



**Fig.S25** Topical Rapamycin treatment effectively alleviates Paget’s Disease-associated pathological symptoms in a cohort of human EMPD patients – Patient 3. **a** Gross image of erythematous lesion of skin around the genital region of a 81-year-old patient (Patient ID: EMPD03) with scrotal EMPD before and after two weeks of topical Rapamycin treatment. The 81-year-old patient was initially diagnosed with scrotal EMPD and metastasis to inguinal lymph nodes by ultrasound and pathological analyses in April 2018. **b** Histopathology of EMPD skin from patient EMPD03 before and after two weeks of topical Rapamycin treatment. **c-f** PAS and immunohistochemical staining against CEA, CAM5.2 and pS6 in EMPD skin from patient EMPD03 before and after two weeks of topical Rapamycin treatment. **g** Reflectance confocal microscopy of lesioned skin from patient EMPD03 before and after two weeks of topical Rapamycin treatment. **h** Ultrasound images of affected skin from patient EMPD03 before and after two weeks of topical Rapamycin treatment. Representative images are shown. Epidermis and dermis are demarcated with broken line. Scale bar: **c-f** – 50  $\mu\text{m}$ .