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Catamenial haemoptysis in females with cystic fibrosis: a case series with review of management strategies

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Abstract

Catamenial haemoptysis, the expectoration of blood during menses, has not been extensively reported in the cystic fibrosis (CF) literature. We describe four cases (age range: 25–34 years) of catamenial haemoptysis across four CF centres in the United States. These cases may represent thoracic endometriosis versus hormonal fluctuations in airway inflammation or infection resulting in bronchial artery bleeding. We identify common and nuanced management strategies including use of pro-coagulants, hormone contraceptives, anti-inflammatories, bronchial artery embolization, and use of the newer cystic fibrosis transmembrane conductance regulator (CFTR) modulators.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Reduction of CFTR function results in mucus retention, chronic infection, and airway inflammation resulting in progressive obstructive lung disease [1]. With underlying airway disease, people with CF can develop bronchial artery hypertrophy and are prone to vessel rupture resulting in haemoptysis [2]. During their lifetime, about 4% of all people with CF will have massive haemoptysis (>240 mL) with an average yearly incidence of 0.87% [3]. The most common cause of haemoptysis in people with CF is a pulmonary exacerbation which often warrants treatment with antibiotics.

Catamenial haemoptysis, the expectoration of blood coinciding with menses, has been reported by women with CF, but studies describing management strategies are limited [4–6]. Hormonal therapy is the standard treatment for catamenial haemoptysis and understanding the clinical response to this treatment in the setting of CF is needed [7,8]. We describe the heterogeneity of clinical manifestations, evaluation, and management strategies used in four cases of women with CF with catamenial haemoptysis across four CF care centres to guide providers when caring for these patients.

Case Series

Case 1

Case 1 is a 27-year-old female with a baseline percent predicted forced expiratory volume in 1 sec ($ppFEV_1$) in the 60s, pancreatic insufficiency, CF-related diabetes (CFRD), and chronic sinusitis. She reported a history of catamenial haemoptysis over five years, specifically occurring monthly immediately prior to her menstrual cycle. She underwent bronchial artery embolization (BAE) two times but continued to suffer from persistent recurrent haemoptysis despite embolization. She was initiated on

vitamin K 5 mg three times per week for bleeding control, which was later increased to 10 mg. This did not resolve her haemoptysis. She was subsequently started on low-dose aminocaproic acid timed with the portion of her cycle when she most commonly bled to decrease haemoptysis, which helped modestly. Ultimately, she was started on the oral contraceptive pill (OCP), norethindrone-ethinyl oestradiol-iron (1.5 mg–30 mcg). She was initiated on a three-week rotating cycle with a skipped placebo week to avoid her menstrual cycle. This improved her haemoptysis; however, within a few months of starting the OCP, her course was complicated by a pulmonary embolism. After lengthy discussions, the patient refused to discontinue the OCP due to the decline in haemoptysis, but she opted to start an anticoagulant, apixaban, simultaneously. She remained on apixaban, OCP, and vitamin K combination. She had no further episodes of pulmonary emboli, but continued to struggle with mild catamenial haemoptysis. She was also started on azithromycin three times a week alternating with 5 mg of prednisone on the non-azithromycin days for the anti-inflammatory effect. She reported an additional improvement with this regimen. She has since started CFTR modulator therapy, elexacaftor–tezacaftor–ivacaftor; continued the OCP, vitamin K, apixaban, azithromycin, and prednisone; and experienced a 5% increase in FEV_1 along with no further haemoptysis.

Case 2

Case 2 describes a 34-year-old female with a baseline $ppFEV_1$ in the 50s, pancreatic insufficiency, CFRD, allergic bronchogenic pulmonary aspergillosis (ABPA), osteopenia, and chronic sinusitis. She had a history of catamenial haemoptysis for over eight years. She had a history of BAE two times previously without resolution of her symptoms. She reported irregular and heavy menses in conjunction with the timing of her haemoptysis. She was initiated on norethindrone–ethinyl oestradiol (1.5 mg–30 mcg) dosed to skip her menstrual cycles. This improved her episodes, but she still experienced a subsequent large bleed requiring BAE. She continued to have minor catamenial haemoptysis. Treatment for her ABPA was initiated due to the ongoing bleeding with prednisone 40 mg daily and itraconazole anti-fungal therapy for a year. She was ultimately started on elexacaftor–tezacaftor–ivacaftor (dose adjusted down due to the Cyp3A inhibition of itraconazole based on prescribing information) [9] at which point she experienced a 20% increase in FEV_1 and has had no further haemoptysis.

Case 3

Case 3 is a 32-year-old female with a baseline $ppFEV_1$ in the 70s, pancreatic insufficiency, and chronic sinusitis. She had a history of recurrent venous thromboembolism (VTE), requiring lifelong anticoagulation with dabigatran. She reported a history of catamenial haemoptysis for over three years. She had large bleeding episodes that were treated by holding anticoagulation, along with intravenous antibiotics, steroids, and tranexamic acid and required up to four BAE resulting in temporary improvement each time. She continued to have minor episodes of catamenial haemoptysis and was then changed from tezacaftor/ivacaftor to elexacaftor–tezacaftor–ivacaftor with significant decrease in the amount and frequency of haemoptysis despite no change in FEV_1. She then started again with moderate amounts of persistent bleeding and ultimately underwent a left upper lobectomy which resolved the haemoptysis for two months before it returned. Lung tissue did not show evidence of thoracic endometriosis (TES). Subsequently, she started decreasing the dabigatran dose and taking tranexamic acid during the time of her menstrual cycles when she most commonly bled. She declined initiation of an OCP due to her history of VTE. A levonorgestrel-releasing intrauterine device (IUD) was placed, but resulted in worsening of her menstrual bleeding and no decrease in her haemoptysis, and was ultimately removed. She is now on dabigatran, elexacaftor–tezacaftor–ivacaftor, and elagolix (GnRH antagonist) with suppression of menses and improvement in the quantity and frequency of haemoptysis to date.

Case 4

Case 4, reported previously [4], is a 25-year-old woman with a baseline $ppFEV_1$ in the 50s and pancreatic insufficiency, with a history of catamenial haemoptysis starting at the age of 13. Notably, her haemoptysis was mild to moderate and she never required BAE. She was initiated on a combined OCP (levonorgestrel-ethinyl oestradiol 0.1–20 mg-mcg) at the age of 15 with cessation of haemoptysis for the subsequent seven years. At age 22, she was started on lumacaftor/ivacaftor, and developed recrudescence of haemoptysis with associated irregular menses and menorrhagia. Her OCP was discontinued and she underwent placement of a levonorgestrel-releasing IUD, but she was maintained on lumacaftor/ivacaftor given pulmonary improvements. Despite IUD insertion, she continued to experience catamenial haemoptysis warranting a six-month treatment with leuprolide acetate. Notably, during this time, she was transitioned to tezacaftor/ivacaftor given the concern of decreased effectiveness of hormonal therapy while on lumacaftor/ivacaftor. She had resolution of her

Table 1. Summary of patient demographics and therapies used.

Patient #	Age (years)	Mutation	Baseline range of FEV_1 %	Hormonal contraception used?	Pro-coagulants tried	Anti-inflammatories tried	Bronchial artery embolization required	Improvement with CFTR modulator
1	27	DeltaF508/V520F	60s	Yes	Vitamin K, aminocaproic acid	Azithromycin, prednisone	Yes—two times	Yes
2	34	DeltaF508/R1162X	50s	Yes	Vitamin K, aminocaproic acid	Prednisone	Yes—three times	Yes
3	32	DeltaF508/DeltaF508	70s	Yes	Vitamin K, tranexamic acid	Prednisone	Yes—four times	Yes
4	25	DeltaF508/DeltaF508	50s	Yes	N/A	Azithromycin	No	Yes

CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 sec.

haemoptysis completely and subsequently had her IUD removed and was restarted on OCP therapy (norethindrone–ethinyl oestradiol 1–20 mg-mcg). Most recently, she transitioned from tezacaftor–ivacaftor to elexacaftor–tezacaftor–ivacaftor with an 11% improvement in FEV_1 and she remains on OCPs with continued cessation of haemoptysis (Table 1).

Discussion

Reports of catamenial haemoptysis are most commonly associated with TES and very few cases are reported in patients with CF [10]. Patients with CF commonly have impaired fat malabsorption leading to vitamin A, D, E, and K deficiency [11]. Therefore, it is a common practice among clinicians to start vitamin K supplementation in those who have bleeding [12]. Other pro-coagulant treatments such as aminocaproic acid or tranexamic acid are also used in CF-related recurrent haemoptysis [13].

Catamenial haemoptysis is generally treated with OCP or gonadotropin-releasing hormone (GnRH) analogues. In our case series, the majority of our patients had some degree of response to the initiation of OCPs. However, it is important to note that OCPs can predispose women to VTE and the risks should be discussed with patients [14]. As reported above, two of the patients experienced VTEs and were started on anti-coagulant medications. Thus, it may be challenging to find the balance of pro- and anti-coagulant medications.

BAE has been performed in patients with brief resolution of symptoms and is recommended by CF guidelines for unstable patients who have massive haemoptysis [3]. However, the efficacy of BAE for control of haemoptysis can range from 75% to 93% with an estimated recurrence rate per episode in the 40% range [15]. The role of BAE remains unclear in CF patients with catamenial haemoptysis as majority of the patients we report had recurrent haemoptysis even after BAE. The higher than typical prevalence of BAE failure may, in part, be due to excessive inflammation but reasons remain unclear.

TES is challenging to diagnosis and is generally established with history. Haemoptysis which occurs along with the menstrual cycle is the most important clue to catamenial haemoptysis; computed tomography (CT) or bronchoscopy is not specific for TES [16]. While TES is a possible aetiology, we propose that another aetiology in CF may be more related to inflammation in the airways occurring in a cyclical nature for these women. This is supported by the variable response to initiation of OCPs noted in these cases and the significant improvement once started on CFTR modulator therapy. Based on recent evidence of sputum inflammatory markers varying in women with CF in a cyclical nature, we believe that dysregulated

inflammation of the airway driven by hormonal fluctuations may play a role in catamenial haemoptysis in CF [17]. Decreased sputum density, dampened airway inflammation and fewer pulmonary exacerbations conferred by highly effective CFTR modulators, such as elexacaftor–tezacaftor–ivacaftor, may be a reason for the significant improvement in several women who experienced haemoptysis after starting this therapy [18].

Special consideration should be paid to the interaction of hormonal contraception and CFTR modulators. Elexacaftor–tezacaftor–ivacaftor does not impact the effectiveness of oral contraceptives. Lumacaftor, on the other hand, is a strong inducer of CYP3A [7,9]. Therefore, lumacaftor/ivacaftor can decrease the effectiveness of hormonal contraceptives and concomitant use should be avoided.

Our step-by-step management strategies for women with catamenial haemoptysis in CF include: optimizing vitamin K supplementation with or without tranexamic acid, a trial of OCP while weighing risks and benefits and the possibility of skipping menses, initiation of CFTR modulators when eligible, BAE when uncontrolled, possible addition of anti-inflammatories, and surgical resection as a last resort.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Author Contribution Statement

Kubra M. Bozkanat, Natalie E. West, Kristina Montemayor, and Maria Gabriela Tupayachi Ortiz were involved in data acquisition, interpretation, and drafting and editing the manuscript. Sigrid Ladores was involved in design of the study and editing the manuscript. Mindy Christianson was involved in editing the manuscript. Raksha Jain was involved in study design and interpretation and drafting and editing the manuscript. All others were involved in revising and editing the manuscript for important intellectual content and gave approval of the final version of the manuscript.

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