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Case Study

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SYSTEMIC SCLEROSIS- A CASE REPORT

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ABSTRACT

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin and internal organs associated with vascular injury and immune system dysregulation. This case report details of the 55 year old female who was diagnosed with **systemic sclerosis on cyclophosphamide treatment**, who is a known case of type 2 diabetes mellitus on oral hypoglycaemic drugs medications for 10 years and was also diagnosed with **ductal carcinoma of right breast** status post modified radical mastectomy 7 years back, came with recurrent episodes of vomiting, loose stools and pain abdomen. This patient was advised for HRCT THORAX to rule out lung fibrosis which revealed extensive honeycombing involving all lobes suggestive of interstitial lung disease possible secondary to systemic sclerosis. Immunological studies were done for the breast carcinoma; RNA – POLYMERASE ANTIBODY IgG was tested positive. Hence this article is adding to the evidence of the relation between systemic sclerosis, carcinoma and RNA- polymerase antibody (IgG).

KEYWORDS: Systemic sclerosis, RNA, polymerase antibody, Carcinoma.

INTRODUCTION

Systemic sclerosis (scleroderma, or SSc) is a heterogeneous, multisystem connective tissue disease that arises as a consequence of a complex interplay of altered immunologic processes involving vascular endothelial cell damage and excessive activation of fibroblasts, culminating in skin sclerosis and fibrotic changes of affected visceral organs.

SSc is a rare condition that affects mostly young and middle-aged women, resulting in disproportionate morbidity and mortality. Vascular injury occurs early in the disease.

SSc can present at any age, the peak age of onset in women with both limited and diffuse cutaneous forms is 65–74 years Subsequent to vascular injury and immune disturbances, fibroblasts activate and produce collagen and extracellular matrix, resulting in organ dysfunction and tissue fibrosis.

Although systemic sclerosis is uncommon, it has a high morbidity and mortality.

Clinical features suggestive for definitive diagnosis are skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon, and SSc-related autoantibodies.

In lcSSc, visceral organ involvement tends to follow an insidious and often benign course, while digital ischemic ulcers, pulmonary arterial hypertension (PAH), hypothyroidism, Sjogren's symptoms, and primary biliary cirrhosis may occur as late complications.

A subset of patients with lcSSc (display the characteristic constellation of clinical findings (limited cutaneous SSc) calcinosis cutis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia), historically termed the CREST syndrome.

The association between SSc and increased cancer risk has been reported in several case series, although this association has not been consistently demonstrated across all studies. Researchers who have conducted recent meta-analyses have reported increased numbers of solid organ malignancies in SSc patients, including lung cancers but not breast cancers. Investigators in other studies, however, have suggested that lung cancers are considered to be common in patients with SSc. The significant heterogeneity and variability in the cancer subtypes reported in these studies may be a consequence of limited patient numbers, patient characteristics and study design. Moreover, the actual role of SSc in the development of cancer remains unclear. For example, it is debatable if SSc patients with severe interstitial lung disease have an increased risk of developing lung cancer.

Few studies have examined the temporal relationship of cancers to the onset of SSc, and the current literature that links breast cancer to the onset of SSc remains contradictory.

The role of autoantibodies and malignancies in other autoimmune rheumatic diseases, however, has been well-described, such as in large population-based studies for inflammatory myositis. Anti-MJ/NXP2 and anti-p155/140 antibodies have been described in cancer-associated myositis. With regard to the latter, its high negative predictive value is potentially helpful to rule out the presence of occult malignancy in patients with dermatomyositis.

It is recently reported that anti-RNA polymerase III (anti-RNAP) antibodies may be associated with malignancy in a small cohort of five patients with early-stage SSc. Airò et al. also described similar clustering of cancer associated with the onset of SSc in a small sample of patients.

CASE REPORT

A 55 year old female presented with complaints of vomiting for the past 2 days a non projectile vomitus which contained recently consumed food particles non bile and non blood tinged content. Patient also had complaint of headache for the past 10 days which was insidious on onset, gradually progressive which was present over bilateral frontal region of forehead non radiating dull aching type.

Patient is a known diabetic (Type 2 diabetes mellitus) for the past 10 years and was on oral hyperglycemic drugs (details unknown).

Patient was diagnosed with ductal carcinoma of right breast in 2016 and mastectomy was performed for the same.

Fig. 1: Sclerosed hands showing stretched and thick skin over digits.

Fig. 2: Puckered face of a patient diagnosed with Systemic sclerosis.

MRI brain was done for the patient which showed Old infarcts with gliotic changes noted involving bilateral basal ganglia, thalamus and right centrum semiovale, right hippocampi with loss of volume with increased t2 and flair intensity and loss of hippocampal digitations and dilatation of the ipsilateral ventricle- to rule out mts.focal area of blooming noted on the pons – old microhemorrhage.

HRCT thorax was done in 2016 status post mastectomy and chemotherapy for right breast carcinoma which showed areas of extensive honeycombing involving all the lobes of the bilateral lungs with peripheral, subpleural and basal predominance causing architectural distortion. Areas of reticulation with intra & interlobar interstitial septal thickening and traction bronchiectasis involving bilateral lung parenchyma predominantly in the bilateral lower lobes.

Minimal ground glass opacification involving the posterior segment of right upper lobe and anterior, apico-posterior segments of left upper lobe Ultrasound abdomen showed grade 1 fatty liver with no other significant findings.

2D echo was done which showed Sclerotic Aortic valve with mild Aortic regurgitation. Mild Mitral regurgitation with annular mitral calcification. There were also findings of trivial tricuspid regurgitation with pulmonary artery pressure of 31mmHg.

Histo–pathology report from MRM specimen of right breast showed infiltrative ductal carcinoma. With lymph node positivity of 4/9 with all free margins with scarff bloom Richard grade 1.

Immuno-histo chemistry report showed tumour cells positive for IR and PR and HER2/nue positive.

DISCUSSION

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis in the skin and internal organs

associated with vascular injury and immune system dysregulation

The most characteristic autoantibodies related to SSc are anti-centromere, anti-topoisomerase 1, and anti-RNA polymerase III.

SSc can also overlap with other systemic autoimmune diseases, particularly with polymyositis. Anti-PM/Scl 75 and PM/Scl 100 are present in sera from patients with polymyositis (PM), systemic sclerosis, and PM/SSc overlap syndromes, and they may characterize distinct SSc subsets.

Antinuclear autoantibodies are detected in almost all patients with SSc. Anti-topoisomerase I (Scl-70) and anti-centromere antibodies are mutually exclusive and highly specific for SSc. Topoisomerase I (Scl-70) antibodies are associated with increased risk of ILD and poor outcomes. Anti-centromere antibodies are associated with PAH, but only infrequently with significant cardiac, pulmonary, or renal involvement.

Nucleolar immunofluorescence pattern may indicate antibodies to U3-RNP (fibrillarin), Th/To, or PM/Scl, whereas speckled immunofluorescence indicates antibodies to RNA polymerase III, associated with increased risk of scleroderma renal crisis and malignancy.

SSc patients who harbour anti-RNAP antibodies have an increased risk of cancer within a short interval of the clinical onset of SSc.

The diagnosis of SSc is made primarily on clinical grounds and is generally straightforward in patients with established disease. Diagnostic criteria developed for classification are >90% specific and sensitive for SSc.

It is also detected enhanced expression of nucleolar RNAP exclusively in the tumoral tissues of SSc patients with anti-RNAP antibodies in whom there was a close temporal relationship between the onset of cancer and SSc.

RNAP is critical for regulation of sustained cellular protein synthesis and is therefore a fundamental determinant of normal cellular growth. Recently, strong evidence has implicated abnormal RNAP activity in cancer cells from breast and lung carcinomas and in fibroblasts transformed by Simian virus 40 or other polyomavirus.

It is postulated that repression of tumour suppressors p53 and retinoblastoma and/or activation of oncogene product c-Myc may lead to enhanced RNAP activity in malignancy. However, the biological basis for an association between specific autoantibody subtypes against NRAP and malignancy in the context of SSc is unclear.

The presence of anti-RNAP antibody may initiate an antitumour immune response that, in the appropriate setting, may cross-react against specific host tissue, resulting in target tissue damage. Proof supporting this hypothesis may provide some insight into the fundamental mechanistic aspects of pathogenesis and highlight the cancer–autoimmunity interface in this particular subset of SSc as a paraneoplastic syndrome.

It is disputed whether SSc onset should be defined from the development of RP or from the first non-RP symptoms. For that reason, the duration of RP prior to SSc onset was considered, and repeat analysis indicated that the association between anti-RNAP antibodies and malignancy remained significant.

The association of breast cancer with SSc may be attributed to the potential role of sex hormones in disease development of SSc and breast cancer. Increased levels of prolactin and low dehydroepiandrosterone in patients with SSc and breast cancer lend further support to this association.

CONCLUSION

It is an orphan disease of unknown aetiology, complex pathogenesis, and variable clinical presentations. SSc frequently follows a progressive course and is associated with significant disability and mortality. Virtually every organ can be affected. SSc is a rare condition that affects mostly young and middle-aged women, resulting in disproportionate morbidity and mortality. The most characteristic autoantibodies related to SSc are anti-centromere, anti-topoisomerase 1, and anti-RNA polymerase III. SSc patients who harbour anti-RNAP antibodies have an increased risk of cancer within a short interval of the clinical onset of SSc. The mainstay of management is NSAIDs.

SSc is a heterogenous disease involving multiple organs and this case report supports the temporal association between the autoantibody subtypes and cancer in SSc, which provides independent confirmation to recent studies that SSc patients who harbour anti-RNAP antibodies have an increased risk of cancer within a short interval of the clinical onset of SSc. Increased awareness among physicians is required to institute appropriate investigations where necessary. Further studies to evaluate the biological link between anti-RNAP antibodies and malignancy in SSc should be undertaken in future studies.

However, it may be appropriate to screen individuals at high risk and those who fail to respond to therapy.

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