Helicobacter Pylori Eradication can induce platelet recovery in chronic refractory idiopathic thrombocytopenic purpura

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Summary: The prevalence of Helicobacter pylori infection and the effect of its eradication on platelet count in 95 Iranian patients with chronic refractory autoimmune thrombocytopenic purpura (CRITP) was investigated. 69 of 95 patients were infected with H.pylori (72.6%). H.pylori eradication was obtained in 69 infected CRITP patients who were not in remission and had platelet count below 100×10^9 at the time of infection assessment. 4 patients failed to eradicate of H.pylori. During follow-up (median 22.5 months). 3 of 33 of responsive patients relapsed after 14 months of eradication. 30 of 65 H.pylori-eradicated patients (46%) showed a significant increase in platelet count accompanied by a significant decrease of platelet-associated immunoglobulin G (IgG). In forteen patients without H.pylori infection, platelet counts did not significantly increase with the same treatment. On the other hand, eradication therapy did not affect platelet counts in 6 patients with gastric ulcer. This response was maintained in all responding patients throughout the follow up period.

The assessment of H.pylori infection and its eradication shoud be attempted in CRITP as this approach could be an effective strategy, at least for some of these patients.

Keywords: chronic refractory idiopathic thrombocytopenic purpura. (CRITP) Helicobacter pylori, eradication therapy

Introduction:

Helicobacter pylori has been conclusively linked to different forms of gastritis, as well as to peptic ulcer diseases of the stomach and duodenum gastric adenocarcinoma and mucosal-associated tissue lymphoma.(1) The chronic inflammation induced by H.pylori upsets gastric acid secretory physiology to varying degrees and leads to chronic gastritis which, in most individuals is asymptomatic and does not progress. In some cases, however, altered gastric secretion coupled with tissue injury leads to peptic ulcer disease, while in other cases, gastritis progresses to atrophy, intestinal metaplasia, and eventually gastric carcinoma or rarely, due to persistent immune stimulation of gastric lymphoid tissue, gastric lymphoma.(2,3) Immunological response to H.pylori infection has been suggested to play a major role in determining gastro-duodenal damage through the production of cytokines and the autoantibodies against gastric epithelial cells.(4, 5) H.pylori has been implicated in the pathogenesis of some autoimmune disease, such as Sjogren's syndrome(6) and Schonlein -Henoch purpura.(7) A B-cell response to H. pylori with production of IgG and IgA antibodies ocures locally in the gastroduodenal mucosa and systemically.(8) Prolonged stimulation of gastric B-cells by activated T-cells can lead to immune stimulation and irregulation it, can lead to autoimmune diseases and MALT lymphoma in rare cases.(8,12) Several lines of direct and indirect evedence suggest that infectious agents may influence the occurrence or course of some auto-immune diseases.(9,10) Two Italian groups studies disclosed a close linkage of H.pylori infection to idiopathic thromocytopenic purpura (ITP).(12,13) They demonstrated a successful improvement of after eradication of H. pylori. We read with interest the report of Kyuhei Kohda et al (2002)(14) dealing with the result they obtained by eradication ITP. However, these studies(14,15) included relatively small number of no refractory ITP patients to immunosupprasive therapy,(12 of 30) and follow-up periods after eradication of H. pylori were relatively short (14.8 months). Furthermore, and some patients (a second group) had secondary thrombocytopenia such as autoimmune hemolytic anemia, hyperthyroidism, non-hodgkin's lymphoma, polymyosits, unclassified collagen disease and sarcoidosis. Because of the bacterium's high genetic diversity and variability of host immune response to bacterium,(11) therefore, we investigated the prevalence of H.pylori infection and the effect of its eradication in slightly larger number of chronic ITP patients (who refractory to immunosupressive agents with full dose for more than 12 months treatment), over a longer observation period (median 24 months).

Patients and method:

Ninty Five patients with chronic refractory ITP who attended the sayed-al Shohada medical center (Esfahan university of medical siencess; Esfahan; Islamic Republic of Iran) between September 1995 and Julay 2002, were evaluated. The patients in-

cluded 29 men and 66 wemen with a mean age of 32.5 years (range 18-71y). ITP was defined as idiopathic thrombocytopenic (platelets<100×10^9/l) (Figure 1) with positive platelet-associated immunoglobuline G (PAIG), when other causes had been excluded, without megakariocytic hypoplasia in the bone marrow.

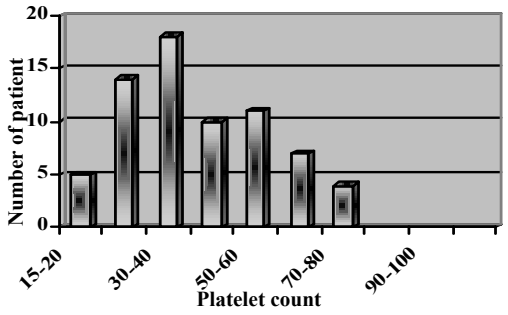

Figure 1. Platelet count of 69 patients with CRITP and H.pylri infection.

Further investigations to exluded secondary thrombocytopenia and correct diagnosis of ITP acording to Bussell.J.B. approaches[10] were done. All paients treated previously with immunosuppressive agents with high dose more than 12 months, and in 14 of those patients splenoctomy were performed but without clearly response.

All patients denied having any specific gastrointestinal symptom or having used antisecretory drugs. H. pylori infection was assessed by C 13 urea breath test (Helicobacter test) infai.Bochum .Germany), detection of serum antibodies IgG, IgM, and IgA (indirect immunofluorescence) and whenever possible, by histologic examination (Giemsa stain) of specimens obtained by an upper gastrointestinal endoscopy (17 cases). 69 of 95 patients were demonstrated for H.pylori infection (72.6%). All immunosuppressive treatment were withdrawn 1 month befor eradication H.pylori.

The sixty Nine infected patients who were H.pylori positive and not in remission (platelet<100×10^9/l) (Figure 1) were assigned to the eradication therapy group immediately after assessment of infection, when informed consent had been obtained. Twenty six patients who were H.pylori negative and not in remission were followed up and in forteen cases of them eradication therapy were done as a control group. Patients (with H.pylori infection) who were not response to treatment Immunosupresive agents (at least 12 months treatment) were stoped treatment and only treated by H. pylori eradication, and followed up for at least 22.5 months.

H. pylori eradication was performed with quadruple therapy consisting of an Amoxicillin (1000mg twice daily), Bismuth subcetrat 240mg (120mg, 2 tablets) QID, Omeprazol 20mg BID, high dose metronidazol 500mg QID, for 10 days.

Outcome definitions:

Helicobacter pylori infection was cured in 59 of 65 patients (93.2%). Thus, 12 men and 47 women, mean age 37.5 years (range 19-68 y), in whom H. pylori infection was cured eligible for evaluation, and 6 patients 1 man 43 years of age and 5 women (mean ages 36.4 y) whom H. pylori infection was not cured were excluded from this study and trated with another methods.

Eradication was assessed by either the negative urea breath test or the negative rapid urease test and confirmed by histology over 2 months after completion of eradication. 33 of 65 (50.8%) patients were defined as an increased platelet count to above 150×10^9/l after four months of eradication (Figure 2). 27 of 33 patients increased platelet above 200×10^9/l. In forteen patients (control group) without H. pylori infection, platelet counts did not significantly increase with the same treatment. On the other hand, eradication therapy did not affect platelet counts in 6 patients with gastric ulcer.

Results:

Prevalence of H.pylori infection in patient with chronic refractory ITP:

H. pylori infection was found in 69 of 95 chronic refractory ITP patient (72.6 %). The prevalence of H.pylori infection of CRITP patients of age>40 years and age<40years was 89.3% (47 of 54) and 53.7% (22 of 41) respectively. There was no defference in age, sex or previous treatment between infected and uninfected patients. All patients were undergoing immunosuppressive therapy befor the time of infection assessment and descovered but these therapy stoped one month befor H.pylori eradication when started.

Platelet response to eradication therapy:

33 of 65 patients (50.8%) responded well to eradication treatment after 4 months (Figure 2).

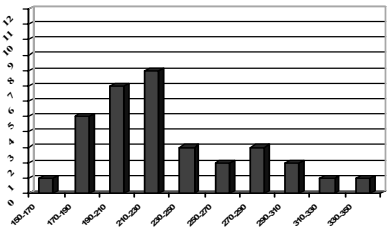

Figure 2. Platelet count in 33 patients with CRITP and H.pylori infection after four months of eradication therapy.

Platelet count in prepheral blood evauated every 15 days after eradication of H.pylori. A response of platelet recovery to H.pylori eradication was defined as increased platelet count to above 150×10^9/l after eradication. 4 of 65 patients showed a partial response (platelet count not higher than 120×10^9/l. The follow-up study, performed for a median 22.5 months range (19-32 m). 3 of 33responsive patients relapsed after 14 months of eradication. In this study showed that 30 of 65 patients (40%) had a significant increase in platelet count after of 22.5 months of eradication of H.Pylori. The patient count was gradually elevated within 2 months of eradication therapy and after four months was maitained above 150×10^9/l in 33 responding patients and in other 4 patients platelet count were between 100-120×10^9/l. There were 3 relapsed seen at 14 months of the follow up period, there patients had not any evidence of secondary infection with Helicobacter pylori.

Statistical analysis:

Statistically significant differences of age, sex, disease duration, and platelet count between H.pylori-positive patients (69 cases) and H.pylori-negative patients (14 cases) were determined by the Fisher Exact–test.

P-Value<0.005. Statistically significant differences in PAIgG level befor and after eradication were analysed by Wilcoxon singed-rank sum test. A P value<0.05 was considered to be statisticaly significant in all these tests.

Discution:

H. pylori has been shown to cause immonological responses with the production of large amounts of pro-inflammatory substances and mucosal damage through auto-immunity (Banford & Andersen 1997, 2,3,11). The rate of some bacterial or viral agents in cause of ITP is well known. It has been demonstrated that the mimicry of human antigens by infection agents represents the mechanism underlying this phenomenon.

Gasbarrini et al (1998) first reported that 61% of 18 ITP cases with H.pylori was eradicated showed significant increases in mean platelet count after 2 and 4 months with disappearance of anti-platelet antibody.Emilia et al (2001)[13] then reported that 43% of 30 ITP patients were H.pylori positive and 50% of 12 eradicated patients showed platelet recovery. The prevelence of H.pylori infection in our series was 72.6% (89.3% in age>40 years and 53.7% in age<40). This appeared to be some what higher than the prevalence of H.pylori in other studies.[13, 14, 15 and 16] In respect to the only nonanecdotal report of the literture by Gasbarini et al,[12] we observed, in our series of ITP patients, a higher prevalence of H.pylori infection (72.6% vs 61.11%) and a lower frequency of platelet response to the eradication (46% vs 72.72%). More over, only 40% of our patients achieved a complet remission versus 100% of eradication patients in the above mentioned report, even though eradication has been obtained in a simelar percentage of patients (93.2% vs 100%). We followed our patients for a median of 22.5 months, versus a maximum of 4 months in the study by Gasbarini et al. This allowed us to document a relapse of ITP in 3 after 14 months of H.pylori eradication. In our study the patients were not new patients an treated previosly with multi-drugs immunosuprassive whom relapsed and resistant ITP patients. Finally, variety in the frequency of H.pylori– associated ITP and in the rate of platelet response to bacterium eradication may be related either to the variability of host immune response to H.pylori or to the bacterium's high genetic diversty, ie, to the existence of different H.pylori strains with possibly differenet pathogenic potentiol. In conclusion, even though the pathogenetic mechanisms of H.pylori induced thrombocytopenia remain abscure, the search for H.pylori infection and an attempt to eradicate bacterium in positive cases appropiate in ITP patients at diagnosis. This approach may be a new good option a nonimmunosuppressive treatment. At least some ITP patients. Further investigations on a large number of patients, with a long follow-up, might allow3 a better definition of the true prevalence of H.pylori infection and the duration of the effect of its eradication in ITP patients.

The mean platelet count in immunotherapy period before eradication therapy in 65 patients

3 months before eradication therapy	6 months before eradication therapy	9 months before eradication therapy	End of immunosuppressive
40000/mm	Mean= 31000/mm	Mean= 18000/mm	Mean= 16000/mm

Table 2, The mean platelet count in 19 patients were splenectomy performed.

10 months after splenectomy	8 months after splenectomy	6 months after splenectomy	4 months after splenectomy	2 months after splenectomy
32000/mm	30000/mm	38000/mm	50000/mm	65000/mm

Table 3: Mean platelets count in 26 patients who were H. pylori negative and not in remission were treated with immunosupressive therapy (26cases) and 14 cases of them eradication therapy were done (as two control groups). mo=month

Groups of patients with H.pylori Negative	After 2 mo.	After 4 mo.	After 6 mo.	After 8 mo.	After 10 mo.	After 12 mo.
Immunosupressive therapy. 26 cases.	32	38	35	28	33	30
Eradication therapy 14 cases	26	35	24	28	25	26

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