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## Abnormalities of gastric mucous membrane in patients with steroid-dependent intractable asthma

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**Abstract:** Recently, we experienced two asthmatic patients with advanced gastric cancer. The two patients had steroid-dependent intractable asthma (SDIA) who had been on administration of corticosteroids for more than 2 years. To determine the influence of pathophysiology of SDIA on stomach mucous lesion, gastroscopic examinations and immunological examinations were performed in eight patients with SDIA, compared with 25 patient with non-SDIA. In patients with SDIA, gastric cancer, its precursor condition and immunosuppressive state were observed. These results suggest that the immunosuppressive state in SDIA induced by the long-term administration of corticosteroids may lead to the risk of gastric cancer development.

**Key words:** steroid-dependent intractable asthma (SDIA), gastric cancer, immunosuppression, lymphocytes, IgG

### Introduction

It has been suggested that patients with bronchial asthma have risk of cancer less frequently compared with the risk of control subjects<sup>1,2)</sup>. However, it is not well known about the incidence of cancer in asthmatics with immunosuppression caused by long-term administration of corticosteroids. Recently we experienced two steroid-dependent asthmatics having advanced gastric cancer. Patients with steroid-dependent asthma may have an increased risk of cancer. In this article, we reported clinical courses of the two subjects, and compared the gastroscopic findings and

immunological examination in steroid-dependent asthmatics with those in non-steroid-dependent asthmatics.

### Subjects and methods

The subjects in this study were 33 patients with asthma. Steroid-dependent intractable asthma (SDIA) was defined when patients were treated with systemic glucocorticoids for more than 2 years. Of these patients, eight subjects had SDIA. Characteristics of patients with SDIA and non-SDIA were shown in Table 1. All patients were underwent gastroscopy examination. To evaluate immunological conditions, mean value of white blood cells count, lymphocytes

ratio and immunoglobulin level in peripheral blood for last three years were examined.

Table 1. Characteristics of patients with SDIA and non-SDIA

SDIA	No. of subjects	Age (years)	Sex M / F
+	8	62.8	5/ 3
-	25	62.4	13/12

**Results**

Case 1: 69-years-old woman with steroid-dependent asthma was admitted at our hospital because of epigastralgia on May 1997. She had been treated with 10mg/day of systemic corticosteroids for eight years. Serum IgE level was 325U/ml. Specific IgE antibodies against common inhalant allergens, such as house dust mite, fungi and pollen were all negative. The gastroscopic examination showed an irregular shape of ulcer lesion on the fornix of the stomach (Fig. 1). Histological examination of the lesion revealed signet ring cell carcinoma. Total gastrectomy was performed. The cancer stage was evaluated as T3N0M0-stage 3.

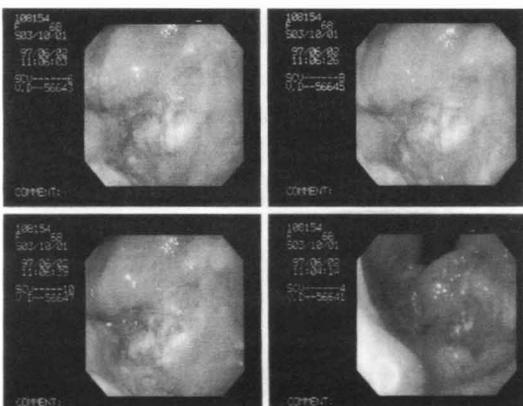


Fig.1. Gastroscopy showed irregular shape of ulcer lesion on the fornix of the stomach. Histological examination revealed signet ring cell carcinoma.

Case 2: 65-year-old man with aspirin-induced asthma was admitted due to severe asthma attacks on November, 1997. He had been treated with 15 mg/day of systemic corticosteroids for sixteen years. Serum IgE level was 90.3U/ml. Specific IgE antibodies against common inhalant allergens, such as house dust mite, fungi and pollen were all negative. In December, he started to complain of abdominal fullness. The abdominal ultrasonography revealed multiple low echoic areas in the liver. The gastroscopic examination showed an elevated tumor lesion on the anterior wall of the stomach (Fig. 2). Histological examination revealed well-differentiated tubular adenocarcinoma. The patient died of multiple organ failure in May, 1998.

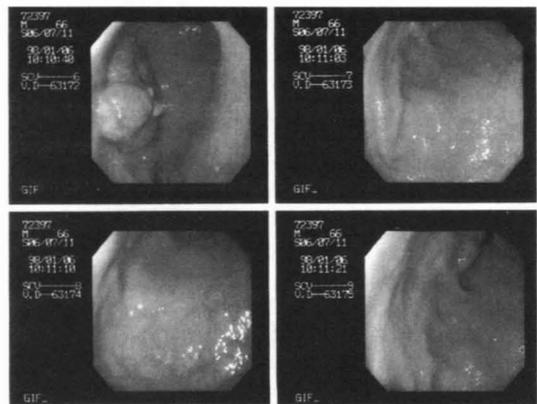


Fig. 2 Gastroscopy showed elevated tumor lesion on the anterior wall of the stomach. Histological examination revealed well-differentiated adenocarcinoma.

From gastroscopic findings in 8 patients with SDIA, two patients with cancer, one with adenoma, one with hyperplastic-polyp, and four with gastritis were found. In contrast, gastroscopic findings showed five patients with hyperplastic-polyp, nineteen with gastritis, and one with ulcer of 25 patients with non-SDIA. Cancer or adenoma were not observed in patients with non-SDIA (Table 2). White blood cell count was

Table 2. gastroscopic findings in patients with SDIA and non-SDIA

	cancer	adenoma	hyperplastic polyp	gastritis	ulcer
SDIA	2	1	1	4	0
non-SDIA	0	0	5	19	1

8425 ± 384.4 /mm<sup>3</sup> in patients with SDIA, and 6273.8 ± 234.3/mm<sup>3</sup> in those with non-SDIA. Significant difference was observed in the two groups (p<0.0001). The percentage of lymphocytes in white blood cells was 15.8 ± 1.98% in SDIA, and 35.47 ± 1.6% in non-SDIA. Significant difference was also observed between the two groups (p<0.0001) (Fig. 3). In SDIA, the level of serum IgG, IgA and IgM were 1179.0 ± 95.61mg/dl, 273.5 ± 48.0mg/dl and 125.0 ± 22.0mg/dl, respectively, whereas 1413.7 ± 61.5mg/dl, 349.5 ± 44.8mg/dl and 130.9 ± 9.0mg/dl in non-SDIA. Serum IgG levels in SDIA were more significantly suppressed than in non-SDIA (Fig. 4).

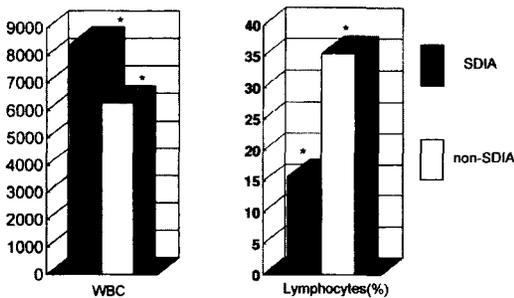


Fig. 3 WBC count and lymphocyte(%) in patients with SDIA and non-SDIA. WBC in SDIA significantly increased and %lymphocyte in SDIA significantly decreased, compared to those in non-SDIA. \*;p<0.0001

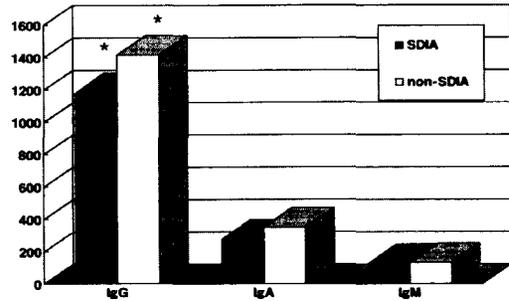


Fig. 4 Immunoglobulin in patients with SDIA and non-SDIA. In SDIA, serum IgG levels were significantly suppressed. No significant differences of IgA and IgM levels were observed between the two groups. \*;p<0.05

Discussion

In patients with bronchial asthma, the incidence of cancer is supposed to be low. Patients with asthma had low incidence of development of lung cancer compared to the general population<sup>3</sup>. The incidence of bronchial asthma in patients with malignancy was significantly lower compared with that in those without malignancy<sup>4</sup>. The results are approximately in agreement with the reports of Allegra et al<sup>2</sup>, McDuffie et al<sup>1,5</sup> and Cockcroft<sup>6</sup> et al, in which the low incidence of atopic disease was observed in subjects with cancer. These results may be due to some enhanced immunological activity preventing the cancer development. However, the precise mechanism of preventing the cancer development in atopic subjects was not clear.

In this article, a relationship between asthma and gastric cancer was investigated. Gastroscopic findings revealed that gastric cancer or precursors conditions were observed in subjects with SDIA, while no malignant or precursors conditions were observed in subjects with non-SDIA. Furthermore, low % lymphocyte and low serum IgG level were observed in subjects with SDIA. These results might suggest the possibility that the suppressed immune system in

SDIA increases the risk of gastric cancer. In the cases of immunodeficiency, the relationship between the immunosuppressive state and the cancer development were reported. Den Hartog, et al have reported that patients with late-onset hypogammaglobulinemia have a very high risk of developing gastric cancer<sup>7)</sup>. In these patients, there was a high frequency of atrophy of the gastric mucosa. They speculated that the immunoglobulin deficiency had not been responsible for the development of the gastric abnormalities, because patients with early-onset hypogammaglobulinemia and X-linked agammaglobulinemia had not shown the increased frequency of gastric abnormalities. According to Yoshitomi and Tanaka, however, patients with ataxia-telangiectasis, who could survive relatively longer than patients with other primary immunodeficiency, had more tendency to have the epithelial tumors, especially gastric cancer, than those with lymphoreticular tumors and leukemia<sup>8)</sup>. Therefore, long-term immunodeficiency may affect the occurrence of gastric cancer. In our subjects with gastric cancer, immune system was suppressed by long term administration of systemic corticosteroids. The immunosuppressive states might correlate with the induction of the gastric cancer. Furthermore, dexamethasone suppressed apoptosis in a human gastric cancer cell line<sup>9)</sup>. Glucocorticoids may have the effects of protecting malignant cell and developing cancer.

Recent epidemiological studies suggest that gastric infection with *H. pylori* may be related to gastric cancer and its precursors conditions, gastric mucosal atrophy and intestinal metaplasia<sup>10,11)</sup>. Patients with immunosuppressive state may be more susceptible to gastric infections with *H. pylori* than those without immunosuppression. However, the incidence of *H. pylori* infections was not investigated in our study.

In conclusion, patients with SDIA have a tendency to develop gastric cancer and precursor mucous lesion. The immunosuppressive state by long-term administration of corticosteroids may induce the development of gastric abnormalities. Therefore, regular endoscopic

screening in patients with SDIA seems to be needed.

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## ステロイド依存性重症難治性気管支喘息症例における胃粘膜病変の検討

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最近, 進行胃癌を合併した気管支喘息症例を2例経験した。2症例ともにステロイド依存性重症難治性喘息 (SDIA) 症例であり, SDIA が胃悪性腫瘍に関与している可能性が考えられた。今回, SDIA 症例における胃粘膜病変の臨床像および背

景因子を検討する目的で, 8例のSDIA症例における胃内視鏡検査, 末梢血液分画, 免疫グロブリン定量を行い, 非SDIA症例と比較検討を行った。

SDIA症例においては胃癌・前癌状態が認められたが, 非SDIA例では認められなかった。SDIA群において, 末梢血白血球は有意に増加し, リンパ球分画・IgGは有意に減少していた。これらの結果より, ステロイド依存性重症難治性気管支喘息症例においては免疫状態が抑制され, 胃悪性腫瘍が発生する危険性があるものと考えられた。

キーワード: ステロイド依存性重症難治性, 胃癌, 免疫抑制, リンパ球, IgG