Scleroderma and the Gut Summary  Dr. Zsuzsanna McMahan

Background

Normal GI motility is stimulated by a bolus of food which is moved by smooth muscle.Circular muscular tone creates radial closure and peristaltic wave. Longitudinal smooth muscle is synergistic, reducing the power needed by circular muscle tone by as much as 1/10.

GI smooth muscle contractions are controlled by the autonomic and enteric nervous systems.

Parasympathetic innervation stimulates peristalsis and secretion in the stomach and proximal 2/3 of the colon. The enteric nervous system (ENS) is housed entirely within the walls of the gut. As food moves through the gut it stimulates the sensory nerves which spreads to the myenteric plexus which activates circular and longitudinal muscle.

In terms of importance, upper GI (Esophageal and stomach) are innervated by vagus nerve>>ENS. In the lower GI tract, small intestine ENS >>vagus, proximal colon Vagus>>ENS and remaining colon ENS>>Vagus

Clinically, it is possible to see patients with a mix of upper and lower symptoms, however, there are two distinct groups. In the upper GI group regurgitation, GERD, early satiety vomiting, and their lower GI tract can be completely normal. The second group, lower GI tract predominant symptoms, severe dilation of bowel filled with stool. Neither seems to necessarily be related to disease duration, but rather might suggest two different mechanisms.

Overview of scleroderma GI dysmotility

Scleroderma dysmotility may affect any GI tract region, however, the frequency with which specific GI regions are functionally impaired differs across the SSc gut. 90% have esophagus involvement, 30-50% have stomach/small intestine, and 50-70X have anorectum involvement. 

The time course of dysfunction is varied.

Using UPMC database (Steen A&R 2000)-Severe GI involvement is rare (8%) in dcSSc and often occurs early, however, mortality rate is 85% at 9 years. Risk factors for severe GI disease (TPN) in SSC is associated with male gender, concurrent myopathy and sicca symptoms while white race was associated with less risk (McMahan AC&R 2017). Predictors of pseudo-obstruction (Dein. Sem Arth Rheu 2019) include male sex, dcSSc, baseline myopathy and opioids (potentially reversible). RNA pol was associated with less risk.

Antibodies associated with severe GI disease

U3-RNP (fibrillarin) 25%, U1-RNP (often associated with MCTD) 14%, and Th/To (often with limited skin involvement) 13%.

Scleroderma GI dysmotility: Pathology and pathogenesis

Muscle atrophy is prominent in the SSc GI tract but is not diffuse across all muscle types. On muscle biopsy there seems to be more atrophy of smooth muscle over skeletal muscle. Also, within smooth muscle it seems that circular muscle is effected more than longitudinal muscle. This raises the question whether all of the pathology is due to fibrosis. On histology, areas of atrophy don’t seem to be near changes of inflammation nor with vascular changes.

Neural abnormalities are identified on pathology in SSc patients w/ fecal incontinence. Structurally normal enteric neurons except for the axon terminals which can be devoid of cytoskeletal elements.
Is autonomic dysfunction playing a role in GI dysmotility?
SSc patients with severe GI disease have more global autonomic dysfunction (based on weight composite patient reported score). Believed to represent parasympathetic under activity and sympathetic overdrive

A pathogenic role for antibodies?
Several groups have reported that Anti Muscarinic 3 acetylcholine receptor antibodies (Anti-M3R) interfere with the neuromuscular junction in patients with SSc and in particular in patients with GI symptoms. There seems to be a subgroup of patients with these antibodies which lead to smooth muscle atrophy over time.

GI microbiome in SSc
Emerging evidence suggests that GI tract dysbiosis is a feature of the SSc disease state. Have decreased beneficial flora (Clostridium/Faecalibacterium/Bacteriodes) and increase pathogenic flora (Fusobacterium, Prevotella, and Erwinia).

Patient cases
40 y.o w/ longstanding lcSSc. Refractory upper GI symptoms. Has had unintentional 10lb weight loss. Attributes weight loss to early satiety and nausea. Already on concurrent PPI and prn H2 blocker therapy. Gastric emptying stomach showed borderline gastroparesis. Was hesitant to try metoclopramide due to concern for tardive dyskinesia. We tried her her on mirtazapine. Originally used for depression. Agonism of 5-HT1A serotonin receptors. This has been studied in multiple double blind RCT in patient’s w/o SSc to improve symptom control.

43 y.o. w/ worsening distention, bloating and intermittent diarrhea. 10lb weight loss over 12 months. Whole gut transit study showed severe colonic delay. Could consider prucalopride (approved as a promotility in SSc). 5-HT4 receptor agonist. Effective in treating chronic constipation unresponsive to laxatives. PROGASS study (Vignone AR&T 2017). Random controlled crossover study in SSc.

Other causes of diarrhea/bloating in SSc
Fructose malabsorption. Consider fructose elimination diet CDif risk kis high due to PPI, abx use, and frequent outpatient care visits

Q&A
Is there any association between SSc ILD and increased GI dysmotility?
Lot of data that shows refractory GERD and worsening ILD. Data hasn’t proven that GERD leads to progression of ILD but the association is definitely there.

Are anti-muscarinic 3 receptor antibodies seen in Sjogren’s w/ gut dysmotility or bacterial overgrowth?
They have been seen in Sjogren’s patient and have been associated with GI dysfunction.

Are M3R ab available at most clinical laboratories?
Not available at most. Mayo panel has some muscarinic antibodies but don’t think it’s M3R antibodies.

Are there any clinical scenario where you would send out for those antibodies?
In patients with rapidly progressive lower GI disease. Would want to study them prospectively see if they respond to IVIG, plasmapheresis or immunosuppression.

Is there any data for early immunosuppression to prevent GI symptoms?
The problem is that we don’t have good measures of GI disease activity. Can’t us mRSS or PFTs etc. Thus, it’s hard to justify starting immunosuppression since we aren’t sure what the endpoints are or if it’s an active immune response causing the damage.