Resolution of paraneoplastic PM/Scl positive systemic sclerosis after curative resection of pancreatic tumour.

Sir, compelling evidence has recently been presented that systemic sclerosis (SSc) may occur as a paraneoplastic disease, especially for cases expressing hallmark anti-RNA polymerase III autoantibodies [1]. Elegant studies have confirmed expression of variant protein by tumours [2] and larger cohort analyses confirm that the association with malignancy is often contemporaneous for ARA [3]. It would be predicted from this model that tumour removal at an early stage could interrupt the autoimmune process and be associated with resolution of the associated SSc. Such clinical improvement would confirm the role of antigen-driven adaptive autoimmunity driving the disease and strongly support current immunosuppressive treatment strategies. Here we describe the case of a 43-year-old lady with malignancy and clinical features of systemic sclerosis (SSc) and polymyositis (CK >2000) associated with PM/Scl antibodies. The presence of tendon contractures, palmar skin thickening and diffuse distribution of skin disease (peak MRSS 11/51) with generalised hyperpigmentation prompted further radiological assessment for underlying malignancy and a cystic pancreatic lesion with a solid component was identified. A distal pancreatectomy and splenectomy successfully excised all tumour tissue and a diagnosis of solid pseudopapillary pancreatic neoplasm was confirmed on histological and immunohistochemical assessment. Following surgical recovery, the patient was rapidly weaned off all immunosuppression and has remained in clinical remission with resolution both of skin sclerosis (MRSS 4/51)and inflammatory muscle disease (normal CK and MRC grade). Immunostaining with anti-exosc10 antibody (anti-PM/Scl 100) demonstrated increased staining in normal exocrine pancreatic cytoplasm (negative in endocrine pancreas) when compared to tumour from this patient. However, nuclear staining was present universally in tumour tissue and found in very few nuclei in the normal pancreas (figure 1, arrow). Clinical remission following full resection and increased nuclear staining for PM/Scl 100 in tumour tissue lends support to a potential

pathogenic link in this case and this has not been previously demonstrated in SSc associated with this antibody subset.

To confirm and extend potential association of this hallmark scleroderma ANA pattern with malignancy we interrogated our SSc research database of 2200 patients and identified 80 patients who tested positive for PM/Scl by Hep-2 immunofluoresecnec and confirmatory counterimmunoelectrophoresis. Data were available for 70 of these patients, of these 70, 80% were female, mean age 58.4±14.0 years and mean age at SSc onset 44.1±14.5 years. 47/70 (67.1%) had limited cutaneous involvement, the remainder had diffuse disease excepting 3 patients for whom this data was missing. More than a third of the population showed the presence of calcinosis (38.6%), inflammatory arthropathy (38.6%), while more than half of the patients in the study population were affected by lung involvement, gastrointestinal involvement and inflammatory myopathy (57.1%, 62.9% and 61.4% respectively). These demographic and clinical data are broadly representative of those published previously for this antibody subset [4]. However, a history of malignancy was found in 14/70 patients (20.0%), with cancer onset within 36 months from SSc diagnosis in 5 patients. This is far higher than seen in the whole cohort (7.1%, [2]) and more consistent with published data from RNA polymerase III positive patients, where a paraneoplastic pathogenic link has been demonstrated [4]. There was no statistically significant difference in exposure to smoking or immunosuppressive therapies when comparing the population with a malignancy to those without fibrosis.

Our analysis also identified 4 PM/Scl positive SSc patients (5.7%) with scleroderma renal crisis (SRC) during their disease course, comparable to broad incidence data across all SSc antibody subsets [5]. In all cases this severe complication was present within 3 years of disease onset, as described previously for this complication of SSc. There was no statistically significant difference in steroid treatment between these 4 patients and the remaining study population. These data are somewhat surprising

given the prevailing view that this antibody type is not associated with SRC. One patient developed both SRC and breast malignancy within 36 months of SSc diagnosis.

Taken together, we propose that a subphenotype of PM/Scl patients develop disease that behaves more aggressively than previously recognised and closely resembles patients with RNA polymerase III antibody positive SSc. A larger scale study is needed to confirm these results and to explore any mechanistic link with malignancy although the case presented here would support a link analogous to that postulated for anti-RNA polymerase III antigen expression in tumour tissue.

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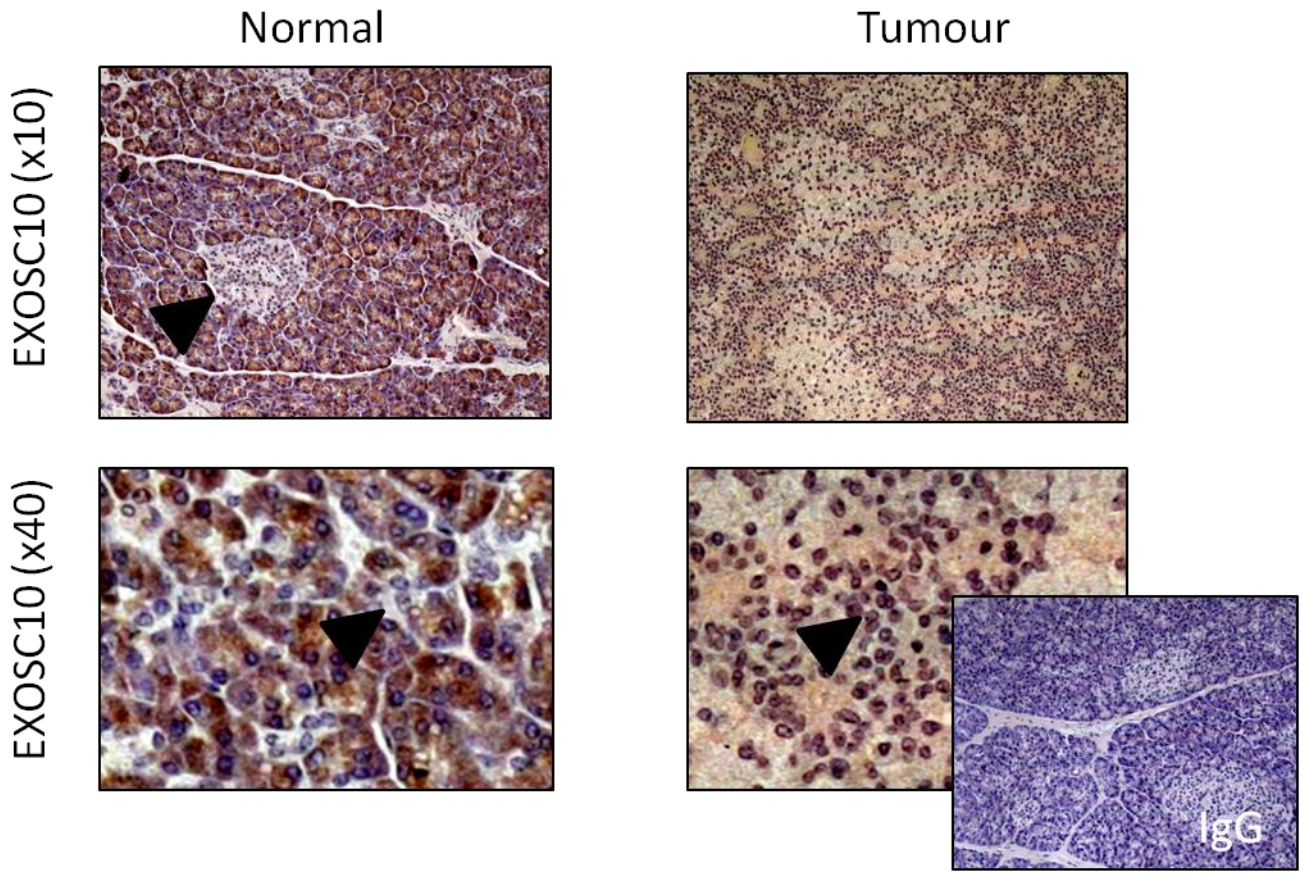

FIGURE 1 with legend

Low (x10) and high (x40) power immunohistochemical images of anti-exosc10 or PM/Scl100 stained tissue demonstrates a marked increase in cytoplasmic staining in normal exocrine pancreas, but islets do not stain strongly for anti-exosc10. Normal counterstained nuclei are present in normal pancreas (blue) and peroxidase positive stained nuclei in tumour tissue demonstrating increased nuclear expression (brown). Inset: Immunohistochemical IgG control.