RESEARCH ARTICLE

Gastric Cancer and Gastrointestinal Stromal Tumors Could be Causes of non-*Helicobacter Pylori* non-NSAIDs Peptic Ulcers in Thailand

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Abstract

Background and aim: *H. pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) remain the major causes of peptic ulcer disease. Nevertheless, non- *H. pylori* non-NSAIDs peptic ulcers or idiopathic peptic ulcer disease (IPUD) constitute a growing problem associated with many complications. Gastric cancer and gastrointestinal stromal tumor (GIST) have also been reported as a cause of IPUD. This study was aimed to investigate prevalence and clinical characteristics of IPUD in Thailand. **Materials and Methods:** Clinical information, histological features, endoscopic findings, history of *H. pylori* status and NSAIDs usage were collected for patients diagnosed with PUD in Thammasat University Hospital during January 2003 – December 2013. **Results:** Total of 1,310 patients was diagnosed with PUD in our institution during the study period, of which 71 (5.4%) had a definitive diagnosis of IPUD (45 men and 26 women, mean age of 59±16.5 years). Common locations were gastric antrum (43.7%), duodenum (25.3%) and gastric body (12.7%). Common causes of IPUD were idiopathic (43.7%) and alcohol consumption (39.4%). Gastric cancer and GIST were also demonstrated in 1(1.4%) and 1(1.4%) respectively. Major complications were upper GI bleeding (73.2%) and peptic perforation (2.8%). Recurrent upper GI bleeding was detected in 23.9%. Interestingly, male patients aged<50 years with alcohol related peptic ulcer were significantly more common than female patients aged ≥ 50 years (57.8% vs 7.7%;P-value= 0.00002, OR= 16.4, 95%CI= 3.5-78 and 68.4% vs 28.9%); P-value= 0.002, OR= 5.3, 95% CI= 1.7-16.7). **Conclusion:** Common causes of IPUD in Thailand are idiopathic followed by alcohol consumption and steroid usage. Gastric cancer and GIST are also possible causes of IPUD. These particular ulcers had a high likelihood of developing severe complications. Appropriate screening and high level of suspicion of fatal causes eg. gastric cancer and GIST should be appropriate ways to reduce complications and improve the treatment outcome.

Keywords: Gastric cancer- non *w*- non-NSAIDs peptic ulcer- Thailand

Asian Pac J Cancer Prev, **18 (1)**, 155-157

Introduction

Helicobacter pylori (*H. pylori*) infection is a major cause of peptic ulcer disease (PUD) worldwide and associated with gastric cancer (Srinarong et al., 2014, Piriyapong et al., 2014, Vilaichone et al., 2014 and Vilaichone et al., 2015). Nationwide survey in all regions of Thailand demonstrated the high prevalence of *H. pylori* infection (34.1%) in Thai dyspeptic patients (Vilaichone et al., 2013). Nonsteroidal anti-inflammatory drugs (NSAIDs) is another major global cause of PUD especially in elderly population (Musumba et al., 2012 and Yoon et al., 2013). However, non-*H. pylori* non-NSAIDs peptic ulcer or idiopathic PUD (IPUD) has been increasingly concerned in many parts of the world. (Adamopoulos et al., 2004, Gisbert and Calvet, 2009). Gastric cancer and gastrointestinal stromal tumor (GIST) have also been reported as a cause of IPUD. In Japan, IPUD was found in one third of PUD patients (Ootani et al., 2006), and up to 40% of PUD patients in Korea were diagnosed with IPUD (Kim et al., 2007). IPUD patients presented with more serious complications than either *H. pylori* infection or NSAIDs users, especially bleeding complication (Wong et al., 2009). In Southeast Asian countries, there had been limited studies of IPUD and the prevalence may be underestimated. We conducted this study for evaluating the prevalence and clinical characteristic of this particular ulcer in tertiary care center in Thailand.

Materials and Methods

All patients aged older than 15 years who had been diagnosed with PUD regardless the cause from *H. pylori* infection or NSAIDs use in Thammasat university hospital

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between January 2003 – December 2013 were enrolled in this study. Non-*H. pylori* non-NSAIDs peptic ulcer or IPUD were defined as gastric or duodenal ulcers diagnosed during upper GI endoscopy without history of taking aspirin, clopidogrel, and/or any NSAIDs within the prior 3 months and without evidence of *H. pylori* infection confirmed by negative rapid urease test and histology. *H. pylori* infection was excluded by negative tests both from rapid urease test and histology. Clinical information (e.g. underlying diseases, current medication, and patient's symptom), endoscopic findings and histopathology of PUD were recorded. We have excluded patients whose medical records were not completed or could not achieve all important information.

Statistical analysis

The statistical analysis was performed by using descriptive statistic to calculate patient demographic data. The clinical information, endoscopic findings, and complications were compared by Student's t-test, Chi-square test or Fisher's exact test where appropriate. The P-value <0.05 was considered as statistical significant. All statistical analyses were performed using SPSS for window version 23 (IBM Corp., Armonk, NY). This study was conducted according to the good clinical practice guideline, and was approved by our local ethics committee.

Results

A total of 1,310 patients were diagnosed as PUD in Thammasat university hospital during the study period, of which 71 (5.4%) had final diagnosis of IPUD including 45 men and 26 women with mean age of 59±16.5 years. Common presenting symptoms were upper GI bleeding (UGIB) in 52/71 patients (73.2%) and dyspeptic symptoms in 16/71 patients (22.5%). The common causes of IPUD were idiopathic (43.7%), alcohol consumption (39.4%) and steroid usage (5.6%). Gastric cancer and GIST were also demonstrated in 1 (1.4%) and 1 (1.4%) respectively. The major complications were UGIB and peptic perforation, which presented in 52/71 patients (73.2%) and 2/71 patients (2.8%) respectively, as detail in Table 1 and 2. Recurrent UGIB was detected as high as 23.9% (17/71 patients). Interestingly, one time recurrent UGIB was detected in 12/71 patients (16.9%), two times recurrent UGIB in 3/71 patients (4.2%), three times recurrent UGIB in 1/71 patients (1.4%) and four times recurrent UGIB in 1/71 patients (1.4%). In idiopathic cause of IPUD, there had recurrent UGIB in 7/31 patients (22.6%). The endoscopic findings mostly found IPUD with Forest classification III in 39/71 patients (54.9%). The common locations of ulcers were gastric antrum in 31/71 (43.7%) patients, duodenal bulb in 18/71 (25.3%) patients, and gastric body in 9/71 patients (12.7%) as described in Table 3.

Interestingly, male patients aged <50 years with alcohol related peptic ulcer were significantly more common than female patients aged ≥ 50 years (57.8% vs 7.7%; P-value = 0.00002, OR = 16.4, 95% CI = 3.5-78 and 68.4 % vs 28.9 %); P-value = 0.002, OR = 5.3, 95% CI = 1.7-16.7). Furthermore, alcohol induced peptic ulcer patients had more underlying diseases than other causes of IPUD (57.1% vs 27.9%; P-value = 0.008, OR = 3.4; 95%CI = 1.3-9.4).

Table 1. Demographic Data and Clinical Characteristic of All Patients

Sex (M: F)	45:26:00
Age (range)	59 (26-91yrs)
Underlying diseases	N=71 (%)
Diabetes mellitus	13 (18.3%)
Hypertension	18 (25.4%)
Dyslipidaemia	12 (16.9%)
Others	22 (31%)
Complications	
UGI bleeding	52 (73.2%)
Recurrent UGIB	17 (23.9%)
Perforation	2(2.8%)

Table 2. Causes of Idiopathic Peptic Ulcer Disease

Causes	N= 71(%)
Idiopathic cause	31 (43.7%)
Alcohol	28(39.4%)
Medications	
Iron supplement	2(2.8%)
Colchicine	2(2.8%)
Steroids	4(5.6%)
Herbal medicine	2(2.8%)
Gastric cancer	1(1.4%)
GIST	1 (1.4%)

Table 3. Location of Idiopathic Peptic Ulcer Disease

Location	N= 71 (%)
Cardia	2(2.8%)
Body	9(12.7%)
Antrum	31(43.7%)
Duodenal bulb	18(25.3%)
Both antrum and body	6 (8.45%)
Both stomach and duodenum	5 (7%)

Discussion

IPUD is now the upcoming problem of PUD and the global prevalence is increasing compare to *H. pylori* and NSAIDs induced PUD (Ciociola et al., 1999 and Konturek et al., 2003). In our study, the prevalence of IPUD was 5.4% which was not as high as other regions. In Thailand, IPUD patients were found in elderly patients and had higher risk of developing severe complications such as recurrent UGIB than previous studies (Chung et al., 2015; McColl, 2009). The majority of IPUD causes in our study were idiopathic and alcohol consumption whereas minority group were caused by medications. Gastric cancer and GIST were also uncommon but fatal

causes of IPUD. The ulcers were mostly located at gastric antrum, body and duodenal bulb similar to other Asian reports (Chung et al., 2015 and Yoon et al., 2013).

Many previous studies demonstrated recurrent UGIB as a major complication of IPUD (Chung et al., 2015, Hung et al., 2005, Wong et al., 2009) like our study. Most of IPUD were found to have multiple lesions and larger ulcer than *H. pylori* and NSAIDs induced PUD which explained why they had more frequent recurrent bleeding complications (Wong et al., 2009). The pathogenesis of IPUD is still in the mystery. Most of IPUD had poorer response to anti-secretory drugs, needed longer duration and higher dose of proton pump inhibitor (PPI) than *H. pylori* and NSAIDs induced PUD to promote the healing process (Chung et al., 2015 and McColl, 2009). Long-term use of PPI might be related with hypergastrinemia, gastric enterochromaffin-like cell (ECL cell) hyperplasia, which could develop gastric dysplasia and gastric cancer in animal model (Solcia et al. 1988, Solcia et al., 2000). However, there was insufficient evidence to support this hypothesis in human study.

In summary, common causes of IPUD in Thailand were idiopathic followed by alcohol consumption and steroid usage. Gastric cancer and GIST were also possible causes of IPUD. These particular ulcers had high likelihood of developing severe complications such as recurrent upper GI bleeding. Appropriate screening of patients at risk and high level of clinical suspicion of fatal causes of IPUD eg. gastric cancer and GIST should be appropriate ways to reduce complications and improve the treatment outcome

Acknowledgements

This study was partially supported by National Gastric Cancer and Gastrointestinal diseases Research Center of Thailand and the National Research University Project of Thailand Office of Higher Education Commission.

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