

Cutaneous Vasculitis Associated to Cystic Fibrosis

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Received date: Apr 1, 2016; Accepted date: Apr 24, 2016; Published date: May 2, 2016

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Abstract

Cutaneous vasculitis is a rare complication of cystic fibrosis. The exact incidence is unknown because there are only isolated cases reported. It usually affects patients with severe lung disease and it is believed to be associated with a worse prognosis. While the skin is the most frequently affected site, vasculitis may involve other organs. We present a patient diagnosed with cystic fibrosis since childhood, with a history of liver transplantation and controlled lung disease. At the age of 18 years, the patient consulted with recurrent episodes of cutaneous vasculitis. Three years later, associated with an increase in skin rash, he evolved with severe respiratory failure and cardiopulmonary transplant requirement.

Keywords: Cutaneous vasculitis; Cystic fibrosis; Autosomal recessive disease

Introduction

Cystic fibrosis is an autosomal recessive disease reported in 1 in 2500 live births in Northern American and Northern European Caucasian populations. Classic disease findings include chronic bacterial infection of airways and sinuses, malabsorption of fat, infertility in men, and elevated concentrations of chloride in sweat. Less well-recognized findings associated with cystic fibrosis include cutaneous findings such as higher prevalence of atopic dermatitis and drug hypersensitivity and early aquagenic skin wrinkling and cutaneous vasculitis, which can be associated with arthralgia. Vasculitis is a disorder that involves venules, capillaries, arterioles and larger blood vessels. It can affect the skin in isolation but also other organs. Palpable purpura is the most common manifestation of cutaneous vasculitis, especially if it affects small and medium vessels. The immunologic origin is indisputable in most cases, with the finding of immune complexes in both serum and in the target organ. We present a patient with a history of cystic fibrosis who consulted with recurrent outbreaks of palpable purpura on the lower limbs.

Case Report

The patient is a male of 18 years of age diagnosed with cystic fibrosis (CF) since birth. As a complication of his illness, he required a liver transplant at age 9 so he was immunosuppressed with tacrolimus and systemic corticosteroids at low doses at the time of consultation. He also had newly diagnosed diabetes mellitus treated with insulin therapy. Regarding respiratory infections the patient required recurrent bronchial toilettes and home oxygen therapy. He had a history of colonization of lung secretions with *Pseudomonas aeruginosa*, *Burkholderia cepaci* and *Aspergillus fumigatus* (Figure 1).

He was hospitalized for having abundant respiratory secretions and he increased the oxygen requirement, performing bronchial passage toilette and he received intravenous ciprofloxacin 750 mg every 12

hours. He also received oral azithromycin 500 mg per day, meprednisone 8 mg per day and endovenous colistin.



Figure 1: Lung X-ray of the cystic fibrosis with hyperinflation and atelectasis with bronchiectasis.

During his hospital stay he had palpable purpura which committed feet, legs and lower thighs (Figure 2). After the interrogation we knew that those skin signs had begun in 2010 with similar lesions and evolved with recurrent outbreaks and increased frequency of them in recent months. Skin biopsy showed findings compatible with leukocytoclastic Vasculitis. Some episodes were treated by increasing the usual dose of corticosteroids with involution of the lesions.

The laboratory tests findings demonstrated an increased serum cryoglobulins, ANCA-c positive (1/80), speckled positive FAN (1/80), positive C-reactive protein (1/4), elevated Beta-2 microglobulin and increased Immunoglobulin A with a value of 957 mg/dl. The patient presented the complement within normal limits and both serological tests for hepatitis B and C were negative. The skin condition was interpreted as autoimmune vasculitis associated with cystic fibrosis (Figure 3). It was indicated rest and elevation of the lower limbs without adding changes to his usual medication. The rash resolved spontaneously within a week.

He was readmitted twice in the following months for spontaneous pneumothorax grade III which required a pleural drainage tube. During the first hospitalization he presented a new episode of palpable purpura which was self-limiting. During the second episode he

presented with severe respiratory failure and mechanical respiratory assistance requirement. After being in list of national emergency for a week, he received a lung transplant and developed a favorably response.



Figure 2: Palpable purpuric rash on his lower limbs.



Figure 3: Cutaneous vasculitis on the leg.

Discussion

Cystic fibrosis (CF) is the most common autosomal recessive disease in the Caucasian population [1]. It is produced by a mutation in the transmembrane regulator gene for cystic fibrosis (TRCF) [1]. Its principal morbidity and mortality is related to the pulmonary progressive deterioration, characterized by colonization and recurrent infection with Gram-negative bacilli mainly the *Pseudomonas aeruginosa* [2]. These episodes lead to irreversible lung damage and respiratory failure associated with oxygen therapy requirement and sometimes even it is necessary for organ transplantation. While lung and pancreatic involvement are the most common organs affected and

have been studied in depth, the skin manifestations of this disease are underestimated and therefore underdiagnosed [3].

It is known the association of ANCA (neutrophil cytoplasmic antibodies) with autoimmune vasculitis, usually with small vessel damaging. The ANCA antibodies are mainly 2 major types; ANCA-P (mostly anti myeloperoxidase) and ANCA-C (mostly anti proteinase 3 antibodies). They play a central role in the pathophysiology of vasculitis and serum dosage is used as a diagnostic tool in these cases [4,5].

In the last decade it has described the presence of ANCA in patients with cystic fibrosis. Although the main ANCA associated with CF is the anti BPI (antibacterial/permeability increase protein), there have also been cases of PR3-ANCA positivity (anti proteinase 3) [6,7] as well as the presence of both antibodies in the same patient [8].

BPI is a protein found in the azurophilic granules of neutrophils and is a major defense weapon against bacteria and lipopolysaccharide (LPS) [1]. It has been shown activity of the N-terminal region of the protein which would neutralize the LPS activity while the C-terminal region would play a role in the opsonization of bacteria [9,10]. The ANCA antibodies against BPI are also found in other vasculitis, in the inflammatory bowel disease and in sclerosing cholangitis [11].

In CF a direct relationship between the presence of this antibody and neutrophilic dysfunction associated with poor immune response to Gram-negative bacteria was found. This would contribute to increased bacterial colonization and greater severity of lung disease [1]. Šedivá and colleagues found that children with CF and ANCA-BPI had worse prognosis of respiratory disease demonstrated a significant difference in FEV1 (Forced expiratory volume 1), and increased frequency of lung colonization chronic Gram-negative bacilli compared to patients without these antibodies, with a total of 28 patients enrolled in the study [2].

The presence of ANCA in CF also has been associated with recurrent episodes of vasculitis. Vasculitis is a recognized but rare complication of CF [12]. The literature research findings were based on case reports and case series. While the exact prevalence is unknown, some authors mention that 2 to 3% of CF patients would be affected [13-15] and the age of onset of the manifestations is above 20 years [13]. The organ most frequently affected when vasculitis appears is the skin. It may also be associated but to a lesser extent the affected joints and neurological or renal involvement [3,12,16].

The pathophysiology of CF-associated with vasculitis is not fully elucidated. The suggested mechanism is multifactorial, including a systemic response to bacterial colonization, a deposit of immune complex secondary to chronic inflammation of the airway and gamaglobulinemia associated and a secondary reaction to drugs commonly used in these patients, such as antibiotics and pancreatic enzymes [14,16-19]. ANCA-BPI has been nominated as one of the antibodies that play an important role in the induction of vasculitis associated with cystic fibrosis [13]. This antibody would block the protective activity against the lipopolysaccharide (LPS), which induce injury on the vascular endothelial cells, facilitating the inflammation of blood vessels (Figure 4) [13].

The usual clinical presentation is purpuric macules that evolve into palpable purpura, which are located in the lower limbs. It can also manifest as vasculitis urticaria and bullous lesions [3,13,19]. It may be associated with intermittent arthralgias [19]. In general the picture tends to be self-limiting, with a mean duration of 2 weeks [3,13].

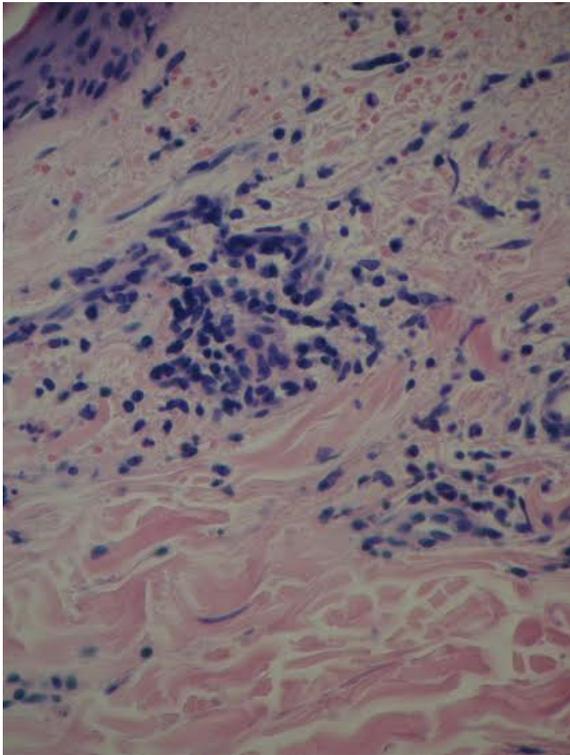


Figure 4: Inflammatory infiltrate predominantly neutrophils in a perivascular and interstitial pattern in addition to those undergoing extravasation from the vessels.

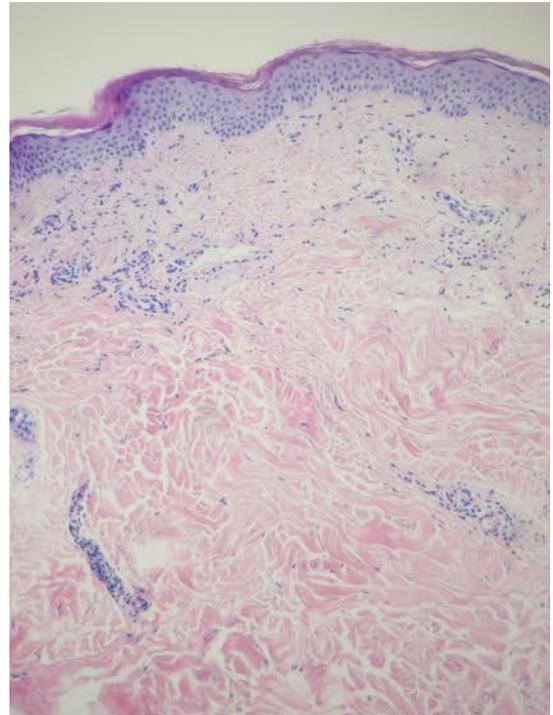


Figure 5: Histopathology of the cutaneous vasculitis (Leucocytoclastic vasculitis).

While the diagnosis is primarily clinical, a skin biopsy histology evidence a leukocytoclastic vasculitis (Figure 5) [14,16]. Direct immunofluorescence demonstrates a deposit of C3, with or without gamma globulin, which is seen within the wall of the blood vessels in the papillar dermis [19].

The disease progresses with recurrent outbreaks. Some authors have suggested that the start of each skin rash would be associated with an episode of pulmonary exacerbation of cystic fibrosis [3,19]. This association is controversial and larger work would be needed to prove this, which is difficult to carry out given the low incidence of the disorder [12].

While cutaneous manifestations do not present major problems to the patients, vasculitis CF has been described associated with severe lung disease and a poor prognosis [13]. This could be explained in part by the pathophysiology that has in common both conditions, due to the impact of antibodies in both organs. In fact 75-90% of patients have less than 2 years of survival after the onset of vasculitis [13,13,20].

Laboratory abnormalities in circulating complexes and vasculitis associated with cystic fibrosis include immune hipergamaglobulinemia [20,21]. It has also been documented the presence of high cryoglobulins and mixed cryoglobulinemia [21]. In patients with CF, the ANCA-BPI was seen more frequently in those with vasculitis compared with those who did not show this condition [3,6,14].

The proposed first-line treatment for cutaneous vasculitis associated with CF is systemic corticosteroids, with a partial response in most cases. There are isolated cases [3,21] reported in the literature which had a successful response to cloroquina [14,16] methotrexate and azathioprine [18] even in cases which were refractory to steroids. Consideration should also be given to the spontaneous resolution in some patients with watchful waiting. Thus the use of immunosuppressants, which could increase the susceptibility to infection, would be prevented.

In case of involvement of other organs it would be required urgent treatment with steroids and other immunosuppressants [18]. For this reason it is important to carry out systematic studies to diagnose all potential target organs of vasculitis. This check should be repeated throughout the disease.

Conclusion

The cutaneous vasculitis associated to cystic fibrosis showed in this case, carries an important learning point for patients with CF who develop skin lesions as palpable purpura or recurrent urticarial disorder. The finding of leukocytoclastic vasculitis as the presence of ANCA supports this diagnosis, especially in cases characterized by ANCA-BPI positive.

Since it is a benign disorder of the skin lesions per se, the most important issue in those cases is to rule out the involvement of vital organs that require systemic immunosuppressive therapy immediately. It should be studied more thoroughly the relationship with lung disease, as it has demonstrated a poor prognosis after onset of cutaneous vasculitis.

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