Research Article

Histopathological characteristic of atretic segments in esophageal atresia with distal eso-traheal fistula

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Abstract

Caracteristica histopatologică a segmentelor atretice în atrezia de esofag cu fistulă eso-traheheală distală

Analiza rezultatelor studiului efectuat privind particularitățile macro- și microanatomice ale componentelor structurale și a celor morfologice ne demonstrează că în cadrul atreziei esofaginene cu fistulă eso-traheală inferioară concomitent cu aspectele macroscopice, histologic sunt prezente o serie de modificări cu importanță predictivă asupra perioadei postoperatorii, care pot fi clasate în două grupe: *primare* – caracterizate de tulburările histiogenerezii la etapa embrionară (displazia fibro-musculară, ectopia cartilajului displazic la nivelul esofagian și a mucoasei gastrice, dublicaturile esofagului, membrana esofagiană incompletă, aganglionoza) și *secundare* – atrofico-hipertrofice evoluate pe parcursul etapei fetale de la 12-13 săptămîni gestație care variază după prezența lor și după localizare (hipetrofia și/sau atrofia fasciculilor musculare, ectaziile varicoase vasculare, procesele inflamatorii, dismaturiția structurilor nervoase. Prezența insulițelor de mucoasă gastrică foveolară în segmentul distal cu fistulă eso-traheală poate servi un substrat morfologic favorabil de dezvoltare a esofagului Barett la bolnavii cu atrezie de esofag sau malignizare, fapt ce impune necesitatea unei evaluări endoscopice de urmărire permanentă.

Cuvinte cheie: atrezia de esofag, displazie fibro-musculară, fistulă eso-traheală

Abstract

The analysis of the results of the study of the macro- and microanatomic peculiarities of the structural and morphological components shows that in the esophageal atresia with inferior eso-tracheal fistula concurrently with the macroscopic, histological aspects there are a number of changes with predictive importance on the postoperative period, can be classified into two groups: primary - characterized by histiogenesis disorders at the embryonic stage (fibro-muscular dysplasia, ectopic dysplastic cartilage at esophageal and gastric mucosa, esophagus diets, incomplete esophageal membrane, aganglionosis) and secondary - atrophic-hypertrophic evolution during the fetal stage from 12-13 weeks gestation that varies according to their presence and location (muscle hypertrophy and / or muscle atrophy, vascular varicose ectasis, inflammatory processes, dismutation of nerve structures. The presence of the islets of foveolar gastric mucosa in the distal segment with eso-tracheal fistula may serve as a favorable morphological substrate for the development of the Barett esophagus in patients with esophageal atresia or malignisation, which necessitates an endoscopic evaluation of permanent follow-up.

***Key words*:** esophageal atresia, fibro-muscular dysplasia, eso-tracheal fistula

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Introduction

Esophageal atresia with eso-tracheal fistula is a severe, relatively common congenital malformation (approximately 1 in 3,000 live births) found in the neonatal period, representing a challenge for the pediatric surgeon both in terms of surgical procedure and management of postoperative morbidity [11]. Although postoperative mortality in this malformation has decreased significantly, a higher incidence of postoperative morbidity is determined by both the anastomotic complications [27] and respiratory and gastrointestinal problems, some of which persist throughout life [7, 12]. Some studies have indicated that the incidence of postoperative complications ranges between 20% and 60% [28]. Fistulae and anastomotic strictures, dysphagia, gastroesophageal reflux, motility disorders, epithelial metaplasia, tracheomalacia represent changes frequently documented radiologically, scintigraphically and endoscopically [14, 18]. In this context, there is a need for complex prospective histopathological studies with the aim of describing more details in the pathogenesis of these postoperative consequences. In the literature there are few reports of histopathology of esophageal atresia with eso-tracheal fistula [1, 3, 12].

The aim of the study was to evaluate the spectrum of morphopathological changes detected in both atresiatic segments of the esophagus in cases of esophageal atresia with lower eso-tracheal fistula.

Materials and methods

The histopathological study was performed on 21 patients, including autopsy materials on unoperated specimens from 8 newborn babies with the presence of esophagus atresia and inferior eso-tracheal fistula in 13 cases - from newborns operated. The evaluation of macro-microanatomic peculiarities in esophageal atresia with inferior esotracheal fistula was performed at 3 levels: the atresia upper segment, the esotracheal fistula and the inferior segment. Serial sections of both the proximal (flanking) segment of the esophagus and of the distal fistula segment were performed The study material, after a preventive fixation in 10% formalin solution, was histologically processed according to the histological standard. The hematoxylin-eosin (H-E), van Gieson (VG) and orcein staining methods were used.

Results and discussions. In the cases of the study group, the presence of a diastase between the esophageal segments ranging from 0.3-0.5cm to 6.8cm (fig. 1A) was established. More frequently, in 14 cases (66.7%) was attested diastasis of 2-2.5 cm.. The length of the upper segment oscillates between 2.3 and 4.5cm with a diameter of 2.0-2.7 cm. Macroscopically, the upper esophageal segment in most cases exhibited a marked hypertrophy of the wall, the thickness of which consisted of 0.3-0.4 cm, the mucosa with bulky longitudinal pleats, frequently oriented chaotically zoned (fig. 1B). In 11 cases (52.4%), were found erosions or exulcerations in the mucosa. The lower esophageal segment was much hypoplastic (fig. 1A), having a diameter of 0.5-0.9 cm over 1-3cm, more commonly the level of tracheal communication being located at 1.0-1.5cm from the bifurcation (fig. 1C), in 16 cases - in the bifurcation region, and in 4 cases - in the main bronchus, including the left one - 3 cases and in the right one - 1 case. More frequently, in 15 cases (71.4%) the vagus nerve had a rectilinear tract, in 5 cases (23.8%) a slightly or moderately undulated or bilateral curve was observed, and in one case (4.8 %) - spiral positioning around the upper atrophied esophagel segment. The histological examinations performed at the level of the upper esophageal atresia segment allowed for a well differentiated structure in the upper and middle third of the esophageal wall in 12 cases (57.1%) (fig. 2A), in 9 cases (42.9%) , in the distal portions of this segment observing the predominance of lax fibrous tissue endowed with a blood and lymphatic vascular network with a decrease of the glandular elements. Closer to the esophageal end, were observed muscle hypertrophy and thickening of the submucosa, the latter being unevenly defined in the bundles by the presence of conjunctive tissue bridges. The muscular tunica of the esophageal wall at this level also marked the presence of hypertrophy (fig. 2B).

Glandular elements were dispersed, with acinar structure, atrophic or dilated acinus. At the same time, inflammatory focal or diffuse processes were observed (fig. 2C), being present in areas with exucerations or eroded. In some areas of the mucosa, could be observed areas with exuceration or erosion. In some areas, its own muscular tunic was made up of atrophied striated muscle fibers. The internal muscle layer contained chaotically distributed muscle fibers, or their zonal deficiency, sometimes being completely substituted by conjuctive tissue (fig. 2D).

In the middle areas of the superior esophageal segment, in some cases, the submucosa was predominantly constituted of densely fibrillated connective tissue or with predominance of collagen fibers in abundance towards the apical atresical segment with a much diminished vascular network. At this level, was documented the diminution of the autonomic and myenteric nerve network. Quite often, muscular fascicles of the esophageal muscles were completely replaced by mesenchymal and collagenous connective tissue, often in the appearance of steeply atrophied beams and monstrous hypertrophies. Such changes have been appreciated that the primary disorder, that fibro-muscular structural-tissulare dysmorphia. In 11 cases(52,4%), malformative modification of the fibro-musculare tissue during superior atresic segment had focal and mosaic aspect.

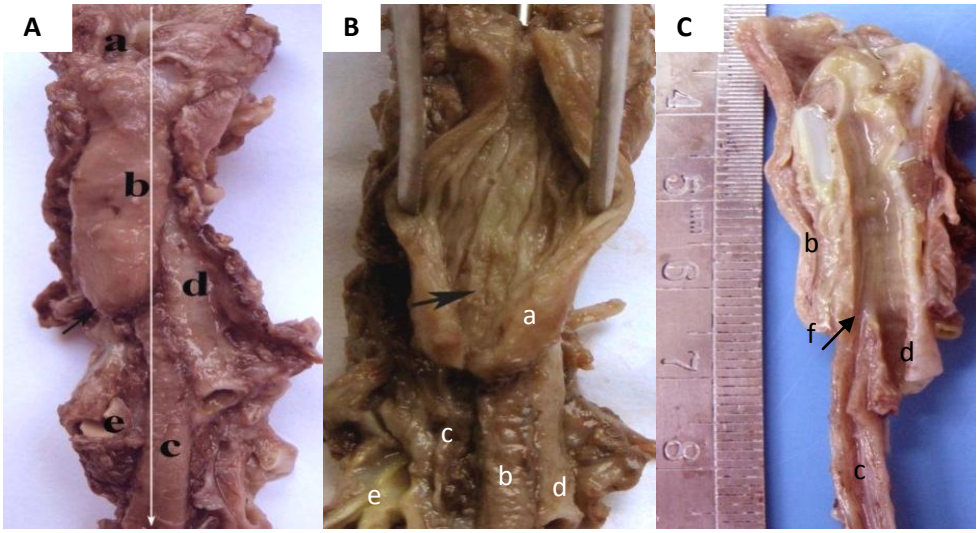

Fig. 1. Macroanatomic aspect of the esophageal tract with inferior tracheoesophageal fistula. A) a - Laryngean region; b - the proximal atresial segment of the esophagus; c - distal esophageal segment; d - trachea; e - cardiac vascular magistral device; **B)** sectional aspect of the proximally attracted segment: a - proximal segment with mucosal follicular hypertrophy (→); b - the distal segment, c - the corrugated vagus nerve (→); d - trachea; e - cardiac vascular magistral device; **C)** sectional aspect of the lower atresized segment: b - proximal proximal esophageal segment; c - distal esophageal segment; d - trachea; f - inferior eso-tracheal fistula (→);

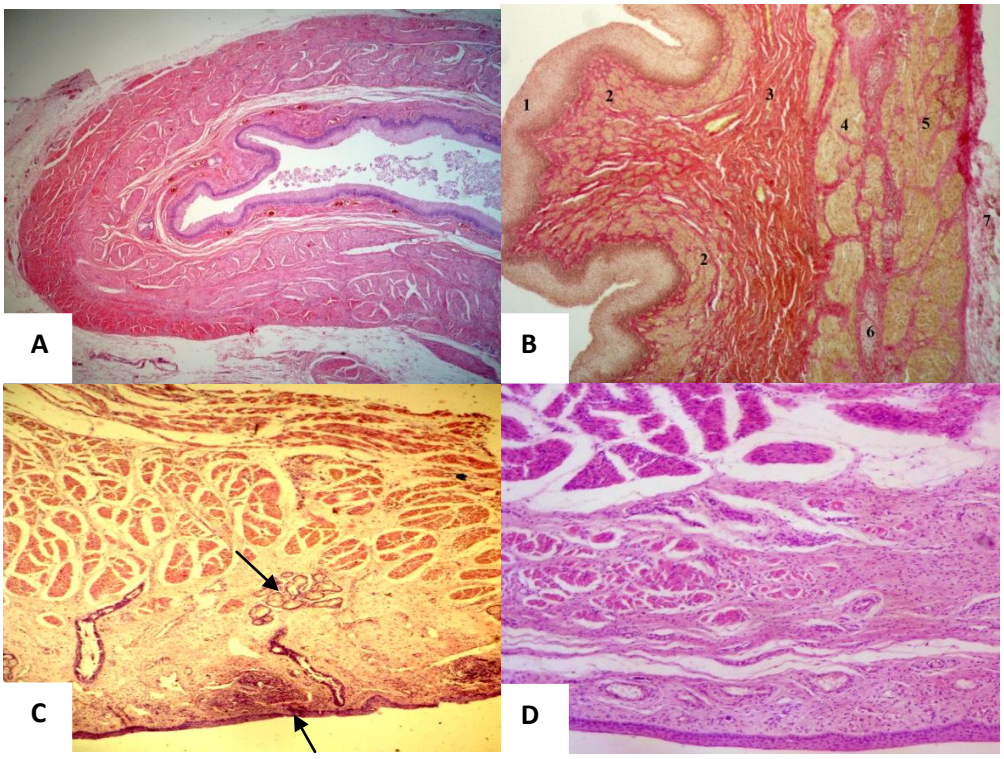

Fig. 2. Microanatomy of the proximal atretic segment: **A**) Hypertrophy of the tunic muscle in the middle portion of the proximal esophageal atretic segment by the fastening of the inner tunic by conjunctive tissue bridges. Color. H-E. x25; **B)** Structure of the proximal atresized segment: 1 - squamos epithelium; 2 - the mucous membrane tunic; 3 - submucosa; 4 - internal circular muscle layer; 5 - external longitudinal muscular layer; 6 - intermuscular nervous plexus; 7 - adventitia. Color. VG. x 25.**C**) Initial area of the proximal esophageal segment – 1) solitary glands with dilated ducts, 2) inflammatory processes at submucosa with epithelial atrophy. Color. H-E. x25; **D**) Abundance of conjunctive tissue with zonal substitution of internal muscle tunic. Color. H-E. x25.

In 16 cases (76,2%), in the apical area of the upper segment and in the area of the wall within 0.5 to 1.2 cm from the apex of the atresia have been registered areas of accentuated fibrosis processes. In this segment, muscular tunic was presented in part by fibers or myocytes chaotic arranged through conjunctive tissue. Frequently, muscle fascicle wer reduced, the present fascicles was disorganized, with different orientation, often in a cross-section with a steep appearance. In 8 cases(38,1%), in the area of the anterior wall of the distal areas of this esophageal segment internal muscular wall, was presented by single fiber or chaotic muscle fascicles, some hypertrophied and others are present only in like shadows, those changes are present and in the external mucular wall, where they could be viewed solitary fiber or hypertrophied fascicles (fig. 3A).

Concomitant with the changes described, in three cases, the wall structure of the upper esophageal segment has been detected the presence of tubular form of duplication of the esophagus with a length of 1.4; 2,0 and 2.1 cm communicating with the esophageal lumen, remaining unrecognized preoperative (fig. 3B,C). In one case, histologically has been detect the presence of a diverticulum in middle part of the upper segment of atresia which have a size of 1.2 x 0.8 cm and a wall thickness of 0.1 cm. Another case is characterized by the presence of a small diverticulum but associated with the membrane, some like fold of the fibro-mucosal wall, at a distance of 1.6 cm from the larynx which partially obstruct the esophageal lumen (fig. 3D).

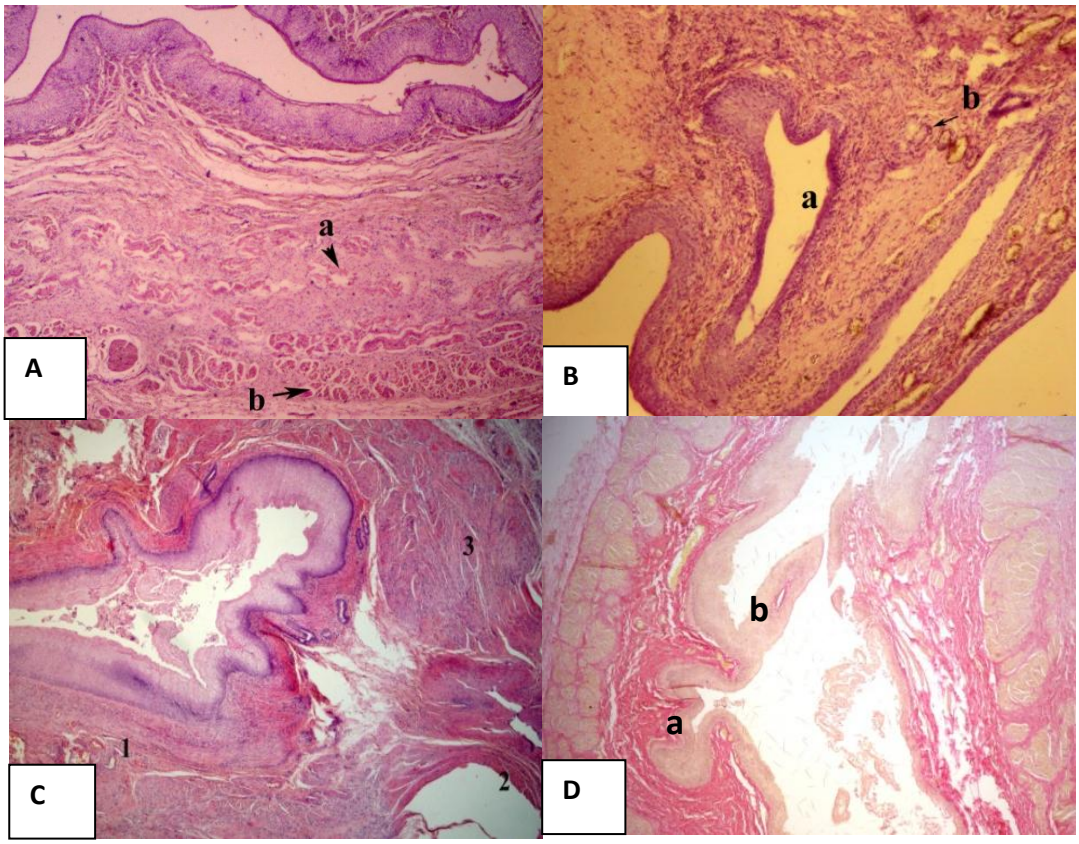

Fig. 4. Histological aspects of the upper esophageal segment. A) Abrasive fascicles and myocytosis chaotic oriented in to fibrous tissue, ganglioneurons with morphological dismutation x75. Color. H-E.B)Intramural tubular duplication of esophagus (a) with solitary glandular structures (b) × 25. Color. H-E. C) Intramural tubular duplication of the proximal segment to the anastomosis dehiscence. Microfoto. 1 - the anterior wall of the esophagus; 2 - suture level of anastomosis; 3 - preanastomotic hypertrophy of muscle tunics x 25. Color. H-E. D) Diverticol (a) associated with a fibro-epithelial transverse membrane.

In 19 cases (90,5%), the lower end compared of the upper esophageal segment, has been registered the volume hypoplasia of the esophageal tube a lengs 1-3 cm, with 0.5-0.9 cm in diameter. In 13 cases (61,9%), the wall thickness varied within 0.15-0.3 cm and in 38,1% of the cases(8 cases) that had a thickness of proximal end 0.3-0.4 cm. In two cases (9,5%) it was found lumen not like tube but fissured fistula. Throughout they, were not observed hypertrophic aspects of mucosal fibro-epithelial ply. Depending on the location of the fistula, in 15 cases (71,4%) the prevalence was found form when eso-tracheal fistula it opening at 1.0-1.5 cm superior to the tracheal bifurcation predominantly on the side wall, in 5 cases (23,8%) - at the level of the bifurcation and in one case (4,8%), fistula in the right bronchus at 0.3 cm from the bifurcation.

The histological examination of the distal segment with fistula (fig. 4), allowed to document the presence of dysplastic changes in microstructure, propensity primary origin, more pronounced than the changes detected in the proximal atresic segment. In 7 cases (33,3%), over a lengt of 0.3 to 0.5 cm in mosaical aspect or totally was found reduction or lack of muscle layers, the wall is presented by a fibro-epithelial-conjunctive plate, the conjunctive part being sclerogenic in varying intensity. The vascular network being diminished and/or with varicosities of the venous component. Glandular structures were cystic or adenomatous. At the tracheo-esophageal junction and adjacent or found the presence of fibrous-cartilaginous dysplasia manifested by immature cartilaginous tissue with glandular structures in various ratios with dilated acinar segments (fig. 4A), those having esophageal and / or tracheal origin. On the tract of the distal segment, towards the stomach the esophageal fistulated tube, gradually in the mosaic aspect took over a normal microanatomic structure. In 14 cases (66.7%), the muscular layers, more frequently in the outbreak, contained muscle fibers or fascicles atrophic, while were observed few hypertrophic muscles, which were frecvently repartisated chaotically in a connective tissue mass (fig. 4B).

At 1-2.5 cm from the eso-tracheal junction of the fistula, were found dysplastic fibrosis processes under sclero-cicatricial aspects with the disordonation of the muscular coats (fig. 4C), which consequently passed into a large or less normal structure of the esophagus but with a hypertrophy of the his own coats of the submucosa (fig. 4D) showing a narrowing of the esophageal lumen.

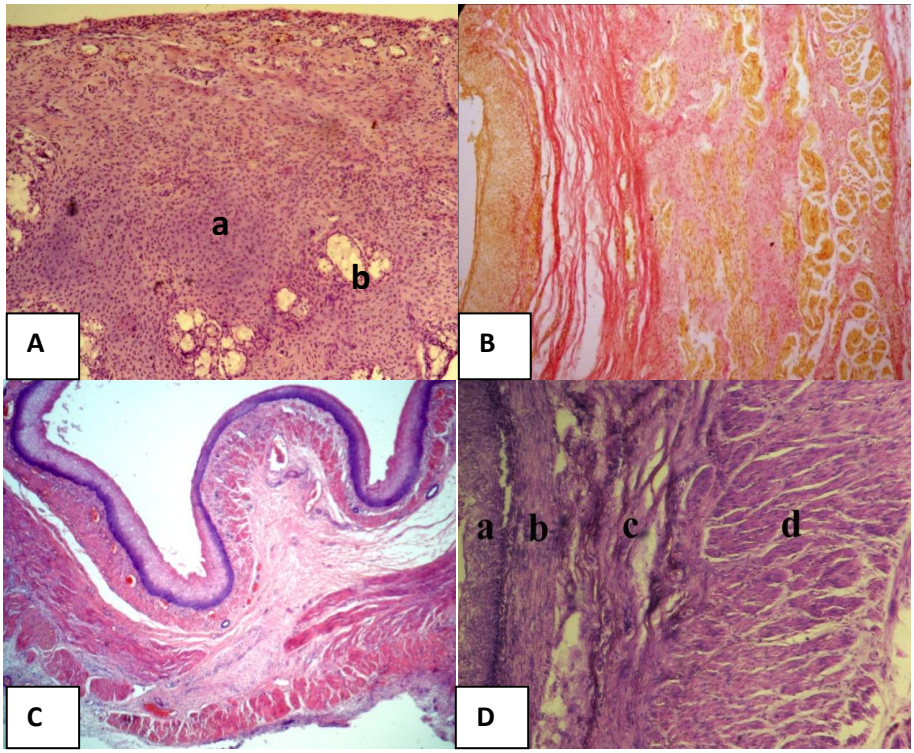

Fig. 4 The proximal segment within 2.0 cm of the fistula. A) immature cartilaginous dysplastic tissue (a) with glandular structures (b) in the fistula x25 area. Color. H-E; B) Fibro-muscular dysplasia of the distal segment within 1.8 cm of the fistula x200. Color. VG; C) Submucosal cicatriceal tissue at the level of a fold x200. Color. H-E; D) Microscopic structure of the distal segment at 2.5 cm from the fistula: a - the epithelial layer, b - the muscular tunic of the mucosal, c - the submucosa, d - the inner muscular tunic. Color. H-E. x 25

In 2 cases(9,5%), it has been observed the presence of tubular esophageal duplication of distal esophageal segment, communicating with the lumen of esophagus (fig. 5).

At the distal esophageal tube, in 3 cases (14,3%), it was observed the presence the inslets of gastric mucosa in sizes from 11 to 15 μ to 0.8-1.2 cm (fig. 6). The vascular network of the distal esophageal segment, especially in the submucosa, was manifested by a much more congestive and microvascular aspect, in which case varicose ectasis and musculature were observed (fig. 6B). The ectopie of gastric mucosa was certified from a distance of 2 cm from the cardiac region to 5-6 cm on the distal esophageal tube.

Examination of the trunk and ganglion-neuronal component of the nerve network at both the proximal atresia segment and the distal segment allowed to cause significant alterations. At the upper and middle third level, the esophageal segment attracted higher structural changes in the trunk and gentle nerve mesenteric nerve network had aspects within the limits of the conventional norm. In the lower third and especially at the apical parts of the atresized segment, including in the areas with a more pronounced fibrous, the mesenteric network appeared to be present in the chaotic aspect, being predominantly attested in the outer layers with a varied morphology of the ganglio-neural structures, which had a polymorphic cell component containing mature neurons, as well as the glia cell component reflecting a dismutation (fig. 7). Nervous plexes at this level were present through thin nerve trunks, more commonly seen in the outside of the tunic. At this level, the nerve plexuses were better evidenced, including in the intramuscular area where they were presented by nerve fascicles in the absence of ganglionuclear cells (fig. 7A). In some sectors, the external muscular tunic could be presented with hypotrophic fibers or bundles compared to the inner tunic, which was conjunctively substituted. Concomitant with these changes, the presence of nerve plexes with fine neuronal cells was found (fig. 7B, C). We note that in the areas with fibromuscular dysplasia, some pathological changes of the mezenteric nerve network and of the ganglioneuronal structures, manifested by granular and vacuolar dystrophy (fig. 7D), were noted. Analogical modification were attested and in the distal segment.

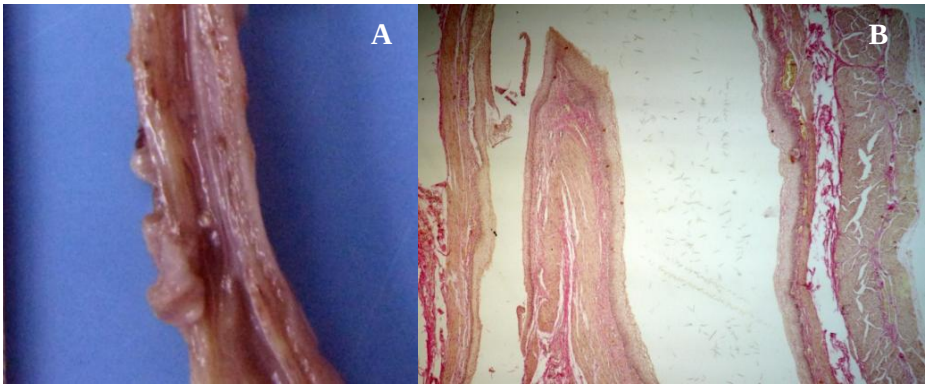

Fig. 5. The macroscopic appearance (A) and microscopic (B) of the communicating

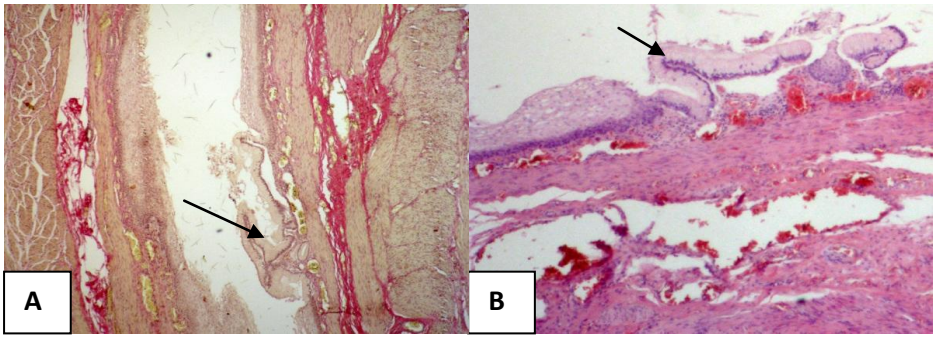

Fig. 6. Histological aspects of the distal segment. A) ectopic gastric mucosa at a distance of 1.5cm from cardia (→). X75. Color. H-E; B) Segmental ectopie of gastric mucosal (→) 4.5 cm from the cardiac region, varicose ectasis of the submucosal and intramural vascular network. x25. Color. H-E.

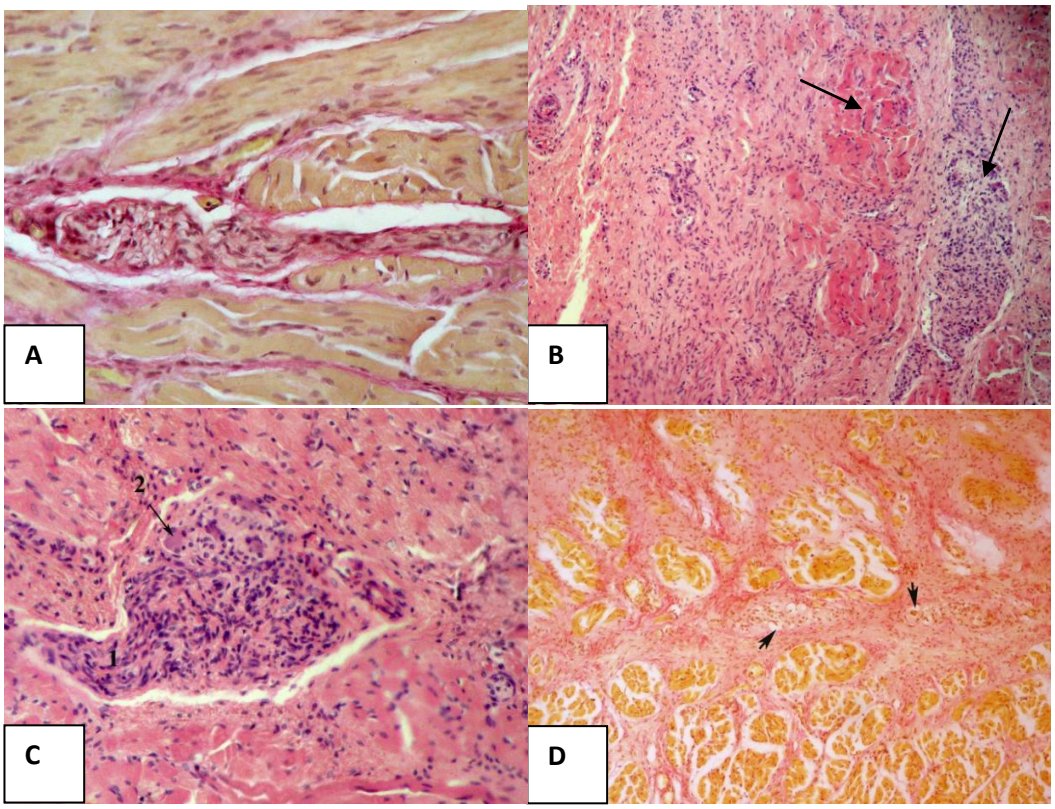

Fig. 7. Microanatomy of the nerve component A) Intramuscular ganglionar aneuronal nerve plexis x200. Color. VG; B) Steep fascicles ans fibres - chaotic oriented miocytes in to connective fibrosive tissue x75. Color. H-E; C) Ganglioneurons of the intermuscular plexus: 1 - nerve fascicles, neural ganglion; 2- neurons x200. Color. H-E. D) Myenteric nerve ganglia with vacuolar dystrophy. Color. VG. x100.

Discussions. Notwithstanding the remarkable results obtained in surgical treatment of esophageal atresia, the incidence of postoperative morbidity remains high, with several factors influencing the prognosis of these patients wase identified [27]. According to some studies, most frecvently wase registrated respiratory problems (about 37%), anastomotic stenosis (22% - 40%), dysphagia (15% -100%), gastroesophageal reflux requiring antireflux surgery (12%), recurrent fistulas 4% -17%) etc. [2, 9, 14, 17].

Postoperative esophageal dismotility in children with esophageal atresia and eso-tracheal fistula are described extensively in the literature, with some controversy over their secondary multifactorial origin due to: abnormal development of the vagus nerve and Auerbach plexus, vagal nerve trauma , surgical mobilization and tauma, ischaemia or major traction on the lower end of the esophagus during surgery or due to congenital architectural anomalies [1, 21]. Some authors believe that the pathological changes found in atretic segments in the case of esophageal atresia with eso-tracheal fistula, including muscular distortion through fibrosis, glandular and neural pathological changes, the presence of tracheobronchial cartilaginous remeniscences may contribute to discomfort and esophageal striction after surgery. The eso-tracheal fistula should be sectioned 3 mm distal from its origin in the trachea, morphological changes in this area being appropriate for primary anastomosis [1, 3].

In children, heterotopic gastric mucosa in the normal esophagus can often be seen in the endoscopic examination (up to 5.9%) in the form of a patch that ranges from a few millimeters to a few centimeters, usually unique or rarely in the form of circumferential ring, asymptomatic or causing dysphagia, odinophagia, esophageal strictures, bleeding and respiratory symptoms. The association of heterotopic gastric mucosa with esofageal atresia with eso-tracheal fistula is rarely described, most of the cases being endoscopically diagnosed after surgical corection of the malformation [8, 23]. There are studies that describe the presence of gastric epithelium in both the proximal oesophageal and distal segment [1, 5]. Some complex studies have found that the Barrett esophagus prevalence is 4 times

higher in young adults treated with esophageal atresia, and the prevalence of esophageal carcinoma is 108 times higher than in the general population, and these findings require the need for an endoscopic follow-up all life [25].

The term "esophageal duplication" includes three morphological variants:

1) cystic (communicating or noncommunicating),

2) tubular and

3) diverticular, developing as a consequence of abnormal tracheoesophageal separation [4, 19]. The association of esophageal atresia with esophageal duplication is quite rare [10, 24]. There are few reports that have detected oesophageal duplications in the muscular tunic of the esophageal wall [20], this type being called segmental intramural duplication of the esophagus [15]. Unique cases have been presented over the years [6, 16, 24, 26]. Usually, non-communicating intramural duplications of the proximal segment remain undiagnosed preoperatively and during surgery, resulting in significant potential for postoperative complications [20], including the failure of anastomosis [24], found by us in 2 cases. Cases of coexistence of esophagus atresia with esophageal fistula and cystic duplication are exceptionally rare, most of them being diagnosed at a later age due to symptoms or complications. The authors argue that it is preferable to resolve both malformations in neonatal surgery at one stage, thus reducing the possibility of developing postoperative complications [13,,22].

Thus, the analysis of the results of the study on the macro- and microanatomic peculiarities of structural and morphological components shows that in the esophageal atresia with inferior eso-tracheal fistula, concurrently with the macroscopic, histological aspects there are a series of changes with predictive importance on postoperative period, which can be classified into two groups: primary - characterized by histiogenesis disorders at the embryonic stage (fibromuscular dysplasia, esophageal dysplastic cartilage ectopia and gastric mucosa, esophagus dysplasias, incomplete esophageal membrane, aganglionosis) and secondary - atrofico-hipertrophy evolved during the fetal stage from 12-13 weeks gestation that varies according to their presence and location (muscle hypertrophy and / or atrophy of the muscles, vascular varicose ectasis, inflammatory processes, dismutation of neuronal structure.

Conclusions.

1. The results of this study allowed to confirm the presence of advanced structural morphopathological changes, which can significantly influence the regenerative-reparative processes of the esophagus after reconstructive operations in cases of esophagus atresia with distal tracheoesophageal fistula.

2. Concurrent fibro-muscular dysplasia changes with morphopathological changes of ganglioneuronal structures are responsible for esophageal motility disorders after reconstructive surgery in cases of esophageal atresia with distal eso-tracheal fistula.

3. In cases of esophageal atresia with distal eso-tracheal fistula, there may be some concomitant structural malformations (intramural communicating duplication of the atresical esophageal segments, diverticulum), which remain undiagnosed preoperatively and during surgery, determining a significant potential for postoperative complications, including the failure of anastomosis.

4. The presence of foveolar gastric mucosa in the distal segment of the eso-tracheal fistula may serve as a favorable morphological substrate for the development of the Barett esophagus in patients with esophageal atresia or malignancy, which necessitates the need for an permanent endoscopic evaluation.

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