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Case Report

A rare case of vasculitis in cystic fibrosis: A clinical case

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ABSTRACT

Introduction: Cystic fibrosis is known to cause serious complications, such as recurrent pulmonary infections, pancreatic insufficiency, and other symptoms related to exocrine gland dysfunction. A rare manifestation of the disease is discussed in this case of a 24-year-old female diagnosed with cystic fibrosis, a purpuric rash was documented during pulmonary infection flares. Skin biopsy shows a leukocytoclastic vasculitis eruption along with infection. Treatment options are limited and not well established. Our patient received a treatment based on colchicine 1mg per day with a total response. The patient was observed during two consecutive pulmonary infection flares separated by a few months, and a total remission without recurrence was found. *Conclusion:* Considering its efficacy and safety, further scientific research about colchicine and vasculitis in cystic fibrosis should be aimed at in order to define a strong consensus between the disease and this treatment option.

1. Introduction

Cystic fibrosis is an autosomal recessive disorder, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel and regulatory protein found in all exocrine tissues, which is responsible of thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract and of the increased salt content in sweat gland secretions [1].

The usual presenting symptoms and signs include persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels.

Vasculitis is an unusual symptom of Cystic fibrosis, considered a severe complication that affects 2–3% of CF patients and is generally associated with a poor prognosis. Managing the rash itself is a challenging entity, as there is no consensus for a specific treatment [2].

We have submitted this case because it is a rare case of cystic fibrosis complication, and also because the treatment used maintained remission during a pulmonary flare up.

2. Case presentation

A 24-year-old female, diagnosed with Cf at the age of 4 months, after sweat testing and DNA mutation analysis, with both pancreatic and pulmonary insufficiency. At the age of 21, she was diagnosed with cystic fibrosis-related diabetes CFRD and treatment was started with long-term subcutaneous Lantus 100UI/mL.

Abbreviations: CFTR, Cystic fibrosis transmembrane conductance regulator.

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She is known to be suffering from recurrent multidrug-resistant *Pseudomonas aeruginosa* pneumonia since the age of 12 and has been treated in an alternate monthly regimen with Colistin (aerosol), tazocin, and Meropenem. She was hospitalized 3times/year in the last two years for IV antibiotic courses.

Her latest episode was in July 2021 and was treated with high dose Meropenem perfusion for 14 days.

Her most recent Lung functions tests (in 2018) show a severe obstructive syndrome: FEV1/FVC = 56 (FEV1 = 26%, FVC 41%)

In February 2022, the patient presented at the pulmonary department with severe dyspnea and desaturation (SpO2 = 60% at room air). She has been suffering from progressive shortness of breath and desaturation (SpO2 fluctuating between 70% and 80%) for a month, but due to financial difficulties, remained home, using 2 L of O2 upon need. No increased cough, no change in sputum, no hemoptysis, and no fever were reported.

In addition, a palpable, purpuric, vasculitic rash was present on the dorsa of the feet, ankles, and tibial surfaces, with marked clubbing of all toenails (Fig. 1).

This rash has first occurred a year ago (July 2021), along with a pulmonary exacerbation, with a spontaneous remission days after antibiotic treatment. Actually, the rash reappeared, has spread to the knees and became painful.

2.1. Investigations

Blood tests showed an elevated white count and a high CRP. ABGs revealed an acute compensated hypercapnia and hypoxia: 7.44/64/60/43/92%. Chest X-Ray demonstrated a consolidation possibly consistent with pneumonia.

Given these results and her history of recurrent multidrug resistant *Pseudomonas aeruginosa* pneumonias, we suspected an acute pulmonary exacerbation due to the same pathogen.

After taking sputum cultures, the patient received an antibiotic treatment (Meropenem 1g/8h), oxygenation and a noninvasive positive pressure ventilation for her hypercapnia.

As for her painful palpable purpuric rash, we performed a skin biopsy, urinalysis and an autoimmune screening. There was no coagulopathy or systemic involvement. The differential diagnosis includes: Vasculitis associated with cystic fibrosis, rheumatic vasculitis, septic vasculitis, drug induced vasculitis, etc …(See Figs. 2, 3 and 4).

1 The specimen exhibits a mild predominantly superficial perivascular lymphoneutrophilic infiltrate with scattered eosinophils and neutrophilic debris. The overlying epidermis is essentially unremarkable. Direct immunofluorescence studies reveal positive immunostaining only with C3 in a granular pattern around superficial blood vessels within the papillary dermis.

2.1.1. Diagnosis

In view of the clinical picture, the findings of biopsy 1 Fig. 2a are consistent with leukocytoclastic vasculitis in spite of the absence of fibrinoid degeneration of the vessel walls. Findings of biopsy 2 Fig. 2b are less specific but may represent the late stages of leukocytoclastic vasculitis. The findings of direct immunofluorescence studies do not support the diagnosis of IgA vasculitis.

Urinalysis was unremarkable and the autoimmune screen was negative for ANCA, including BPI-ANCA. The technique used for ANCA detection is Immunofluorescence using granulocyte smears as substrate, which can detect antibodies against all antigens, including cANCA, anti–BPI, CAP57, and pANCA.

2.1.1.1. Outcome and follow-up. Following thorough investigations, a treatment with colchicine 1.5 mg per day was administered shortly after. The rash started to resume on the third day of treatment. The dose of colchicine was decreased to the lowest effective dose of 1mg/24h with no relapse.

One month after, the patient was again hospitalized for an infectious exacerbation. No rash was observed (Fig. 4).

3. Discussion

Cystic fibrosis (CF) is a multi-organ disease caused by an autosomal recessive gene, It is produced by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene, which is located on the long arm of chromosome 7 that causes airway obstruction, recur-

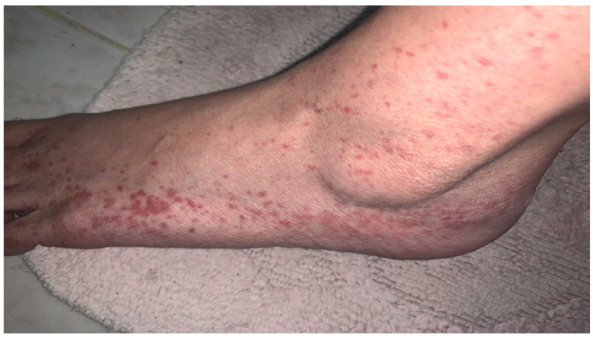

Fig. 1. Purpuric rash on the dorsa of the feet of a patient hospitalised for a pulmonary infection.

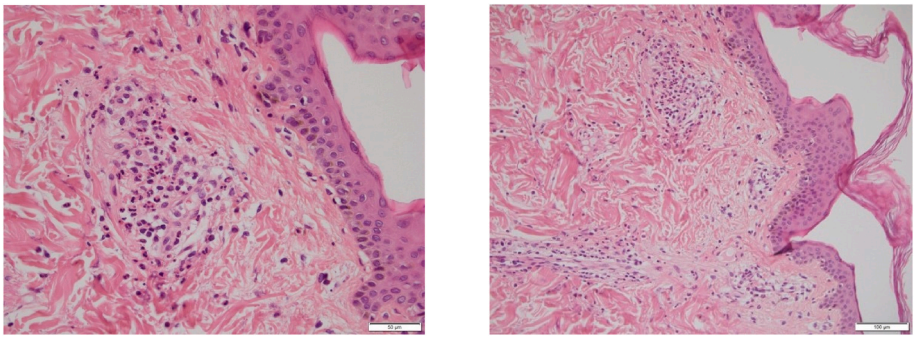

Fig. 2. Two photos of H&E (x200 and x400): fig 2a and fig 2b showing the neutrophilic and eosinophilic perivascular infiltrate. (2a) Skin biopsy exhibiting a mild predominantly superficial perivascular lymphoneutrophilic infiltrate with scattered eosinophils and neutrophilic debris. The overlying epidermis is essentially unremarkable. Direct immunofluorescence studies reveal positive immunostaining only with C3 in a granular pattern around superficial blood vessels within the papillary dermis. (2b) Skin biopsy exhibiting a mild superficial perivascular lymphocytic infiltrate with scattered siderophages. The overlying epidermis is unremarkable.

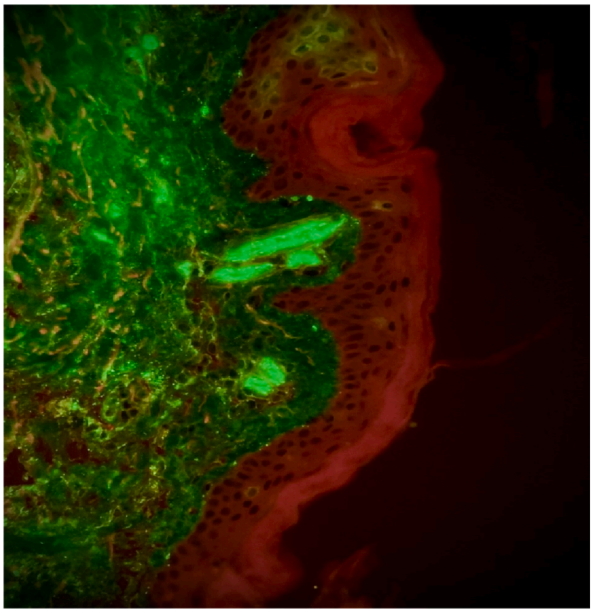

Fig. 3. Photo of DIF with C3 (x400) showing perivascular C3 deposits.

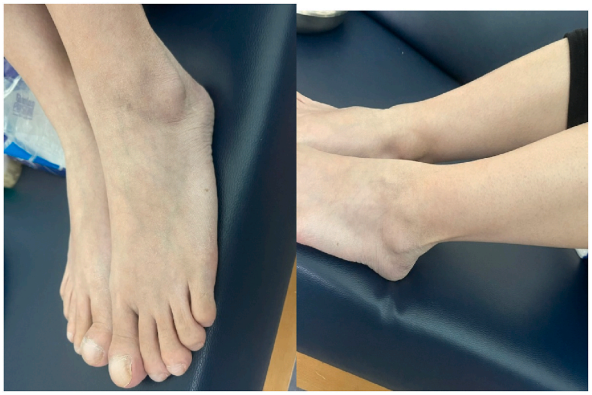

Fig. 4. Complete macroscopic resolution of the purpuric rash after one month of colchicine regimen instauration, despite a new cystic fibrosis infectious flare-up.

rent bacterial infections of airways and sinuses, malabsorption of fat, infertility in men, systemic inflammation and less-well recognized cutaneous manifestations.

Patients exhibit more drug hypersensitivity and atopic reactions compared to the general population, although other seldom dermatological features include early aquagenic skin wrinkling and cutaneous vasculitis [3].

The development of CF-related vasculitis is due to various mechanisms. Bacterial colonization leads to persistent activation of neutrophilic granulocytes, inflammation, and damage, contributing to the production of antineutrophil cytoplasmic autoantibodies (ANCAs) [4].

Cutaneous vasculitis can be induced by some medications. Despite some eosinophilic infiltrate seen in the skin biopsy, the clinical features and the review of the patient's medication, do not support this entity (drug-induced vasculitis) [5].

Continuous inflammation, ongoing immune cell activation, the use of numerous medications, and the presence of pathogens may result in immune complex development and deposition in CF-associated vasculitis, which in turn may cause leukocytoclastic vasculitis [2].

The leukocytoclastic pattern of the vasculitis suggests an inflammatory process which correlates with the patient's current condition.

In fact, ANCA-associated Leukocytoclastic vasculitis was described in many types of infections and chronic inflammation conditions. For example, ANCA positivity is seen in 60–80% of patients with ulcerative colitis and the related disorder primary sclerosing cholangitis, and were found to bedirected against myeloperoxydase, BPI, lactoferrin, cathepsin G, elastase, lysozyme, and PR3 [6].

De novo ANCA-associated vasculitis has been reported in the setting of coronavirus disease 2019 (COVID-19) [7] as well as following administration of COVID-19 mRNA vaccines Vasculitis seen in our case can be attributed to the chronic infection condition seen in cystic fibrosis. Although ANCA were found to be negative using the Indirect immunofluorescence assay, the optimal approach was to perform both immunofluoresence and ELISA, which wasn' t available. The clinical association between vasculitis and the presence of ANCA in Cystic fibrosis has been proposed in many studies. In a cross-sectional study, between 66 Cf patients, none had autoantibodies to the major ANCA antigens, proteinase 3 or myeloperoxidase. However, the majority had autoantibodies to bactericidal/permeability-increasing protein (BPI) (60/66 (91%) CF samples contained IgG, and 55/66 (83%) IgA). Furthermore, anti-BPI levels were inversely correlated with the observed reductions in FEV1 and FVC (IgA anti-BPI & FEV1: $r = -0.508$, $p < 0.0001$). Thus BPI is the major ANCA antigen in CF. Furthermore, the anti-BPI autoantibody levels, especially for the IgA isotype, significantly correlated with reductions in pulmonary function and the presence of secondary vasculitis [8].

Many type of treatments have been proposed, in case reports and small case series, for infection associated Vasculitis, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, hydroxychloroquine, and/or disease-modifying anti-rheumatic drugs (DMARDs), without a clear consensus. As immunosuppression increases the risk of infection and/or malignancy, which are both already increased in people with CF, possible alternative medications may involve the blockade of individual cytokine or inflammatory pathways, or the use of novel CFTR modulators. Based on these criteria, and on its anti-inflammatory properties, we chose colchicine as an alternative treatment option.

The exact mechanism of action is not clearly understood but may involve reduced eicosanoid production via inhibition of phospholipase A_2 or interference with proinflammatory cytokines [9]. In our case, we used a minimal dose, 1mg/day, without corticoids, and there was a dramatic improvement in the appearance of the rash. No previous reports in the literature of cases where colchicine has been successfully used to treat CF associated vasculitis were found.

Leukocytoclastic vasculitis associated with cystic fibrosis can resolve spontaneously, however there is a need for treatment in severe cases in order to interrupt the viscous cycle of bacterial amplification, and thus limiting the recurrence, as it was seen in this case.

4. Conclusion

We reported the case of a CF patient who presented painful palpable purpuric rash, secondary to a Vascultis associated with cystic fibrosis. This rash respond very well to colchicine 1mg/day for 3 months without any relapse even with infectious relapse.

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Declaration of competing interest

All authors have declined no conflict of interest.

References

[1] S.M. Rowe, S. Miller, E.J. Sorscher, Cystic fibrosis, N. Engl. J. Med. 352 (19) (2005 May 12) 1992–2001 https://doi.org/10.1056/NEJMra043184, PMID: 15888700.

[2] F. Sposito, P.S. McNamara, C.M. Hedrich, Vasculitis in cystic fibrosis, Front Pediatr 8 (2020 Nov 12), 585275 https://doi.org/10.3389/fped.2020.585275, PMID: 33282799; PMCID: PMC7690646.

[3] M.L. Bernstein, M.M. McCusker, J.M. Grant-Kels, Cutaneous manifestations of cystic fibrosis, Pediatr. Dermatol. 25 (2) (2008 Mar-Apr) 150–157 https://doi.org/10.1111/j.1525-1470.2008.00620.x, PMID: 18429769.

[4] J.C. Jennette, R.J. Falk, P. Hu, H. Xiao, Pathogenesis of antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis, Annu. Rev. Pathol. 8 (2013 Jan 24) 139–160 https://doi.org/10.1146/annurev-pathol-011811-132453, PMID: 23347350; PMCID: PMC5507606.

[5] C.J. Laversuch, D.A. Collins, P.J. Charles, B.E. Bourke, Sulphasalazine-induced autoimmune abnormalities in patients with rheumatic disease, Br. J. Rheumatol. 34 (5) (1995 May) 435–439 https://doi.org/10.1093/rheumatology/34.5.435, PMID: 7788172.

[6] H. Locht, T. Skogh, A. Wiik, Characterisation of autoantibodies to neutrophil granule constituents among patients with reactive arthritis, rheumatoid arthritis, and ulcerative colitis, Ann. Rheum. Dis. 59 (11) (2000 Nov) 898–903 https://doi.org/10.1136/ard.59.11.898, PMID: 11053069; PMCID: PMC1753037.
[7] N.N. Uppal, N. Kello, H.H. Shah, Y. Khanin, I.R. De Oleo, E. Epstein, P. Sharma, C.P. Larsen, V. Bijol, K.D. Jhaveri, *De novo* ANCA-associated vasculitis with glomerulonephritis in COVID-19, Kidney Int Rep 5 (11) (2020 Nov) 2079–2083 https://doi.org/10.1016/j.ekir.2020.08.012, Epub 2020 Aug 20. PMID: 32839744; PMCID: PMC7439090.
[8] M.H. Zhao, D.R. Jayne, L.G. Ardiles, F. Culley, M.E. Hodson, C.M. Lockwood, Autoantibodies against bactericidal/permeability-increasing protein in patients with cystic fibrosis, QJM 89 (4) (1996 Apr) 259–265 https://doi.org/10.1093/qjmed/89.4.259, PMID: 8733512.
[9] J. Bondeson, The mechanisms of action of disease-modifying antirheumatic drugs: a review with emphasis on macrophage signal transduction and the induction of proinflammatory cytokines, Gen. Pharmacol. 29 (2) (1997 Aug) 127–150 https://doi.org/10.1016/s0306-3623(96)00419-3, PMID: 9251892.