CukurovaMedicalJournal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

CukurovaMed J 2023;48(1):145-152
DOI: 10.17826/cumj.1162996

RESEARCH

Evaluation of upper gastrointestinal system endoscopy screening in patients with acromegaly: a single center experience

Akromegali hastalarında üst gastrointestinal system endoskopi taramasının değerlendirilmesi: tek merkez deneyimi

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Abstract

Purpose: The prevalence of precancerous or cancerous lesions in the upper gastrointestinal tract in acromegalic patients is not well known. The aim of this study is to evaluate the endoscopic findings of the upper gastrointestinal system (GIS) of patients with acromegaly and to assess whether the pathological findings are related to the disease and the use of somatostatin analogs.

Materials and Methods: Between January 2010 and October 2021, patients diagnosed with acromegaly were identified by retrospective medical record scanning. This study included 49 patients with acromegaly who underwent upper GIS endoscopy. The acromegaly patients were divided into two groups: those who were taking somatostatin analogs at the time of endoscopy and those who were not. It was investigated whether there was a difference between these two groups in terms of lesion development. The patients with acromegaly and the control group were compared in terms of endoscopic findings and biopsy results.

Results: Of these patients, 53% (n=26) were male and 46.9% (n=23) were female. The incidence of Helicobacter pylori (HP) was significantly higher in the acromegaly patients than in the control subjects. In the acromegaly group, 62.5% (n=15) of the 24 patients with antral and pangastritis were taking somatostatin analogs. There was no significant difference between the use of somatostatin analogs and the development of gastritis. The development of esophagitis was statistically higher in patients with acromegaly taking somatostatin analogs.

Conclusion: The incidence of HP was higher in patients with acromegaly than in the normal population. No clear results were found regarding the development of gastritis. The incidence of esophagitis was high in acromegalic patients taking somatostatin analogs. Large-scale studies

Öz

Amaç: Akromegalik hastalarda üst gastrointestinal sistemdeki prekanser öz veya kanserlilezyonların prevalansıiyi bilinmemektedir. Çalışmamızda Akromegali hastalarının üst gastrointestinal sistem(GİS) endoskopi bulgularının incelenmesi ve patolojik bulguların hastalık ve somatostatin analoğu kullanımı ile ilişkisinin olupol madığının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Ocak 2010 ile Ekim 2021 arasında akromegali tanısı konulan hastalar tıbbi kayıtlar geriye dönük taranarak belirlendi. Bu çalışmayaüst GİS endoskopisiyapılan 49 akromegali hastası dahil edildi. Akromegali hastaları endoskopi anında somatostatin analogu kullanan ve kullanmayanlar olarak iki gruba ayrıldı. Bu iki grup arasında lezyon gelişimi açısından fark olup olmadığı incelendi. Akromegali hastaları ve control grubu endoskopik bulgular ve biyopsi sonuçları açısından karşılaştırıldı.

Bulgular: Hastaların %53'ü (n=26) erkek, %46,9'u (n=23) kadındı. Akromegali hastalarında Helicobakterpilori (HP) insidansı kontrollere göre anlamlı derecede yüksekti. Akromegali grubunda antral ve pangastriti olan 24 hastanın %62,5'i (n=15) somatostatin analoglarıalıyordu. Somatostatin analoglarının kullanımı ile gastrit gelişimi arasında anlamlı bir fark yoktu. Somatostatin analogları kullanan akromegali hastalarında özofajit gelişimi istatistiksel olarak daha yüksek saptandı.

Sonuç: Akromegali hastalarında HP görülmesıklığı normal popülasyona göre yüksek saptanmıştır. Gastrit gelişiminde ise net sonuçlar ortaya konamamıştır. Somatostatin analogları kullananak romegali hastalarında özofajit sıklığı yüksek bulundu. Etyolojisinin hastalık ve kullanılan ilaçlarla ilişkisinin net bir şekilde ortaya konulabilmesi açısından geniş çaplı çalışmalara gereksinim duyulmaktadır.

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Received: 18.08.2022 Accepted: 30.01.2023

are needed to uncover the relationship between the etiology of the disease and the drugs taken.
Keywords:. Acromegaly, esophagitis, somatostatin analogs, upper gastrointestinal system endoscopy

Anahtar kelimeler: Akromegali, özofajit, somastostatin analogları, üst gastrointestinal sistemendoskopisi

INTRODUCTION

Acromegaly is caused by excessive secretion of growth hormone (GH), usually by an adenoma in the pituitary gland. Excess GH stimulates the hepatic secretion of insulin-like growth factor-1 (IGF-1), which causes many of the clinical manifestations of acromegaly. Acromegaly is considered a rare disease with an estimated prevalence of 30 to 70 individuals per million population in Europe[1]. The diagnosis is delayed by an average of 5-7 years because of the slow progression of the disease and serious comorbidities may be identified at the time of diagnosis. The risk of cardiovascular and respiratory problems, as well as cancer, is increased 2-4-fold in patients with acromegaly compared with healthy individuals[2].

The most common comorbidities of acromegaly are hypertension, diabetes, sleep apnea, osteoarthritis, and colon polyps[3]. In addition, the incidence of colon carcinoma, adenomatous polyps, and diverticular disease in the gastrointestinal tract increased with the duration of active disease and high IGF-1 levels[4]. In the male gender, based on the results of a cohort of 1041 men with acromegaly, an increase in cancers such as colon, gastric, esophageal, and melanoma was also found [5]. In the meta-analysis of 529 patients with acromegaly, in which 23 studies were evaluated and the incidence rates of cancers were compared, it was found that this group of patients has an increased risk of gastric cancer as well as many other cancers[6]. On the other hand, the prevalence of precancerous or cancerous lesions in the upper gastrointestinal tract in patients with acromegaly is not well known. Therefore, it is not clear whether upper endoscopy should be included in the routine screening program.

In addition to the disease, the agents used for treatment also affect the gastrointestinal system. Somatostatin analogs used in medical treatment slow gastric emptying by decreasing secretion of gastric inhibitory peptides, cholecystokinin, neurotensin, gastrin, motilin, and pancreatic polypeptides; prolong small intestinal transit time; and cause stone formation by decreasing gallbladder contraction[7].

This study aims to evaluate the upper GIS endoscopy findings of patients with acromegaly and investigate the relationship between pathological findings and disease and somatostatin analogs. In patients with acromegaly, endoscopy screening may need to be included in the routine program, as well as colonoscopy screening. Because the effects of the disease itself on the upper gastrointestinal system are not clearly known, and somatostatin analogues used also have many effects on this system.

MATERIALS AND METHODS

Sample

This retrospective study was conducted between January 2010 and October 2021 at the Department of Endocrinology and Metabolic Diseases, Karadeniz Technical University in Turkey. Patients diagnosed with acromegaly were identified by scanning medical records with ICD code E22.O- (acromegaly and pituitary gigantism). Between January 2010 and September 2021, 84 patients diagnosed with acromegaly were identified. The diagnosis of acromegaly was made based on IGF-1 level, magnetic resonance imaging of the pituitary gland, and GH suppression test after 75 grams of a load of oral glucose. 35 patients who did not undergo endoscopy were excluded. This study included 49 patients with acromegaly who underwent upper GIS endoscopy in the Department of Gastroenterology.

Procedure

Ethical approval was obtained from the College Ethics Committee for Health Sciences, Scientific Research, and Publications (Decision: 11/24/2021) to conduct the study, and written permission was obtained from the institution where the study was to be conducted. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients included in the study were selected from those who underwent upper GI endoscopy at the same time as colonoscopy after diagnosis of acromegaly. Pangastritis, antral gastritis, bulbitis, esophagitis, lower esophageal sphincter laxity, hiatal hernia, peptic ulcer, deformed pylorus, fundic gland polyp, esophageal mucosal lesion, anastomotic line

polyp, and esophageal polyp were diagnosed by direct endoscopic examination; and chronic gastritis, submucosal edema, squamous cell papilloma, intestinal metaplasia and Helicobacter pylori infection were diagnosed by pathological examination.

Laboratory tests

Patient age and sex, initial GH and IGF-1 levels at diagnosis, IGF-1 levels during upper GIS endoscopy, upper GIS endoscopy, and biopsy findings were retrospectively evaluated. The time between the diagnosis of acromegaly and the time of endoscopy was calculated.

Patients with acromegaly were divided into two groups: those who were taking somatostatin analogs at the time of endoscopy and those who were not. No difference was found between these two groups in terms of lesion development. CLIA (chemiluminescence immunoassay) was used to measure IGF-1 and GH.

The control group was retrospectively selected from age- and sex-matched patients who had undergone endoscopy for dyspepsia (postprandial fullness, early satiety, bloating, and/or epigastric pain/burning). Patients who underwent endoscopy for possible malignancies with findings such as anemia and weight loss were excluded. None of the patients were regularly taking proton pump inhibitors, nonsteroidal anti-inflammatory drugs/steroids, and acetylsalicylic acid. The patients with acromegaly and the control group were compared in terms of endoscopic findings and frequency of intestinal metaplasia and HP infections in the biopsy results.

Statistical analysis

The Number Cruncher Statistical System (Kaysville, Utah, USA) version 2007 was used for statistical tests. Continuous variables were evaluated for normal distribution using histogram, Q-Q plot, and Shapiro-Wilk test. Other continuous variables were presented with median values (minimum-maximum), and the nonparametric Mann-Whitney U test was used to compare groups. The independent T-test was used for parametric analysis. Categorical variables were presented as frequencies and percentages, and the Pearson chi-square test or Fischer exact probability test was used to compare groups. Tests with a p-value of 0.05 and below at the 95% confidence interval were considered statistically significant.

RESULTS

Upper GIS endoscopy was performed in 49 patients with acromegaly. Of the patients who underwent upper GI endoscopy, 53% (n=26) were male and 46.9% (n=23) were female. The mean age of patients who were later on examined with endoscopy was 45.97±12.38 at the time of diagnosis, while it was 50.16±12.5 at the time of endoscopy. Upper GI endoscopy was performed at a median of 7 months (12 days-28 years) after the diagnosis of acromegaly. Among systemic diseases, the two most common comorbidities were diabetes mellitus (n=18) and hypertension (n=15). Of the acromegaly patients who underwent endoscopy, 46.9% (n=23) were treated with surgery alone, 42.8% (n=21) with a somatostatin analog after surgery, and 10.2% (n=5) with a somatostatin analog alone (Table 1).

Table 1. Demographic and clinical characteristics of patients with acromegaly who underwent endoscopy

Variable	Acromegaly (n=49) N (%)
Age(years), mean ± SD	45.97 ± 12.38
Gender Female	23 (46.9)
Male	26 (53.1)
History of gastrectomy	3 (6.1)
Systemic Diseases	
Diabetes mellitus	18 (36.7)
Hypertension	15 (30.6)
Hypopituarism (Postoperative)	9 (18.4)
Colon Cancer	2 (4.1)
Hypothyroidism	1 (2)
Papillary Thyroid Cancer	1 (2)
Coronary Artery Disease	1 (2)
Cerebrovascular Event	1 (2)
Gastric Cancer	1 (2)
Treatment	49
Surgery only	23 (46.9)
Surgery + SA*	21 (42.8)
SA* only	5 (10.2)

*Somatostatin analogs

The endoscopy of 67.3% of these patients (n=33) showed an abnormal finding. The three most common findings were 26.5% pangastritis (n=13), 22.4% antral gastritis (n=11), and 16.3% bulbitis (n=8). Pathological evaluation of 28 patients revealed 85.7% (n=24) chronic gastritis, 7.1% (n=2) normal findings, 3.6% (n=1) submucosal edema, 3.6% (n=1) squamous cell papilloma, 14.3% (n= 4) intestinal metaplasia and 53.6% (n=15) HP (Table 2).

The median level of IGF-1 at the time of endoscopy of patients undergoing upper GI endoscopy was measured as 337.5 (29-1084).

Twenty-six patients received somatostatin analogs. A gastric biopsy was performed in 14 of these patients, and 64.2% (n=9) were HP-positive. There was no difference between medication use and H. pylori incidence (p=0.759). While no significant difference was found between the use of the somatostatin analog and the development of gastritis (p=0.256), all acromegalic patients with esophagitis were using somatostatin analogs. There was a correlation between the development of esophagitis and somatostatin use (p=0.024) (Table 3).

Variable	Upper GI endoscopy (n=49) n (%)
Pangastritis	13 (26.5)
Antral gastritis	11 (22.4)
Bulbitis	8 (16.3)
Esophagitis	6 (12.2)
LOS relaxation*	4 (8.2)
Hiatal hernia	3 (6.1)
Ulcer	2 (4.1)
Deformed pylori	2 (4.1)
Fundic gland polyp	1 (2)
Esophageal mucosal lesion	2 (4.1)
Anastomotic line polyp	1 (2)
Esophageal polyp	1 (2)
Intestinal metaplasia	4 (8.2)
Helicobacter pylori	15 (30.6)

*Lower esophageal sphincter

Table 2. Upper GI endoscopy findings in patients with acromegaly

Table 3. Comparison of endoscopic findings in acromegalic patients using and not using somatostatin analogs.

Variable	Somatostatin (-) n	Somatostatin(+) n	p
Esophagitis			0.024
No	23	20	
Yes	0	6	
Hiatal hernia			1
No	22	24	
Yes	1	2	
Antral gastritis			0.506
No	19	19	
Yes	4	7	
Pangastritis			0.532
No	18	18	
Yes	5	8	
Bulbitis			1
No	19	22	
Yes	4	4	
Deformed pylori			0.276
No	23	24	
Yes	0	2	

There were 24 patients with antral gastritis or pangastritis as a comorbidity of acromegaly. Biopsy was obtained in 21 of 24 patients and 52.3% (n=11) were HP positive. A statistically significant association was found between the development of gastritis and HP (p=0.001).

When we compared the endoscopy results of the acromegaly patients and the control group, we found that the incidence of hiatal hernia was higher in the acromegaly patients (p=0.049). It was found that esophagitis and pangastritis were statistically significantly more frequent in the control group (p-value 0.038 and 0.005, respectively). Based on the results of 28 pathological examinations, it was found that the incidence of H. pylori was higher in patients with acromegaly (p=0.001) (Table 4).

Table 4. Comparison of endoscopic findings in patients with and without acromegaly

	Acromegaly		
Variable	**Present (n= 49) n (%)**	**Not Present (n= 83) n (%)**	**p value**
LOS relaxation	4 (8.2)	1 (1.2)	0.063[a]
Hiatal hernia	3 (6.1)	0 (0)	0.049[a]
Esophagitis	6 (12.2)	23 (7.7)	0.038[b]
Antral gastritis	11 (22.4)	28 (33.7)	0.170[b]
Pangastritis	13 (26.5)	43 (51.8)	0.005[b]
Bulbitis	8 (16.3)	8 (9.6)	0.255[b]
Deformed pylori	2 (4.1)	0 (0)	0.136[a]
Fundic gland polyp	1 (2)	0 (0)	0.371[a]
Ulcer	2 (4.1)	0 (0)	0.136[a]
Gastric operation (Gastrectomy)	3 (6.1)	1 (1.2)	0.144[a]
Helicobacter pylori	15 (57.7)	16 (20.3)	0.001[b]
İntestinal metaplasia	4 (15.4)	16 (20.3)	0.775[a]

[a]Independentvariables t-test, [b]Mann-Whitney U test

DISCUSSION

Acromegaly is a rare disorder usually caused by benign somatotroph adenomas. Due to chronically elevated IGF-1 and GH levels, it causes systemic complications such as organomegaly, arthralgia, and various comorbidities including diabetes mellitus, hypertension, and sleep apnea. The most common cause of mortality is cardiovascular disease[8]. The incidence of gastric cancer is increased 3.3-fold in patients with acromegaly compared to the normal population[9].

Gastritis is an inflammation associated with damage to the gastric mucosa. The damage and regeneration of epithelial cells without inflammation is called gastropathy. Gastritis is usually caused by infectious agents (e.g., HP) or is immune-mediated in many cases, although the cause of gastritis is unknown[10]. Gastric and duodenal ulcers are lesions that can be identified by endoscopy. The sensitivity of endoscopy is approximately 90%, depending on the location of the ulcer and the experience of the endoscopist[11]. In the study conducted by Borch et al. in which the prevalence of gastroduodenitis in the normal population was investigated, the prevalence of gastritis was 50%[12]. In our study, the incidence of pangastritis was 26.5% (n=13) in patients with acromegaly and 51.8% (n=43) in the control group. Although the incidence of gastritis in the control group was similar to that in the study by Borch et al, it was found to be lower in patients with acromegaly. Since upper GIS endoscopy is performed during screening colonoscopy without any symptoms in patients with acromegaly, we think that normal results are obtained more frequently in endoscopies performed in these patients in our study.

Somatostatin has an important effect on gastrointestinal endocrinology. Although it was originally discovered as an inhibitor of growth hormone secretion, it is now known to inhibit various gastrointestinal processes[13]. Somatostatin is produced by paracrine cells in the gastrointestinal tract and inhibits the secretion of many gastrointestinal endocrine hormones. It accelerates the early phase of gastric emptying and slows the late phase. It also prolongs the transit time of the small intestine. Although it is known to alter upper GIS physiology, there are insufficient data on its effect on gastritis and gastroduodenal development[7]. Because the half-life of endogenous somatostatin is very short (less than 3 minutes), somatostatin analogs (octreotide) have been developed for use in medical therapy. Somatostatin analogs are used in the medical treatment of patients whose GH levels do not respond to surgical treatment of acromegaly[14]. In the study by Plockinger et al. on the prevalence of gastritis, gastritis was found in all 9 acromegaly patients treated with a somatostatin analog for 2 years and HP was positive in the antrum biopsy of these patients. However, gastritis is common in the general population and its prevalence increases with age. The efficacy of the somatostatin analog remains uncertain because the extent of gastritis present before treatment in this study is unknown. [15]. In our study, 62.5% (n=15) of 24 patients with antral gastritis or pangastritis were taking somatostatin analogs. There

was no difference in the development of gastritis between acromegaly patients taking or not taking somatostatin analogs (p=0.256).

HP is the most common chronic bacterial infection associated with peptic ulcer disease, chronic gastritis, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma (MALT)[16]. Although the disease can occur at any age, it is found in more than 80% of the population in developing countries, whereas in developed countries it is found in about 50% of the population over 60 years of age[17]. Octreotide therapy used for acromegaly may create a suitable environment for H. pylori by reducing gastric acid and pepsin secretion[18]. However, there are conflicting publications on this topic in the literature. In the study by Şahin et al., no difference was found in the incidence of HP in patients treated with octreotide[19]. Similarly, in the acromegaly patients of Jones et al., there was no difference in HP positivity between the groups of patients who received treatment and those who did not[20]. In our study, the gastric biopsy was performed in 14 of 26 patients receiving somatostatin analog, and HP was positive in 64.2% (n=9). There was no difference in the incidence of HP between patients with acromegaly taking somatostatin analogs or not (p=0.759). It was also found that the frequency of HP was significantly higher in patients with acromegaly compared to the control group (p=0.001). This suggests that the development of HP is higher in acromegaly patients compared with the control group because the octreotide treatment used in acromegaly patients provides a favorable environment for the development of HP. Since HP positivity and somatostatin analog use affect each other in the etiology of gastritis, it is difficult to evaluate these two entities independently.

According to studies in the literature, the prevalence of intestinal metaplasia ranges from 3.4% to 29.6% [21]. In another study conducted in Turkey, the frequency of intestinal metaplasia in patients with acromegaly was found to be 30.7% [22]. In our study, this frequency was 15.4%. Although there are insufficient data to show that acromegaly itself increases intestinal metaplasia, because a precancerous lesion is also detected in these patients, screening of the upper GI may be useful for early detection.

In our study, gastric cancer was found in one patient, colon cancer in two patients, and papillary cancer in one patient. The coexistence of two cancers at the same time was not detected in our patients. However, there are patients in the literature in whom multiple cancers coexist that have been presented as case reports. In a case report presented by Aleksandra et al., although no genetic predisposition was found, GIST, non-small cell lung carcinoma, clear cell renal carcinoma, multiple myeloma, medulla oblongata tumor, adrenal adenoma, and follicular thyroid nodules were detected in the same patient [23]. In a case report presented in 1997, four types of tumors were found in the same patient: gastric cancer, colon tubular adenoma with moderate atypia, pancreatic mucinous cystadenoma, and subcutaneous lipoma [24]. In addition to spontaneous comorbidities, patients with acromegaly may also have genetic-based comorbidities, such as multiple endocrine neoplasms. Therefore, it is important to perform additional screening for other malignancies when any malignancy is detected in patients.

Esophagitis results from prolonged exposure to acid, pepsin, bile, and cytokine-induced inflammation [25]. Insufficiency of the gastroesophageal junction is the most commonly cited etiology. Somatostatin analogs contribute to insufficient contraction of the lower esophageal sphincter due to their suppressive effect on many systems in the gastrointestinal tract. This is one of the factors facilitating the development of esophagitis. In our study, although the frequency of esophagitis was higher in the control group compared to acromegaly patients, the presence of esophagitis was found to be higher in acromegaly patients on somatostatin.

The limitations of our study are the deficiencies in the records due to the retrospective nature of the study, the lack of symptom surveys, and the inability to obtain information from the records about other factors that may cause gastritis, such as smoking and alcohol consumption. Furthermore, since upper GI endoscopy is not part of the routine acromegaly screening program, there was no standardization of endoscopy appointments.

Acromegaly is a disease that affects many systems in the body and requires a multidisciplinary approach. Comorbidities and complications of the disease require lifelong follow-up. The disease itself and the drugs used to treat it have many effects on the gastrointestinal system. In our study, the incidence of HP development was higher in patients with acromegaly than in the normal population. As for the development of gastritis, there are no clear results. The frequency of esophagitis was found to be high in

acromegalic patients using a somatostatin analog. In light of all the data obtained, upper GIS endoscopy may be necessary to be aware of the disease itself and the effects of the drugs used. However, since there are not enough studies investigating upper gastrointestinal tract endoscopy, further studies are needed to analyze these associations.

Yazar Katkıları: Çalışma konsepti/Tasarımı: YEG, SD, AMC, ÖÜ; Veritoplama: YEG, SD; Veri analizi ve yorumlama: SD; Yazı taslağı: YEG, SD; İçeriğin eleştirel incelenmesi: ÖÜ, AMC; Son onay ve sorumluluk: YEG, SD, OU, AMC; Teknik ve malzeme desteği: -; Süpervizyon:-; Fon sağlama (mevcutise): yok.
Etik Onay: Bu çalışma için Karadeniz Teknik Üniversitesi Bilimsel Araştırma ve Yayın Etiği Kurulundan 24.11.2021 tarih ve 2021/24237859-848 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Author Contributions: Concept/Design :YEG, SD, AMC, ÖÜ; Data acquisition: YEG, SD; Data analysis and interpretation: SD; Drafting manuscript: YEG, SD; Critical revision of manuscript: ÖÜ, AMC; Final approval and accountability: YEG, SD, OU, AMC; Technical or material support: -; Supervision: -;Securing funding (if available): n/a.
Ethical Approval: For this study, ethical approval was obtained from the Karadeniz Technical University Scientific Research and Publication Ethics Committee with the decision dated 24.11.2021 and 2021/24237859-848 numbered.
Peer-review: Externally peer-review.
Conflict of Interest: The authors have declared that there is no conflict of interest.
Financial Disclosure: Authors declared no financial support.

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