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Original Article

Endoscopic and histopathological features of Tibetans with high-altitude polycythemia

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Abstract: Aim: To evaluate endoscopic and histopathological features of upper gastrointestinal lesions in Tibetans with high altitude polycythemia (HAPC). Methods: Twenty-two native Tibetans with high altitude polycythemia (HAPC) and 24 healthy controls who lived on the Tibet Plateau at an average altitude of between 3650 m to 4800 m, were randomly selected and enrolled. Gastroscopy was performed in both groups. Mucosal biopsies of the gastric antra were carried out and both histopathological changes and ultrastructural characteristics were observed. Results: Endoscopic findings showed significant greyscale values for color of the upper gastrointestinal mucosa compared with that observed in the control group, with evident mucosal hyperemia and edema. The number of micro-vessels in the gastric mucosa, the average diameter of blood vessels, and the number of red blood cells inside micro-vessels and the incidence of inflammatory lesions in the gastric mucosa was significantly higher, including cases of intestinal metaplasia in the high altitude polycythemia group compared with those in the control group. Transmission electron microscopy revealed markedly impaired epithelial cell structures of the gastric mucosa in the high altitude polycythemia group, compared with the control group, in which the epithelial cell structure of the gastric mucosa appeared normal (90.9% vs 8.3%, $p < 0.001$). Conclusions: High altitude polycythemia has characteristic morphological and pathological tissue changes including obvious microcirculation disturbance of the gastric mucosa, significantly damaged structure of the gastric mucosa, and severe and widespread inflammation. This study provides basic information on effects of high altitude polycythemia on the upper gastrointestinal tract.

Keywords: High altitude polycythemia, upper gastrointestinal tract, gastric mucosa, histopathological structure, endoscopy

Introduction

The Tibetan plateau is a special ecological environment, characterized by low atmospheric oxygen partial pressure, low atmospheric pressure, a low mean daily termperature, a low temperature difference between day and night, and a long cold winter [1]. Various altitude sickness syndromes are major health problems for individuals living on the plateau [1]. Among them, high altitude polycythemia (HAPC) is the most common chronic mountain sickness (CMS) [2], and can have many detrimental and severe effects on various body systems. Long-term high-altitude hypoxia can cause varying degrees of damage to the human digestive system. Upper gastrointestinal lesions are commonly caused by HAPC in the Tibetan population [1, 3]. Patients often complain of abdominal pain, abdominal distention, acid reflux, nausea, poor appetite or loss of appetite, and sometimes, hematemesis and melena. Clinically, lesions can be slow healing, predisposed to relapse, and difficult to cure. The effect of the special plateau environment and how it affects the structure and physiological function of the gastrointestinal mucosal barrier of the human digestive system, is not clear. The aim of the

current study was to accurately record endoscopic and histopathological findings of upper gastrointestinal lesions in patients with HAPC.

Materials and methods

General information

Subjects were randomly included from Departments of Mountain Sickness and Gastroenterology in our Tibetan Autonomous Region People's Hospital (Lhasa, China) from October 2012 to June 2014. HAPC is defined by the 2004 Qinghai International High Altitude Medicine Conference as hemoglobin (Hb) concentration ≥21 g/dl (male) and ≥19 g/dl (female) [4]. Twenty-two patients, that lived on the Tibetan Plateau at an average altitude of between 3600 to 4800 m, with a definite diagnosis of high altitude polycythemia (HAPC) were enrolled in the HAPC group, and all had symptoms that justified gastroscopy. In addition, 24 healthy Tibetans living at the same altitude, who had voluntary medical screening requirements (screening to eliminate the upper digestive tract disease) for gastrointestinal endoscopic examination during the corresponding period, were considered as a control group. All subjects were from Lhasa, Naqu, Shannan, and Rigaze in Tibet and all of them were indigenous and had lived in their regions for at least 30 years. Their places of residence, customs and culture, lifestyle and diet were very similar.

Questionnaire design

General information and lifestyle of subjects were acquired by questionnaires, including physical examinations by physicians from the Endoscopy Department of the People's Hospital of Tibet autonomous region, Tibet, China. Before endoscopy, peripheral venous blood was sampled for blood routine tests in order to clarify whether people had HAPC. Pulse oximetry was used to measure the oxygen saturation of arterial blood. The inclusion criterion for the study was: the presence of HAPC as defined by the 2004 Qinghai International High Altitude Medicine Conference [4]. Exclusion criteria were: 1 Chronic pulmonary diseases: emphysema, bronchitis, bronchiectasis, alveolar fibrosis, lung cancer and other serious pulmonary diseases. 2 Chronic respiratory disorders or secondary polycythemia due to hypoxemia caused by certain chronic diseases. 3 Severe diseases of the heart, brain, lungs, liver, kidneys, endocrine system and hematopoietic system. 4 Alcohol abuse, drug addiction, use of NSAIDs, poor mental health or other conditions inappropriate for gastroscopy. 5 Pregnant or lactating women. 6 Obstructed gastrointestinal tract. The diagnosis of chronic gastritis was made according to the Chinese Consensus on Chronic Gastritis, formulated in Shanghai in 2006 [5]. The histopathological diagnosis was based on the Operative Link on Gastritis Assessment (OLGA) staging system [5]. This study was approved by the Tibet Autonomous Region Hospital's Institutional Review Board, and signed informed consent was obtained from all study subjects before enrolment in the study.

The infection status of Helicobacter pylori (H. pylori) for all subjects was determined by a C^{14}-urea breath test (C14-UBT) before gastroscopy. HAPC assessment using 10 mL of viscous lidocaine hydrochloride Mucilage (Jiangsu Ji-chuan Pharmaceutical Co., Ltd., China) was orally administered to study subjects. A gastroscope (OLYMPUS GIF-260) was used for examination. All of the subjects were examined, and the photos of the upper gastrointestinal tract were taken using the same model of endoscope by an experienced endoscopist. The tract photos were collected, and then converted into tif format. Three positions of the tract photo without light spots were selected to calculate the mean grayscale value, which refers to the degree of shade of color. The color image ratios of R, G, B (3:6:1) refer to a weighted transformation into black and white image pixel value by a gray level difference analysis method IMAGE J (Image processing software, Institutes of National Health), and expressed as INT [Integrated Density] (value) per mm^2. The color of esophageal, gastric and duodenal mucosal lesions were carefully assessed. The color changes of the upper gastrointestinal mucosa for patients with HAPC were obtained by direct endoscopic observation. Photos were taken of the upper gastrointestinal tract, including the esophagus, cardia, gastric fundus, gastric antrum and body, the duodenal bulb and the descending portion. Endoscopic mucosal biopsy was performed in all subjects. Two specimens of antral mucosa from the lesser and greater curvatures in each subject were collected randomly. After that, the specimens were immediately put into 2 ml 4% paraformaldehyde for fixation for 2 h. Afterwards, one of the two specimens was trans-

Table 1. Clinical Symptoms of Study Subjects

Variable	Cases n=22	Controls n=24	*P* value
Poor appetite or loss of appetite	7 (31.8)	2 (8.3)	P < 0.05
Abdominal distention	13 (59.1)	4 (16.7)	P < 0.05
Abdominal pain	11 (50.0)	4 (16.7)	P < 0.05
Acid reflux	7 (31.8)	3 (12.5)	P < 0.05
Heartburn	6 (27.3)	2 (8.3)	P < 0.05
Nausea	2 (9.1)	1 (4.2)	P > 0.05
Vomiting	1 (4.5)	1 (4.2)	P > 0.05
Hiccups	1 (4.5)	1 (4.2)	P > 0.05
Hematemesis	1 (4.5)	0 (0.0)	P < 0.05
Melena	3 (13.6)	0 (0.0)	P < 0.05

Table 2. Characteristics of Study Subjects

Variable	Cases n=22	Controls n=24	*P* value
Age (yr)	46.90±6.40	47.46±6.67	P > 0.05
Gender			
Male	20 (90.9)	19 (79.2)	
Female	2 (9.1)	5 (20.8)	P > 0.05
Place of residence			
Altitude of 3650 m	8 (36.4)	11 (45.8)	
Altitude of 4800 m	14 (63.6)	13 (54.2)	P > 0.05
Clinical biomarkers			
WBC (10^9/L)	6.11±1.30	5.55±0.96	P > 0.05
RBC (10^{12}/L)	7.31±0.68	5.42±0.35	P < 0.001
Hb (g/L)	239.7±10.71	154.7±13.57	P < 0.001
HCT (%)	68.81±3.95	46.53±3.47	P < 0.001
PLT (10^9/L)	109.13±34.36	214.7±40.68	P < 0.001
SaO2 (%)	80.3±1.21	90.9±1.20	P < 0.001
H. pylori infection			
C^{14}-UBT	18 (81.8)	16 (66.7)	P < 0.05

WBC: white blood cell. RBC: red blood cell. Hb: hemoglobin. HCT: hematocrit. PLT: platelet. SaO2: oxygen saturation of blood. C^{14}-UBT: C^{14}-urea breath test.

ferred to 3% glutaraldehyde for pre-fixation, and further subsequent electron microscopic examination.

Paraffin embedding, HE staining, and histopathological observations

The specimen underwent 5 μm slicing, gradient ethanol dehydration, hematoxylin-eosin (HE) staining, and neutral gum mounting [6]. Under a 400X high magnification microscope, blood vessels and red blood cells inside micro-vessels were counted manually, and the diameter of five vessels were randomly observed and measured. All the results were judged by a pathologist who was blinded to the clinical data i.e. case or control.

Sample preparation for electron microscopy, ultrathin section production, and electron microscopy observation

The preserved samples were pre-fixed in 3% glutaraldehyde, followed by 1% osmium tetroxide fixation, with gradual dehydration in gradient acetone, before Epon812 embedding, optical positioning of semi-thin sections, slicing of ultrathin sections, and double staining with both uranyl acetate and citrate lead [7]. Finally, the sections were photographed by a transmission electron microscope (Hitachi H-600IV).

Statistical analysis

All the data were analyzed with SPSS 13.0 statistical software. Quantitative data were expressed as mean ± standard deviation (SD) and qualitative data were subject to the analysis of variance (ANOVA). A two-tailed *p* value less than 0.05 was considered statistically significant.

Results

Clinical symptoms in HAPC patients and healthy control group

The main complaints of HAPC patients were poor appetite or loss of appetite (31.8% vs 8.3%, p < 0.05), abdominal distention (59.1% vs 16.7%, p < 0.05), abdominal pain (50.0% vs 16.7%, p < 0.05), acid reflux (31.8% vs 12.5%, p < 0.05), heartburn (27.3% vs 8.3%, p < 0.05), hematemesis (4.5% vs 0.0%, p < 0.05), melena (13.6% vs 0.0%, p < 0.05) and these were significantly higher than those in the control group. There were no statistically significant differences in symptoms of nausea (9.1% vs 4.2%, p > 0.05), vomiting (4.5% vs 4.2%, p > 0.05) or hiccups (4.5% vs 4.2%, p > 0.05) between the two groups (**Table 1**).

Physiological indicators in HAPC patients and healthy control group

In this study, gender (male, 90.9% vs 79.2%, p > 0.05), age (46.90±6.40 yr vs 47.46±6.67 yr p

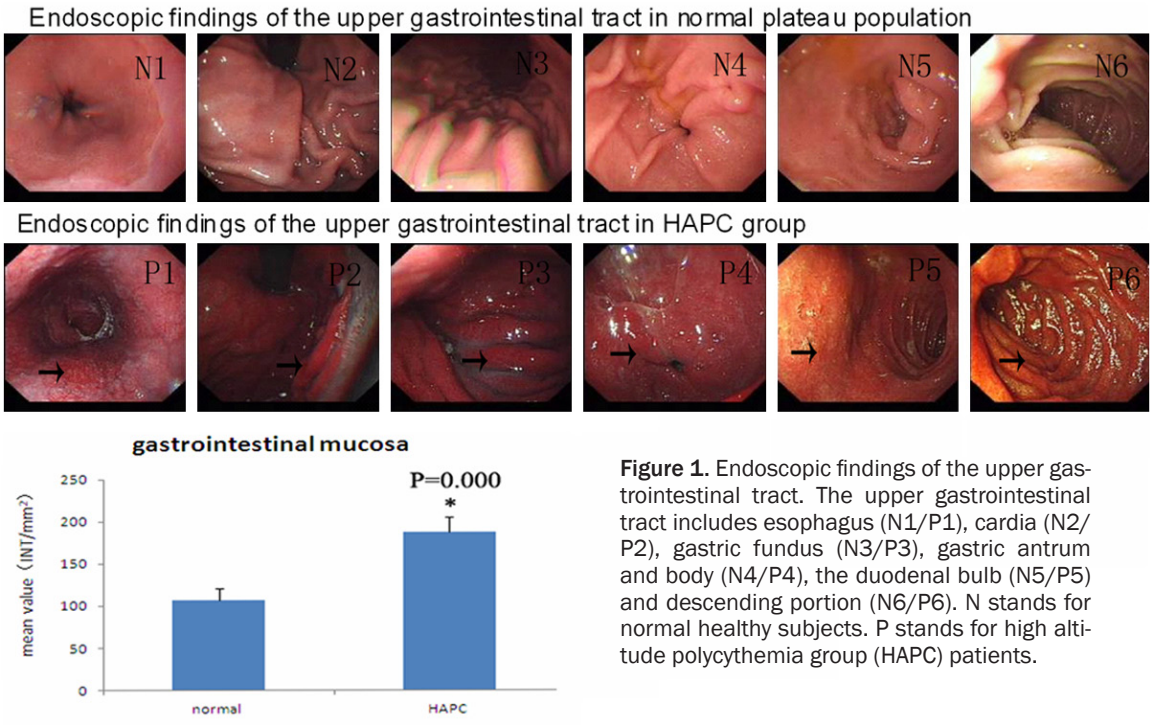

Figure 1. Endoscopic findings of the upper gastrointestinal tract. The upper gastrointestinal tract includes esophagus (N1/P1), cardia (N2/P2), gastric fundus (N3/P3), gastric antrum and body (N4/P4), the duodenal bulb (N5/P5) and descending portion (N6/P6). N stands for normal healthy subjects. P stands for high altitude polycythemia group (HAPC) patients.

> 0.05), and place of residence (3650 m, 36.4%, 4800 m, 63.6% vs 3650 m, 45.8%, 4800 m, 54.2%, p > 0.05) were non-significantly different between the HAPC group and the control group. In the HAPC group, red blood cell (RBC) ($7.31\pm0.68\times10^{12}$/L vs $5.42\pm0.35\times10^{12}$/L) counts, hemoglobin (Hb) (239.7±10.71 g/L vs 154.7±13.57 g/L) and hematocrit (HCT) (68.8±3.95% vs 46.5±3.47%) were significantly higher than those in the control group ($p < 0.001$), while the oxygen saturation of blood (SaO2) (80.3±1.21% vs 90.9±1.20%) and platelet (PLT) ($109.1\pm34.36\times10^{9}$/L vs $214.7\pm40.68\times10^{9}$/L) counts were significantly lower than those in the control group ($p < 0.001$). No statistically significant difference in white blood cell (WBC) ($6.11\pm1.30\times10^{9}$/L vs $5.55\pm0.96\times10^{9}$/L) counts was observed ($p > 0.05$). The C^{14}-UBT showed that the rate of infection of H. pylori in HAPC patients was significantly higher than that of the control group (81.8% vs 66.7%, $p < 0.05$) (**Table 2**).

Endoscopic findings of the upper gastrointestinal mucosa

In the HAPC group, endoscopic findings commonly showed a significant greyscale value in the upper gastrointestinal mucosa compared with that observed in the control group (187.75±18.11 vs 107.11±13.19, $p < 0.01$), with evident mucosal hyperemia and edema. This includes the esophagus (N1/P1), gastric fundus (N2/P2), gastric body (N3/P3), gastric antrum (N4/P4), duodenal bulb (N5/P5), and descending duodenum (N6/P6). The color of the esophageal mucosa was dark red, compare to pink in the control group. Moreover, in the HAPC group, the mucosa was thin and red and a fine meshwork of vessels could be observed under the mucosa as cord-like and branch-like structures. Furthermore, congestion was detected in areas where veins were slightly wider. In addition, due to the significantly deepened pink appearance of the esophageal mucosa, there were no evident boundaries that could be distinguished between esophageal mucosa and gastric mucosa. The color was orange below the Z-line line. In the HAPC group, the color of the gastric mucosa was deeper and darker, mainly manifesting as a dark red, red-purple, and diffuse hyperemia and edema as well as obvious changes of congestion, were observed. Also, in the bulb and descending part of the duodenum in the HAPC group, the mucosal color was significantly browner and resembled a brownish red color compared to the control group. In addition, the villi of the duodenal bulb were slightly enlarged with marked hyperemia and swelling (**Figure 1** and **Table 3**).

Table 3. Endoscopic and Histopathological Findings of the Upper Gastrointestinal Mucosa

Variable	Cases n=22	Controls n=24	*P* value
Endoscopic findings			
Esophageal mucosa dark red	22 (100.0)	2 (8.3)	P < 0.001
Esophageal veins congested and slightly wider	20 (90.9)	2 (8.3)	P < 0.001
Gastric mucosa deeper and darker red	22 (100.0)	3 (12.5)	P < 0.001
Gastric mucosal hyperemia and edema	19 (86.4)	5 (20.8)	P < 0.001
Duodenal mucosa browner	17 (77.3)	0 (0.0)	P < 0.001
Duodenal villi slightly enlarged and hyperemic and swollen	17 (77.3)	0 (0.0)	P < 0.001
Pathological manifestations			
Changes in gastric mucosal vascular tissue	20 (90.9)	2 (8.3)	P < 0.001
Number of vessels in the gastric mucosa	24.68±4.38	11.79±2.43	P < 0.001
Average diameter of vessels in the gastric mucosa	3.92±1.15	1.59±0.45	P < 0.001
RBC counts in the gastric mucosa	160.91±62.53	30.33±15.98	P < 0.001
Gastric mucosal inflammation	21 (95.5)	7 (29.2)	P < 0.001
Gastric mucosal atrophy	9 (40.9)	2 (8.3)	P < 0.05
Gastric mucosal intestinal metaplasia	7 (31.8)	1 (4.2)	P < 0.05
Changes of gastric mucosal ultrastructure	20 (90.9)	2 (8.3)	P < 0.001

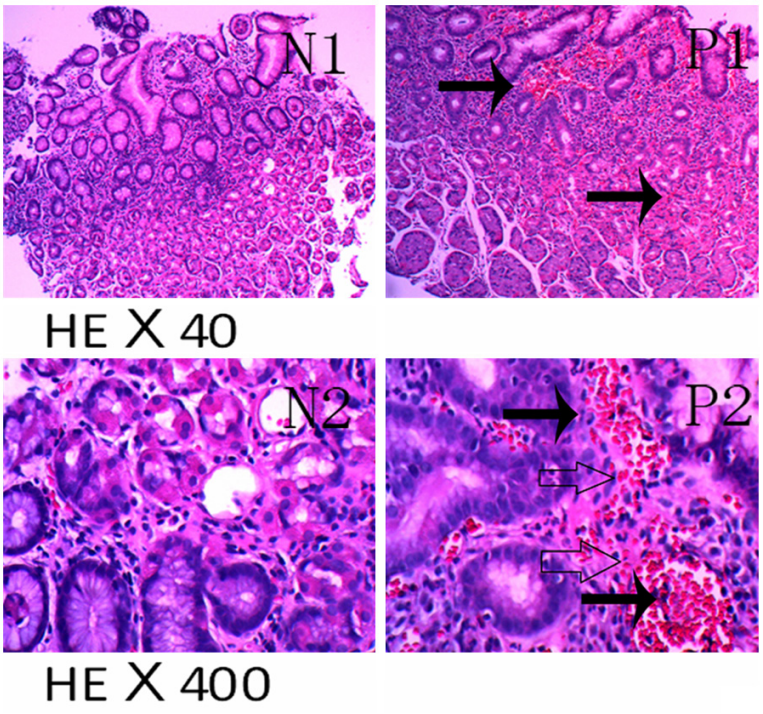

Figure 2. Histopathological findings of the gastric mucosa in the high altitude polycythemia group. The black arrows indicate red blood cells distributed in vessels while the open arrow indicate red blood cells distributed in interstitial spaces in the gastric mucosa of high altitude polycythemia patients. N1 and N2 are from normal subjects and P1 and P2 are from HAPC patients.

Changes in vessel counts in the gastric mucosa, average vessel diameter, and RBC counts

Under low magnification microscopy, in the HAPC group, a variety of changes in vessels within the gastric mucosa were observed such as dilation and distortion accompanied by hyperemia and bleeding which was statistically different from the control group (90.9% vs 8.3%, p < 0.001). Under high magnification, in sections of the gastric mucosa, the number of vessels per high power field was statistically significant between the groups (24.68±4.38 vs. 11.79±2.43, p < 0.001). Results of the statistical analysis for average vessel diameter showed that in sections of the gastric mucosa, the average vessel diameter per high power field in the HAPC group was significant higher than that in the control group (3.92±1.15 vs. 1.59±0.45, p < 0.001). Results of the statistical analysis for RBC counts showed that in sections of the gastric mucosa, RBC counts in the HAPC group were higher than those in the control group (160.91±62.53 vs. 30.33±15.98, p < 0.001) (**Figure 2** and **Table 3**). Histopathological findings of the gastric mucosa designated N1 and N2 were from normal subjects, and P1 and P2 were from HAPC patients.

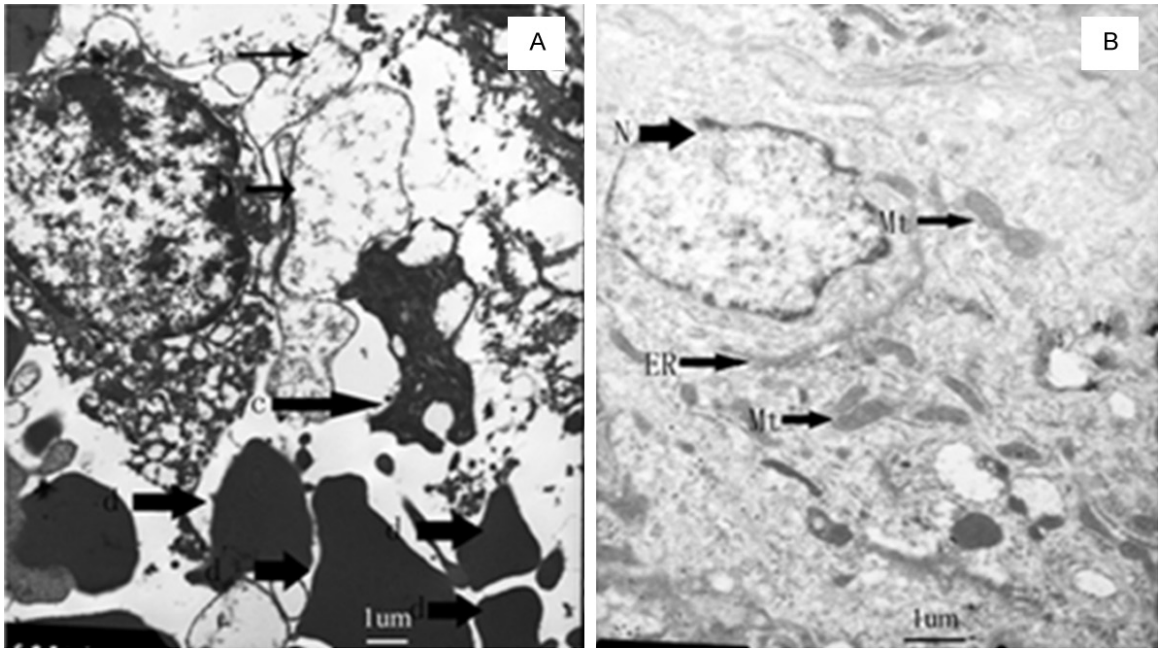

Figure 3. Ultrastructure of the gastric mucosa in the high altitude polycythemia group. Double staining of both uranyl acetate and lead citrate ×10 000. Transmission electron microscopy of epithelial cells of the gastric mucosa in high altitude polycythemia group (A), swelling of endoplasmic reticulum (a), mitochondria edema and the loss of the ridges (b), pyknosis (c), hemorrhage (d); control group (B), epithelial cell structure of the gastric mucosa: the endoplasmic reticulum (ER), nuclei (N), mitochondria (Mt).

Changes in gastric mucosal structure

By light microscopy, after HE staining, gastric mucosal inflammation was widespread and severe (95.9% vs 29.2%, $p < 0.001$) in HAPC subjects. Atrophic antral gastritis (mild to moderate) (40.9% vs 8.3%, $p < 0.05$) accompanied by intestinal metaplasia (31.8% vs 4.2%, $p < 0.05$) was significantly more common in the HAPC group compared to controls. Transmission electron microscopy revealed various degrees of expansion in the endoplasmic reticulum, and mitochondrial swelling in epithelial cells of the gastric mucosa in the HAPC group. In addition, parts of epithelial cells disappeared and demonstrated development of vacuolar degeneration and intracellular micro-cysts. Parts of the cell nuclei were damaged. Intestinal metaplasia of the microvilli was observed on the surface of epithelial cells. In contrast, in the control group, the epithelial cell structure of the gastric mucosa appeared normal (90.9% vs 8.3%, $p < 0.001$) (**Figure 3** and **Table 3**).

Discussion

The Qinghai-Tibetan Plateau is the largest and highest plateau, and contains the largest resident high plateau population in the world [1]. Due to an abnormal increase in RBC, there is a significantly increased blood viscosity and systemic microcirculation disturbances. HAPC can affect almost every organ system, but has the greatest influence on the respiration, circulation, nerve, blood and digestive system [1]. However, no effective prevention and control measures have yet been identified [1, 3]. In general, the incidence of HAPC increases with the elevation of altitude. However, because of differences in living environments, place of residence, altitude differences, and diverse ethnic groups, the incidence of HAPC is uneven around the world [8-10]. Significant ethnic differences and individual predispositions have been confirmed in different populations [11-13].

The pathogenesis of HAPC is complex. Previously, it had been widely believed that increased synthesis and release of erythropoietin (EPO), induced by long-term exposure to high-altitude hypoxic conditions stimulates bone marrow erythropoiesis, which is a key factor in the development of HAPC [14, 15]. In the current study, Hb concentration, RBC counts, and hematocrit (HCT) in the HAPC group were significantly higher than those in control group.

This was also in line with the notion that the initiating factor of HAPC was the high-altitude hypoxia-induced enhancement of bone marrow erythropoiesis, which induced RBC hyperplasia and related clinical manifestations. There was no significant difference in white blood cell (WBC) counts detected between the two groups, suggesting that high-altitude hypoxia might have no significant effects on bone marrow leukocytes. However, it was found that platelet (PLT) counts in the HAPC group were lower than those in control group. It is not clear if this observation is related to the decline in platelet regeneration caused by severe high-plateau hypoxia. In addition, the oxygen saturation of arterial blood in the HAPC group was significantly lower than that in control group, which was more or less consistent with previous reports [16-19], showing that this might be associated with excessive RBC hyperplasia as well as increased blood viscosity and flow resistance in HAPC patients [1].

In this study, HAPC patients often have abdominal pain, distension and many other digestive symptoms. In the current study, patients with HAPC showed characteristic morphological changes. Studies have shown that in the presence of high-altitude hypoxia, the dynamic equilibrium between in vivo nitric oxide and endothelin is broken, causing enhanced vasoconstriction and increased systemic peripheral resistance. This leads to the dilation of mucosal vessels. Meanwhile, high-altitude hypoxia-induced HAPC caused increased blood viscosity, slow blood flow, and severe local mucosal congestion, resulting in severe vascular hyperemia and even rupture. As a consequence there was microcirculation disturbance of the gastric mucosa [20, 21]. Considering the environment which contributes to long-term high-altitude hypoxia, secondarily increased numbers of RBC could cause damage to the gastrointestinal mucosa and might compromise normal physiological functions such as digestion and absorption.

Additionally we also found that in the HAPC group, the rate of chronic gastritis was higher than that in control group. Gastric atrophy and intestinal metaplasia was also evidently higher than those in control group. HAPC patients showed characteristic ultrastructural changes. Previous studies have speculated that the reasons for gastric mucosal lesions of HAPC patients might be due to long-term chronic hypoxia, local gastric mucosal congestion, microcirculation disturbance, accumulation of metabolites, and local mucosal malnutrition, which compromises the function of metabolism and regeneration of mucosal epithelial cells. This may result in severe damage to the mucosal barrier after a long period [22-24]. In the current study, the H. pylori infection rate in the HAPC patients was significantly higher than that of controls. Of course, H. pylori infection is also an important cause of gastric mucosal inflammation, and may have contributed to some of the findings. Thus, in HAPC patients, the weakened function of protection and restoration in the gastric mucosal barrier might be more susceptible to various precipitants, and may increase destructive effects on the gastric mucosal barrier. This could cause significant increases in the incidence of gastritis, atrophy, and intestinal metaplasia in the plateau population.

In summary, we observed characteristic changes of the upper gastrointestinal mucosa in native Tibetans with HPAC including obvious microcirculation disturbance of the gastric mucosa, significantly damaged structure of the gastric mucosa, and severe and widespread inflammation. HAPC was associated with pathological damage to the upper gastrointestinal organs and tissues of the digestive system. This study provides basic clinical information on the effect of HAPC on the digestive system which might be useful for understanding the pathogenesis and organ damage caused by HAPC. However, the sample size of this study is small, and the relationship between the upper digestive tract pathological damage and clinical symptoms caused by HAPC is not very clear. Therefore, we need to expand the sample size in future clinical studies.

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Disclosure of conflict of interest

None.

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