Gastrointestinal and Hepatic Disease in Systemic Sclerosis

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KEYWORDS

• Scleroderma • Systemic sclerosis • Therapeutics • Gastrointestinal diseases
• Mouth diseases • Esophageal diseases • Stomach diseases • Liver diseases

KEY POINTS

- The gastrointestinal tract (GIT) is the most commonly involved internal organ in systemic sclerosis (SSc).
- GIT management involves an integrated approach of patient education for lifestyle modification, medical therapies, and ancillary services for nutrition support.
- Medical therapeutics for SSc have several important considerations that require an understanding of potential adverse effects.

EPIDEMIOLOGY

Systemic sclerosis (SSc, scleroderma) is a connective tissue disease characterized by vasculopathy, fibrosis, and immune dysfunction with a prevalence varying from 30 to 443 per million population.[1] SSc classification criteria[2] do not incorporate the gastrointestinal tract (GIT) manifestations that are often present in this disease, despite the fact that GIT involvement produces substantial morbidity and is the most commonly involved internal organ in SSc.[3] The GIT is the presenting disease feature in 10% of SSc, occurs during disease course in up to 95% of individuals, and is responsible for 6% to 12% of mortality in SSc patients.[4] Malabsorption, gastroesophageal reflux (GERD), nausea, vomiting, diarrhea, and constipation are some of the GIT complications that occur in

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this population, and despite varying degrees of disease severity from mouth to anus, SSc GIT involvement significantly impairs quality of life in almost all patients.[5,6] Severe GIT involvement in up to 8% of SSc patients is associated with a high morbidity and poorer outcome.[7,8]

PATHOGENESIS AND PATHOPHYSIOLOGY

The specific pathogenesis of GIT involvement is complex and not adequately understood, but neuropathy progressing to myopathy with eventual fibrosis has been proposed.[8] The pathophysiology of GIT involvement is thought to parallel other organ involvement in SSc with fibroproliferative vascular lesions of small arteries and arterioles, increased production of various profibrotic growth factors, and alterations of innate, humoral, and cellular immunity.[9,10] Although the role of immune dysfunction has not been adequately characterized, environmental factors may trigger the initial endothelial cell injury, which results in release of reactive oxygen species, chemokines, and cytokines that activate and recruit chronic inflammatory cells, including T- and B-lymphocytes and macrophages.[8]

Animal models for SSc described in the literature demonstrate that there are several induced and spontaneous systems mimicking certain inflammatory, immunologic, or fibrotic aspects of the disease, which provide contexts in which to study various aspects of this complex disorder.[11] However, the most extensive GIT work has been done in the transgenic (TG) mouse strain TβRIIΔk-fib, which is characterized by ligand-dependent upregulation of transforming growth factor-β (TGF-β) signaling. Quantitative polymerase chain reaction results of TG GIT fibroblasts showed evidence of upregulated collagen transcription and noncanonical TGF-β signaling pathways.[12]

The concept of GIT cell-mediated immunity in SSc is supported by biopsy specimens that demonstrate an increase in endothelial/lymphocyte activation leading to a pronounced increase in the $CD4^+/CD8^+$ ratio, and type 2 helper (Th2) polarization.[13] The classic Th2 cytokines interleukin (IL)-4 and IL-13 are not only profibrotic but also upregulate humoral immunity by inducing immunoglobulin production.[14] Of interest, immunoglobulins isolated from the serum of SSc patients interfere with cholinergic-mediated contraction of the GIT, a phenomenon that is most intense early in the disease and more extensive later in the disease, when both smooth muscle and myenteric neurons are involved.[15–17] These circulating antimuscarinic 3 receptor autoantibodies block cholinergic neurotransmission by inhibition of acetylcholine release and thus the ability of the smooth muscle in the GIT to respond to stimuli. As fibroblasts become activated into myofibroblasts by TGF-β, excess collagen is produced, which causes structural damage and also impaired motility. The result of these processes is a dysfunctional GIT, which contributes to Barrett esophagus, gastroparesis, malabsorption, and fecal incontinence.

ANATOMIC DISTRIBUTION OF INVOLVEMENT

Oral Cavity

Oral involvement in SSc may include perioral fibrosis, sublingual frenulum thickening, or secondary Sjogren syndrome, all of which can predispose patients to malnutrition because of reduction of oral aperture and intake.[18,19] Dental changes because of bone reabsorption may affect mastication and result in tooth loss.[20]

Esophagus

In SSc patients, the esophagus is the most commonly affected organ of the GIT, occurring in up to 90% of patients and resulting in symptoms of heartburn,