Chapter 13

Histopathological Change of Esophagus Related to Dysphagia in Mixed Connective Tissue Disease

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Additional information is available at the end of the chapter

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1. Introduction

Dysphagia is one of the symptoms in patients with connective tissue diseases (CTDs), although it is not directly fatal and is a frequent complication. The frequency of esophageal dysmotility is 46-92%, 30-88%, 21-72%, and 50% in patients with systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematosis (SLE), and polymyositis/dermatomyositis (PM/DM), respectively [1-8]. While the cause of esophageal dysfunction in patients with CTDs has been unclear, there are some reports that suggest the accumulation of extracellular matrix, neuropathy, and autoantibody as the cause of esophageal dysfunction in patients with SSc [9-11]. On the other hand, there are few reports relating to the cause of esophageal dysfunction in MCTD patients, despite its frequency. Therefore, we examined the histopathological characteristics of esophageal lesions in MCTD patients using 27 autopsy cases in Japan [12].

2. Histopathological analysis of esophagus in MCTD patients

2.1. Comparison between changes in the upper, middle, and lower portion of the esophagus.

To date, there have been studies demonstrating a high frequency of esophageal symptoms in patients with MCTD [1-7,13] (Table 1). In our study, evidence of histological changes was found in 25 of the 27 cases examined (91%). The differences may be due to differences in the method of measurement. Esophageal dysmotility in MCTD patients is sometimes associated with the dilatation of the distal esophagus (Figure 1). The main sites of esophageal change were generally different between CTDs [8]. In patients with SSc and MCTD, the lower portion of the esophagus changes histologically. Therefore, we examined 3 different regions of the

esophagus, which we defined as follows: 1) upper, at the height of the ring around the cartilage of the trachea; 2) middle, at the height of the bifurcation of the trachea; and 3) lower, just above the esophago-cardiac junction. We compared histological changes for each portion. Of 12 cases examined, 9 showed slight to severe changes in the lower portion, 3 showed slight to severe changes in the middle portion, and none showed histopathological changes in the upper portion. According to these results, the lower portion was involved in many cases of MCTD.

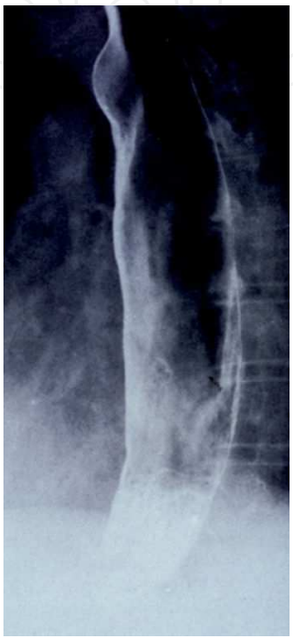

Figure 1. X-ray photograph of esophagus in MCTD patients.

Symptoms and dysmotility	Actual number (Frequency)	Reference
Abnormal esophageal motility	8/17 (47.1%)	Bennett (1980) [1]
Esophageal symptoms	11/17 (64.7 %)	Gutierrez (1982) [2]
• Heartburn	10/17 (58.8%)	
• Regurgitation	6/17 (35.3%)	
• Dysphagia	1/17 (5.9%)	
Abnormal esophageal motility	14/17 (82.4%)	
Esophageal symptoms		Dantas (1985) [3]
• Dysphagia	6/12 (50%)	
Abnormal esophageal motility	6/12 (50%)	
Esophageal symptoms		Marshall (1990) [4]
• Heartburn or regurgitation	29/61 (47.5%)	
• Dysphagia	23/61 (37.7%)	
Abnormal esophageal motility	21/35 (60.0%)	
Esophageal symptoms	14/21 (66.6%)	Doria (1991) [5]
• Heartburn	5/21 (23.8%)	

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Symptoms and dysmotility	Actual number (Frequency)	Reference
• Regurgitation	5/21 (23.8%)	
• Dysphagia	4/21(19.0%)	
Abnormal esophageal motility	15/21 (71.4%)	
Abnormal esophageal motility	15/17 (88.2%)	Lapadula (1994) [6]
Abnormal esophageal motility	10/18 (55.6%)	Rayes (2002) [7]
Esophageal symptoms		Calerio (2006) [15]
• Heartburn	9/24 (37.5%)	
• Dysphagia	18/24 (75%)	
Abnormal esophageal motility (cine-esophogram)	23/24 (95.8%)	

Table 1. The frequency of esophageal involvement in patients with mixed connective tissue disease.

2.2. Comparison between changes in the inner circular muscular layer and outer longitudinal muscular layer of the esophagus

As regards histological changes in the muscular layers, the inner circular muscular layer (IM) exhibited more severe changes than the outer longitudinal muscular layer (OM) in 17 of 27 cases (63%). Eight cases (30%) showed similar changes. Two cases (7%) showed no pathological changes in either IM or OM, and no cases (0%) showed more severe involvement of OM than IM. Muscular dynamisms of IM and OM in esophageal motility are different. The IM is fairly active and subject to greater stress than the OM [14]. Furthermore, esophageal regurgitation often occurs and exerts direct effects on the IM, particularly in the lower esophagus. Thus the IM in the lower portion may carry a larger physical stress than the OM. Therefore, more severe histological changes may occur in the IM of the lower portion than in the OM.

2.3. Cellular and tissue change

In our study, the most striking change of the esophagus in MCTD was severe atrophy and occasional disappearance of muscular fibers followed by fibrosis in muscular layer (Figure 2). In contrast to smooth muscle, however, striated muscle of the upper esophageal portion exhibited no marked changes. Similar histopathological changes occur in SSc [15,16]. In SSc patients, histological features are also characterized by degeneration and disappearance of smooth muscle cells with fibrosis, especially in the IM of the lower portion [17]. In our study, ganglionic cells had not decreased in number and were not particularly atrophic except in severely fibrotic areas. Vascular changes were also not overly severe in non-fibrotic regions, although slight intimal thickening of small vessels was sporadically found in the fibrotic area. The vein wall was injured and smooth muscle cell disruption and inflammatory cell invasion were observed (Figure 3).

2.4. Pathogenesis of esophageal lesions

The factors that seem to be associated with esophageal dysfunction have been reported in some studies, and include extracellular matrix degradation, disorder of blood circulation, and

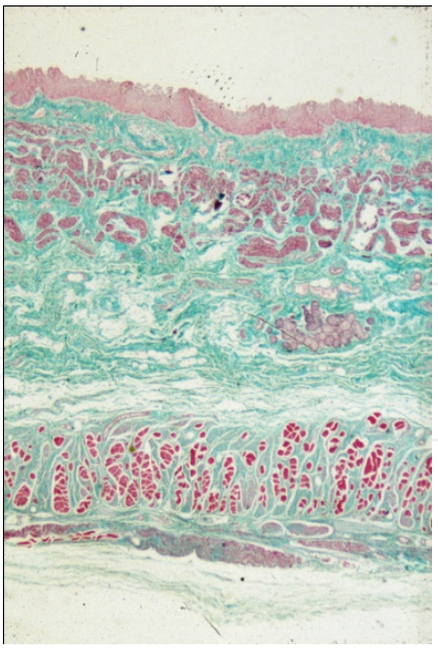

Figure 2. Esophageal muscle degeneration and fibrosis in MCTD patients.

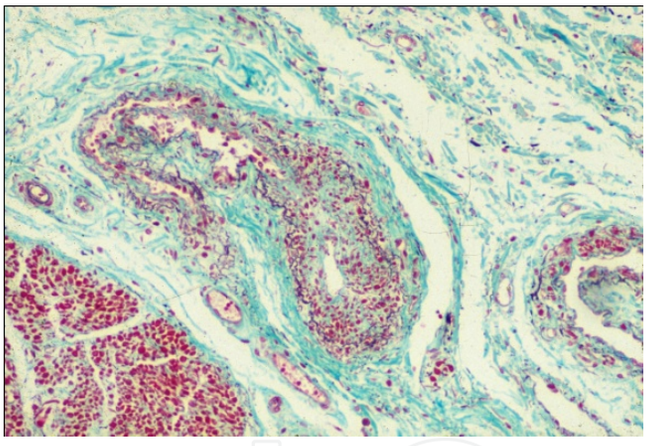

Figure 3. Vascular changes in the esophagus of MCTD patients.

autoantibodies [10,18-20]. Our hypothesis was that autoantibodies are associated with the pathogenesis of esophageal lesions. In immunohistochemical studies, anti-human IgG and anti-C3 antibodies reacted positively with muscle tissues showing a myolytic appearance accompanied by edema and inflammatory cell infiltration in MCTD autopsy case (Figures 4). No IgM deposition was found (Figure 4). The reactivity of IgG extracted from sera of MCTD patients against normal esophageal tissues was then assessed. Esophageal tissues used here were non-cancerous parts taken intraoperatively from esophageal cancer patients without specific immunological disorder. The IgG reacted with smooth muscle cells in the muscularis mucosa, muscular layer and venous wall, the ganglion cells in Auerbach's plexus, and squamous epithelium of the esophagus (Figure 5), but did not react with striated muscle in upper portion (Figure 5 A,B). IgG from MCTD patients also reacted with primary-cultured

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smooth muscle cells prepared from surgical specimens of esophagus (unpublished data) (Figure 6). These results suggested that antibodies in the serum of patients with MCTD attack smooth muscle tissues as well as other tissues of the esophagus.

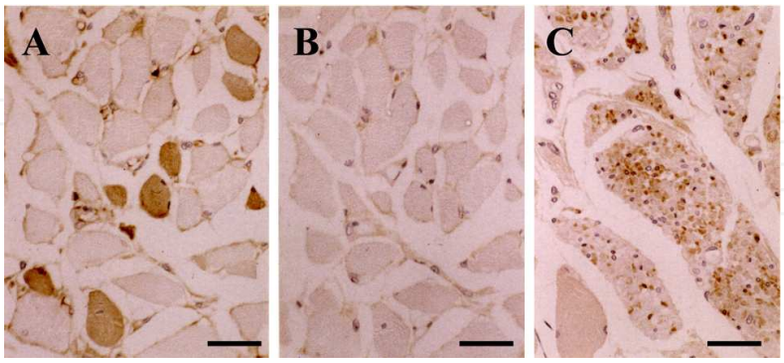

Figure 4. Immunoglobulin and complement deposition in the muscular layer of the esophagus from MCTD patients. Deposition of IgG (A), IgM (B), and complement C3 (C).

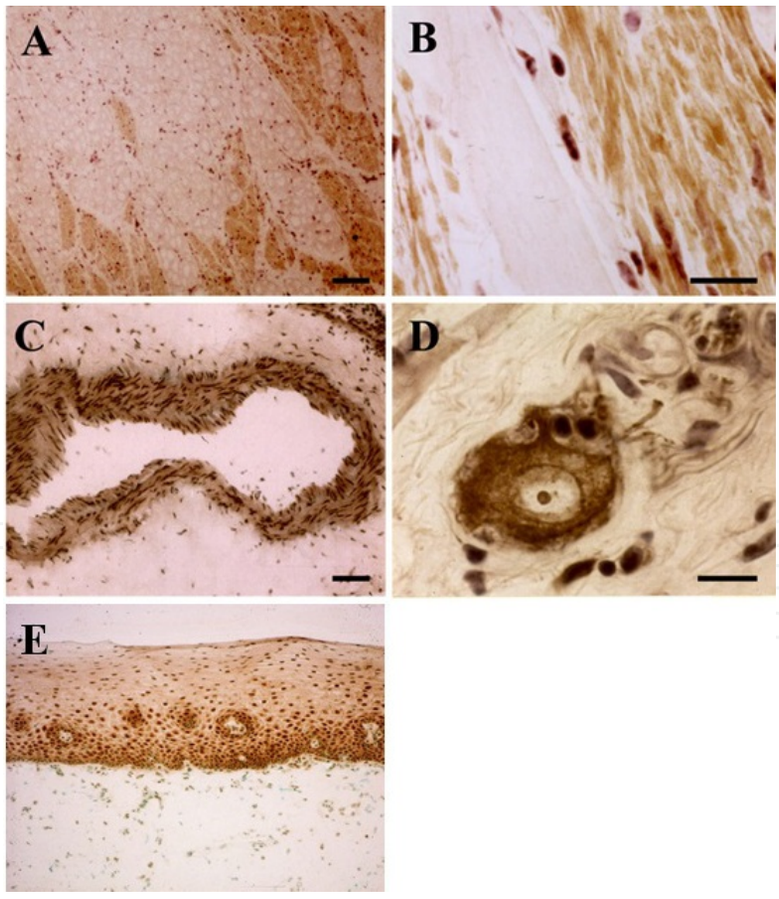

Figure 5. Reaction of IgG from MCTD patients with smooth muscles and other cells composing the esophagus. (A) Esophageal smooth muscle tissue, (B) Higher magnification of esophageal smooth muscle tissue, (C) Medial smooth muscle of the venous wall, (D) Ganglionic cell in Auerbach's plexus, (E) Squamous epithelium of esophagus

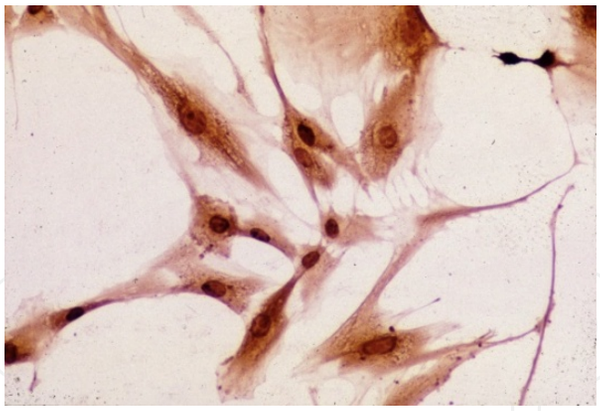

Figure 6. Reaction of IgG from MCTD patients with primary-cultured smooth muscle cells from esophagus.

3. Discussion

Histopathological features of the esophagus in SSc and MCTD patients are similar, but muscular change in SSc is more progressive than in MCTD patients in our study. It has been suggested that there is no association between manometric abnormality and cutaneous symptoms in MCTD patients, and the characteristics of SSc are not always linked to esophageal dysfunction [5]. The pathological mechanism of esophageal dysfunction in MCTD may be similar but not always identical to that in SSc.

In patients with CTDs, autoimmune inflammation occurs in systemic organs such as kidney, lung, skin and blood vessels, and so on. The gastrointestinal tract is also involved though the histological features and grades are different from disease to disease even in the same CTD.

In CTDs, many kinds of autoantibodies may play an important role in causing the various symptoms and diseases, whether they are fatal or not. These differ from disease to disease and from tissue to tissue. We showed that IgG from MCTD patients reacts to various tissues such as kidney and lung (unpublished data) (Figure 7). It is well known that pulmonary hypertension is the fatal cause of MCTD. Anti-endothelial cell antibody (AECA) was identified in the serum of MCTD patients, and was especially high in patients with pulmonary hypertension [21]. We now examine the antigen of AECA in endothelial cells of small pulmonary vascular vessels [22]. As for the autoantibody of MCTD against esophagus, our study revealed that IgG extracted from MCTD patients showed a positive immunohistochemical reaction not only for the smooth muscle cells of esophagus, but also for the ganglion cells in Auerbach's plexus, the vascular walls in esophageal muscular tissues, and squamous epithelium of the esophagus. Dysphagia in MCTD and SSc patients may be one of the symptoms often occurring as an autoimmune reaction.

The reason why the inner layer of the lower portion incurs more severe damage than other portions has not been clarified. Esophageal manometry shows that this portion sustains more intense mechanical stress in peristalsis than the outer layer or upper portions. Thus autoanti-

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bodies, mechanical stress and regurgitation may induce the severe dysphagia in MCTD and other CTDs.

Motility dysfunction is not a direct cause of death, but a strong association between esophageal dysmotility and interstitial lung disease in patients with MCTD is indicated [23]. Therefore, care must be taken with diagnosis.

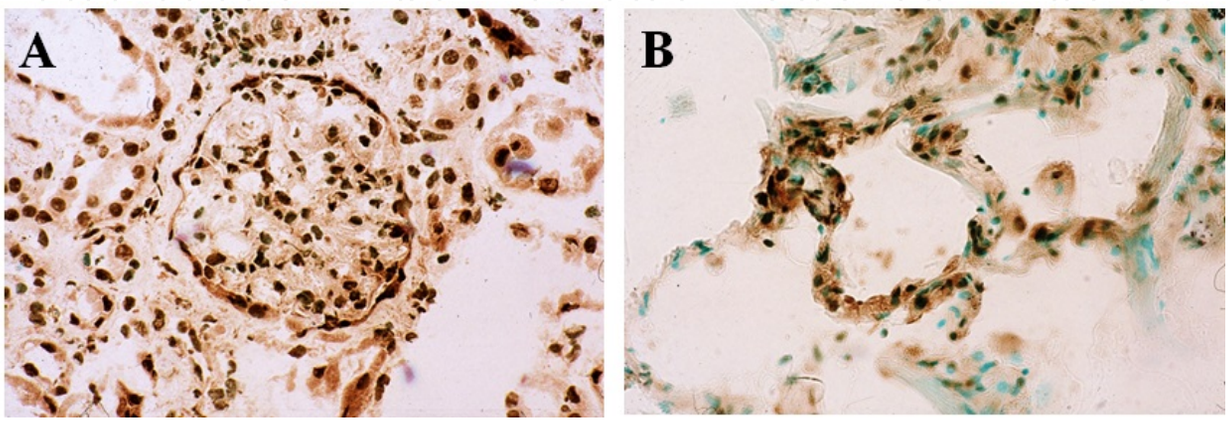

Figure 7. Reaction of IgG from MCTD patients with various tissues. (A) kidney, (B) lung

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