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Central Compartment Atopic Disease: What Are the Defining Clinical Features?

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Abstract

Purpose of Review The goal of this narrative is to educate clinicians on the pathophysiology, clinical presentation, radiologic findings, and treatment strategies of central compartment atopic disease.

Recent Findings Central compartment atopic disease (CCAD) is a relatively recently described chronic rhinosinusitis phenotype involving polypoid changes of central sinonasal compartment related to inhalant allergy exposure. This review highlights the current understanding of the pathophysiology of CCAD, relevant history, physical exam findings, and radiologic hallmarks in order to allow for appropriate clinical management.

Summary CCAD is a diffuse type 2-mediated inflammatory phenotype that initially includes polypoid changes of central sinonasal compartment. This is a response to inhalant allergen deposition in the area. Initial treatment includes management of their allergy via immunotherapy. In cases with sinus obstruction from edema of the central compartment, management includes endoscopic sinus surgery. There are differing views on the extent of surgery for these patients.

Keywords Polypoid edema · Immunotherapy · Inhalant allergy · Type 2 inflammation · Endoscopic sinus surgery · CCAD · CRSwNP

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory condition involving the sinonasal mucosa with an estimated prevalence of 5 to 12% of the US population [1]. Traditionally, CRS was further divided into 2 main phenotypes, chronic rhinosinusitis without polyposis (CRSsNP) and chronic rhinosinusitis with nasal polyposis (CRSwNP). Chronic rhinosinusitis with nasal polyposis (CRSwNP) represents approximately 20% of CRS patients and approximately 5.7 billion dollars in yearly costs [2]. CRS represents an estimated healthcare cost of more than $60.2–64.5 billion dollars in 2011 in the USA alone [3]. These patients have an average estimated annual cost > $11,000 more per patient than those without CRS. This is likely related to the high rate of concomitant inflammatory comorbidities, disease chronicity, and need for systemic treatments [4]. Within this cohort of patients, there are several different endotypes with corresponding phenotypes including allergic fungal rhinosinusitis (AFRS), aspirin-exacerbated respiratory disease (AERD), eosinophilic chronic rhinosinusitis (eCRS), and central compartment atopic disease (CCAD). Central compartment atopic disease (CCAD) is a more recently described phenotype first described and named by DelGaudio [5]. CCAD involves edematous and polypoid changes of the central sinonasal cavity (middle turbinate, septum) resulting from deposition of inhalant allergens [5]. Phenotypic classifications of sinus related disease have followed the dichotomy of type 2 and non-type 2 inflammatory patterns. CCAD is classified in the type 2 inflammatory pathway along with AFRS, AERD, and eCRS [6, 7].

As with all subtypes of chronic rhinosinusitis, understanding the pathophysiology of CCAD is vital to providing individualized treatment strategies [7–9]. The initial association between atopy and middle turbinate polypoid edema was first described by White et al. [10] and Hamizan et al.

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[11]. Due to the course of normal nasal airflow, allergens are deposited in the central sinonasal compartment. Here, these allergens stimulate T helper 2 (TH2) and type I immunoglobulin E (IgE)-mediated mucosal edema and inflammation [12]. DelGaudio et al. created a computational fluid dynamics model of allergen deposition which demonstrated that allergens preferentially deposit along the middle turbinate and nasal septum [13]. This explains the involvement of the superior nasal septum (NS), middle turbinate (MT), and superior turbinate (ST) in CCAD [14]. Although this is a disease affecting mainly the central sinonasal compartment, progressive inflammation may lead to lateralization of the MT and/or extension of polypoid changes of the lateral aspect of the MT. This can subsequently lead to obstruction of the sinus outflow, but spare the actual sinus mucosa [15]. This results in post-obstructive secretions in sinuses rather than true atopic/polypoid changes of the underlying sinus mucosa [5]. Recognition of this pattern of disease radiographically, endoscopically, and symptomatically is crucial for differentiating CCAD from other sinonasal inflammatory conditions.

Investigations for Central Compartment Atopic Disease

Clinical History

A systematic approach to obtaining a detailed sinonasal and allergy history is often required when delineating central compartment atopic disease from other Th2 mediated sinonasal disorders, which have a detailed history. Central compartment atopic disease has been characterized by rhinorrhea, sneezing, itching, and conjunctival reactivity [9]. These symptoms are also synonymous with systemic allergy, which has a strong association with CCAD. Smell loss is not standard for these patients as the olfactory cleft is typically spared from the polypoid changes of the central compartment. Allergic sensitization has been reported in 74–100% of patients with [5, 10, 11]. The prevalence of allergic rhinitis (AR) and CCAD is reported to be 97.6%. As the main driver for this pathology is thought to be inhalant allergies, one would expect this number to be closer to 100%. This may be explained by the fact that patients with subclinical allergy symptoms may have sinonasal inflammation [14].

These patients may have a history of allergic asthma that has persisted from childhood and is not adult-onset. However, the incidence of comorbid asthma in CRS conditions has not been as strong as originally postulated. The incidence was found to be to be 17.1% for CCAD, 19% for AFRS, 30.8% for CRSwNP NOS, and 100% for AERD [14]. This may be explained by the attempt of the body to filter these allergens in the central compartment, reducing exposure to the lower airway.

Clinical Findings

Nasal Endoscopy

One of the earliest findings of CCAD found on rigid nasal endoscopy is watery polypoid edematous changes of the middle turbinate. Inhaled allergens are first deposited along the middle turbinate head which can induce a localized inflammation response (Fig. 1A). It is theorized that as the edema increases, the normal function of the MT mucosa is reduced. This allows aeroallergens to advance to surfaces of the superior turbinate (ST), posterosuperior nasal septum (PSNS), and middle turbinate. Hamizan et al. demonstrated that patients with more severe findings of polypoid edema demonstrated on nasal endoscopy, had the strongest association with inhalant allergy, and that MT edema on nasal endoscopy had an excellent positive predictive value for the presence of inhalant allergy [11]. As inflammation progresses, this edema may secondarily obstruct sinus outflow tracts leading to retained secretions. Importantly, this inflammation involves mainly central sinus cavities (medial ethmoids, maxillary sinus ostium), whereas clearance is maintained at the skull base or periphery. In late-stage CCAD, it may be difficult to diagnose based upon nasal endoscopy alone. Therefore, additional testing may be needed. AERD and eCRS may also involve the central compartment, but this is distinguished by more diffuse sinus polyposis, no sparing of the roof or anatomic location, thick eosinophilic mucin, and more fibrous polyps [5, 16]. In patients who undergo surgery, the involvement of the lateral sinuses is typically mucus trapping alone without edema of the sinus mucosa [15].

CT Imaging

Clinical history and exam findings of patients with CCAD often overlap with many subtypes of CRSwNP. Therefore, computerized tomography (CT) imaging is a useful diagnostic tool to help differentiate CCAD from these other subtypes. Unique radiologic findings include nasal septal thickening and obliquely positioned MTs, with relatively aerated sinuses (Fig. 1B–D) [17]. Lund-Mackay (LM) scores are typically low in early CCAD due to its centrally located disease and the lack of major sinus involvement [17–19]. These findings differentiate CCAD from other inflammatory sinus diseases. As described earlier, long-standing CCAD may lead to progressive inflammation resulting in obstruction of sinus outflow tracts (Fig. 2A, B). In this pattern of sinusitis, soft-tissue thickening is noted to begin in the medial aspect of the ethmoid sinuses,

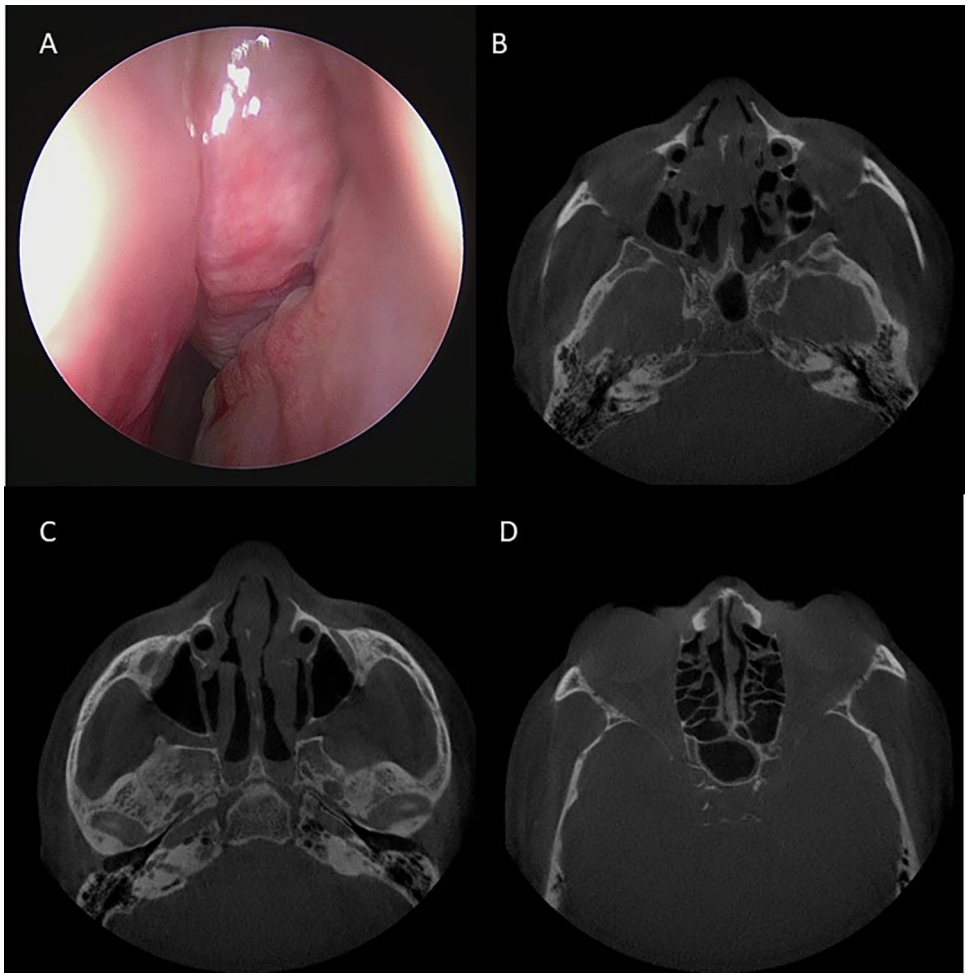

Fig. 1 **A** Inhaled allergens are first deposited along the middle turbinate head which can induce a localized inflammation response. **B**–**D** Unique radiologic findings include nasal septal thickening and obliquely positioned MTs, with relatively aerated sinuses

with sparing of the lateral portion [20]. There will typically be a halo of aeration along the orbits and skull base, commonly referred to as the "black halo sign" (Fig. 2C, D) [21]. Advanced sinus involvement, higher LM scores, and olfactory opacification are key radiologic findings to differentiate AERD from CCAD. Olfactory cleft opacification is only found in very advanced CCAD [17].

Lab Findings

These patients will often have elevated serum specific IgE and have positive testing on skinprick or Immunocap testing. These positive allergens are often correlated with atopic symptoms. Given the high rate of allergen sensitization (74–100%) with CCAD [5, 10, 11], it is important to consider allergy testing in these patients [15]. Prior studies have demonstrated that the allergen profiles between CCAD and AR are very similar, with the exception of weed allergy prevalence. Ninety-six percent of CCAD patients had at least 1 aeroallergen sensitivity [22]. As inhalant allergens are theorized to be the main trigger for the localized inflammation seen in CCAD, it would be expected that 100% of patients with CCAD would demonstrate allergen sensitization. This slight variation may be because these patients have subthreshold doses of allergens which, over long periods of exposure, can cause central compartment inflammation.

This is further evidenced by the increased level of allergen specific IgE (sIgE) found localized to the sinonasal mucosa. Edwards et al. demonstrated that 28.6% of patients with CCAD had positive testing to sIgE on localized sinonasal mucosa, but negative on skin and serum sIgE testing, as evidence of local allergen sensitivity [23]. Allergen sensitivity in the diagnosis of CCAD can be complex and may need further evaluation to determine the allergic profile. Prior meta-analysis found that patients may have negative sIgE and skin prick testing, but have positive nasal allergen provocation testing (NAPT) indicating local mucosal allergic responses. However, systemic testing may also mischaracterize the allergic profile leading to inaccurate allergen sensitization information or may lead to the patient being misdiagnosed as non-allergic [24]. In these situations, it is paramount for the clinician to evaluate the whole picture of the patient including clinical history, endoscopic findings, and allergen testing when making the diagnosis of CCAD.

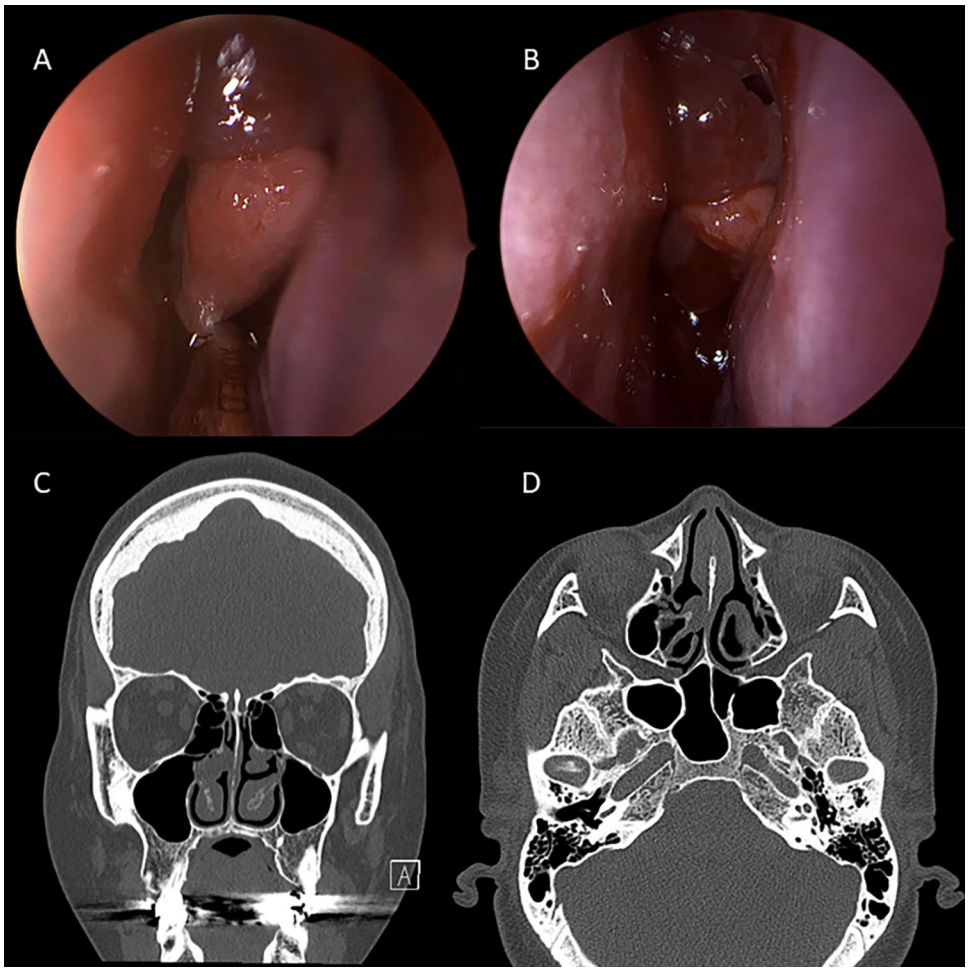

Fig. 2 **A**, **B** Long-standing CCAD may lead to progressive inflammation resulting in obstruction of sinus outflow tracts. **C**, **D** Halo of aeration along the orbits and skull base, commonly referred to as the "black halo sign"

Treatment

Medical

While CCAD is a more recently described sinonasal inflammatory disorder, definitive treatment paradigms have not been clearly defined. However, the goals of medical management are clear. As inhalant aeroallergens are proposed to be the dominant pathologic mechanism driving CCAD, medical treatment strategies are aimed at reducing inflammation and exposure. The standard therapies recommended for management of CRSwNP can be employed including intra-nasal corticosteroid spray (evidence A), followed by intra-nasal steroid irrigations (evidence B) [16]. In addition to these management strategies, treatment of the underlying sensitization is paramount to prevent persistent atopic symptoms. In patients who are able to undergo allergy testing and immunotherapy, these should be utilized early in the management. However, if polypoid change has already occurred, neither corticosteroid irrigations nor immunotherapy will reverse these changes and surgical intervention may be needed up front to overcome nasal symptoms with medical therapy to follow. In patients with predominant systemic allergic symptoms and reactive nasal symptoms, medical management should be initiated first (corticosteroid application and immunotherapy) and surgical intervention reserved for later if needed.

Surgical

There are debates surrounding the extent of surgical intervention in patients with CCAD. Some postulate that limited endoscopic sinus surgery in those with refractory symptoms on maximal medical management is the appropriate plan. This limited approach involves targeted sculpting of central nasal compartment structures, removal of polyps, and only opening sinuses if they are secondarily involved. This methodology is meant to preserve protective capabilities of the central compartment structures in their role to filter inhalant allergens. This also minimizes exposure of unnecessary additional sinonasal mucosa to inhalant allergens. The goal of surgery should be to allow delivery of topical steroid via nasal irrigations. The ability to control polyp formation and decreased need for revision

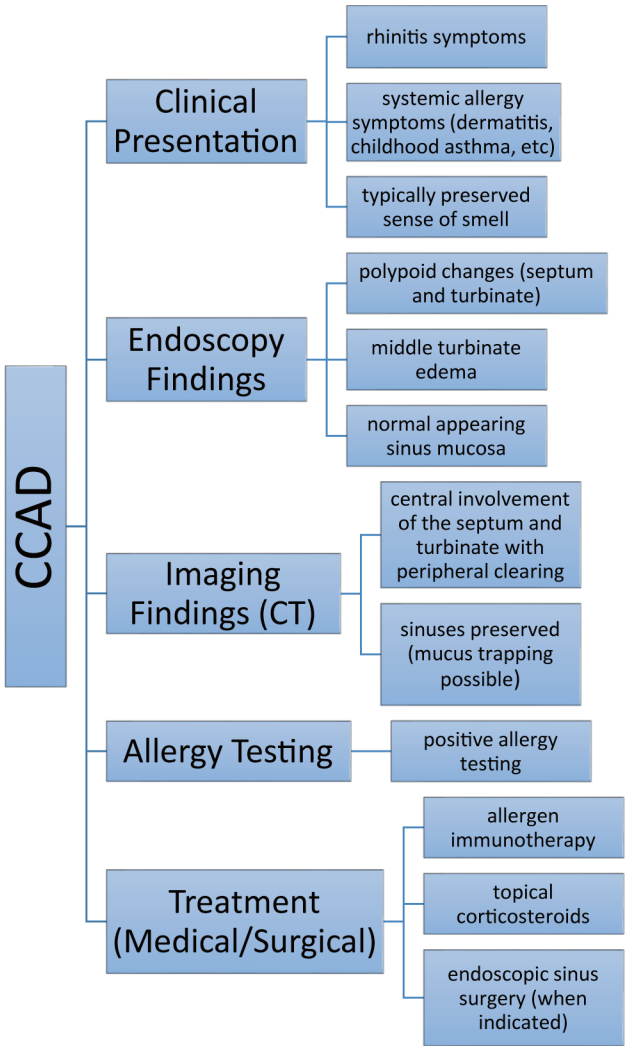

Fig. 3 Management includes topical corticosteroids, immunotherapy, and endoscopic sinus surgery in those with advanced polypoid changes that will not be completely managed with medical therapies or that are obstructing the lateral sinus cavities

surgery were demonstrated to be particularly favorable in the CCAD group, unlike disease recurrence and persistent symptoms for other subtypes of CRSwNP. The rate of revision surgery of ESS in CCAD patients was found to be 5.3%. This is a significantly lower rate when compared to CRSwNP group as a whole (21.2% and 18.6%) in previously reported studies [25, 26]. DelGaudio et al. demonstrated that this limited approach followed by topical steroid rinses and allergy treatment resulted in dramatic symptomatic improvement [5].

Shih et al. demonstrated statistically significant improvement in SNOT-22 scores in CCAD patients after ESS [27]. Interestingly, this study also demonstrated that CCAD patients experienced excess blood loss during surgery when compared to patients with other subtypes of CRSwNP. This is thought be attributed to severe local Th2-mediated inflammation. It is important to note that although symptoms may initially improve after surgical intervention, in the absence of medical therapy, further exposure of the sinonasal mucosa may inadvertently result in increased disease burden. Others may recommend a "full-house ESS" to open all of the sinuses to allow for maximum topical corticosteroid exposure and controlled healing to decrease irrigation limiting post-operative scarring. Interestingly, patients with CCAD may be more likely to experience sinus barotrauma or "sinus squeeze." This most commonly affects the frontal sinus and is an indication to extend surgery to include the affected sinuses. Despite the debate about extent of surgery, ultimately, a definitive extent of surgery plan, diligent patient selection, and patient counseling are important prior to surgical intervention.

Conclusions

Given the extensive sub-types of CRSwNP, a structured approach is needed to determine which sub-type best fits each patient and their symptoms. Determination of CRS phenotype is critical for appropriate medical and surgical therapies to maximize patient outcomes. Central compartment atopic disease is a Th2-mediated inflammatory subclass of CRSwNP. It is characterized by atopic history and symptoms, middle turbinate, posterior nasal septum and superior turbinate edema on endoscopy, and sparing of the superior and lateral sinus walls on imaging in the early phases. Management includes topical corticosteroids, immunotherapy, and endoscopic sinus surgery in those with advanced polypoid changes that will not be completely managed with medical therapies or that are obstructing the lateral sinus cavities (Fig. 3).

Declarations

Competing Interests Emily Miller, MD, has no relevant disclosures. Do-Yeon Cho, MD, has no relevant disclosures. Bradford A, Woodworth, MD, serves as a consultant for Medtronic and Cook Medical. Jessica Grayson, MD, has no relevant disclosures.

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