous lesions which could become the target of screening and early treatment. Our aim was to check whether esophagitis could serve as a relevant histological precursor of ESCC in Northern Iran.

METHODS

During 2001–2005, all adult patients who were referred to Atrak clinic for upper gastrointestinal endoscopy and biopsy were enrolled. Atrak clinic is a major center for upper gastrointestinal cancer research in eastern Golestan. All subjects had been complaining of upper GI symptoms and were under further investigation to rule out cancer. Biopsies from the endoscopically normal mid-esophagus and also just above the esophago-gastric junction were obtained in all subjects whose esophagus appeared normal during endoscopy and from endoscopically normal appearing mucosa at the proximal vicinity of any detected mass. Microscopic examinations for the verification of the presence or absence of esophagitis was performed by independant histological examination of the samples by two pathologists. All the discrepant diagnoses were resolved in joint diagnostic sessions.

RESULTS

During the study period 836 patients were enrolled including 419 non cancer patients (endoscopy clinic controls), 387 cancer patients, and 30 subjects with clinical diagnosis of malignancy referred for histological reconfirmation of diagnosis by repeated biopsy. Mild or marked mid-esophagitis was diagnosed in 39 (9.3%), 47 (12.5%) and 12 (40%) of endoscopy clinic controls, cancer patients and those who were suspicious for upper gastrointestinal malignancies.

CONCLUSION

Our observation does not show evidence for esophagitis to be a predisposing factor for ESCC in Gonbad region In North Eastern Iran.

KEYWORDS

Esophagus; Squamous cell carcinoma; Esophagitis

INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) is the ninth most common malignancy and ranks the sixth most frequent cause of cancer mortality responsible for over 300,000 annual global deaths. The global incidence of ESCC shows considerable variations in different geographical locations. One of the well known high risk areas is the so-called Asian esophageal cancer belt extending from eastern Turkey to Northern and Western areas of China covering parts of Northern Iran, Turkmenistan, Kazakhstan, Uzbekistan and Tajikistan.

The other major high incidence areas include Hong Kong, Japan, Southeastern Africa, Southern France and parts of South America.[1,2] The Eastern part of Golestan province in Northern Iran, was reported to have one of the highest incidence rates for esophageal cancer in the world.[1,2]

Age standardized rates (ASR) of 109/100,000 in men and 175/100,000 in women were reported by Mahbobi and co-workers from this area 38 years ago.[3] The new investigations, however, report a sharp decline in the incidence rate to 43.4 per 100,000 for men and 36.3 for women, which is still among the highest in the world.[4]

Between 1992 and 1999, the five year relative survival rate for esophageal cancer in the United States was 14%[5] During 2001-2007 five-year survival was 3.3% in Northeast Golestan.[6] The tumor usually remains asymptomatic, and hence undetected, before occurrence of its major clinical symptoms of dysphagia and weight loss and usually by that time the lesion has already progressed to advanced and unresectable stages.[5,7] Therefore, identification of the precancerous lesions is essential for early detection and successful treatment of this lethal disease.

In 1982 Munoz, Crespi and co-workers conducted two endoscopic surveys in two high risk areas on in Golestan at Gonbad district from North-Eastern Iran and Northern China. They reported a high incidence of esophagitis by histological examination of the esophageal biopsy specimens obtained from the residents of both areas and concluded that esophagitis was the first step in the multiple events which lead to development of ESCC in human beings.[8,9,10] More recent investigations, however, questioned the role of esophagitis as a precursor lesion for ESCC.[5,11]

In the present study we reinvestigated the prevalence of esophagitis in the ESCC patients and normal population of the Gonbad district to determine whether mid-Esophagitis could be considered a precancerous lesion in Northern Iran.

MATERIALS AND METHODS

In 2001 The digestive Diseases Research Centre (DDRC) affiliated to Tehran University of Medical Sciences established the Atrak Clinic in the city of Gonbad to serve as a referral point for the diagnosis, management and research on the cancers of the upper gastrointestinal (GI) tract in that area.[7] During the initial phase of a case control study[7,12] the investigators contacted all of the local medical practitioners and asked them to refer their patients with upper GI symptoms suspicious of cancer to the Atrak Clinic.

Study population and endoscopy

During 2001-2005, all adult patients who were referred to Atrak clinic and underwent endoscopy and biopsy for histologic diagnosis were enrolled. Those with tumors in other organs, those who received any therapy due to the tumor, and patients who did not tolerate endoscopy were excluded. After signing an informed consent, patients underwent physical examination followed by esophago-gastro-duodenal videoendoscopy.

Endoscopic examinations and biopsy were conducted based on a standard protocol previ-

ously described elsewhere.[12] Briefly in every subject biopsy samples were obtained from normal appearing mid esophagus, cardia, gastric body and antrum. In patients with a tumoral lesion, in addition, several samples from the tumor and biopsy of the endoscopically normal appearing esophageal mucosa in the proximal vicinity to the mass were obtained using a 2.8 mm biopsy forceps. Biopsies were fixed in 10% buffered formalin, processed and embedded in paraffin, cut into 3-4 μm sections and stained with haematoxylin and eosin.

Histological examination

Biopsy slides were examined independently by two pathologists (MS, BA). Pathologists were not completely blinded to the clinical diagnosis of subjects and if discrepancy in histologic diagnosis was found, slides were read jointly to reach an agreement.

Based on one biopsy sample from mid-esophagus diagnosis of esophagitis was confirmed when one or more of the following three criteria[5] were present:

1. Basal cell zone exceeding 15% of the whole thickness of epithelium plus elongation of the connective tissue papilla from lamina propria to the upper third of the whole epithelial thickness.
2. Focal or diffuse infiltration of the epithelium by PMN leukocytes (> 2 PMN leukocytes per tissue section) or eosinophils (> 5 eosinophils per tissue section)
3. Dense non-follicular infiltration of mononuclear inflammatory cells and/or an easily recognized infiltrate of neutrophils in lamina propria.

Esophagitis was graded as mild or moderate /severe based on the degree and type of the three criteria. Esophagitis was graded as mild when basal zone hyperplasia and elongation of the papilla were the only finding. Cases that showed small number of PMN leukocytes and/or eosinophils and those with moderate number of intraepithelial lymphocytes and/or moderate non-follicular lymphocytic infiltration of lamina propria with/without elongation of rete ridges were regarded as moderate esophagitis. Presence of severe neutrophil infiltration in lamina propria and/or epithelium usually associated with erosion and ulceration had to be graded as severe esophagitis.

Moderate and sever esophagitis were grouped and categorized as marked esophagitis. For further analysis, mid-esophagitis diagnostic criteria were categorized to three groups including regenerative changes in basal cells, epithelial inflammation, and lamina propria inflammation (including those with inflammation in both lamina propria and epithelium).

The difference in demographic or diagnostic variables between each group was evaluated using chi-Square statistics. $p < 0.05$ was considered as significant level. Statistical calculation was done using Stata 11.0 (Statcrop USA).

RESULTS

During study period 836 patients were enrolled including 419 non cancer patients (considered as the endoscopy clinic controls), 387 cancer patients, and 30 subjects with clinical diagnosis of malignancy and need for repeating biopsies for histological confirmation of diagnosis. Mild or marked mid-esophagitis was diagnosed in 39 (9.3%), 47 (12.5%) and 12 (40%) of endoscopy clinic controls, cancer patients and those who were suspicious for upper gastrointestinal malignancies, respectively. Table 1 summarizes the characteristic of the patients.

The proportion of criteria components for diagnosis of mid-esophagitis was equally distributed among non-cancerous, cancerous, and those subjects who needed rebiopsy for confirmation of cancer ($p = 0.6$) (Table 2). In only 3 subjects esophagitis was diagnosed based on just presence of eosinophils in epithelium.

Marked mid esophagitis among non-cancer

Table 1: Characteristics of patients with and without mid-esophagitis (mild and marked) by diagnosis.

	Mean age (SD)		Female/male	
	No esophagitis	Esophagitis	No Esophagitis	Esophagitis
Non cancer patients	54.7 (13.0)	61.3 (15.2)	216/162	14/25
Cancer patients	65.4 (11.1)	67.7 (9.9)	138/202	20/27
Suspicious for malignancy	71.4 (8.1)	63.0 (12.9)	6 /12	3/9

Table 2: Occurrence of each diagnostic criteria for mid esophagitis among cancerous and non-cancerous endoscopy clinic patients.

	Non cancer patients (n=39)	Cancer patients (n=47)	Suspicious for malignancy (n=12)
Regenerative changes	3 (7.7)	1 (2.1)	0 (0)
Epithelial inflammation	16 (43.6)	19 (40.4)	6 (50.0)
Lamina propria inflammation	19 (48.7)	27 (57.5)	6 (50.0)

Table 3: Prevalence of mid esophagitis among consecutive series of endoscopy clinic patients by anatomic site of cancer.

		Mid esophagitis		
	No of subjects	None	Mild	Marked
Non cancer patients	419	380 (90.7)	25 (6.0)	14 (3.3)
Cancer patients				
Esophageal SCC	234	202 (86.4)	20 (8.5)	12 (5.1)
Esophageal adenocarcinoma	16	14 (87.5)	0 (0)	2 (12.5)
Gastric adenocarcinoma	137	124 (90.5)	7 (5.1)	6 (4.4)
Suspicious for malignancy	30	18 (60)	6 (20)	6 (20)

subjects, esophageal cancer and gastric cancer cases was observed in 3.5%, 4.6%, and 6.1% patients, respectively ($p = 0.33$).

Even after splitting esophageal cancer to adenocarcinoma and squamous cell carcinoma, the difference in presence of mid esophagitis did not reach the significance level although marked esophagitis was observed in 2 (12%) of esophageal adenocarcinoma. There was no difference in proportion of patients with esophagitis in esophageal or gastric cancer patients ($p = 0.4$).

Of the 30 patients with suspicious diagnosis for gastroesophageal malignancies 9 and 17 had suspicious esophageal and gastric lesions respectively. None of these patients were found to have cancer after rebiopsy and histological examination of the suspected lesions. After adding these patients to the non-cancer patients, the percentage of mild or marked mid esophagitis raised to 13% which was not statistically different from cancer patients ($p = 0.38$).

DISCUSSION

Clustering of ESCC in certain geographical areas of the world has attracted the attention of cancer investigators to probe different aspects of the disease with hope to elucidate the etiology and pathogenesis of this malignant neoplasm. High incidence areas in Northern Iran and China have been two of the major focal points in this regard.

ESCC is a highly malignant tumor. Most of the patients are diagnosed when in advanced incurable stages and succumb to the disease within a year after the diagnosis.[6]

A number of endoscopic surveys on asymptomatic residents in high risk areas for ESCC have been performed to look for the possible pre-neoplastic lesions of this cancer. In 1979, Crespi and Monez from International Agency for Research on Cancer (IARC) reported an 86% prevalence of "chronic esophagitis" without clinical evidence of reflux disease on the histological sections of the samples obtained from patients and asymptomatic residents of

Gonbad region.[8] Crespi and co-workers diagnosed mild esophagitis when they observed mild infiltration of lamina propria by lymphocytes, plasma cell and segmented neutrophils (PMN) and severe esophagitis was diagnosed when the infiltration was heavy associated with edema. Any inflammatory change between the two extremes was interpreted as moderate esophagitis.[8] In a similar study performed in China they also reported a rate of 84% chronic esophagitis with similar endoscopic and histologic features observed in Iran.[9]

They suggested that esophagitis could be the first step in the pathogenesis of esophageal squamous cell carcinoma progressing to atrophy, dysplasia and cancer in Northern Iran and China.[8,9] Later on, the data obtained from other endoscopic surveys from high and low risk populations challenged these observations and showed inconsistent results for the prevalence of esophagitis in relation to the occurrence of esophageal cancer.[5,12]

One of the largest and longest prospective endoscopic follow up studies that looked for the development of ESCC from Linxian China showed no evidence of association between increased risk of developing ESCC within 13.5 years after the initial diagnosis of esophagitis [relative risk 0.8 (95% CI 0.2–3.2)]. The authors suggested it is unlikely that esophagitis be an important and significant precursor lesion in this very high risk population.[5]

Our present investigation performed in the same area studied by Crespi and Monez shows a rate of only 9.3% esophagitis in mid-esophageal biopsies of non-cancer subjects which is far less than the figure of 86% reported in 1970's.

Interestingly, new information obtained from a local cancer registry set up in Gonbad area also indicates a significance decrease in the incidence rates of ESCC compared to those reported by Mahbobi and co-workers almost four decades ago.[4] The new rates for esophageal cancer are 43.4 and 36.3 per 100,000 population per year for males and females, respectively.[4] Although the possibility of misclassification of some of the cardia tumors in 1970's as esophageal squamous cancers might have occurred, the considerable decrease in incidence of ESCC can mostly be attributed to improvements in socioeconomic status including higher incomes, availability of electricity, access to safe drinking water and natural gas for heating and cooking, telephone communication and transport coverage of 98% in the urban areas and 92% in the rural areas in today's Golestan.

Changes in environmental risk factors and life style including better housing and hygiene, improvements in the processing and refrigeration of food and increased intake of fresh fruits and vegetables could also have a contribution.[4]

The decrease in the rate of histologically detected esophagitis in our study, however, is not proportional to the decrease in rate of ESCC and is significantly more prominent. Difference in the histological criteria used by the two groups might explain this difference to some extent.

The most important histological criteria for diagnosis of esophagitis used by the Crespi group were presence of the submucosal inflammation.[8,9] Today, scattered mononuclear inflammatory cells and occasional follicular clusters of lymphoid cells in the lamina propria and submucosa of the esophagus are considered as normal histological findings. Only dense non-follicular aggregation of mononuclear inflammatory cells or easily recognized neutrophils and eosinophils in lamina propria are considered as part of the histological diagnostic criteria of esophagitis.[5]

The minimum degree of the sub mucosal inflammation considered by Crespi and co-workers as a criterion for the diagnosis and grading of esophagitis is not clearly defined in their article.[8,9] It is very likely that even small

numbers of lymphocytes in lamina propria had been considered significant and this might have led to over diagnosis of esophagitis by that collaborative group.

We observed scattered mononuclear cells in lamina propria in almost all of those samples in which parts of the lamina propria were included in the biopsy. Another likely scenario is that the normal intraepithelial lymphocytes, could have been mistakenly diagnosed as PMN leukocytes by Crispi's group; due to the peculiar nuclear morphology of these so-called squiggle cells[5] they sometimes could mimic the nuclei of neutrophils. The other criterion used by Crespi for the diagnosis of esophagitis was clear cell acanthosis.[9] We did not detect this lesion in our biopsy samples and it is not accepted as a histological sign of inflammation at the present time.

We did not have the chance to review the histological sections prepared by Crespi and coworkers to re-evaluate the histological findings by the criteria we used for our diagnoses.

Chronic inflammation is considered an important risk factor and companion of cancer[13,14] and is almost always observed along with the malignant cells in different tumors of the human body. However, this could be a consequence rather the cause of cancer. Presence of neoplastic cells in any organ, including esophagus, could trigger a secondary inflammatory reaction at the vicinity or even remote from the tumor. This can be due to the reaction of cellular and humoral immune system against the tumor cells.[14]

Destruction of the native parenchymal cells and vascular channels leading to localized ischemia is the other major possible cause of inflammatory reaction. Esophageal cancer, in particular, causes obstruction and stagnation of ingested food material proximal to the site of the tumor. This leads to irritation of the mucosa and bacterial overgrowth which could also contribute in the process of inflammation.

Our recent case control study has demonstrated evidences for several predisposing conditions and etiologies for ESCC in the Gonbad area. Life style and environmental factors including, tobacco smoking, opium abuse,[12] drinking of hot tea,[15] polycyclic aromatic hydrocarbons,[16] low consumption of fresh fruit and vegetable,[17] Low socioeconomic status[18] poor oral hygiene,[19] and positive family history of ESCC[20] have been and still remain as main suspected risk factors for the development of ESCC.

Considerable changes in the life style and living environment in the last 40 years could explain the significant decrease in the rate of the disease in this area both in males and females.

In conclusion the results of our present study do not give substantial evidence for inclusion of esophagitis in the list of predisposing factors of ESCC in the Gonbad area, northeast of Iran.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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