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Neutrophilic asthma: a complex phenotype of severe asthma

Abstract

Asthma is a common chronic airway disease affecting about 334 million people worldwide, and an estimated 7 million children globally. Approximately 10% of patients with asthma have severe refractory disease, which is difficult to control on high doses of inhaled corticosteroids and other modifiers. Among these, are patients with severe neutrophilic asthma. Neutrophilic asthma is a phenotype of asthma that is very severe and persistent, with frequent exacerbations, and characterized by fixed airway obstruction. It is associated with comorbidities such as respiratory infections, obesity, gastroeosophageal reflux disease, and obstructive sleep apnoea. Immunopathologically, it is characterized by the presence of high levels of neutrophils in the lungs and airways. Neutrophils and the interleukin-17 family of cytokines play a pivotal role in the pathogenesis of severe neutrophilic asthma. Most patients with the disease do not achieve control with high dose inhaled corticosteroids, and probably to novel IgE, interleukin and interleukin monoclonal antibodies.

Keywords: neutrophilic asthma, neutrophils, inflammatory mediators, interleukins-17, monoclonal antibodies

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Nightingale Syabbalo
Department of Medicine and Physiology, Copperbelt University, Zambia

Correspondence: Nightingale Syabbalo, Professor of Medicine and Physiology, Copperbelt University, M. C. Sata School of Medicine, P. O. Box 21692, Kitwe, Zambia, Tel +260 966 486117, Email nightsya@gmail.com

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Abbreviations: IL, interleukin; TSLP, thymus stromal lymphopoietin; Th, T helper cells; FENO, fractional exhaled nitric oxide; FEV1, forced expired volume in 1 second, LABAs, long-acting β2-agonists; AERD, aspirin-exacerbated respiratory disease; EIA, exercise-induced asthma; ICSs, inhaled corticosteroids

Introduction

Asthma is a complex chronic airway disease with several distinct phenotypes with different immunopathological pathways, clinical presentation, physiology, comorbidities, biomarker of allergic inflammation, and response to treatment.[1–4] There are several distinct clinical proposed asthma phenotypes, such as childhood-onset allergic asthma, adult-onset eosinophilic asthma, neutrophilic asthma, exercise-induced asthma (EIA), obesity-related asthma, and aspirin-exacerbated respiratory disease (AERD).[5–12] Among these phenotypes of asthma, there are patients whose asthma is very severe and refractory to the standard treatment including high doses of inhaled corticosteroids (ICSs), and long-acting β2- agonists (LABAs) and/or any other modifier.

Severe refractory asthma represents about 5-10% of patients with asthma.[9–11] The guidelines on the definition, evaluation and treatment of severe refractory asthma are discussed in detail by the American Thoracic Society, the European Respiratory Society, and the World Health Organization.[13–15]

Severe refractory asthma encompasses several molecular phenotypes of asthma, including neutrophilic asthma phenotype. Neutrophilic asthma is characterized by severe refractory disease, with fixed airway obstruction, and poor response to standard treatment with inhaled corticosteroids (ICSs), long-acting β2-agonists (LABAs), and other modifiers. [7, 16–18]

Eosinophilic asthma is adequately investigated and established phenotype of asthma.[5, 6, 9, 10] By contrast, neutrophilic asthma has complex pathogenesis and is not fully understood phenotype of asthma. However, about 30%-50% of the patients with symptomatic asthma have this phenotype.[19]

Neutrophilic asthma

Characterizing the phenotypes of severe asthma has clinical and therapeutic implications in the development of novel biologics for the personalized treatment of different phenotypes of asthma.[5–7, 10, 14, 19] Approximately 50% of patients with asthma have Th2-driven eosinophilic asthma, whereas the remaining 50% have non-eosinophilic asthma phenotypes which can be subdivided into neutrophilic, and paucigranulocytic subtypes.[5, 6, 20] Eosinophilic asthma is one of the well-characterized clinical phenotype of asthma,[8,, 10, 20–24] whereas, neutrophilic asthma phenotype is less-well defined.[25, 26]

The pathophysiology of neutrophilic asthma is complex and less clearly understood. Patients with neutrophilic asthma have high neutrophil count in the sputum ranging from 40% to 76% of sputum cells,[25–27] or a neutrophil count of 500 x 10^4/ml.[26] Conversely, they have less sputum eosinophil count which has been quoted to be between less than 1.9% and 3% by various authors.[6, 23]

Increased neutrophils in sputum have been associated with severe persistent asthma,[6, 7, 14, 27, 28] fixed airway obstruction,[27, 29, 30] with very low forced expired volume in 1 second (FEV1), and post-brochodilator FEV1.[30] Shaw and collagues[30] reported that both patients with eosinophilic asthma and neutrophilic asthma had low pre-bronchodilator FEV1, but only patients with neutrophilic asthma had lowest post-bronchodilator FEV1, indicating persistent airflow limitation.

Neutrophilic asthma is associated with more frequent exacerbations, although the exacerbations are not as severe as those encountered in patients with eosinophilic asthma.[3, 31–33] On the sick note, patients with neutrophilic asthma have frequent urgent visits to emergence rooms, hospitalization and intubation.[13] This phenotype of asthma has been associated with sudden-onset fatal asthma in about 23% of the

patients.[34] Furthermore, patients with severe bronchial neutrophilia are more likely to be admitted to hospital for noninfectious status asthmaticus.[35] Intriguingly, the disease tends to be worse at night (nocturnal asthma).[36] Martin and collegues[36] found a greater than three-fold increase in the number of granulocytes in bronchoalveolar (BAL) fluid at 04:00 hr compared with 16:00 hr. This has clinical implication in the management of patients with neutrophilc asthma who may require chronotherapy for the treatment of their nocturnal symptoms.[37]

Additionally, neutrophilic asthma is typically associated with a worse quality of life, and has a poor prognosis.[7, 13, 14, 17, 21, 30, 38] Patients with neutrophilic asthma are unresponsive to high-dose ICSs,[39–41] and possibly to the newly introduced targeted biologics.[11, 12, 16] Currently, no specific biomarkers are readily available to support the diagnosis and phenotyping of these patients,[42] for personalized precision medicines.[43]

Neutrophilic asthma phenotype is an adult-onset disease and usually starts after 12 years.[9] Patients are less likely to be atopic,[9, 22, 30, 44] and have less responsiveness to bronchoprovocation testing with methacholine.[9, 22, 42] The underlying mechanisms of neutrophilic asthma are not fully understood. The clinical characteristics of neutrophilic asthma are summarized in Table 1.

Table 1 Characteristics of neutrophilic asthma

Adult on-set, after 12 years
Less atopic
Less severe exacerbations compared to eosinophilic asthma
Less sub epithelial basement thickness - indicator of IL-13 and TSLP responses
Th17 cytokine milieu - IL-6, IL-8, IL-21, IL-23, IL-17A, IL-17F, IL-1β, TNF-α, TGF-β
Chemo attractant chemokines – CXCL1 (Gro-α), CXCL2 (Gro-β), CXCL5, CXCL6, CXCL8 (IL-8), MCP-1
Prostaglandins - prostaglandin E2
Low FENO - biomamarker of eosinophilic asthma
Low periostin levels - indicator of IL-13 inflammatory activity
High hydrogen sulfide levels
Fixed airway obstruction (low FEV1)
Low post-bronchodilator response to β2-agonists
Less responsive to methacholine bronchoprovocation tests
Corticosteroid unresponsiveness

Comorbidities and associated features of neutrophilic asthma

Neutrophilic asthma is associated with comorbidities and confounding factors which may contribute to the severity of the disease and exacerbations. These include: respiratory infections (viral, bacterial and fungal), rhinosinusitis, obesity, gastroeosophageal reflux disease, obstructive sleep apneas, and occupational asthma. Table 2 shows the comorbid and cofounder conditions associated with neutrophilic asthma.

Table 2 Comorbidities and confounders associated with neutrophilic asthma

Respiratory infections (viral, bacterial and fungal)
Rhinosinusitis
Obesity
Gastroeosopghageal reflux disease
Obstructive sleep apneas
Occupational asthma
Nocturnal asthma
Smoking
Pollution

Upper and lower respiratory tract infections including respiratory syncytial virus, and human rhinovirus have been associated with both the onset and exacerbations of asthma including the neutrophilic phenotype, especially in children.[45–47] Respiratory infection due to influenza can lead to severe refractory asthma exacerbation requiring intensive care unit (ICU) admission.[48]

Bacterial infection has been associated with the pathogenesis of neutrophil corticosteroid-refractory severe asthma.[49–53] Refractory asthma is characterized by increased number of neutrophils, inflammasomes and pro-neutrophil biomarkers in the airways. The airway neutrophilia in this phenotype of asthma is unlikely to be due to bacterial infection or to corticosteroid use which is known to prevent apoptosis of neutrophils in favour of eosinophils. Wood et al[53] found several potentially pathogenic bacteria in the sputum from patients with stable asthma, as well as increased sputum counts, and IL-8 levels. This may suggest the presence of a specific lung microbiota and subsequent effect on immunity.[53]

Fungal respiratory infection with *Aspergillums fumigates* and other fungi has been identified in severe asthma, with fungal sensitization and neutrophilic response in order to combat the infection.[54]

Rhinosinusitis coexist with asthma in 34% of patients with different phenotypes of severe asthma.[55] However, patient with neutrophilic asthma have an increased prevalence of rhinosunisitis (>64%) compared to those with eosinophilic asthma.[56] Sinupulmonary

infection is also reported to be high in patient with neutrophilic asthma.[7] Patients with asthma should be investigated for chronic rhinosinusitis and nasal polyps. Medical and surgical therapy of chronic rhinosinusitis improve the clinical course of asthma, with medical treatment being superior to surgical procedures in patients with chronic rhinosinusitis and nasal polyps.[57]

Obesity is extremely common in patients with asthma,[58–63] and the risk of severe asthma in obese patients appears stronger for central than for generalized adiposity.[64–66] Obesity is associated with more symptoms, more frequent severe exacerbations of asthma.[60, 67] Patients with obesity-related asthma have less favourable response to reliever and controller medication compared to normal weight patients.[67–70] Similar to neutrophilic asthmatic patients, patients with obesity-related asthma have a poor response to corticosteroids,[71–75] and a worse quality of life.[67–69]

Obesity-related asthma phenotype represent a distinct clinical phenotype,[23, 61, 76] but with some identical clinical features and biomarkers as neutrophilic asthma (Table 1). It present with a particular set of characteristics that include late onset, predominantly female, severe asthma, less atopic to bronchoprovocation tests, lower pulmonary function, and poor responsiveness to corticosteroids.[9, 23, 66]

Obesity-related asthma has been associated with increased airway neutrophilia.[77, 78] Scott et al[78] have shown that neutrophils but not eosinophils were higher in the sputum of obese asthmatic than non-obese patients. The high levels of sputum neutrophil counts in obese patients has been confirmed by Marijsse and colleagues,[79] who also demonstrated higher levels of sputum neutrophils than eosinophils in obese versus lean subjects with poorly controlled asthma. This group also reported higher levels of IL-17A protein in obese asthmatic patients that in the lean patients.[79]

The mechanisms and relationship between obesity-related asthma and severe steroid-resistant asthma are described in detail elsewhere,[58, 60, 67, 79–83] however, the inflammatory cascade due to the activation of the Th17 cell/IL-17A axis may partly contribute to the pathogenesis of airway neutrophilic inflammation in patients with obesity-related asthma. It is important to investigate patients with asthma for comorbidities such as obesity and syndrome X.

Bariatric surgery, by either sleeve gastrectomy or Roux-en-Y gastric bypass has been reported to improve asthma control, lung function, and related-quality of life.[84, 85] Bariatric surgery has also been shown to reduce airway hyperresponsiveness.[85] Hasegawa et al,[86] have reported that, bariatric surgery lead to nearly 60% reduction in the risk of asthma exacerbations.

Obese individuals usually have co-existing comorbidies such as hypertension, gatroeosophageal reflux disease (GERD), sleep obstructive apnoea (OA), type 2 diabetes mellitus, dyslipidaemia,[27,87–88] metabolic syndrome,[66] and depression (Table 3). These coexisting diseases may aggravate the symptoms of obesity-related asthma, and make it difficult to control.

Table 3 Clinical conditions associated with obesity

Gastro esophageal reflux disease
Obstructive sleep apnoea
Hypertension
Type 2 diabetes
Dyslipidemia
Metabolic syndrome
Depression and anxiety

Several studies have indicated that up to 50% of patients with asthma have either evidence of esophagitis or increased esophageal acid exposure assessed on a 24-hr ambulatory pH monitoring.[89–92] Gastroesophageal reflux disease has been found to be very common in patient with neutrophilic asthma.[7, 86, 93, 94] Immunopathologically, GERD is characterized by airway neutrophilia.[93] Patients with GERD and neutrophilic asthma have severe refractory disease, lower lung function, and poor symptom control.[7, 56, 86] Several reports have documented that medical treatment with prokinetics and H2-antagonists, proton-pump inhibitors, and antireflux surgery improve asthma symptom and reduce exacerbations in asthmatic patients with GERD.[95] Prokinetics and H2-receptor antagonists have been reported to reduce symptoms, [96] and nocturnal asthma in patients with GERD.[97] Similarly, proton-pump inhibitors have been shown to improve symptom control and pulmonary function.[98, 99] Antireflux surgery in patients with severe asthma and GERD has been documented to improve respiratory symptoms and peak expired flow rates (PEF),[100, 101] and decrease the need or dose of systemic corticosteroids.[102]

There is a high prevalence of obstructive sleep apnoea of about 80% in patients with severe asthma.[103,104] The frequency of severe asthma exacerbation is also reported to be higher is asthmatics with OSA than those without.[104] Teodeorescu and colleagues,[105] have reported that OSA is associated with severe asthma which is difficult to control. The same authors found that OSA was associated with neutrophilic airway inflammation.[108] Taillé et al[107] have also reported increased sputum neutrophil counts and airway remodeling in asthmatic patients with mild OSA.

Obstructive sleep apnea is treated with continuous positive airway pressure (CPAP). CPAP has been shown to reduce systemic inflammation and airway responsiveness.[85,109] Long-term use of CPAP has also been reported to decrease symptoms of asthma,[110] and the use of rescue β2-agonists.[108] Noteworthy, the quadruple disease of obesity, obstructive sleep apnea, gastroesophageal reflux, and severe asthma has a worse clinical outcome.

Patients with neutrophilic asthma are at a higher risk of developing occupational asthma,[111] particularly due to low molecular weight (LMW) agents.[112] Patients who develop work-related asthma from LMW agents have bronchial neutrophilic inflammation.[113] The mechanisms by which LMW sensitizers induce neutrophilic airway inflammation require further investigations. Patients with occupational asthma and comorbid conditions associated with neutrophilic airway inflammation should be suspected of having neutrophilic asthma, and at least be treated for the coexisting diseases.

Smoking is associated with severe asthma, frequent exacerbation, life-threatening asthma attacks, and worse asthma-specific quality of life.[114] Shimoda et al.[115] reported that smokers with asthma had very low FEV1/FVC ratio, lower fractional expired NO (FENO), and higher sputum neutrophil counts than eosinophils compared to non-smokers. Furthermore, smoking is associated with poor response to inhaled corticosteroids.[116,117] All these are typical characteristics of neutrophilic asthma. Siew et al[118] have reported that the expression of IL-17A and IL-8, and neutrophil counts are significantly elevated in the bronchial mucosa of smokers compared to nonsmokers. Furthermore, IL-17A levels correlated with that of IL-8 and the

neutrophil numbers.[118] This emphasizes the importance of airway neutrophilic inflammation and IL-17A in the pathogenesis of severe asthma in smokers.

Airway neutrophilic inflammation in neurophilic asthma

The pathogenesis and immunopathology is complex and is not fully understood. The hallmark of neutrophilic asthma and its coexisting diseases such as obesity, GERD and OSA is infiltration of the airway with activated neutrophils. The driving mechanism for neutrophilic asthma has been associated with altered innate immune response and activation of Th17 cells.[119–121] Unlike eosinophilic asthma, which has clearly been identified as a Th2-driven phenotype,[20, 21, 24] and associated with IL-3, IL-4, IL-5, IL-13, IL-25, IL-33, and TSLP,[122–128] the relationship between Th17 cells and its family of cytokines is becoming much clear. Interleukin 17A (synonymous to IL-17) and IL-17F are the signature cytokines implicated in neutrophilic airway inflammation and in the pathogenesis of neutrophilic asthma. There are also other surrogate cytokines such as IL-6, IL-8, IL-23, IL-1β, TNF-α, TGF-β and many more other cytokines, chemokines and inflammasomes which aid IL-17A in orchestrating neutrophilic airway inflammation in patients with severe neutrophilic asthma.[129–132] This review has just discussed briefly IL-17A, but this kingpin cytokine and its other five siblings are implicated in a myriad of autoimmune and inflammatory diseases. Table 4 lists the several diseases implicated by activation of the Th17 cells/IL-17A axis. It is hoped in future to find a suitable IL-17 A and/or IL-17RA monoclonal antibody specific for the targeted personalized treatment of neutrophilic asthma, similar to the other phenotypes of asthma.[43, 132, 133]

Table 4 Conditions and diseases in which interleukin 17A and IL-17F are implicated

Rheumatoid arthritis
Ankylosing spondylitis
Psoriatic arthritis
Psoriasis vulgaris
Neutrophilic asthma
Inflammatory bowel disease
Multiple sclerosis
Epilepsy
Autism spectrum disorders
Alzheimer's disease
Atherosclerosis
Depression and anxiety
Allograft rejection
Anti-tumour immunity

Conclusion

Neutrophilic asthma is a complex phenotype of asthma characterized by high levels of neutrophils in sputum, BAL fluid, and bronchial biopsy specimen. Th17 cells and IL-17A and IL-17F cytokines play an important role in the pathogenesis of neutrophilic airway inflammation. Neutrophilic asthma is characterized by severe disease, frequent exacerbations, near-fatal asthma, fixed airflow obstruction with low FEV1. Patients with neutrophilic asthma have poor response to corticosteroids, and have worse quality of life. Cormobid disease coexisting with NA, such as respiratory infections, rhinosinusitis, obesity, gastroesophageal reflux disease, obstructive sleep apnoeas aggravate the symptoms, and contribute to the poor response of neutrophilic asthma to controller and modifier medications. Treatment of of some of these coexisting diseases improve the symptoms, lung function, reduce frequent use of rescue medication, and improve the quality of life. There are no readily available biomarkers for the diagnosis of neutrophilic asthma for targeted precision medicines.

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Conflicts of interest

The author declares there is no conflicts of interest.

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