GENETICS AND GENODERMATOSES

URINARY CATHEPSIN C AND PROTEINASE 3 EXPRESSION ON NEUTROPHILS IN PAPILLON LEFEVRE SYNDROME WITH HOMOZYGOUS NONSENSE MUTATION IN CATHEPSIN C GENE: IMPORTANCE AND IMPLICATIONS IN AUTOIMMUNE VASCULITIS

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Background: The main target of autoantibodies in granulomatosis with polyangitis (GPA) is membrane-bound proteinase 3 (PR3), a neutrophil serine protease (NSP). Cathepsin C (CatC) is the physiological activator of several NSPs. Papillon-Léfèvre syndrome (PLS) is an autosomal recessive disorder caused by homozygous mutations in the gene encoding lysosomal protease, CatC (CTSC). A strong reduction of proteolytic activity of NSPs has been demonstrated in PLS.

Observations: A 15-year-old boy born out of 3rd degree consanguineous marriage presented to the dermatology clinic with thickening of palms and soles since the age of 6 months. There was no history of premature loss of primary dentition. At the age of 12 year patient noticed toothache and swelling of gums associated with severe halitosis. On examination, bilaterally symmetrical diffuse thickening with punctuate lesions and scaling affecting palms and soles extending into Achilles tendon, dorsa of hands and feet was present. Well demarcated erythematous scaly plaques were seen on knees, elbows and sacro-coccygeal area. Dental examination revealed diffuse redness, swelling and marked recession of gingiva with heavy plaque and calculus accumulation, and loosening of teeth suggestive of periodontitis. The genetic analysis showed homozygous nonsense mutation p.Y304X in exon 7 of CTSC. The CatC activity and CatC antigen was absent in urine sample. The activity of CatC and PR3 in white blood cell lysates in both case and control was studied. It showed reduced activity of CatC and PR3. The PR3 exposure on the surface of activated neutrophils was also impaired compared to control.

Key message: Absence of CatC activity and CatC antigen in urine helps in prevention of severe periodontitis in PLS by early diagnosis and treatment. The reduced activity and exposure of PR3 on activated neutrophils in PLS suggests pharmacological inhibition of CatC activity as a novel therapeutic approach to GPA.