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ZAZDRAVNOV A.A.  
Kharkiv National Medical University, Kharkiv, Ukraine

## ESOPHAGEAL COMPLICATIONS IN PATIENTS WITH ANKYLOSING SPONDYLITIS: ENDOSCOPIC AND HISTOMORPHOLOGICAL FEATURES

**Summary.** On the basis of clinical and endoscopic examination of 31 patients with ankylosing spondylitis (AS) with clinical signs of esophageal lesions, we have found that in these patients erosive lesions of the esophagus occur much more often than in simple gastroesophageal reflux disease (GERD). Esophageal lesions in patients with AS are more severe than in simple GERD — severe erosive esophagitis (of C and D grade) is detected in 43.8 % of patients with erosive and ulcerative lesions of the esophagus against AS. Microscopic examination of biopsy material taken from esophageal mucosa suggests multifactorial mechanism of esophageal lesions in AS, including systemic and local immune inflammation, abnormal microvasculature, excessive proliferation of connective tissue, disseminated sclerotic processes in the wall of the esophagus, reduced number of esophageal glands.

**Key words:** esophageal lesion, ankylosing spondylitis, erosive esophagitis, morphology, histology.

### Introduction

Ankylosing spondylitis (AS) is a systemic disease of the connective tissue, mainly affecting the joints and ligaments of the spine and may be related to pathological process of internal organs. Approximately 0.2–2 % of general population suffer from AS, predominantly young and middle-aged. Chronic immune-inflammatory process causes not only functional impairment of musculoskeletal system, but also reduces the duration of life of the patients. The successes of recent years in the study of the pathogenesis of this disease, the introduction of new classes of therapeutic drug improved the prognosis of patients with AS and reduced the number of the most severe forms of the AS. However, keeping the disease under control still remains a difficult task that is largely dependent on the presence and expression of systemic symptoms of AS.

Dysfunction or even failure of the digestive system frequently is an extra-articular manifestation of rheumatic diseases, including AS. The vast majority of research in this area is devoted to the intestinal lesions in patients with AS [1–3]. The most common gastroenterological disease today is gastroesophageal reflux disease (GERD). The diagnosis of GERD — primarily clinical, and a large

number of patients does not exhibit endoscopic evidence of disease [4–6]. Heartburn, the main clinical symptom of GERD, is observed among patients with rheumatological diseases 1.6 times more often than in the population [7]. There are certain specific preconditions for the formation of GERD in patients with AS. One of them is deformation of the cervical spine, with changed topography of the esophagus affecting its peristaltic function. Another symptom observed in patients with AS is visceral and diaphragmatic compression due to the strain in the thoracic and lumbar spine. In systemic connective tissue the disease is manifested in development of hyposalivation, which may also trigger esophageal complications [8]. All of the above gives reasons to expect observation of specific features of histomorphological changes in esophageal mucosa in patients with AS.

**Objective.** To identify and investigate the endoscopic features, histological and morphological changes in the esophageal mucosa in patients with AS, who had clinical manifestations of esophageal lesions.

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## Materials and Methods

Study was conducted in compliance with the principles of Good Clinical Practice (GCP), based on the Declaration of Helsinki of the World Medical Association. The study was conducted on 31 (including 27 men and 4 women) patients with AS and esophageal complications. Diagnosis of AS was based on the modified New York criteria (1985), the diagnosis of GERD is based on the requirements of the Montreal Consensus (2006). Duration of the AS was  $(17.0 \pm 4.8)$  years. In all cases GERD symptoms appeared within few years from the debut of AC. Therapy was conducted using the anchor drugs (sulfasalazine, in some cases methotrexate) and non-steroidal anti-inflammatory drugs (indomethacin, diclofenac, celecoxib); treatment of esophageal lesions was conducted using proton pump inhibitors (omeprazole mainly, more rarely — esomeprazole, rabeprazole).

For all patients endoscopy with biopsy was conducted. Fence biopsies performed at the lower esophageal sphincter at the level of Z-line and at 3–4 cm above the Z-line, as well as in the sites of visually changed mucosa. Fixation and sectioning of biopsies was performed by the standard technique. The histological preparations were stained with hematoxylin and eosin (H & E), following van Gieson method.

Patients with AS with significant deformation of the cervicothoracic spine (kyphosis thoracic and cervical spine hyperlordosis) were excluded from the observed sample, because for these patients endoscopy could be potentially dangerous.

## Results and Discussion

Analysis of the endoscopic picture found that the erosive form of esophageal lesions in patients with AS occurs much more frequently than in the classical course of GERD (Table 1).

Higher prevalence of erosive form of esophageal lesions in AS patients showed existence in the mucosa of the esophagus background that leads to epithelial damage and generated by systemic autoimmune inflammatory process. There

were no significant differences in the clinical symptoms of erosive and non-erosive GERD forms, but the prognosis for patients with erosive and ulcerative lesions of the esophagus is much worse. It is believed that the vast majority of non-erosive GERD is not prone to progression, while erosive, in the absence of adequate treatment, is accompanied by complications and transformed in Barrett's esophagus [9].

The next phase of the study consisted of an evaluation of erosive changes in the esophageal mucosa. Grading reflux esophagitis by severity was performed according to the Los Angeles classification (1998): Grade A — one or more defects in the mucosa of less than 5 mm, which are located between the tops of two mucosal folds; Grade B — one or more defects mucosa than 5 mm which are located between two tops of the folds of mucous; Grade C — one or more mucosal defects that apply to two or more mucosal folds, but cover less than 75 % of the circumference of the esophagus; Grade D — one or more mucosal defects, which are distributed over 75% of the circumference of the esophagus.

Assessing the severity of endoscopic evidence of erosive esophagitis in patients with AS it was noted that almost 44 % of these patients had high severity (C and D), which is significantly higher than in the classical course of GERD (Table 2).

The high incidence of erosive esophagitis (especially its more severe forms) in the structure of esophageal lesions in patients with AS requires special attention to such patients and lifelong appointment of proton pump inhibitors in high doses, with availability of functions «on demand» or «step-down». Inadequate treatment of esophageal lesions may result in re-epithelialization of erosions and ulcers of the esophagus in the stratified squamous epithelium. In this case there is increased proliferation and disruption of cell differentiation, which can lead to dysplasia and eventually to cancer of the esophagus. On histological basis, in 90 % of cases of esophageal cancer is squamous, process that cause disruption of differentiation of squamous cells, and require careful clinical observation with the obligatory morphologi-

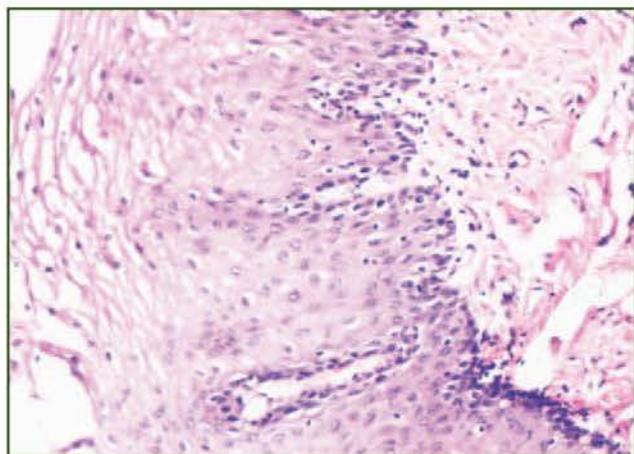
**Table 1 — The detection rate of erosive and non-erosive forms of esophageal lesions**

| Index                 | Population studies: classical GERD |                         |                    | Own data: AS complicated by esophageal lesions |
|-----------------------|------------------------------------|-------------------------|--------------------|--|
|                       | M.S. Rosaida, K.L. Goh [6]         | J. Ronkainen et al. [5] | N.R. Ha et al. [4] |  |
| Number of patients, n | 388                                | 400                     | 792                | 31   |
| In fact including:    |                                    |                         |                    |  |
| — non-erosive GERD, % | 65.5                               | 62.2                    | 63.1               | 48.4   |
| — erosive GERD, %     | 34.5                               | 38.8                    | 36.9               | 51.6   |

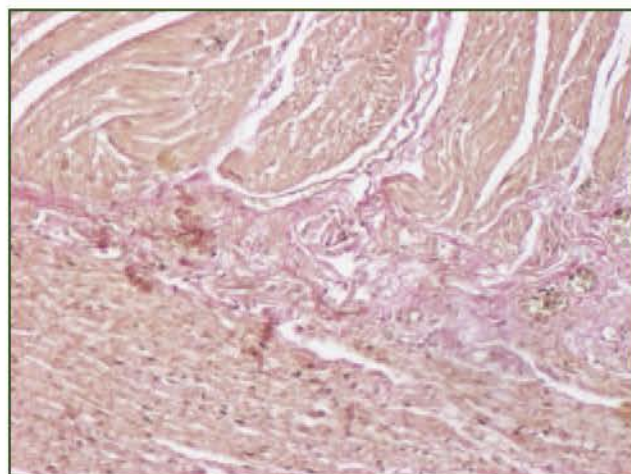
**Table 2 — Distribution of patients (%) with erosive esophagitis depending on its severity**

| Grade | Population studies: erosive esophagitis as a component of classical GERD |                             | Own data: AS complicated by erosive esophagitis, n = 16 |
|-------|--|-----------------------------|---|
|       | J. Labentz et al., n = 2766 [10]   | N.R. Ha et al., n = 292 [4] |   |
| A     | 32.5   | 74.0                        | 31.2  |
| B     | 44.4   | 20.9                        | 25.0  |
| C     | 18.6   | 4.5                         | 25.0  |
| D     | 4.6  | 0.7                         | 18.8  |





**Figure 1 – Erosive esophagitis. Degenerative changes in the epithelium, intraepithelial lymphocytes, small lymphogistioplasmacytic infiltrates in the stroma, in vessels of small caliber – fibrinoid necrosis. H & E stain, magnification 94**



**Figure 2 – Erosive esophagitis, focal perivascular sclerosis, multiple sclerosis initial manifestations of the muscular layer. Van Gieson's stain, magnification 75**

cal control [11, 12]. Another feature of erosive esophagitis degrees C and D in AS patients is erosions spread beyond the area of the lower esophageal sphincter. Significant relationship between the frequency of erosive esophagitis and the using of particular nonsteroidal anti-inflammatory drugs or anchor drugs in treatment of AS was not observed. Absence of association between the esophagus lesions and possible iatrogenic effect of particular drugs points to the benefit of systemic autoimmune lesions of the esophagus.

Analysis of biopsies of the esophagus of patients with AS complicated GERD reveals changes inherent in classical GERD – erosion, intraepithelial and subepithelial lymphoplasmacytic, neutrophilic and eosinophilic infiltration, hyperplasia of the basal layer, elongation of papillae, stratification of the epithelial layer and thinning of the epithelium.

Along with these changes there are peculiarities that are specific to the AS. This is, above all, the mandatory involvement in the inflammatory process of the microvessels with the formation of perivascular sclerosis. Observed thickening of the vascular wall with homogenization, fibrinoid necrosis of small vessels and sclerotic changes of the arterioles (Figure 1).

In all cases observed excessive proliferation of connective tissue submucosal spread to all the structural components of the esophagus wall (Figure 2).

In some cases in areas of sclerosis destruction of macrophages and fibroblasts was observed. Number of esophageal glands was significantly reduced, with compressed connective tissue formations and lymphoplasmacytic infiltrated.

Thus, esophageal damage in patients with AS characterized by overproduction of connective tissue, which extends over all layers of the esophageal wall, with adverse influence on blood circulation and irritation of the esophageal mucosa, which creates area with depressed reparative potential. The formation of ulcers on the mucosa occurs in a microcirculatory deficiency, which leads to local hypoxia. Hypoxia promotes the proliferation of connective tissue followed by restructuring of the wall. Due to the destruction of the muscle layer effectiveness obdurate function of the lower esophageal sphincter decreases.

In addition to systemic overproduction of proinflammatory cytokines (observed in AS) was observed local activation of fibroblasts (caused by alternative changes esophageal mucosa), responsible for production of matrix of fibrous connective tissue.

## Conclusions

Findings suggest that in patients with AS erosive lesions of the esophagus occur much more frequently than in the classical course of GERD. Severe erosive esophagitis was revealed in 43.8 % of patients with erosive and ulcerative form of GERD on a background of AS. Analysis of biopsies of esophageal mucosa indicates a multifactorial mechanism of esophageal lesions in the AS, including systemic autoimmune process of microvessels pathology, proliferation of connective tissue, disseminated sclerotic processes in the esophageal wall, reduced number of esophageal glands.

Further research is planned to explore endoscopic and histologic features of esophageal mucosa in patients with other connective tissue diseases.

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Заздравнов А.А.

Харьковский национальный медицинский университет

### ЭЗОФАГЕАЛЬНЫЕ ПОРАЖЕНИЯ У БОЛЬНЫХ С АНКИЛОЗИРУЮЩИМ СПОНДИЛОАРТРИТОМ: ЭНДОСКОПИЧЕСКИЕ И ГИСТОМОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ

**Резюме.** На основании клинического и эндоскопического обследования 31 больного анкилозирующим спондиллоартритом (АС) с клиническими признаками поражения пищевода установлено, что у этой категории пациентов эрозивные поражения пищевода встречаются значительно чаще, чем при традиционной гастроэзофагеальной рефлюксной болезни (ГЭРБ). Эзофагеальные поражения у больных АС протекают более тяжело, чем при обычной ГЭРБ, — тяжелые степени эрозивного эзофагита (С и D) выявляются у 43,8 % пациентов с эрозивно-язвенными поражениями пищевода на фоне

АС. Микроскопическое исследование биопсийного материала слизистой оболочки пищевода свидетельствует о многофакторном механизме эзофагеальных повреждений при АС, включающих системный и локальный иммунный воспалительный процесс, патологию микроциркуляторного русла, избыточную пролиферацию соединительной ткани, диссеминированные склеротические процессы в стенке пищевода, уменьшение количества пищеводных желез.

**Ключевые слова:** поражение пищевода, анкилозирующий спондиллоартрит, эрозивный эзофагит, морфология, гистология.

Заздравнов А.А.

Харківський національний медичний університет

### ЭЗОФАГЕАЛЬНІ УРАЖЕННЯ У ХВОРИХ НА АНКІЛОЗІВНИЙ СПОНДИЛОАРТРИТ: ЕНДОСКОПІЧНІ ТА ГІСТОМОРФОЛОГІЧНІ ОСОБЛИВОСТІ

**Резюме.** На підставі клінічного та ендоскопічного обстеження 31 хворого на анкілозівний спондиллоартрит (АС) із клінічними ознаками ураження стравоходу встановлено, що у цієї категорії пацієнтів ерозивні ураження стравоходу зустрічаються значно частіше, ніж при традиційній гастроєзофагеальної рефлюксії хвороби (ГЕРХ). Езофагеальні ураження у хворих на АС перебігають більш тяжко, ніж при звичайній ГЕРХ, — тяжкі ступені виразкового езофагіту (С та D) виявляються у 43,8 % пацієнтів з ерозивно-виразковими ураженнями

стравоходу на тлі АС. Мікроскопічне дослідження біопсійного матеріалу слизової оболонки стравоходу свідчить про багатофакторний механізм езофагеальних ушкоджень при АС, що включають системний і локальний імунний запальний процес, патологию мікроциркуляторного русла, надлишкову проліферацію сполучної тканини, дисеміновані склеротичні процеси в стінці стравоходу, зменшення кількості стравохідних залоз.

**Ключові слова:** ураження стравоходу, анкілозівний спондиллоартрит, ерозивний езофагіт, морфологія, гистологія.