American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Concise Details of RADS

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To Cite This Article: *Stuart M Brooks, Concise Details of RADS. Am J Biomed Sci & Res. 2019 - 6(3). AJBSR.MS.ID.001029. DOI:* 10.34297/AJBSR.2019.06.001029.

Received: November 05, 2019; **Published:** November 22, 2019

Abstract

Reactive Airways Dysfunction Syndrome (RADS) is an abrupt-onset asthmatic disorder of a non-allergy origin. Its mechanism relies on innate immunity that permits the airways to deal with non-microbiological constituents. The massive exposure causes a severe airway injury with ensuing detachment of damaged and dead epithelial cells. There is the release of Molecules of Damage-Associated Molecular Patterns (DAMPs) by stressed or dying cells. Hematopoietic and bone marrow-derived cells migrate to renew the denuded cellular barrier. Soluble growth factors, interleukins, chemokines, arachidonic acid products, and discharges from airway smooth muscle cells aid epithelial and tissue repair. Metalloproteases and extracellular matrix influence the epithelial-to-mesenchymal matrix. Lung macrophages contribute to the repair and influence airway hyperresponsiveness. Airway wall thickening, subepithelial fibrosis, mucus metaplasia, myofibroblast hyperplasia, muscle cells hyperplasia and hypertrophy, and epithelial hypertrophy are characteristic features of the airway remodeling (136-word count).

Introduction

Reactive Airways Dysfunction Syndrome (RADS) is an abrupt-onset asthmatic disorder of a non-allergy origin [1]. RADS development involves the inhalation of a single high-level irritant exposure [2]. Innate immunity plays a critical role in RADS pathogenesis. Implementation of innate immunity permits the airways to deal with non-microbiological constituents arising after a massive irritant inhalation exposure [3-5]. Allergy, antigen-antibody interaction, and actions by immune Th2 lymphocyte are not part of the pathogenetic processes of RADS. Causative agents causing RADS are irritating gases, vapors, aerosols and/or fumes, as well as solvent vapors and acid mists [6,7]. There generally is need for prompt medical assistance within the first 24 hours after the inhalation exposure [8]. The foremost clinical characteristics of RADS are asthma-like symptoms and nonspecific airway hyperresponsiveness, which may be transient or present for a longer period [9,10]. Table 1 presents the diagnostic criteria of RADS [2].

Table 1: Diagnostic Criteria for RADS

S.no	Diagnostic Criteria for RADS
1.	Absence of pre-existing respiratory disorder, asthma symptomatology or a history of asthma in remission and exclusion of conditions that can simulate asthma.
2.	Onset of asthma occurs after a single high-level exposure or accident.
3.	Exposure is to an irritant vapor, gas, fumes, aerosols, or smoke present in very high concentrations.
4.	Onset of asthma occurs within minutes to hours and always less than 24 hours after the exposure.
5.	Finding of a positive methacholine challenge test (<8 mg/ml) after the exposure when tested.
6.	Airflow obstruction on pulmonary function testing is common.
7.	Another pulmonary disorder to explain the symptoms and findings is excluded.

Humans and Rads

RADS ensues following an unforeseen or unexpected excessive irritant chemical release. There may be unanticipated explosions or circumstances where there is the sudden accidental release of irritant(s) held under pressure [11-20]. Dangerous inhalation events occur in the workplace, the home surroundings, and in

various community environmental situations [21]. Accomplishing workplace activities within a confined space having reduced rates of air exchanges and/or a space with reduced fresh air make-up are potentially unsafe situations. Elevated irritating emissions accompany a fire with smoke [22]. Workers engaged in repairing damaged workplace structures or malfunctioning machines are in potential danger. Cleaning activities become risky when a worker is not properly equipped, trained, or aware of potential hazardous risks while performing a job [23].

Adverse pulmonary consequences transpire after accidents involving trains or trucks transporting chemicals. The Bhopal release disaster, involving methyl isocyanate, caused serious lung consequences to workers and surrounding residents [24-26]. Intentional inhalational casualties occurred because of chemical warfare attacks during World War I and the Iran–Iraq War. A RADS-like condition affected rescue workers involved with the collapse of New York's World Trade Center on September 11, 2001 [27]. The originally reported causative agents of RADS were uranium hexafluoride gas, floor sealant, spray paint containing significant concentrations of ammonia, heated acid, 35-percent hydrazine, fumigating fog, metal coating remover, and smoke.

When a massive exposure suddenly materializes, like a bolt from the blue, an oncoming exposure cloud quickly gains the attention of witnessing individuals. The expanding suspension may force persons to retreat in fear. Persons in attendance at a worksite or in a community location where a catastrophic massive irritant exposure emerges become frightened and surprised by the unannounced exposure. Panic may ensue. Vocal communications warn of a looming "danger." Finally, the disastrous exposure envelops victims who breathe in its dangerous constituents, which enter the airway striking the bronchial epithelial cells and mucosal surfaces; both are the first lines of airway defense [5,28]. Serial bronchial biopsies were obtained on an injured individual at three and 15 days after an accidental workplace inhalational of chlorine gas [29]; bronchial biopsies were also taken at three and five months after the exposure. The earliest bronchial biopsy depicted sloughing of epithelial cells, and infiltration of the submucosa with a fibrinohemorrhagic exudate. Basal and parabasal cells proliferation and deposition of collagen took place early on. Mononuclear cell inflammation, denuded epithelium, and edematous mucosa were reported for the originally reported cases of RADS [1]. Mucosal squamous cell metaplasia, thickening of the basement membrane with reticulum, and collagen-associated bronchial wall fibrosis tended to be later pathological findings [30,31]. An individual who inhaled sodium hypochlorite and hydrochloric acid disclosed bronchial biopsy pathological findings of cellular destruction, lymphocytic inflammation and subepithelial fibrosis several months after the exposure [30].

An investigation utilizing Sprague-Dawley rats mirrored a human RADS exposure. The laboratory rats sustained a single exposure to 1,500 parts per million of chlorine gas for 5 minutes [32,33]. The massive exposure caused a severe airway injury with ensuing detachment of damaged and dead epithelial cells; the first line of defense is laid bare [5,28]. At 24 hours after the exposure, the rat's airway tissue exhibited a severe injury to the bronchial mucosal with sloughing of damaged or dead epithelial cells, and cellular detachment from the basement membrane. Bronchoalveolar lavage fluid identified an initial neutrophilic inflammation. There were mucosal regenerative changes by the third day after the exposure. Cellular regeneration changes persisted for the next 7-14 days. There was the appearance of increasing numbers of mucus-secreting cells. Reparative pathological abnormalities disappeared by 90 days after the exposure.

Discussion

Human and animal pathological surveys afford clues to what happens biomedically. Pathological specimens reveal sloughing of damaged and dead epithelial cells; there is and cellular detachment from the basement membrane. In response to the inhalation injury, activated innate repair genes proceed without reliance on an adapted immunity route that requires an antigen-antibody trigger and contributions by Th2 lymphocytes. Hematopoietic and bone marrow-derived cells migrate to renew the denuded cellular barrier [34-38]. Damage-Associated Molecular Patterns (DAMPs) are released by stressed or dying cells [39-45]. A variety of cytokines and chemokines, arachidonic and prostaglandin products, and nitric oxide emissions appear [41,42,46-48]. Soluble growth factors, G-protein-coupled receptor agonists, and liberations from airway smooth muscle cells contribute to epithelial and tissue repair [34,38,41,42,46-50]. The mononuclear lymphoid-type cell, noted in RADS, may embody innate lymphoid cells that lack T-cell and B-cell receptors.

Type 2 innate lymphoid cells produce cytokines IL-5 and IL-13 in response to IL-25 or IL-33. These type cells are involved in the pathogenesis of airway hyperreactivity [51,52]. RAGE (Receptor for Advanced Glycation End-products) molecules, expressed on macrophages, influence the inflammatory response through DAMPs [38,40,53-56]. RAGE triggers NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and numerous MAPKs (Mitogen-activated protein kinases) [57-59]. NF-κB controls genes involved in inflammation while MAPKs transduce a wide range of cellular responses. HMGB1 (High Mobility Group Box 1), a chromatin-associated, non-histone protein and DAMP, kindles cellular proliferation, angiogenesis, neovascularization, and cellular differentiation of bone marrow-derived mesenchymal stem cells with RAGE binding [60].

Adenosine triphosphate (ATP) influences migration of vascular smooth muscle cells and in "cleanup" operations [42]. The chemokine RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted) plays a role in the inflammatory process

[61,62]. The amount of RANTES contained in bronchoalveolar lavage fluid is higher in patients with non-allergic asthma [63]. Lung macrophages assist the repair and clean-up processes; and influence airway hyperresponsiveness [64-67]. The presence of nonspecific airway hyperresponsiveness (AHR) is a cardinal feature of RADS. Components of metalloproteases and extracellular matrix improve the epithelial-to-mesenchymal matrix [68,69]. Airway wall thickening, subepithelial fibrosis, mucus metaplasia, myofibroblast hyperplasia, muscle cells hyperplasia and hypertrophy, and epithelial hypertrophy are characteristic features of the airway remodeling response described in cases of RADS [70].

Conclusion

The massive exposure causing RADS initiates detachment of damaged and dead epithelial cells. Molecules of Damage-Associated Molecular Patterns (DAMPs) enter the extracellular space after being release by stressed or dying cells. Hematopoietic and bone marrow-derived cells migrate to renew the denuded cellular barrier. Soluble growth factors, interleukins, chemokines, arachidonic acid products, and discharges from airway smooth muscle cells aid epithelial and tissue repair. Lung macrophages contribute to the repair and influence airway hyperresponsiveness. Type 2 innate lymphoid cells release important cytokines. Proteases and extracellular matrix influence the epithelial-to-mesenchymal matrix. Further airway remodeling entails airway wall thickening, subepithelial fibrosis, mucus metaplasia, myofibroblast hyperplasia, muscle cells hyperplasia and hypertrophy, and epithelial hypertrophy.

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