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CASE REPORT

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Bronchiectasis in a patient with Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy: a case report

Margherita S. Silani[1,2], Edoardo Simonetta[3*], Andrea Gramegna[1,2], Alessandro De Angelis[3,4], Francesco Blasi[1,2] and Stefano Aliberti[3,4]

Abstract

Background The rare monogenic syndrome Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) leads to multisystemic autoimmunity with possible lung involvement. Autoimmune pneumonitis is a rare manifestation, with bronchiectasis being the most frequent radiologic pattern, and may lead to fatal outcome. The Sardinian population in Italy has a high incidence of APECED, although no case of lung manifestation has been reported yet in this cohort. This is the case of a Sardinian APECED patient referred to a bronchiectasis clinic. Our aim is to raise awareness and screen these patients earlier for pulmonary involvement and to initiate multidisciplinary treatment for better outcome.

Case presentation A 49-year-old female native of Sardinia from consanguineous parents was diagnosed with APECED in childhood and was referred to our bronchiectasis clinic in March 2023. In addition to typical APECED features, she reported recurrent respiratory infections since childhood, chronic purulent sputum and a hospitalization for pneumonia. She came to our attention with a recent isolation of *P. aeruginosa* on sputum culture and diffuse cylindrical and varicoid bronchiectasis on her first CT scan. She underwent aetiologic screening for bronchiectasis with no evidence of another cause of disease. Lung treatment was optimized according to bronchiectasis guidelines, and during follow-up the patient developed methicillin-resistant Staphylococcus aureus (MRSA) infection and *M. intracellulare* pulmonary disease. The patient was offered *P. aeruginosa* eradication treatment with intravenous antibiotics and initiation of antimycobacterial therapy.

Conclusion This is the first documented lung involvement case of APECED in a Sardinian patient, and the first patient reported to enter a bronchiectasis program. The patient was prescribed lung imaging late in time when bronchiectasis complications were already present. Our case report highlights the need for early pulmonary screening and multidisciplinary management in patients with APECED.

Keywords Bronchiectasis, APECED, Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy, Autoimmune polyendocrine Syndrome-1, APS-1, Autoimmune pneumonitis, Treatable traits, Case report

*Correspondence:
Edoardo Simonetta
edoardo.simonetta@humanitas.it
Full list of author information is available at the end of the article

Background

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) is a rare monogenic syndrome caused by more than 100 loss-of-function mutations in the autoimmune regulator (AIRE) gene, which is essential for central immune tolerance [1, 2]. Due to peripheral activity of self-reactive T-lymphocytes, patients develop multisystemic autoimmunity from early childhood with lymphocyte infiltration of endocrine and non-endocrine tissues with a very heterogeneous clinical presentation [3]. Classical disease manifestations include of adrenal insufficiency, chronic mucocutaneous candidiasis and hypoparathyroidism. If two manifestations of the classic triad are present, a diagnostic work-up through AIRE gene sequencing and Type I interferon autoantibody testing may be performed [4]. In addition to the clinical management of already existing manifestations, an active surveillance of novel organ involvements is also mandatory.

APECED is also characterized by extra-endocrine manifestations, including autoimmune pneumonitis. Although this clinical manifestation has been considered rare, *Ferre* et al. reported a prevalence of 42% in a cohort of 50 individuals with APECED who were prospectively assessed [4–6]. In terms of clinical manifestations, cough was the leading clinical symptom and bronchiectasis the most frequent radiologic manifestation, reported in up to 81% of this group [6]. A fatal outcome for this condition has been also reported [4, 7–9]. In a limited number of cases, azathioprine and rituximab or mycophenolate mofetil have been administered with positive effects on respiratory symptoms, radiologic alterations and airway microbiology [6, 9, 10].

Bronchiectasis is a respiratory disease characterized by a persistent enlargement of bronchi associated with chronic respiratory symptoms [11, 12]. The disease pathophysiology is characterized by a vicious vortex of impaired mucociliary clearance, chronic infection, airway inflammation leading to recurrent pulmonary exacerbations [13]. The majority of these patients undergo daily respiratory physiotherapy, monitoring of chronic respiratory infections and treatment of pulmonary exacerbations [11]. International guidelines recommend that every patient should undergo etiological screening at bronchiectasis diagnosis to identify causes of disease such as immunodeficiency [11, 14, 15]. Addressing treatable traits in bronchiectasis could lead to early treatment and better disease outcomes [16].

As far as we know, APECED is not recognized among possible etiologies of bronchiectasis. Here, we report the case of a young female with bronchiectasis in the context of APECED syndrome.

Case presentation

A 49-year-old female was referred to a pulmonary service because of recurrent respiratory infections. She was born in Sardinia, Italy to consanguineous parents, and she was diagnosed with APECED in her early childhood (R139X/R139X genotype). Two of her seven siblings and one nephew were affected by the same syndrome (Fig. 1). She also suffered from G6PD deficiency, familial hip dysplasia, osteopenia, and gastroesophageal reflux disease. She presented typical APECED features from childhood such as hypoparathyroidism, mucocutaneous candidiasis, hypergonadotropic hypogonadism, kidney stones, recurrent otitis media, and autoimmune gastritis. From a respiratory point of view, she presented with a history of recurrent episodes of pneumonia since childhood and daily purulent sputum since 2018. In 2019 she reported a single episode of hemoptysis and was hospitalized due to pneumonia secondary to an episode of purulent otitis media. Since October 2022, her symptoms worsened with exertional dyspnea, night sweats and serotine fever. From the beginning of 2023 she had been reporting three pulmonary exacerbations treated with empiric oral antibiotics. In February 2023, she underwent her first chest

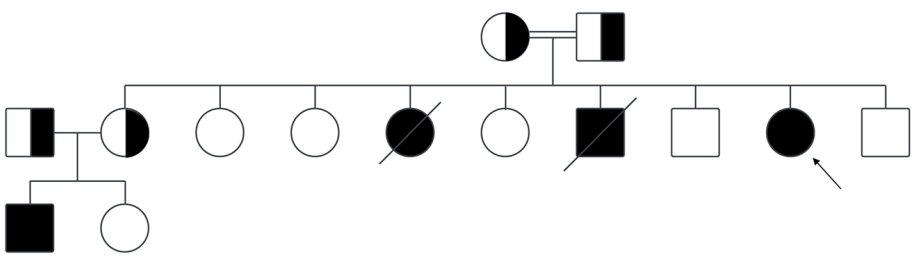

Fig. 1 The patient's pedigree

The patient (indicated by the arrow) is the seventh daughter of two consanguineous parents (first cousins) of Sardinian heritage. Two of her older siblings were affected by APECED: the fourth sister died due to hypercalcemia as first manifestation of disease, the sixth brother died due to hematologic malignancy. The oldest sister had two children with a non-consanguineous partner, their oldest son is also affected by APECED

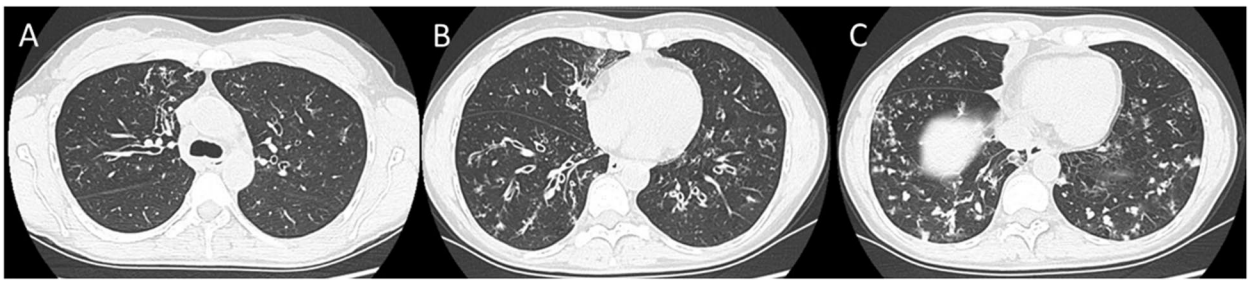

Fig. 2 The patient's first Lung HRCT

The patient's first lung CT showed diffuse cylindrical and varicoid bronchiectasis (**A-C**), tree- in- bud alterations (**A-C**) and bibasilar mucous impaction (**C**)

CT which showed evidence of diffuse cylindrical and varicoid bronchiectasis, tree-in-bud and mucus impaction (Fig. 2). The first sputum culture was performed in January 2023, with the isolation of *Pseudomonas aeruginosa*.

After being lost to follow up due to SARS-CoV-2 pandemia, she came to our attention in March 2023. She reported daily mucopurulent sputum (ca. 20 ml/day) and persistent cough, at PE she presented bibasal rhonchi and wheezing at forced expiration. She was prescribed an extensive etiological screening for bronchiectasis which revealed low IgG_2 levels (189 mg/dl, reference 200–600 mg/dL), an increased T4/T8 ratio, inverted kappa/lambda ratio, positivity for both antinuclear (1:320 nucleolar homogeneous pattern -AC-8) and anti-cyclic citrullinated peptide antibodies (Table 1).

She received indication for PEP bottle and daily nasal lavages, as recommended by guidelines for the management in bronchiectasis patients [11]. She underwent spirometry with the identification of a moderate obstructive syndrome (Forced Expiratory Volume in the 1st second: 63%, Tiffeneau-Pinelli index: 59%), and repeated sputum cultures. Microbiology was positive for a second identification of *P. aeruginosa*, indicating chronic infection, and first isolation of *M. intracellulare*, which was confirmed in a later sputum culture. At the end of this initial evaluation, Bronchiectasis Severity Index (BSI) was 11 [17]. Because of the poor clinical conditions and recurrent exacerbations, a two-week intravenous antibiotic therapy with meropenem 2 g TID was prescribed in May 2023 for *Pseudomonas* eradication. In addition, MRSA was isolated in the same period on bronchoalveolar lavage, but no treatment was indicated. In consideration of no improvement following intravenous antibiotic course and consistent radiological manifestations, she was diagnosed with MAC-pulmonary disease and treatment for *M. intracellulare* (three times weekly regimen of azithromycin 500 mg, rifampicin 450 mg and ethambutol 1000 mg) was started. At the following

Table 1 The patient's extended bronchiectasis etiologic screening

Exams	Results
Blood count	WBC 8.26 × 10^9 cells/L (reference, 4.0–10.0 × 10^9 cells/L), Hb 13.7 g/dl (reference, 13–16 g/dL), PLT 324 × 10^9 cells/L (reference, 150–400 × 10^9 cells/L), eosinophils 0.1 × 10^9 cells/L (reference, 0.1–0.5 × 10^9 cells/L)
Inflammation	CRP 1.89 mg/dl (reference, less than 0.5 mg/dL), ESR 58 mm/h (reference, 3–20 mm/h)
Aspergillus screening	Total IgE 6 kU/L (reference, < 10 kU/L), IgE and IgG A. fumigatus negative (reference, < 10 kU/L)
Autoimmunity	ANA 1:320 nucleolar homogeneous (AC-8), anti-CCP antibodies 1.2 units/ml (positive), ENA screening and ANCA antibodies negative
Immunity panel	IgA 240 mg/dl (reference, 70–400 mg/dL), IgG 1226 mg/dl (reference, 700–1600 mg/dL), IgM 79 mg/dl (reference, 40–230 mg/dL), IgG1 784 mg/dl (reference, 500–1200 mg/dL), IgG2 189 mg/dl (reference, 200–600 mg/dL), IgG3 80 mg/dl (reference, 40–120 mg/dL), IgG4 434 mg/dl (reference, 30–90 mg/dL), lymphocyte subpopulations with altered T4/T8 ratio, inversion of kappa/lambda ratio
Alpha-1 antitrypsin	202 mg/dl (reference, 90–200 mg/dL, considered normal if > 110 mg/dL)
CF testing	Negative sweat test
PCD testing	no indication

Table 1: The patient's results for extended bronchiectasis etiological screening are reported. The alterations in the autoimmunity and immunity panel are compatible with APECED syndrome. PCD testing was not performed for inconsistent clinical history. No other cause for bronchiectasis was recognized. *WBC* White Blood Cells, *Hb* Hemoglobin, *PLT* Platelets, *CRP* C Reactive Protein, *ERS* Erythrocyte Sedimentation Rate, *ANA* Antinuclear Antibodies, *CCP* Cyclic Citrullinated Peptide, *ENA* Extractable Nuclear Antigen, *ANCA* Anti-Neutrophilic Cytoplasmic Autoantibody, *CF* Cystic Fibrosis, *PCD* Primary Ciliary Dyskinesia

clinical evaluation after 6 months, she reported clinical improvement and is still under follow-up. Then the patient was scheduled for a clinical encounter every 6 months and a new CT scan after 18-months.

Discussion and conclusions

Although APECED is a rare genetic disease, its prevalence and incidence are higher in Sardinia in comparison with the rest of Europe. Our patient is a biallelic carrier of the distinctive Sardinian mutation R139X [18]. Although the Sardinian patient group has been well characterized as a foundational cohort in clinical research on APECED, this may be the first case of pulmonary involvement in this population [18].

Diagnostic delay is a significant challenge in the management of people with bronchiectasis, with a possible impact on clinical and patient-reported outcomes [19–21].

Bronchiectasis is the most frequent radiological manifestation in the context of autoimmune pneumonitis in APECED patients and a possible evolution of the lung involvement of this genetic disease [6]. Consistent with our description, chronic pulmonary infections with either *Pseudomonas* or non-tuberculous mycobacteria have already been described in APECED patients and associated with negative outcomes [4, 8].

Regarding the diagnosis, our report is limited by the potential post-infectious etiology in a patient with a history of recurrent pulmonary infections. However, the prevalence of autoimmune pneumonitis has been reported high in APECED patients and its early occurrence may have been possibly mistaken for bronchitis, infectious pneumonia or asthma [6, 8]. In addition, the pattern of diffuse, cylindrical, and varicoid bronchiectasis may be in favor of a systemic etiology.

Further tests for the recognition of autoimmune pneumonitis may include bronchial biopsies reporting the presence of submucosal and intraepithelial lymphocytic inflammation of both T and B cells [6, 22]. However, due to poor clinical conditions, invasive diagnostic testing was not recommended for our patient.

To the best of our knowledge, this is the first APECED patient reported in literature who entered a bronchiectasis program and who was initiated to both microbiological monitoring and respiratory physiotherapy according to international recommendations [11]. We speculate that, according to clinical, radiological, and microbiological complexity of this genetic disease, outcomes of people with APECED and bronchiectasis may benefit from a multidisciplinary evaluation, including respiratory physiotherapists and pulmonologists.

The rational for lymphodepleting treatment with rituximab and azathioprine or mycophenolate mofetil in APECED patients with autoimmune pneumonitis lies in the observation of submucosal and intraepithelial lymphocytic inflammation but may be complicated by serious microbiological complications as shown in our case. The option of initiating lymphodepleting treatment after a multidisciplinary discussion could be successfully implemented.

Another characteristic aspect of autoimmune pneumonitis is the presence of activated neutrophils in the airways, which have been demonstrated to be promoted by the parenchymal lymphocyte infiltrates [6]. Neutrophils are known to be drivers in Th1-mediated bronchiectasis, and there is growing experience targeting neutrophilic inflammation with DPP1 inhibitors [23, 24]. According to these observations, a still unanswered question is whether targeting neutrophils could also have an ameliorating effect in symptomatic patients with APECED and be an alternative to lymphodepleting agents, if these are contraindicated.

The importance of this clinical case lies in the fact that autoimmune pneumonitis in APECED could lead to development of bronchiectasis with a potential impact on clinical outcomes and quality of life. Some APECED patients may require a chest CT scan as well as specific testing to identify bronchiectasis and start effective treatment in an experienced bronchiectasis center.

On the other hand, respiratory physicians should keep APECED in mind as a possible rare cause of bronchiectasis. Young patients showing the classic diagnostic triad should be considered for adequate genetic and serologic testing for APECED diagnosis.

Abbreviations

CT	Computed Tomography
BID	Bis In Die
DPP1	Dipeptidyl Peptidase 1
HRCT	High Resolution Computed Tomography
MAC	Mycobacterium Avium Complex
MRSA	Meticillin Resistant Staphylococcus Aureus
NTM	Non-Tuberculous Mycobacteria
PE	Physical Examination
TID	Ter In Die

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03149-9.

Supplementary Material 1. Supplementary Fig 1. Timeline of the patient's respiratory symptoms and history.

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Authors' contributions

MSS has analyzed and interpreted the patient's data regarding the pulmonary disease and was the major contributor in writing the manuscript. ES, ADA and SA have contributed extensively in the patient's follow-up.ES, AG, ADA, FB and SA have contributed in writing and reviewing the manuscript. All authors read and approved the final manuscript.

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All data and materials are available for sharing, if needed, by the corresponding author.

Declarations

Ethics approval and consent to participate
Ethics approval is not applicable. Consent to participate was obtained from the participant in writing.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The editor in chief for this journal has a copy of this written consent and the ability to review.

Competing interests
MSS, ES and ADA have no conflicts of interest or competing interest to report;
AG reports personal fees from Chiesi, Foodar, Insmed, Neupharma, Vertex;
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Author details
[1]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy. [2]Internal Medicine Department, Respiratory Unit and Cystic Fibrosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano, Milan, Italy. [3]Respiratory Unit, IRCCS Humanitas Research Hospital, Rozzano, Italy. [4]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy.

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