SAR Journal of Medicine

Abbreviated Key Title: *SAR J Med*
Home page: https://sarpublication.com/journal/sarjm/home
DOI: 10.36346/sarjm.2022.v03i02.001

ISSN 2707-773X (P)
ISSN 2709-6920 (O)

Review Article

The Role of Mycotoxin in Myecetoma Pathogenesis

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Article History: | Received: 21.02.2022 | Accepted: 03.04.2022 | Published: 09.04.2022 |

Myecetoma is one of the neglected tropical diseases, most prevalent in tropical and subtropical regions in the area known as myecetoma belt. It is caused either by fungi (eumycetes) or bacteria (actinomycetes). We suggest that, through their strong and stable, mycotoxin inhibits pain and aryl hydrocarbon receptor actions and promotes IL-17 release. Furthermore, it affects Catechol-O-methyltransferase (COMT), which is responsible for male sexual orientation and this explains the predominance of myecetoma among men and we suggest that the size of lesion is related to the strength of COMT activity in male patients. Due to the absence of laboratory facilities, we are not able to achieve more than these suggestions, so experimental studies are recommended.

Keywords: Myecetoma, Mycotoxin, Pain receptors, Aryl hydrocarbon receptor, IL-17, Catechol-O-methyltransferase.

INTRODUCTION

The word mycotoxin is resulting from the Greek word *mykes* for fungus or mold and the Latin word *toxicum*, which means poison or toxin. Therefore, the term mycotoxin factually means fungus poison and is a broad term for mold-produced toxins, or simply mold toxins, which contain a wide group of toxic compounds that are injurious to both humans and animals. They are secondary mold metabolites, which means that they are not ingredient of the primary metabolic growth courses of the mold, and they are difficult to classify owing to their diverse chemical structures and biosynthetic origins, their countless biological effects, and their production by a board number of diverse fungal species. They are comparatively stable compounds that resist destruction [1].

Mycetoma is a chronic, specific, granulomatous, progressive inflammatory, disfiguring and mutilating ailment; it frequently involves the subcutaneous tissue, most probably after traumatic inoculation of the causative agent. It may be caused by true fungi (eumycetes) or by certain bacteria (actinomycetes) and, therefore, it is frequently classified into eumycetoma and actinomycetoma, respectively.

The painless subcutaneous mass, multiple sinuses and purulent or seropurulent discharge that may contain grains is characteristic of mycetoma. It usually spreads to involve the skin and the deep structures resulting in destruction, deformity and loss of function; occasionally it could be fatal [2]. *Mycetoma* is *more* frequently reported in *males* than females [3].

Aryl hydrocarbon receptor (AhR) is a transcription factor existed in all skin cells type. It reacts with exogenous and endogenous chemicals by inducing/repressing the expression of numerous genes with toxic or protective effects in a broad range of species and tissues. In well skin, AhR signalling participates to keratinocytes differentiation, skin barrier function, skin pigmentation, and mediates oxidative stress. In the most recent years, some reseaech have shown that AhR seems to be concerned in the pathogenesis of some skin diseases, even if the currently accessible data are conflicting. Indeed, while the blocking the AhR signalling activity could prevent or treat skin cancer, the AhR activation seems to be advantageous for the treatment of inflammatory skin diseases [4].

As confirmed before, activation of AHR has immunomodulatory effects through interaction with NF-κB. Compelling evidence has accumulated supporting a role for the AHR in regulating adaptive immune responses relevant to the pathogenesis of

diseases, for example inflammatory bowel disease (IBD), multiple sclerosis (MS), rheumatoid arthritis (RA), cancer, and obesity. These observations have led to the hypothesis that the AHR participates in innate immune responses to microbial invasion of barrier tissues [5].

The most frequent etiologic agent of eumycetoma worldwide is *Madurella mycetomatis*. Causative agents of eumycetoma can be classified based on the kind of grain formed. Most frequently categorized into those producing black grains, white or pale unstained grains, yellow or yellow-brown grains [6]. We hypothesized that causative agents of myecetoma whether fungal or bacterial inhibit pain receptors via its toxins.

Poisons have developed to induce or suppress pain by aiming a broad range of ion channels and receptors [7].

Administration of Ochratoxin A is demonstrated to reduce *N*-methyl-D-aspartate (NMDA) [8]. Which is Ochratoxin A (OTA) is a naturally occurring foodborne mycotoxin found in a wide range of agricultural commodities globally, ranging from cereal grains to dried fruits to wine and coffee. It is produced by numerous dissimilar fungi counting *Aspergillus ochraceus, A. carbonarius, A. niger* and *Penicillium verrucosum*. These fungi differ in their optimal growing temperatures and water activity, and contaminate different commodities [9].

Study done by Skov L *et al*., [10] showed that staphylococcal enterotoxin B induce selective accumulation of T cells. Proof from a murine model of mycetoma suggests that IL-17 producing T cells, called Th17 cells may play a role in mycetoma pathogenesis. IL-17 is a pro-inflammatory immune modulating agent which can play a role in tissue inflammation and can indirectly participate to neutrophil infiltration. IL-17 can also encourage neutrophils to release reactive oxygen species, which can contribute to tissue injury. IL-17 has also been shown to up-regulate matrix metalloproteases (MMPs), which play a role in tissue remodelling [11]. Study done by Gong W *et al*., [12] showed that ABCG2 overexpressing lentiviral vector transfection significantly increased the MMP-9 activity.

Study done by Tan KP *et al*., [13] suggested that AHR is a direct transcriptional regulator of human ABCG2 and provide an unprecedented role of AHR in cellular adaptive response and cytoprotection by up-regulating a vital ATP-binding cassette efflux carrier. Both AHR and ABCG2 are highly expressed in barrier and excretory tissues [14].

OTA increased the release of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α in activated murine macrophages and supported the differentiation of naïve T cells into Th1 cells, while treatment of CD4+T cells with the supernatant from mycotoxin-exposed macrophages induced IL-17 production. Study done by Jahreis S *et al*., [15] demonstrated that mycotoxins increase the susceptibility to develop RA via an enhanced stimulation of macrophages and promotion of Th1/Th17 cell differentiation by initiation of Stat signalling pathways and down-regulation of the Socs-mediated feedback inhibition. Study done by Mazzarella L *et al*., [16] suggested that IL-17 is involved in severe immune-related neuroendocrine toxicity, this supported by the study done by *et al*., [17] demonstrated that knockdown of AHR significantly enhances IL-17 levels.

Study done van de Sande WW by *et al*., [18] among Myecetoma patients showed that significant difference in allele distribution for Catechol-O-methyltransferase (COMT) and cytochrome p450 subfamily 19 (CYP19). Catechol-O-methyltransferase (COMT) polymorphism was associated with lesion size.

Stimulation of the aryl hydrocarbon receptor (AhR) by interfering with the control of oestrogen homeostasis and the estrogen receptor α (ERα) signalling pathway. Augmentation of AhR signaling reliant on ERα was noticed providing evidence for increased cytochrome P450 (CYP) induction to promote E2 metabolism.

However, relative mRNA levels of major E2-metabolizing CYP1A1 and 1B1 and the main E2-detoxifying catechol-O-methyltransferase were not affected by the co-treatments [19]. Study done by Yu W *et al*., [20] showed that The COMT Val158Met variant might be associated with male sexual orientation. Although opportunistic fungal infections occur commonly in immunocompromised hosts, *mycetoma* has never been reported in association with HIV infection [21], the majority of HIV-infected persons are homosexual [22] Castro LG and his colleagues reported first myecetoma lesion in the right elbow of HIV patient and attributed it to the use of contaminated needles and syringes for HIV drug injection [21].

Study done by Collins JM and Wang D [23] showed that ESR1 as a master regulator for the expression of several CYP enzymes. So, aspects disturbing ESR1 expression may have broad influence on drug metabolism through altered expression of CYP enzymes.

It has been recommended that dioxin-mediated toxicity may, in fact, reproduce disturbance of the endogenous function of this receptor by inducing sustained and inappropriate AhR signaling due to the stability of the toxin, and thus causing dysregulation of physiological functions [24].

DISCUSSION

It seems that bacterial and fungal species cause myecetoma by secretion of potent and stable mycotoxin [5, 21] which enables these pathogens to overcome the immune system by inhibition of pain receptors [6] and dysregulation of aryl hydrocarbon receptors[15, 17]. And we suggest that Myecetoma occurs in men more than in females[3], due to the direct effect of pathogens on Catechol-O-methyltransferase (COMT) [16], which is responsible for male sexual orientation [19], and it's not appear as opportunistic infection in HIV male patients due to their abnormal sexual orientation (homosexuality) [22]. We disagreed with Castro LG and his colleagues [21] whom attributed myecetoma infection to the contaminated needles and syringes for HIV drugs, we suggest that patient acquired HIV infection through sharing of needles with addicts and then exposed the causative agent of myecetoma.

CONCLUSION

We conclude that the pathogenicity of Myecetoma causative agents is attribute to its secretion of a powerful stable mycotoxins which injure pain and aryl hydrocarbon receptors and affect it affect males more due to its interference with their sexual orientation enzyme Catechol-O-methyltransferase (COMT) and the size of the lesion determine the strength of male sexual orientation.

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