

Oesophageal involvement in scleroderma

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Systemic sclerosis (SSc) is an autoimmune disease characterized by vascular lesion, and abnormal fibrotic process affecting skin, lung, heart, kidney, musculoskeletal system and the gastrointestinal tract. The pathology of internal organ involvement is complex (several organs are involved at the same time), heterogenous (the extent of involvement is variable in each patient), and often the onset of organ damage is very early in the course of the disease. Clinical management of scleroderma patients is a difficult task for several reasons. Scleroderma patients are diagnosed using the classification criteria developed by the American College of Rheumatology in 1980. There is a substantial lack of sensitivity of these criteria, since many patients mostly with limited cutaneous involvement do not fulfill them. Sensitivity can be enhanced with the involvement additional data, *e.g.* nailfold capillary abnormalities (2) and specific autoantibody tests, but there is an obvious need to establish new diagnostic criteria for SSc. SSc has a very strong negative impact on quality of life resulting in a severe functional impairment in comparison with not only healthy population but another connective tissue diseases as well (3). Use of the hands and walking are the most severely impaired functions (3). It is very difficult to assess quality of life in SSc patients. General instruments such as HAQ-DI are useful tools, and seem to provide accurate data on this field showing a positive correlation with outcome measures of whole disease process (*e.g.* modified Rodnan skin score) or single organ manifestations (Raynaud's Condition Score, lung function tests, cardiovascular performance tests etc.) (4). Although there are many new therapeutic modalities in the prevention of single organ damage, SSc still frequently ends with a premature death. Analysis of mortality data

of different cohorts have shown a 2.7-fold to 4.7-fold increase of death risk (5). Subsequent analysis have shown that diffuse form with high baseline skin score, multiple organ involvement (lung, kidney, heart), male sex, older age at diagnosis and some laboratory abnormalities (leukocytosis, anti-Scl70 positivity, impaired kidney function, proteinuria) predict fatal outcome (5). Although the involvement of the gastrointestinal tract does not seem to severely enhance SSc-related mortality (5), its impact on quality of life seems to be substantial. A symptom-based self-reporting questionnaire was developed to assess the involvement of the gastrointestinal tract (6), but the evaluation of a single organ involvement including the gastrointestinal tract is still not complete.

Gastrointestinal involvement in SSc is a very frequent complication, and it is one of the earliest events. Furthermore, functional tests frequently show gastrointestinal dysfunction before the onset of GI-associated symptoms. Gastrointestinal manifestations equally affect both the limited and the diffuse subset of SSc (1). Cross-sectional prevalence of different organ damages caused by systemic sclerosis was recently published. The most frequently involved internal organ was the oesophagus in both limited cutaneous and diffuse cutaneous forms, 66.8% and 68.2%, respectively (7).

With regard to the gastrointestinal manifestation, the typical pathological changes are probably due to a complex interaction among the vascular, immune and neural systems. Vasculopathy is the early key event, which impairs the blood supply to the internal organs including the gastrointestinal tract. Hypoxia, compression of neural fibres caused by connective tissue deposition (8) and antineuronal antibodies inhibiting muscarinic neurotransmission are

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the main contributing factors for the development of neuropathy (9). Furthermore, the inflammatory cytokines released upon the stimulation of the immune system may alter different gastrointestinal functions as well.

Scleroderma involves each part of the gastrointestinal tract (10, 11) but the frequency of involvement of different segments of the gastrointestinal tract is different (12). The oesophagus is the most frequently damaged portion of the gastrointestinal tract (12), up to 90% of the patients have an oesophageal manifestation. Most of the patients have oesophageal dysmotility (13, 14), and subsequent oesophageal reflux disease (15). Oesophagus involvement is characterized by abnormal motility. The striated muscle of the upper part is mostly spared by the disease, and only the lower two-thirds of the oesophagus body composed of smooth muscle is affected. Most of the studies presented similar results and conclusions regarding oesophageal dysmotility: 1. the distal oesophagus shows low amplitude contractions or aperistalsis; 2. the resting pressure of the lower esophageal sphincter (LOS) is decreased or absent; 3. there is a lack of coordination between oesophageal peristalsis and LOS relaxation (13). Oesophageal dysmotility in association with delayed gastric emptying (16) results in impaired oesophageal clearance of refluxed gastric content and the development of oesophageal reflux disease (12, 14, 15). The typical symptoms of oesophageal reflux disease are dysphagia, odynophagia, heartburn and regurgitation. Severe and long lasting reflux disease is complicated by oesophageal ulcers, strictures, development of Barrett's metaplasia. Interstitial lung disease seems to develop as an organ manifestation of scleroderma, but oesophageal reflux disease complicated by small aspirations of acidic stomach content may contribute to the development of interstitial lung disease. Patients with advanced and progressive oesophageal motor abnormality had a faster progressing lung disease than those with less severe dysmotility (17). Patients with esophagitis and/or Barrett's oesophagus require a very strict suppression of gastric acid secretion (18).

The suitable methods to assess oesophageal involvement are manometry, pH monitoring, scintigraphy, endoscopy, and cine/video barium esophagogram (19). Barium swallowing is preferred since it is a simple and feasible test to demonstrate oesophageal dysmotility. If there is a suspicion of mucosal disease (inflammation, gastric type metaplasia or adenocarcinoma), an esophagoscopy must be performed. If dysphagia is the presenting symptom, barium swallowing must always precede esophagoscopy. Oesophageal manometry usually serves research purposes and adds little information to the diagnosis and the treatment of oesophageal manifestation of SSc. Endoscopy provides valuable information about erosive gastroesophageal reflux disease and its complications. 24-hr pH metry is an accurate diagnostic tool of acid reflux into the oesophagus. It may be combined with Bilitec® to show bile reflux as well. A recent technology, oesophageal impedance examination was introduced to distinguish between gas and fluid reflux. These tools are useful to diagnose reflux disease in those cases in which the symptoms are not typical or extra-oesophageal symptoms are present and a precise diagnosis is required (20). Furthermore, therapy refractory reflux disease needs a very detailed approach to measure the outcome of therapy. Proton pump inhibitor test seems an appropriate method to diagnose most of the patients with reflux disease. A double dose of proton pump inhibitor must be used for four weeks. If the symptoms are completely resolved due to this treatment, then oesophageal reflux disease can be considered to be established.

Managing gastrointestinal involvement of SSc is difficult and not yet solved due to several reasons.

First, there is no doubt that basic pathological processes in the background in a particular problem (*i.e.* oesophageal dysmotility and reflux esophagitis) are very similar in SSc and non SSc patients, but SSc may modify the development and propagation of a disease with other contributing factors as well. Second, the standardization of gastrointestinal diagnostic procedures in SSc patients is not complete this time.

The evaluation of the symptoms is difficult, since validated symptom questionnaires are lacking. Confirmation of the validity of functional tests to measure different gastrointestinal functions is still an ongoing process (20).

Third, the symptoms do not usually correlate with functional tests and morphological examinations. On one hand, many patients present gastrointestinal symptoms with no or hardly detectable pathologic changes. On the other hand, patients with severe pathologies do not present any symptoms at all.

Fourth, the treatment options available to cure gastrointestinal involvement in SSc must be also validated. We do not know whether SSc patients respond to any treatment with the same result, intensity and side effects as non-SSc patients would do. The most typical example of this phenomenon is the treatment of polyarthralgia/polyarthritis accompanying SSc. Non-steroidal antiinflammatory compounds were a good option to reveal inflammatory symptoms, but the presence of gastrointestinal mucosal vascular malformations do not allow the use of such drugs because of the high risk of gastrointestinal bleeding.

Fifth, the outcome measures also lack a standardization. There have been several attempts made to measure treatment results, but a consensus agreement as to how to estimate different treatment modalities still needs further investigations. A symptomatic questionnaire (6) was developed, but its validation procedure needs to be completed.

Due to the reasons above there is only a little evidence supporting the management of gastrointestinal involvement of SSc. The EULAR Scleroderma Trial and Research group (EUSTAR) has recently released a set of recommendations for the treatment of systemic sclerosis (21). Based on a widespread literature research and the opinion of experts and patients, optimal treatment plans are suggested to cure the most threatening organ involvements including oesophageal manifestations:

1. Proton pump inhibitors (PPIs) should be used for prevention of SSc-related gastroesophageal reflux disease, oesophageal ulcers and strictures. Recently, American Gastroenterological

Association (AGA) has released a position statement on the management of gastroesophageal reflux disease (20). The use of antisecretory compounds is strongly recommended to provide symptomatic relief and heal esophagitis. Lifestyle modifications are effective in selected groups of patients. Overweight or obese patients should lose some weight and patients with heartburn or regurgitation should elevate the head of the bed. Other modifications including avoiding late meals, specific foods or activities should be individualized.

2. Prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early response in satiety, bloating, pseudoobstruction, etc.). The drugs currently available to stimulate intestinal motility are non-selective 5-hydroxytryptamine agonists, dopamine D2 receptor antagonists (metoclopramide and domperidone), and motilides (erythromycin) (22). However metoclopramide is not recommended by AGA to treat GERD symptoms, its effectivity or failure in the treatment of scleroderma associated oesophageal dysmotility/reflux disease awaits further confirmation. The paper by Pakozdi *et al.* published in the current issue addresses several of these questions to this particular problem: oesophageal involvement in SSc. The aim of this study was to assess the long term efficacy of acid suppression on oesophageal symptoms of SSc patients, and to find a correlation between symptoms and oesophageal scintigraphy. Although lansoprasole was able to improve symptoms 6 months after the initiation of therapy, its effectivity was not established 6 months later. Symptoms of gastrointestinal involvement, radiologic abnormalities, endoscopic findings and motility disorders do not correlate in scleroderma patients, and even the subset of disease had impact only on the overall incidence of endoscopic esophagitis (23). Endoscopic esophagitis or Barrett's oesophagus is still frequent finding in those patients who are receiving proton pump inhibitor therapy (18). The findings of Pakozdi *et al.* confirm that the symptoms of oesophagus involvement of scleroderma

do not depend purely on the reflux of acidic stomach content, and suggest that long term complaints are rather determined by the underlying dysmotility which is left unchanged by proton pump inhibitors. A selection of patients may improve the rate of success, since those who have mucosal rupture (erosive esophagitis or oesophageal ulcers) may have a greater benefit from the suppression of acid production. Scintigraphy confirmed the importance of oesophageal dysmotility, since a progressive deterioration was observed 12 months after the baseline observation. This finding confirms that proton pump inhibitors may provide a symptomatic improvement, but do not influence the progression of the disease. To find an effective disease-modifying drug which may influence the natural course of the disease still requires further studies.

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