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Evaluating the association of central centrifugal cicatricial alopecia (CCCA) and fibroproliferative disorders

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Abstract

Background: In central centrifugal cicatricial alopecia (CCCA), a lymphocytic scarring alopecia that primarily affects black women, it has been postulated that there is a "pro-fibrotic" tendency and increased risk for systemic fibroproliferative disorders.

Objective: To determine whether women with biopsy-proven CCCA have a greater likelihood of systemic fibroproliferative disorders (FPDs) of the lungs (interstitial lung disease), arteries (atherosclerosis of the aorta), liver (non-alcoholic steatohepatitis), kidney (end stage renal disease), or uterus (uterine leiomyoma).

Methods: We conducted a retrospective matched cohort study evaluating 427 cases with biopsy-proven CCCA and 1281 age- and sex-matched controls.

Results: Black women with biopsy-proven CCCA, were not more likely to have interstitial lung disease (ILD), atherosclerosis of the aorta, non-alcoholic steatohepatitis (NASH), end stage renal disease (ESRD), or uterine leiomyoma. Central centrifugal cicatricial alopecia was associated with a history of never smoking and higher body mass index.

Conclusion: In this large cohort of biopsy-proven women with CCCA, there was no association with specific fibroproliferative disorders when compared with age and sex matched controls. Future longitudinal studies may help confirm these results.

Keywords: central centrifugal cicatricial alopecia, fibrosis, fibroproliferative disorders

Introduction

Central centrifugal cicatricial alopecia (CCCA) is a primary lymphocytic scarring alopecia, characterized by a perifollicular lymphocytic infiltrate that results in replacement of the pilosebaceous unit with fibrotic tissue (**Figure 1**). Patients with CCCA develop an area of thinning at the crown or central area of their scalp which can gradually enlarge and spread outward, hence the descriptor, "central centrifugal." This condition is almost exclusively seen in women of African descent mostly in the third or fourth decade of life, although onset can be as early as the second decade. The true prevalence of CCCA remains elusive with studies predicting a rate as low as 2.7% and as high as 47.6% in women of black ancestry [1-4].

Although the pathogenesis of CCCA is unknown, the permanent destruction of hair follicles may be the end result of a destructive inflammatory attack on follicular stem cells and a collapse of the normal "immune privilege" [5,6]. The severity of hair loss has been associated with maternal central scalp hair loss and it has been postulated that hair care practices may lead to low grade but chronic inflammation of

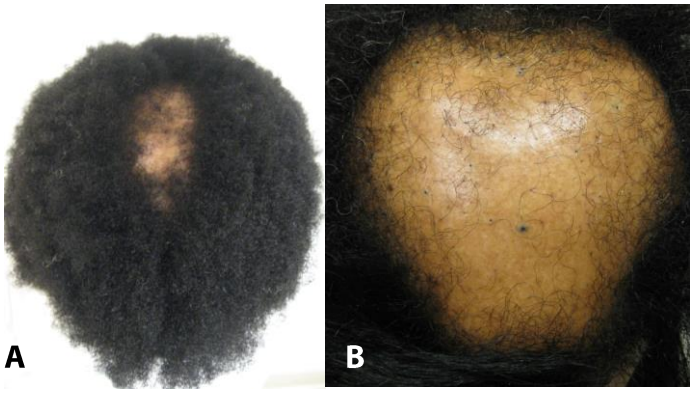

Figure 1. ***A)*** *Central centrifugal cicatricial alopecia. In early central centrifugal cicatricial alopecia there is loss of hair on the scalp vertex.* ***B)*** *In more advanced central centrifugal cicatricial alopecia hair loss is extensive. Follicular markings are absent and signs of cutaneous inflammation are mild/absent.*

the hair follicle [1,2]. A recent study found that the prevalence of mutations in the *peptidyl arginine deiminase 3* (*PADI3*) gene, which encodes a protein that is essential to proper hair-shaft formation, was higher among patients with CCCA than in a control cohort [7]. Thus, it is plausible that both environment and genetics play pivotal roles in the development of CCCA; in genetically susceptible individuals, an aberrant response to inflammation may eventually lead to more destructive fibrotic changes. This model of low-grade injury/inflammation leading to tissue damage is analogous to those changes that occur in some of the fibroproliferative disorders of other tissues such as idiopathic pulmonary fibrosis and end stage renal disease.

Fibroproliferative disorders (FPDs) are characterized by persistent inflammation resulting in replacement of normal tissue architecture with fibrosis. Recent research has helped identify some common molecular pathways in FPDs, raising the prospects of disease markers and treatment targets. Some systemic FPDs that have similar inflammatory cascades include interstitial lung disease, idiopathic pulmonary fibrosis, liver cirrhosis, end stage renal disease, atherosclerosis, and uterine leiomyomas. It has been proposed that the risk of certain FPDs is increased in people of African descent related to profibrotic alleles that provide a protective effect against helminths found in Sub-Saharan Africa [9]. Others have hypothesized that patients with CCCA may have a "pro-fibrotic" tendency and thus may have a higher risk of developing FPDs, not just in the skin of the scalp but in other tissues as well [10-12]. In this study, we aimed to determine whether Black patients with biopsy proven CCCA had an increased risk of the following FPDs: atherosclerosis of the aorta, interstitial lung disease, non-alcoholic steatohepatitis, end stage renal disease, and uterine leiomyoma.

Methods

This study was conducted after approval from the Kaiser Permanente Division of Research's Institutional Review Board. We performed a retrospective matched (3:1) case-control cohort study of adult Black female Kaiser Permanente Northern California (KPNC) members to evaluate whether FPDs are more common among subjects with biopsy-proven CCCA compared to a control population of adult Black female KPNC members with no type of alopecia. We also assessed whether there was a relationship between the use of medications known to be associated with fibrosis and the diagnosis of CCCA. We identified all newly diagnosed, biopsy-proven CCCA cases in Black females between 1/1/2008 and 12/31/2017 and selected three controls for each case. Medication usage and clinical factors were assessed at the study entry date. All indications of FPDs were based on diagnosis codes in the two years prior to study entry and year 1 post-study entry, during which all study members were continuously enrolled in the health plan.

Study population

We identified all potential CCCA cases in Black females within KPNC electronic databases using ICD 9/ICD 10 codes for alopecia (704.09, 704.0, L65.9, L66.9, L66.8). Race and ethnicity are self-reported by the patient. We then identified the pathology reports associated with the alopecia diagnoses using the diagnosis date and Systematized Nomenclature of Medicine (SNOMED) codes for alopecia and scalp. The texts of the pathology reports of possible CCCA cases were reviewed by the two co-investigators who confirmed those with CCCA versus other types of alopecia. Those confirmed with CCCA were our cases and the date of diagnosis was the subject's index date.

Each case was assigned three randomly selected Black, female controls matched on birth year and having KPNC membership on the date of the case diagnosis (index date) as well as two years prior to and 1-year post index data. Each control was required to have at least two medical visits (outpatient, inpatient, or emergency) in the year prior to their index date to indicate they were utilizing KPNC health care services. All controls were at least 18 years of age on the index date with no previous diagnosis of any type of alopecia. Controls with any alopecia diagnosis were excluded from the study.

Organizational context

Kaiser Permanente Northern California is a large, community-based, integrated health care system that reflects the demographics of the community of Northern California [13]. Starting in 2008, the organization has used an Epic®-based electronic health record (EHR) for membership records and healthcare information.

Outcomes and predictors

We identified FPDs of cases and controls through the KPNC electronic database using ICD9/ICD10 codes as follows: atherosclerosis of the aorta (440.20/170), lung (Interstitial lung disease [516.34/J84.9], Idiopathic pulmonary fibrosis [516.31/J84.112]), liver (cirrhosis [571.5/K74.69], non-alcoholic steatohepatitis (NASH), [571.8/573.3/K75.81]), ESRD (585.6/N18.6), and uterine leiomyoma (9218.9/D25.90). The FPD diagnoses were all verified by chart review by the two co-investigators. We then calculated the percentage of subjects having these fibrotic disorders.

We used the KPNC electronic pharmacy database to identify patient prescriptions (prior to index date) of medications with known association of fibrosis: methotrexate, bleomycin, cyclophosphamide, amiodarone, procainamide, penicillamine, gold, and nitrofurantoin.

Potential confounders

Clinical factors (diabetes, body mass index [BMI], hypertension, antinuclear antibody (ANA) test results, medications, and smoking status, prior to or on CCCA diagnosis date, were identified using the KPNC electronic databases. Smoking status was classified as ever smoked cigarettes versus never smoked cigarettes.

Analyses

Descriptive statistics (frequencies, percentages, means and standard deviations) were used to report the distributions of predictors and control variables for the cases and controls. Comparisons between the cases and matched controls were calculated using conditional logistic regression. We used bivariate and multivariable conditional logistic regression to investigate whether differences in CCCA diagnoses could be explained by smoking status, BMI, or FPDs. The multivariable models include variables at least marginally ($\alpha<0.1$) associated with the outcome in bivariate models. All statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, North Carolina, USA). All tests were two-sided and P values less than 0.05 were considered significant. The Kaiser Foundation Research Institute's institutional review board approved this study with waiver of consent.

Table 1 *Demographic and clinical characteristics of study cohort.*

Characteristic	Full Cohort N (%)	Cases N (%) N=427	Controls N (%) N=1281	P value*
Ever smoked cigarettes	321 (18.8)	63 (14.8)	258 (20.1)	0.01
BMI				0.04
16-24.9	264 (15.5)	52 (12.2)	212 (16.6)	
25-39.9	1205 (70.8)	321 (75.2)	884 (69.3)	
40+	233 (13.7)	54 (12.7)	179 (14.0)	
Diabetes	347 (20.3)	79 (18.5)	268 (20.9)	0.26
Hypertension	991 (58.0)	240 (56.2)	751 (58.6)	0.34
Fibrotic Diseases				
Lung disease	12 (0.7)	0 (0.0)	12 (0.9)	0.97
Atherosclerosis	341 (20.0)	89 (20.8)	252 (19.7)	0.55
Liver disease	42 (2.5)	8 (1.9)	34 (2.7)	0.38
Cirrhosis	1 (0.1)	0 (0.0)	1 (0.1)	0.98
NASH	41 (2.4)	8 (1.9)	33 (2.6)	0.42
ESRD	20 (1.2)	5 (1.2)	15 (1.2)	1.0
Leiomyoma	434 (25.4)	121 (28.3)	313 (24.4)	0.10

*Conditional maximum likelihood

Results

A total of 3,313 pathology reports were reviewed resulting in 427 biopsy-proven cases of CCCA identified as part of the cohort. The demographics and clinical characteristics are listed in **Table 1**. The average age of the cases was 50.1 years with a range of 20-83. Looking at the age distribution by quartiles, 25% of the cases were younger than 41 and 25% were older than 59, with 50% being between 41-59 years at diagnosis. The 1281 age- and gender-matched controls were significantly more likely to have a BMI of 25+ but were less likely to have had a history of ever smoking. The rates of comorbid diseases of hypertension and diabetes did not differ significantly between the cases and controls, nor did the rates of a positive ANA. Of the medications that were evaluated, only nitrofurantoin was prescribed at a frequency that could be statistically evaluated, but there was no difference noted between cases and controls.

In our cohort there were no reported cases of idiopathic pulmonary fibrosis and only one case of cirrhosis, so these diagnoses were eliminated in the final analysis. Multivariable analysis indicated that never smoking and higher BMI are characteristics associated with increased odds for CCCA.

Discussion

The results of this case-control study of women with biopsy-proven CCCA suggest that this dermatologic condition is not associated with an increased likelihood of developing ILD, NASH, ESRD, atherosclerosis of the aorta, and uterine leiomyomas. Additionally, CCCA in our cohort was not associated with use of nitrofurantoin. To our knowledge, this is the largest cohort of biopsy-proven CCCA reported in the literature.

The average age in our cases was 50 and the majority had a diagnosis of CCCA between ages 41 and 59, in keeping with other studies that suggest the prevalence of CCCA increases with age [1]. This observation suggests there may be a cumulative burden or a threshold effect for environmental or inflammatory processes before clinical disease or hair loss is diagnosed.

A study of Black women from the Johns Hopkins database found a significantly higher rate of uterine leiomyomas in women with a diagnosis of CCCA versus those without (13.9% versus 3.3%), [10]. Although our study did not find a specific association between CCCA diagnosis and uterine leiomyomas, there were certain differences in our study design. First, in our cohort, the diagnosis of CCCA was confirmed by biopsy and by manual chart review, thus eliminating any discrepancies in diagnosis due to coding but potentially biasing the study for those with more severe disease. Secondly, the rate of uterine leiomyomas in our study was higher, 28% in cases and 24% in controls compared to the previous study. Since we manually validated the individual FPDs, including uterine leiomyomas, both by diagnosis code and by manual chart review, we suspect that our results may be more representative of the true prevalence of clinically diagnosed or symptomatic uterine leiomyomas. Indeed, other estimates suggest that between 20 and 50 percent of all women develop symptomatic fibroids by age 50 with African American women having disproportionately higher rates than white women [14].

Another study of 72 patients with ESRD found central scalp hair loss was prevalent in 68% of patients [11]. This was higher than the 2.7% prevalence reported in the African American population [11]. Again, we did not find a specific association between CCCA and ESRD in our cohort, though the prevalence of this condition was low (1.2%) in both cases, and controls.

Some studies have suggested that there is an association between CCCA and diabetes in Black women [3,4,15]. We did not find such an association. However, approximately 20% of the cases and controls did have a diagnosis of diabetes, suggesting that this diagnosis, along with hypertension, which was seen in approximately 50% of the women, are common comorbidities in this population. The finding that a history of smoking as "protective" was unexpected. Since the duration and quantity of smoking was not evaluated, this result may be a reflection of the limitation in how the data for this variable was collected (ever versus never). There was no difference in cases and controls regarding

autoimmune tendency as ANA was not significantly different amongst cases and controls in those who were tested.

Obesity, as measured by BMI, was associated with an increased risk of CCCA. Prior studies have suggested that there may be a link between hair loss and obesity [16]. Since excess adipocytes are associated with changes in the metabolic milieu in the body, such as insulin resistance and chronic inflammation, this modifiable risk should be addressed in women with CCCA. Interestingly, the same model of a chronic inflammatory state related to obesity has also been implicated in the fibrotic disorder NASH [17]. On a molecular level, genes involved in regulation of lipid metabolism and biosynthesis of fatty acids have been shown to be downregulated in affected scalp tissue in patients with CCCA as well as other cicatricial alopecias [9,18,19]. Recently, treatment with topical metformin has been shown to be effective in two women with CCCA [20].

Limitations

Owing to the retrospective design of our study it is possible that some of the control patients may have had undiagnosed CCCA. Additionally, although hair care practices may play an important role in the pathogenesis of CCCA, this was not specifically addressed in our study. Delineation of hair care practices, their frequency, and age of onset of these practices within our cohort might help determine if there is an association between these practices and CCCA. Although one prior study showed no association of severity of CCCA with relaxer or hot comb use or reaction to a hair care product, there was a statistically significant association between *age* of first relaxer use or prolonged use and extensive hair loss [2]. More severe patterns of CCCA have also been associated with an increase in use of traction hairstyles (braids, weaves), [1].

Conclusion

Our study found that women with CCCA did not have an increased likelihood of having interstitial lung disease, non-alcoholic steatohepatitis, aortic atherosclerosis, and uterine leiomyoma. Never smoking and a higher BMI were associated with a higher risk of CCCA. Future longitudinal studies may help confirm these results.

Potential conflicts of interest

The authors declare no conflicts of interest.

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