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The heterogeneity of lung involvement in vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome: a case of hypersensitivity pneumonitis-like pattern

C. Iannone[1,2], M.R. Pellico[1,2], C. Campochiaro[3,4], L. Tescaro[2,5], M. Zompatori[6,7], A. Caminati[4], S. Harari[2,4], R. Caporali[1,2]

[1]Division of Clinical Rheumatology, ASST Gaetano Pini-CTO Institute, Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan, Italy; [3]Vita-Salute San Raffaele University, Milan, Italy; [4]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy; [5]Operative Unit of Pneumology and Semi-Intensive Respiratory Therapy, Respiratory Pathophysiology and Pulmonary Hemodynamics Service, Ospedale San Giuseppe, MultiMedica IRCCS, Milan, Italy; [6]Operative Unit of Radiology, Department of Diagnostic Imaging, MultiMedica IRCCS, Milan, Italy; [7]DIMES University Department, University of Bologna, Italy

SUMMARY

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a recently characterized disease associated with somatic mutations in the *UBA1* gene, which cause dysregulation of ubiquitin-mediated processes. This case describes a 71-year-old male patient with VEXAS syndrome who presented with refractory lung inflammation with a pattern similar to computed tomography hypersensitivity pneumonitis, a novel finding in VEXAS syndrome. The presented clinical case highlights the protean involvement of the lung in VEXAS syndrome and emphasizes the importance of considering interstitial lung disease in the differential diagnosis.

***Key words**: VEXAS, interstitial lung disease, hypersensitivity pneumonitis.*

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INTRODUCTION

Since its first description, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome has been reported as a multifaceted disease involving different organs, such as bone marrow, skin, vessels, joints, and lungs, and mimicking acknowledged diseases, namely relapsing polychondritis, Sweet's syndrome, vasculitides, and myelodysplastic syndrome (1, 2). It is caused by somatic mutations of the UBA1 gene encoding the major E1 enzyme ubiquitin, a cytoplasmic enzyme starting the ubiquitination, a post-translational change of proteins regulating intracellular signaling, and protein degradation required for autophagy (1, 3). The exact mechanism by which the cellular defective ubiquitination leads to dysregulation of the inflammasome and a syndromic picture is still unknown, but different point mutations of UBA1 have been reported in patients with VEXAS syndrome. It should be suspected in elderly male individuals with unexplained fever and constitutional symptoms, hematologic abnormalities with vacuolization of myeloid and erythroid precursors in the bone marrow, and confirmed by detecting a somatic mutation of methionine-41 (p.Met41) in the UBA1 gene, located on the X chromosome. Within its clinical broad-spectrum picture, the lung can also be involved in roughly 50% of VEXAS patients, with a tendency to increase over time (3, 4). Pulmonary manifestations have been reported to be heterogeneous, with a wide array of findings at chest computed tomogra-

Corresponding author:
Claudia Iannone
Division of Clinical Rheumatology,
ASST Gaetano Pini-CTO Institute,
Piazza Cardinal Ferrari, 1 - 20122 Milan, Italy
E-mail: claudia.iannone@unimi.it

phy (CT). We hereby report a case of VEXAS syndrome with refractory pulmonary inflammation and a hypersensitivity pneumonitis-like pattern at CT scan, never been reported so far.

CASE REPORT

A 71-year-old male patient with VEXAS syndrome was referred to the interstitial lung disease (ILD) clinic due to worsening respiratory symptoms. The diagnosis was made in 2020 upon the appearance of fever, widespread joint pain, macrocytic anemia, myelodysplastic syndrome, positron emission tomography evidence of mediastinal lymph node uptake, and increased inflammatory markers.

The diagnosis was then confirmed by gene analysis by Sanger sequencing and peptide nucleic acid-clamping PCR of *UBA1,* which revealed a variant in the *UBA1* gene c.122T>C, p.Met41Thr. He was thus started on medium-dose glucocorticoids (GCs) (prednisone 12.5 mg/d) with benefit, but clinical relapses occurred when GCs were tapered. Multiple steroid-sparing treatments were attempted, including anakinra, discontinued due to severe skin reactions, tocilizumab, stopped because of severe neutropenia, and eventually canakinumab 300 mg every 4 weeks in combination with cyclosporin 300 mg/day, which allowed tapering of the GCs dose (to prednisone 5 mg/day). In 2017, due to the appearance of dyspnea, cough, fever, and a CT scan reporting ground glass areas and widespread micronodules, he was diagnosed with ILD.

In the previous 3 months, the patient was complaining of worsening fatigue, dry cough, exertional and at-rest dyspnea. He was admitted to our unit for further evaluation. A blood test showed macrocytic anemia (hemoglobin 8.6 g/dL, mean corpuscular volume 109.7 fL, hematocrit 24.8%) and a low platelet count (51000/mmc). Pulmonary function tests showed mild restrictive deficit (forced vital capacity 2.84 L, % predicted 79, forced expiratory volume in 1 second 2.3 L, % predicted 83) and severe diffusing capacity of the lungs for carbon monoxide reduction (8.1, % predicted 33), with no desaturation detected at the 6-minute walking test. Nocturnal oximetry showed mild respiratory failure. High-resolution chest CT demonstrated a non-fibrotic hypersensitivity pneumonitis-like pattern (Figure 1). Serum anti-dust and anti-fungal precipitins resulted in negative results, and after an extensive work-up both on serology and bronchoalveolar lavage samples, any other infectious, autoimmune, or neoplastic causes were ruled out. Due to the high hemorrhagic risk, lung criobiopsy was not carried out. The patient was started with a higher GCs dose, titrated up to prednisone 12.5 mg/day, with clinical benefit.

DISCUSSION

As previously mentioned, VEXAS syndrome may be caused by different somatic mutations of the *UBA1* gene encoding the major E1 enzyme ubiquitin (1, 5). A cluster analysis of 116 French patients with VEXAS syndrome tried to identify different

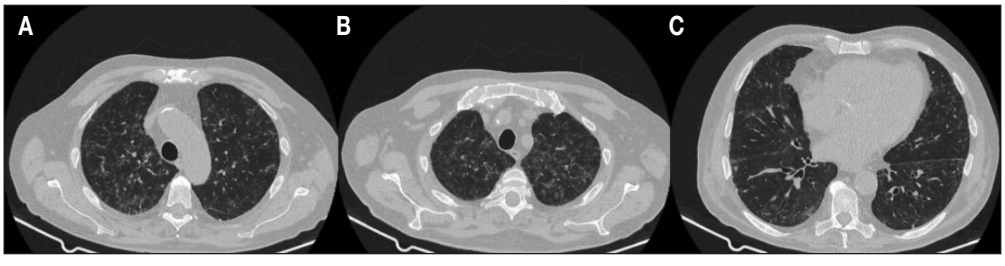

Figure 1 - Chest tomography scan of the patient. a, b) extensive areas of ground glass density with prevalent upper lobe and centrilobular distribution; c) no signs of irreversible fibrosis were seen and particularly no honeycombing. In the lower lobes and in dorsal, subpleural regions, the study also demonstrated millimetric nodules with calcium density, suggestive of diffuse pulmonary ossification.

clinical profiles according to the *UBA1* mutation. Three VEXAS clusters were identified, and a better 5-year overall survival was associated with *UBA1* p.Met41Leu, while p.Met41Val and p.Met41Thr were associated with a worse prognosis (6). This genetic heterogeneity may be a possible explanation of the variety of clinical manifestations of this syndrome and, as such, may also account for the different CT-ILD patterns recently described in two series of VEXAS patients with lung involvement ranging from organizing pneumonia to pulmonary fibrosis with diffuse alveolar densities.

CONCLUSIONS

We cannot exclude a casual association between the two diseases, but as all the known causes of ILD associated with this CT pattern in this patient were adequately excluded, we suggest that a hypersensitivity pneumonitis-like pattern should also be included in the VEXAS syndrome clinical picture and that ILD experts should be aware of this possibility during the differential diagnosis work-up.

Contributions
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare no potential conflict of interest.

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Not applicable.

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