A new terminal nonsense mutation of Cathepsin C gene in a patient with atypical Papillon-Lefèvre Syndrome

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Papillon-Lefèvresyndrome (PLS, OMIM 245000) is a rare autosomal recessive disorder caused by mutations of *CTSC*, a gene located in 11q14.2 that encodes the enzyme cathepsin C [1]. Cathepsin C activates proinflammatoryproteases(e.g., NE, PR3, CatG, NSP4,chymases, tryptases, granzymes), regulates the function of immune cells [2-4] and the formation of the envelopeof corneocytes.

PLS is characterized by symmetric palmoplantar keratoderma and severe, early-onset periodontitis, leading to the premature loss of dentition [1]. Other manifestationsinclude recurrent pyogenic skin infections, nail dystrophy, hyperhidrosis, liver abscesses, mild mental retardation, intracranial calcifications and increased susceptibility to infection [1,5]. *CTSC* loss of function results in reduced neutrophil response bacteria [2,3]. PLS is found in all ethnic groups with estimated prevalenceof 1-4per million individuals and a male/female ratio of 1/1 [1].

More than 75 biallelichypomorphic variants in the *CTSC* gene have been described in PLS, Haim-Munk Syndrome (OMIM 245010) and aggressive periodontitis-1(OMIM 170650) [6].The majority of the PLS pathogenic variants are located in exons 5–7, that encode the heavy chain of the cathepsin C, suggesting that tetramerization is important for the enzymatic activity [7]. Due to the high allelic heterogeneity, most patients are compound heterozygotes, with the exception of consanguineous families. Identical mutations of the *CTSC* gene can result in different phenotypes, and no straight genotype-phenotype correlations have been established [7,8]. Intra-familial variable penetrance has been described [7].

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We describe a 26 years-old Caucasian male, born to consanguineous Portuguese parents (coefficient of consanguinity (r) = 1/32) that developed the first symptoms at the age of 20 months: persistent gingivitis, palmoplantar skin thickening, periungual desquamation, recurrent episodes of furunculosis in the buttocks, knees and arms, and severe maxillary rhinosinusitis.

Dental caries were evident in the deciduous teeth and only mild symptoms of periodontitis during adolescence, but no loss of dentition occurred. Oral and radiographic examinations at 26 years-old showed preserved dentition with mild localized chronic periodontitis (less than 30% of tooth and probing pocket depth of 4 to 5 mm).

During adolescence,the patient maintained mild palmoplantar trangredienskeratoderma with erythema, psoriasiform plaques and hyperhidrosis. At this age, recurrent skin abscesses and exuberant furunculosisrequired several courses of antibiotics and prophylaxis, with no benefit.

Significant worsening of the skin infections occurred at 21 years of age, with several skin abscesses in the axillae and groin areas needing surgical drainage, with transient response to oral rifampicin and nasal mupirocin. Bacterial swabs from the abscesses were positive for *Staphylococcus aureus*.

At 25 years-old, he had a severe episode of pneumonia with several isolations in the sputum of *Staphylococcus aureus* and*Klebsiella pneumonia*, requiring prolonged hospitalization. Chest computed tomography scan 4 months afterthe pneumonia episode showed sequalaecavities suggesting pneumatoceles and left hilar lymphadenopathies(Figure 1).

Currently, he ison prophylaxis with oral cotrimoxazole and annual flu vaccination, maintains three courses of antibiotics and one surgical drainage per year. Other manifestations include seborrheic dermatitis, allergic rhinitisand lactose intolerance. Both parents and an older brother are healthy and there is no reported family history of recurrent infections.

Full blood counts and immunoglobulins classes and subclasses were unremarkable, except for IgE (213 Ul/mL). Skin prick tests were positiveto *Dermatophagoides pteronyssinus*. HIV test was negative.

Flow cytometry of peripheral blood showed normal levelsand distribution of cells and normal lymphocyte activation phenotypes. Expression of leukocyte CD119, B cell CD40, leukocyte adhesion molecules CD11a/CD18 and CD54were normal, except for low CD62L inlymphocytes and neutrophils. Neutrophil Oxidative Burst Assay was normal.

Sanger sequencing of *CTSC* gene identified a novel homozygous nonsense variant in exon 7 (NM_001814.5:c.1339G>T; NP_001805.3: p.Glu447Ter), located in a conserved sequence (7 species, Ensembl), leading to a premature stop codon predicted to cause a terminally truncated protein. The variant is not on ClinVar (accessed 07.05.2019) but is referenced in SNP

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data base (rs569702051) and is described in ExAC with a frequency of 0,001‰ (http://exac.broadinstitute.org/gene/ENSG00000109861, accessed 07.05.2019). Both parents were heterozygous for the variant. The patient's brother refused genetic testing.

The patient presents an atypical course of PLS whereas both hyperkeratosis and periodontitis are notably mild, and the patient has an increased susceptibility to severe infections.

The variant of *CTSC* present in this patient supports the clinical diagnosis of PLS. This newly described variant can be considered likely pathogenic as it is found in very low frequencies in the population and causes a premature stop-codon with truncation of a conserved region in the light-chain domain, and although very terminal, may interfere with the tetramerization of the mature enzyme. Importantly, another missense variant in the same residue was described in PLS (p.E447G),albeit compound heterozygous [5-7].

The reasons for the dissociation between mild hyperkeratosis/dental manifestations and the important infectious manifestationsare unclear and may include particularities of the CTSC mutation or other gene-gene interactions and/or environmental. Despite extensive immunological work-up no other immunology deficiencies were found. The absence of significant immunological anomalies is consistent with previous reports and more subtle functional defects may be present. Reduced cathepsin Cenzymatic activity results in diminished activity and stability of neutrophil-derived serineproteases [9], such as elastase and cathepsin G, that are thought to play a role in the regulation of innate immune responses against bacteria. However, neutrophils in PLS do not uniformly have a defect in their ability to kill bacteria, suggesting that serine proteases do not represent the major mechanism used by human neutrophils for killing common bacteria [3]. Other roles in neutrophil function have also been described [9,10].

PLS NK cells contain inactive granzyme B and have a cytolytic defect, failing to induce the caspase cascade in target cells [4]. However, in vitro activation of PLS NK cells with interleukin-2 restores cytolytic function and granzyme B activity by a cathepsin C-independent mechanism [4]. Recently, PLS patients were shown to have an impaired autophagy caused by*CTCS* mutation and insufficientlysosomal function [10].

The increasing number of reported atypical PLS cases, including those with isolated keratosis or periodontitis, prompts the establishment of the correct diagnosis. Early diagnosis is beneficial for the treatment and the long-term quality of life for the patient.

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Conflicts of interest

Dr. Moura has nothing to disclose.

Prof.Regateiro has nothing to disclose.

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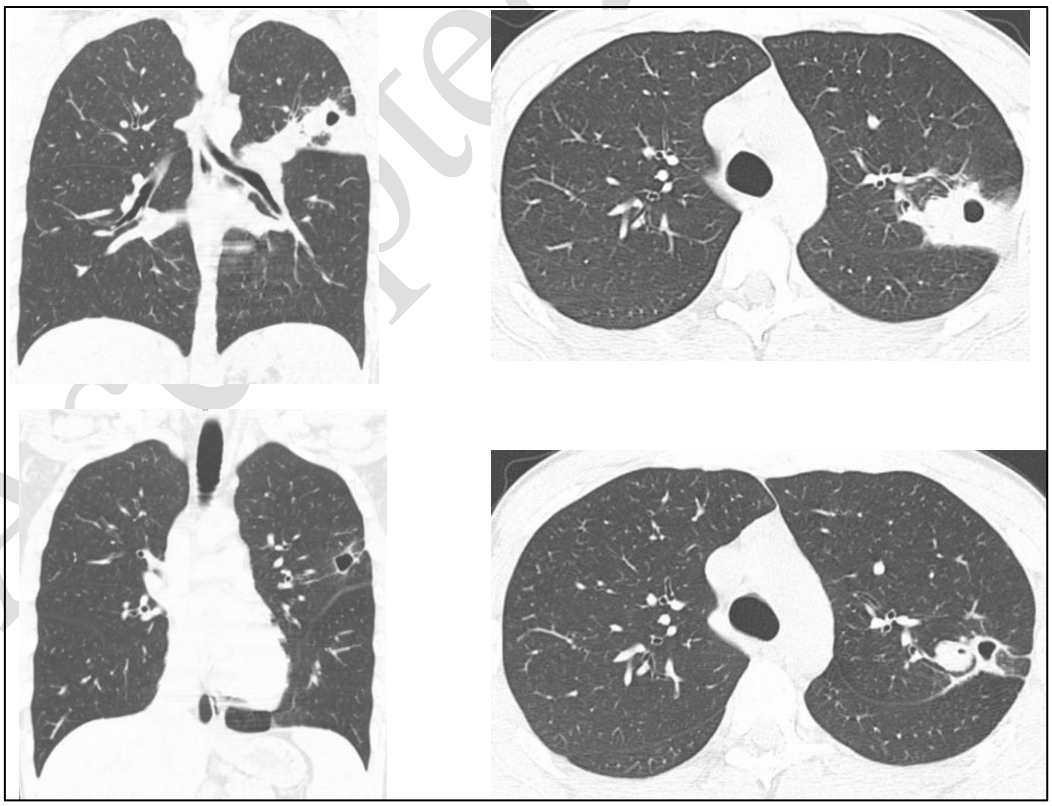
Figure 1. Images from a chest computed tomography scan four months after the pneumonia episode showing sequalae cavities, pneumatoceles and left hilar lymphadenopathies.



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