Case report

Protective role of interleukin-6 in systemic sclerosis gastrointestinal tract involvement: case report and review of the literature

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ABSTRACT

Objective. Systemic sclerosis (SSc, scleroderma) is characterised by complex multi-organ pathogenesis, including gastrointestinal tract (GIT) disease that remains poorly characterised. Immunosuppression is commonly used to treat inflammatory manifestations of SSc, including the skin, lungs and joints. There is a paucity of data on the effects of immunosuppression on GIT disease in SSc.

Methods. This case report and review of the literature presents two clinical cases in which interleukin-6 (IL-6) antagonism was used for early, diffuse skin disease.

Results. In these two cases, IL-6 antagonism was associated with an exacerbation of GIT symptoms.

Conclusion. We postulate that IL-6 is important in the repair of GIT mucosa and further studies are warranted to better understand the effects of immunosuppression on SSc-GIT disease.

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterised by immune dysregulation, proliferative vascular lesions and fibrosis of the skin and internal organs. The gastrointestinal tract (GIT) is the most common extra-cutaneous organ system involved in SSc. It is the presenting feature in 10% of patients and, over the course of the disease, affects up to 90% of patients (1). It is associated with significant morbidity and mortality (2). Immunosuppression is commonly used to treat the inflammatory manifestations of SSc. Common side effects of immunosuppressive drugs include GIT symptoms. As such, choosing an immunosuppressive drug for treatment of a disease characterised by GIT disease, such as SSc, can be particularly challenging. In addition, the role of immunosuppressive drugs to prevent or treat GIT disease in SSc remains largely unknown. There is a pressing need to address the effect of these therapies on GIT symptoms.

Pathogenesis of systemic sclerosis gastrointestinal disease

The GIT in SSc is a challenge to study due to limited data on pathophysiology, and considerable practice variation in approach for diagnostics as well as empiric treatment for GIT symptoms (3, 4). In particular, the role of ischaemia, inflammation, fibrosis, and neural function in the spectrum of mild to severe GIT dysfunction is unclear. Histology studies of the oesophagus, small intestine, and large bowel have important limitations (3), in particular the fact that they were conducted in subjects with long SSc disease duration and with heterogeneous disease severity. As such, large gaps in our understanding of the pathogenesis of SSc-GIT disease remain (Fig. 1).

Clinical presentation

The first patient is a 56-year-old female who received tocilizumab, an interleukin-6 (IL-6) antagonist, for rapidly evolving skin (modified Rodnan skin score; mRSS 22) and inflammatory joint disease. Her antinuclear antibody (ANA) was 1:160 and she had a positive RNA polymerase III antibody. Her antinuclear antibody (ANA) was 1:160 and she had a positive RNA polymerase III antibody. While her skin score improved (mRSS 17) after several months on this therapy and weight remained stable, her GIT 2.0 developed severe scores for reflux, bloating, diarrhoea and soilage. Tocilizumab was thus discontinued and the patient was referred to gastroenterolo-
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Fig. 1: Potential interaction of dysbiosis with systemic sclerosis gastrointestinal disease and immunosuppression (IS)

Fig. 2. Pseudoobstruction in a systemic sclerosis patient receiving tocilizumab.

Is there an association between interleukin-6 inhibition and GIT disease?

During GIT homeostasis, a continuously renewing single layer of epithelial cells and its associated layer of mucus provide a barrier between the intestinal microflora and the resident immune cells in the submucosa. Normal regulation of intestinal inflammation in the GIT microenvironment includes the production of interleukin (IL) 6 (5). IL-6 is a cytokine produced by many cell types, which has pleiotropic effects. Anti-IL6 therapy (tocilizumab) reduces systemic and joint inflammation, hepatic acute phase proteins, and has anti-angiogenic effects (6).
Although rare, tocilizumab has been associated with bowel perforation in rheumatoid arthritis (RA) (7), in particular in association with diverticulitis and steroid use. Indeed, in RA, this adverse event had an event rate of 2.8 per 1000 patient-years in subjects treated with tocilizumab, with no events reported in control or placebo groups. On the other hand, post-marketing reports of serious gastrointestinal events for patients on tocilizumab for RA were similar to anti-tumour necrosis factor treated population derived from a US-based health care insurance claims and published literature (8).

Until recently, the pathophysiology of bowel perforation was largely unknown. However, a study published in 2014 suggests a novel role for IL-6 in intestinal injury repair (9). In animal models of bowel injury substantial IL-6 expression was induced by intraepithelial lymphocytes shortly after injury. This was required for cellular proliferation and epithelial repair. In addition, IL-6 inhibition resulted in decreased epithelial proliferation and impaired wound healing. Finally, in intestinal tissue obtained from patients who had undergone surgical resection of the colon due to traumatic perforation, IL-6 was also observed within the area of perforation. These results were interpreted as consistent with a beneficial role of IL-6 for intestinal wound healing early after injury. Although the role of IL-6 in chronic intestinal inflammation also remains to be better defined, in a small, pilot study, treatment of patients with active Crohn’s disease with a humanised monoclonal antibody to IL-6R was associated with improvement in disease activity but not endoscopic and histologic scores, suggesting that IL-6 blockade was helpful at reducing systemic symptoms but not intestinal wound healing. In a recent phase II trial, tocilizumab was shown to have promising effects on skin and lung disease in SSC (10). It is possible that IL-6 and IL-6 blockade may vary by tissue type and microenvironment. While further data will help to identify the precise risk associated with tocilizumab use, caution would seem to be indicated in SSC patients with GIT inflammation (11). A phase III trial of tocilizumab in SSC is planned, in which case special attention to GIT disease could provide important new information on the role of IL-6 blockade in this complex disease.

Conclusion

Many GIT symptoms are non-specific and are associated with both SSC and immunosuppressant drugs. Thus, overlapping symptomatology may in part explain “worsening symptoms” associated with exposure to immunosuppression in SSC. Whether SSC is associated with dysbiosis and whether immunosuppression also contributes to dysbiosis is largely unknown. Studies to understand the role of gut dysbiosis, the effect of immunosuppression in SSC-GIT disease and the role of microbial directed therapies in SSC are urgently needed (12). In the meantime, close monitoring of SSC subjects exposed to immunosuppression is warranted.

Key message

- Understanding the role in interleukin 6 (IL-6) in systemic sclerosis gastrointestinal tract (SSC-GIT) disease is warranted.
- Studies to understand the effect of immunosuppression in SSC are urgently needed.

References

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