Anti-NOR90 antibody associated with paraneoplastic systemic sclerosis

Sirs,

The anti-NOR90 antibody, which is a nucleolar type of anti-nuclear antibody may be found in patients with systemic sclerosis (SSc) even if its clinical relevance remains unclear. Recently, in 1252 patients with systemic autoimmune rheumatic diseases, anti-NOR90 antibodies were found in 0.4% and were significantly more frequently found in patients with SSc-spectrum disorders and in patients with SSc (1). In another cohort of 131 patients with SSc, anti-NOR90 antibodies were found in 6.1% and were associated with the presence of interstitial lung disease (2). A 72-year-old female patient was followed for 10 years in our department for autoimmune neutropenia. During the follow-up any treatment was required as neutrophil count number exceeded 500/mm3 and as she did not experience infectious events. Patient's characteristics are shown in Figure 1. She suddenly developed Raynaud's phenomenon, puffy fingers, sclerodactyly as well as hands arthralgia (Fig. 1A). She concomitantly developed anti-nuclear antibodies (1/5120) showing a typical AC-10 punctate nucleolar pattern suggestive of anti-NOR-90 auto-antibody that was further confirmed using Euroimmun EUROLINE SSc profile kit (Fig. 1B-C). No other specific SSc auto-antibodies were detected. Highly specific abnormalities for SSc pattern were observed at nailfold capillaroscopy with several giant capillaries associated with avascular areas (Fig. 1D). High resolution CT and echocardiography were normal, diagnosis of limited cutaneous SSc was done with an 11 modified Rodnan skin score (mRSS). At the same time, she developed moderate anaemia and thrombocytopenia. Bone marrow analysis showed myelodysplastic syndrome (MDS) characterised by multilineage dysplasia and 8% blasts. Three months later cytopenia worsened, bone marrow blasts were over 20% defining acute myeloid leukaemia. Conventional karyotyping did not find any cytogenetic abnormality but myeloid NGS panel found mutation in IDH1 gene (Arg132Cys). She was placed under IDH1 inhibitor with a dramatic haematological efficiency. After a few weeks of treatment, we observed a pronounced improvement of scleroderma phenotype (mRSS=2) except for Raynaud's phenomenon. A close temporal relationship between SSc onset and cancer has been reported in anti-RNA polymerase III-positive patients (3). Recently, data from the Canadian Scleroderma Research Group registry found that synchronous cancer was rare and

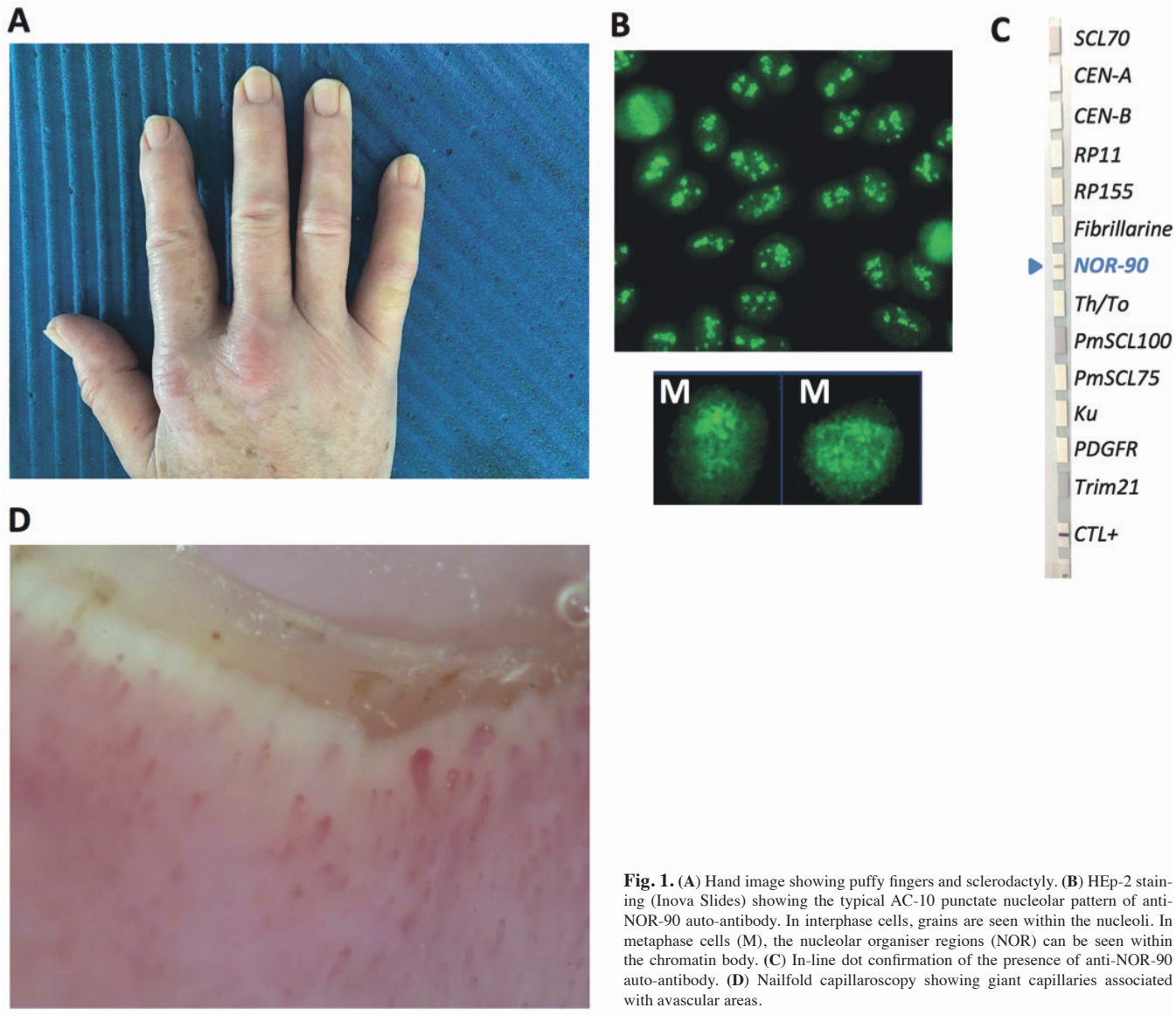

Fig. 1. (**A**) Hand image showing puffy fingers and sclerodactyly. (**B**) HEp-2 staining (Inova Slides) showing the typical AC-10 punctate nucleolar pattern of anti-NOR-90 auto-antibody. In interphase cells, grains are seen within the nucleoli. In metaphase cells (M), the nucleolar organiser regions (NOR) can be seen within the chromatin body. (**C**) In-line dot confirmation of the presence of anti-NOR-90 auto-antibody. (**D**) Nailfold capillaroscopy showing giant capillaries associated with avascular areas.

that the risk of cancer within 2 years was increased among anti-topoisomerase and anti-U1-RNP-positive patients but not with other autoantibodies associated with SSc including anti-NOR90 antibody (4). The same year another group found that cancer (stomach, colon, lung) were relatively frequently found in anti-NOR90-positive patients with limited SSc phenotype (1). Autoimmune disorders (AID) are observed in 10–20% of MDS, typically diagnosed concomitantly or shortly before or after MDS. Most common AID associated with MDS include relapsing polychondritis, vasculitis especially in case of VEXAS syndrome recently described as well as non-erosive seronegative arthritis and Sweet's syndrome (5, 6). SSc has also been associated with MDS even rare (7). Interestingly, azacitidine in numerous case reports as well as retrospective studies frequently seems effective in controlling AID associated with MDS suggesting that AID in the context of MDS are of paraneoplastic origin. IDH1 is a key metabolic enzyme that convert isocitrate to alpha-ketoglutarate (α-KG). IDH1 mutations disrupt the balance between α-KG and 2-hydroxyglutarate (2-HG) production leading to increased production of 2-HG, a competitive inhibitor of α-KG notably for the binding into the active site of histone demethylase. Interestingly, recent reports in SSc indicate that α-KG and dimethyl- α-KG suppress TGF-β induced profibrotic response and migration of myofibroblasts (8, 9). This suggests that metabolic perturbations affecting α-KG and its metabolite may favour fibroblast-to-myofibroblast reprogramming and tissue fibrosis during SSc. Whether mutated IDH1 induced metabolic imbalance contributed to the development of SSc in our patient or inhibition of IDH1 directly influenced the SSc course remains still an open question.

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