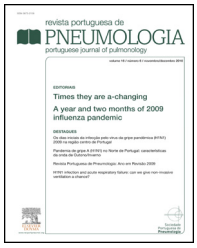
Rev Port Pneumol. 2014;20(5):273–278

revista portuguesa de PNEUMOLOGIA
portuguese journal of pulmonology
www.revportpneumol.org



CASE REPORT

A novel immunodeficiency syndrome as a rare cause of secondary pulmonary alveolar proteinosis: A diagnosis after 5 decades

Pedro G. Ferreira[a,*], **Lina Carvalho**[b], **Fernanda Gamboa**[a]

[a] *Pulmonology Department, Coimbra Hospital and University Centre, Coimbra, Portugal*
[b] *Anatomopathology Department, Coimbra Hospital and University Centre, Coimbra, Portugal*

Received 11 July 2013; accepted 22 August 2013
Available online 13 April 2014

KEYWORDS
Alveolar Pulmonary Proteinosis;
Immunodeficiency;
Parenchymal lung disease;
Systemic disease with lung involvement

Abstract Case report of a male patient with a five-decade follow-up history in a tertiary care hospital distinguished for malabsorption syndrome, failure-to-thrive, meningitis and recurrent bacterial, fungal and mycobacterial pulmonary infections. Additionally, he developed epidermodysplasia verruciformis, several in situ spinocellular carcinomas and an uncharacteristic parenchymal lung disease. Surgical lung biopsy suggested pulmonary alveolar proteinosis with fibrotic change. Retrospectively, severe monocytopenia had been overlooked in the past, as well as low B and NK cell blood counts. Flow cytometry confirmed the absence of the previous cell subsets along with an undetectable population of dendritic blood cells.

Dendritic cell, monocyte, B and NK lymphoid Human Deficiency Syndrome (DCMLS) is a novel rare immunodeficiency described in 2010, linked to GATA-2 mutation. This syndrome should be highlighted as a rare cause of acquired PAP, with a radiological pattern encompassing potential fibrotic change. Failure to recognize monocytopenia may impede the chance to diagnose.

PALAVRAS-CHAVE
Proteinose Alveolar Pulmonar;
Imunodeficiência;
Doença pulmonar parenquimatosa;
Doença sistémica com envolvimento pulmonar

Uma nova síndrome da imunodeficiência como causa rara de proteinose alveolar pulmonar: um diagnóstico após 5 décadas

Resumo Relato de um caso clínico de um doente do sexo masculino com um historial de acompanhamento de cinco décadas, num hospital de cuidados terciários, caracterizado por um síndrome de malabsorção, insuficiência de crescimento, meningite e infecções pulmonares bacterianas, fúngicas e micobacterianas recorrentes. Além disso, desenvolveu epidermodisplasia verruciforme, diversos carcinomas espinocelulares in situ e uma doença pulmonar parenquimatosa não definida. Uma biópsia pulmonar cirúrgica sugeriu uma Proteinose Alveolar Pulmonar com alterações fibróticas. Em retrospectiva, uma monocitopenia grave negligenciada no passado,

* Corresponding author.
E-mail address: p_goncalof@hotmail.com (P.G. Ferreira).

0873-2159/$ – see front matter
http://dx.doi.org/10.1016/j.rppneu.2013.08.006

bem como uma baixa contagem de células B (linfócitos B) e NK (células 'natural killer'). Uma citometria de fluxo confirmou a ausência dos subconjuntos de células anteriores, juntamente com uma população indetectável de células dendríticas sanguíneas.

A Síndrome de Deficiência Humana de células dendríticas, monócitos, linfóides B e NK é uma rara imunodeficiência descrita recentemente em 2010 e relacionada com a mutação do gene GATA-2. Esta síndrome deverá ser referida como uma causa rara de PAP (proteinose alveolar pulmonar) adquirida, com um padrão radiológico que poderá apresentar uma potencial alteração fibriótica. A ausência de reconhecimento da monocitopenia pode impedir a oportunidade de chegar a este diagnóstico.

We present the case report of a 61-year-old male patient with a five-decade history of medical follow-up in a tertiary care University Hospital who is a non-smoker without relevant family history or occupational exposures. The history of the present illness started at the age of 9, with a diagnosis of pulmonary tuberculosis (PT) for which standard antibacillary treatment was completed. He presented failure to thrive in his early childhood, and at the age of 18, he was admitted twice in the Internal Medicine Department for diarrhea, malabsorption syndrome and acute tracheobronchitis. By the age of 20 he had pneumococcal meningitis, but had recovered without neurological sequelae. During the following decade he had further admissions for community-acquired pneumonias, ''middle lobe syndrome'' and otitis media.

At the age of 37 he was again diagnosed with PT and completed standard treatment, supervised by the Tuberculosis District Center. In his forties he started presenting recurrent processes of bronchitis with isolation of *Haemophilus influenzae* and *Streptococcus pneumoniae*. He also started dermatological consultations for epidermodysplasia verruciformis that gradually developed on his hands, upper limbs, torso, and neck, and severe perineal condylomas that were repeatedly treated with electrodessication and curettage (Fig. 1). Since then, he has been diagnosed six times with in situ cutaneous spinocellular carcinoma. His skin biopsies typically revealed dyskeratotic spinocellular carcinomas and ''bowenoid papulosis'' of a verruciform nature, with abnormalities in the granulosa cell layer suggesting infection by human papillomavirus (HPV).

At the age of 47, one of his admissions to the Pulmonology Department was for *Aspergillus fumigatus* lung infection (the patient did not fulfill the criteria for allergic bronchopulmonary mycosis). A complete investigation for cystic fibrosis was performed and, after a borderline sweat test, he showed normal spermogram and negative Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) genotype mutation study.

Gradually, he started developing parenchymal lung disease, initially with reticulomicronodular pattern with upper lobe predominance on chest radiograph. In his fifties, computed tomography (CT) scan showed a septal thickening pattern with reticulation, traction bronchiectasis and micronodulation. Pulmonary function tests presented moderately severe restriction by spirometry (*Tiffeneau* index of 0.74, Forced Vital Capacity 57.2%, forced expiratory volume in one second 52.8%), corrected to normal by plethysmographic lung volumes (total lung capacity 80.8%, residual volume 109.2%), with a moderately affected diffusion capacity (DLCO 54%), while maintaining satisfactory blood gas analysis at room air (pO_2 80 mmHg, pCO_2 41 mmHg, SaO_2 96%).

At his last admission, at the age of 61 years, he presented a more pronounced diffuse interstitial reticulomicronodular pattern and progressive emaciation. He complained of productive cough with high volume purulent sputum and worsened dyspnea (grade III mMRC). High-resolution chest CT showed a more profuse septal thickening, micronodular pattern of random distribution, ''tree-in-bud'' images, along with apical subpleural blebs, linear fibrotic lines and distortion of the normal bronchovascular architecture (Fig. 2). Flexible bronchoscopy presented inflammatory changes of the mucosa and mucopurulent sputum. BAL, in the context of infection, showed a concordant neutrophilic cellular profile (860,000 total cells/mL, with 84% neutrophils). The cytopathological study was negative and microbiological workup allowed for the identification of *Corynebacterium species* and *Acinetobacter baumannii*. Serum immunoglobulins were normal, as were complement levels and serum angiotensin-converting enzyme titers. There were positive anti-nuclear antibodies with positive anti-cytoskeleton fibers and anti-vimentin antibodies, and negative anti-neutrophil cytoplasmic antibodies (ANCAs). His serological panel was negative for syphilis, B and C hepatitis and Human Immunodeficiency virus (HIV)-1/2 infection, but presented high IgM and IgG titers for cytomegalovirus, Epstein–Barr and herpes simplex virus-1.

He underwent a multiple-lobe surgical lung biopsy, which was suggestive of alveolar proteinosis with some fibrotic trace. It revealed aspects of diffuse alveolar occupation by eosinophilic, Periodic-Acid-Schiff positive proteinaceous material, with a light macrophagic reaction, together with abnormal lobular architecture, diffuse septal fibrosis with focal collagen deposition and some multinucleate foreign body giant cells with cholesterol crystal clefts (Fig. 2). There were no granulomas.