# Undiagnosed Systemic Sclerosis causing exaggerated radiation-induced fibrosis

## Background

In systemic sclerosis, overproduction of extracellular matrix macromolecules by fibroblasts in the skin and internal organs is thought to lead to fibrosis and dysfunction. Presenting symptoms are variable and include: pruritis, Raynaud’s phenomenon, dysphagia, joint and muscle pain, and weakness. Prognosis is dependent on the type of systemic sclerosis, with stability of the condition common in multiple types.

Ionizing radiation is widely used for the treatment of head and neck cancer. While fibrosis is a common sequel to radiation, when therapeutic doses and targeted radiation fields are used, this fibrosis is typically limited in extent and does not progress. Certain connective tissue disorders are considered relative contraindications for radiation therapy, as systematic reviews have suggested that patients with connective tissue disorders have an increased risk of chronic radiation-induced normal tissue toxicity\(^1\). Connective tissue disorders include: rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, and systemic sclerosis. Of these disorders, systemic lupus erythematosus and systemic sclerosis have been noted to have increased chronic toxicity even when compared to other connective tissue disorders\(^2\). We present a case of a patient with undiagnosed systemic sclerosis who presented with a severe fibrotic reaction in response to radiation therapy.

## Objectives

- To present a case report and review of the literature showing exaggerated radiation induced fibrosis in a patient with undiagnosed systemic sclerosis who received radiation for oropharyngeal squamous cell carcinoma.
- To demonstrate that caution should be used when administering radiation therapy to patients with connective tissue disease.

## Methods

The patient is a 51 year-old male with a history of a T2N0M0 squamous cell carcinoma of the palatine tonsil. He was treated at an outside institution with tonsillectomy with subsequent 70 cGy of radiation in 35 fractions to the bilateral neck and tonsil area and concurrent cisplatin every 3 weeks. Three months after completing treatment, the patient began having severe trismus, dysphagia, reflux with aspiration, and hand and foot swelling. He presented to our clinic 9 months after finishing treatment with the above symptoms and a 50 pound weight loss. Physical exam and swallow study showed severe neck fibrosis, near laryngeal fixation, and aspiration. The patient was diagnosed with systemic sclerosis with Raynaud’s phenomenon and an exaggerated fibrotic response to radiation.

## Results

The patient underwent an esophageal dilation and swallowing therapy with some modest benefits in dysphagia and aspiration. A gastrostomy tube was placed in order to supplement the patient’s nutrition. After ten months of regular swallowing therapy with speech pathologists, the patient was tolerating a soft solid and nectar-thick liquid diet without need for gastrostomy tube supplementation. He will continue a home exercise program for swallowing. The patient is cautioned that the fibrosis related to the radiation is typically progressive and his oral intake make be further compromised in the future.

## Discussion

Although the patient experienced some improvement in regards to his dysphagia with esophageal dilation, swallow therapy, and better control of his systemic sclerosis, his long term functional prognosis remains guarded. As the patient is determined to be free of a gastrostomy tube and eat by mouth, he is at continued risk of aspiration pneumonia, which is a common cause of death in patients with exaggerated fibrotic reactions in response to radiation therapy.

The relationship between systemic sclerosis and excessive fibrosis with radiotherapy is not clear at this time. TGFβ is a cytokine produced by most inflammatory cells and has a potent effect on stimulation of collagen synthesis by fibroblasts. TGFβ has been implicated in the pathogenesis of systemic sclerosis and other connective tissue disorders. It is postulated that TGFβ is activated excessively in patients with systemic sclerosis when they undergo radiation therapy. The mechanism for an exaggerated fibrotic reaction is supported by findings of TGFβ being markedly elevated in irradiated non-tumor-bearing tissue several months after radiation treatment. While this pathway may account for a part of the fibrotic response, other cellular processes, such as those involving endothelium injury, mast cells, or lymphocytes, may play a contributory role\(^2\).

There have been several case reports and small series illustrating the connection between systemic sclerosis and exaggerated fibrotic responses to radiation, often demonstrating fatal outcomes. Larger systematic reviews have looked at the relationship of patients with connective tissue disease who underwent radiation and experienced increased chronic toxicity. It is suspected that systemic lupus erythematosus and systemic sclerosis, in particular, have increased rates of chronic toxicity\(^3\). Systematic reviews have shown that there is a trend towards the severity of connective tissue disease, as measured by the number of involved organ systems, correlating with the rate of chronic toxicity\(^4\). Given the low number of patients with systemic sclerosis who undergo radiation, it has been difficult to show correlation with higher level data. Currently, most radiation oncologists recommend caution when initiating radiation therapy in patients with connective tissue disease, in particular, systemic sclerosis.

## Conclusions

Patients with systemic sclerosis may have exaggerated responses to therapeutic doses of radiation. This can be progressive, extend beyond irradiated fields, and eventually fatal in severe cases. Patients with connective tissue disease, especially systemic sclerosis, and cancer should be counseled on the risks of an exaggerated fibrotic response and overall increased risk of chronic toxicity prior to a decision on treatment.

## References