Review Article Pol J Public Health, Vol. 134 (2024): 30-33

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Cutaneous infections in Atopic Dermatitis (AD) – a literature review

Abstract

Atopic dermatitis (AD) is a chronic inflammatory disease that affects people of all ages, usually with onset in childhood. It is a multifactorial, complex disorder that causes disruption of the skin barrier and is associated with an abnormal immune response that can predispose to both cutaneous and extracutaneous infections with the potential to become systemic infections.

The aim of this article is to present cutaneous infections as the most common complications of atopic dermatitis (AD). Atopic dermatitis (AD) increases susceptibility to skin viral and bacterial infections. These include Staphylococcus aureus colonization, molluscum contagiosum (MC), eczema herpeticum (EH) and human papilloma virus (HPV) infection. Among them, Staphylococcus aureus infection is the most frequently observed. Molluscum contagiosum (MC) and AD are considered risk factors for each other. However, studies on the relationship between MC and AD are divergent and there is a need for further research. Eczema herpeticum and systemic infections can be life-threatening nevertheless they are not common. Individuals with AD are more prone to HPV infections with various subtypes. Research shows that AD increases the risk of cervical cancer. Cutaneous infections are the most common complication of atopic dermatitis (AD) and are associated with various health risks. Preventive therapy in AD emphasizes improving the skin barrier. Early recognition of skin infections and introduction of adequate therapy is important to prevent serious medical complications.

Keywords: Staphylococcus aureus, Eczema Herpeticum, HPV, Molluscum Contagiosum.

DOI: 10.12923/2083-4829/2024-0007

INTRODUCTION

Atopic dermatitis (AD), also known as eczema, is the most common chronic inflammatory skin disease that can affect people of all ages, but it is particularly prevalent in children [1]. AD affects approximately 10% to 30% of children and 2% to 10% of adults in developed countries. In recent decades, the incidence of this phenomenon has increased two to three times [2]. In most cases, AD is treated in childhood, although the disease can persist into the old age. In most patients in adolescence or adulthood, the disease persists from a younger age (persistent AD), but can also begin in adolescence or adulthood (adolescent-onset AD or adult-onset AD) [3]. Recently, a distinct subgroup of AD with onset in old age (aged ≥60 years) has been described [4].

Patients with atopic dermatitis have a defective skin barrier that is susceptible to dry skin and environmental irritants and allergens that lead to inflammation, itching, and the classic clinical symptoms of atopic dermatitis [5,6,2]. In addition to skin symptoms, there are also sleep disturbances and fatigue, as well as mental health problems. Symptoms can contribute to severe functional impairment that limits the ability to perform daily activities and causes psychosocial distress and stigma [7-9].

The disease usually begins in infants or children (early-onset AD) and may represent the initial stage of the so-called "atopic march", in which AD is followed by progression to other IgE associated disorders like allergic rhinitis (AR), asthma, and food allergies (FA) [10]. Patients with the atopic triad have damaged skin and upper and lower respiratory barriers, leading to their symptomatology [6]. If one parent suffers from atopy, the risk of atopic symptoms in the offspring is more than 50%. If both parents are affected, up to 80% of offspring are affected [6].

Although atopic dermatitis (AD) is primarily a dermatological condition, its impact can extend beyond the skin and affect various aspects of a person's health, including susceptibility to other diseases [2]. Disruption of the skin barrier, immune dysregulation, increased symptoms and iatrogenic complications can lead to other comorbidities [11]. According to previous reports, infectious, autoimmune, respiratory, neuropsychiatric, musculoskeletal, and potentially cardiovascular diseases can be distinguished [12]. Some of these diseases are likely related to the severity of atopic dermatitis and inadequate treatment of the disease [12]. Considering the observed prevalence of other comorbidities with AD, it can be speculated that it is a systemic disease whose symptoms go beyond skin signs and symptoms [13].

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Previous studies have suggested that atopic dermatitis (AD) is associated with an abnormal immune response, which can predispose to both cutaneous and extracutaneous infections [14]. It is worth noting that cutaneous infections are reported to be the most common type of complications of atopic dermatitis [15]. In this paper, we would like to concentrate on presenting the skin infections described in the literature, which have a higher risk in the AD population compared to those without the disease [14-15].

Infections

Predisposition to recurrent skin infections is known to be a secondary criterion of Hanifin and Rajka's diagnostic standard for atopic dermatitis (AD) [17]. In both children and adults, the incidence of skin and systemic infections in patients with AD is significantly higher than in those without AD [14,16)]. Studies have shown that infectious complications of AD include skin and soft tissue infections (SSTI), eczema herpeticum (EH), bacteremia, osteomyelitis, septic arthritis and endocarditis [18]. AD is also associated with higher rates of extracutaneous infections, such as upper and lower respiratory tract infections, ear infections and urinary tract infections [16,19].

It is well-established that the barrier disruption associated with AD is associated with more frequent cutaneous infections [12]. People with atopic dermatitis are more prone to skin infections, especially bacterial and viral infections, due to impaired cutaneous barrier function and immune dysregulation and alterations in the skin microbiome [12,20,21]. These include Staphylococcus aureus colonization, molluscum contagiosum, eczema herpeticum (EH) and possibly warts [16,22]. Because of the compromised skin barrier and underlying inflammation, infections can spread quickly and lead to complications that can be serious and potentially life-threatening if not treated quickly and effectively. Staphylococcal and herpes simplex virus (HSV) infections are commonly recognized infections in AD [23]. Some studies suggest a higher prevalence of chickenpox and herpesvirus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections among patients with AD, but the prevalence of these other herpesvirus infections in AD remains unknown [23].

Staphylococcus aureus colonization

Staphylococcus aureus is a gram-positive bacteria that cause a wide variety of clinical diseases. It is the most common pathogen involved in skin infections worldwide, regardless of the patient's age, the climate or geographical area [24]. However, S. aureus colonizes about 30% of the human population asymptomatically in the nostrils, either temporarily or permanently, and can therefore also be considered a human commensal, although carriage increases the risk of infection [25]. Studies shown that S. aureus colonizes the skin in 60-100% of AD patients compared to 5-30% of healthy controls [26]. However, in people with atopic dermatitis, the skin barrier is impaired, making it easier for S. aureus to colonize and cause infection. Previous research indicates that there are many factors on AD-affected skin that increase the risk of skin colonization [27]. One paper outlining the interaction between atopic dermatitis and Staphylococcus aureus infection concluded that this bacteria exacerbates skin inflammation in AD by releasing superantigens, PSMs, toxins and lipoproteins that affect keratinocytes and immune cells [26]. Additionally, colonization of skin lesions in AD has been shown to correlate with disease severity [28].

S. aureus infection can aggravate symptoms of atopic dermatitis and contribute to exacerbations of the disorder. This can lead to increased inflammation, increased itching and sometimes purulent blisters or lesions [29]. This can create a vicious cycle, as scratching the affected areas can further compromise the skin barrier and increase the risk of additional infections. Patients with severe exacerbations of AD tend to have more generalized skin symptoms. These include erythema, swelling, oozing and tenderness, all of which can also be signs of skin infection [20]. S. aureus infection also plays a role in infectious complications such as impetigo, cellulitis and abscesses [30]. Importantly, S.aureus colonization can cause both superficial and invasive skin infections, leading to bacteremia and sepsis, which can be life-threatening [29]. It is worth noting that the detection rate of multidrug-resistant S. aureus (MRSA) in AD patients is higher than in the healthy population, making treatment much more difficult [26,28].

Remarkably, recent studies have shown that S. aureus colonization in AD patients is associated with food allergy, including peanut, egg white and cow's milk in children with AD. However, further studies are needed to clarify how S. aureus colonization affects atopic march and food allergy in children with AD [47].

Skin colonization by S. aureus, particularly MRSA, is one of the major challenges commonly encountered in the treatment of AD [30]. Treatment of eczema to reduce the number of S. aureus on the skin includes antibiotics, over-the-counter treatments and antibacterial soaps/baths. Whether these treatments are helpful is unclear. A review that evaluated the effects of interventions to reduce S. aureus in the treatment of eczema found insufficient evidence for the efficacy of anti-staphylococcal treatment in treating people with infected or uninfected eczema. It also indicates that topical combinations of steroids and antibiotics may be associated with a possible small improvement in good or excellent symptoms compared to topical steroids alone [25].

The second most common cause of skin and soft tissue infections and systemic infections in AD is Streptococcus pyogenes [48]. Infection can be caused by S. pyogenes in AD patients alone or in combination with S. aureus [48]. These skin infections usually manifest as eczema or impetigo. In AD, there is a rapid onset of exacerbation, rapid development of lesions, fever, and enlarging pustules. The lesions may also resemble eczema herpeticum (EH) [48,49].

Molluscum contagiosum (MC)

Molluscum contagiosum (MC) is caused by poxvirus molluscum contagiosum virus (MCV) and is a viral disorder of the skin and mucous membranes characterized by discrete single or multiple, flesh-colored papules [31]. It affects primarily pediatric patients, sexually active young adults, and immunocompromised people of all ages [32]. MCV is transmitted mainly by direct contact with infected skin, which can be sexual, non-sexual, or autoinoculation [33]. MC occurs all over the world, making up about one percent of skin disorders and appears to be increasing in prevalence [32]. In most healthy individuals, the disease can resolve spontaneously over a period of several months to several years, often with the development of new lesions and/or spread to others [34].

Of particular importance in both adult and pediatric patients with MC is atopic dermatitis (AD) – MC and AD are considered to be risk factors for each other. Atopic dermatitis (AD) has

been found to be common in children with MC and the prevalence of AD is higher in children with MC than in the general population [35]. However, the causal relationship between MC infection and AD onset or aggravation has not been widely explored. Studies show that this viral infection appears to exacerbate symptoms of atopic dermatitis (AD) in some children and adolescents [22,36]. In susceptible children, the first symptoms of AD may occur during MC infection [22]. In individuals with pre-existing AD, MC has been found to exacerbate their condition, resulting in a higher occurrence of widespread lesions [36]. Exacerbations of atopic dermatitis can occur at any age, but seem to occur mainly in preschool children and are usually not prevented by treatment of AD or MC [22].

An association between the presence of atopic dermatitis (AD) and MC has been shown. It is common that children with MC also present with atopic eczema to primary and secondary care. However, the subsequent risk of developing MC in children with a diagnosis of AD is not known. It is unclear whether there is a higher incidence of MC infection in patients with AD, a higher number of MC lesions when MC infection and AD coexist [37,35]. In one study which prospectively follow a retrospective cohort in order to determine whether children with a diagnosis of AD have an increased risk of subsequent MC. The study was able to demonstrate that children with AD are 13% more likely to develop MC than children who do not have this diagnosis [35]. Most previous studies have also found an association between AD and MC. Some research has also been conducted that did not show a relationship [35]. In recent study aimed to compare molluscum patients with and without atopic dermatitis, it was concluded that AD did not increase molluscum morbidity, inflammatory markers, treatment outcomes or relapse rates [36]. Considering that the association between molluscum contagiosum and coexisting atopic dermatitis and its impact on clinical features and treatment outcomes remains unclear, there is a need for further research.

If not treated, MC can lead to molluscum dermatitis, which allows the virus to spread more readily on the skin. Besides, there are additional reasons to treat MC, such as preventing AD exacerbations, reducing the risk of spreading to others, and preventing adverse psychosocial sequelae. Also adequate treatment of atopic dermatitis provided a more rapid improvement in skin barrier function, thereby reducing the risk of developing other skin diseases, including MC [38].

Eczema herpeticum (EH)

Eczema herpeticum (EH) is a disseminated cutaneous viral infection caused by superinfection of the skin with herpes simplex virus (HSV) type 1 or 2, usually HSV-1, in patients with atopic dermatitis [39]. Cases caused by HSV reactivation are more common than the original infection [40]. Local skin infection with the virus can progress to disseminated vesicles with skin damage, leading to EH. It is a widespread skin infection and usually manifests itself with the sudden appearance of monomorphic blisters and erosions with hemorrhagic scabs on eczematous areas [20, 39]. It can progress to systemic EH infection, which may present with fever, malaise, lymph node enlargement, viremia and complications including keratoconjunctivitis, encephalitis and septic shock [20, 39]. It has been reported that disseminated systemic HSV infections leading to bone marrow suppression, disseminated intravascular coagulation and death [41]. EH can lead to skin superinfection as a complication which can include Staphylococcus aureus, Streptococcus pyogenes and molluscum contagiosum virus [14].

Exposure to HSV-1 is common in the general population and is present in 60% of adults and 20% of children [42]. Studies show that although most adults show serologic evidence of previous HSV exposure, EH occurs in less than 3% of AD patients [42]. Although previous cross-sectional studies also suggested that EH is rare among patients with AD but tends to be more common in those with severe AD [23]. The disorder affects infants and children more often than adults [39]. The unexpected rarity of EH in AD patients suggests that multiple host factors influence the development of EH.

AD patients with EH tend to have a more severe course of AD, an earlier onset of AD, high levels of peripheral eosinophils and the presence of other atopic diseases, such as food or environmental allergies, asthma and history of Staphylococcus aureus and molluscum contagiosum infections compared to their peers with AD without EH [39,43]. Patients with AD, who have a history of S. aureus skin infections, are also more likely to develop EH. Research shows that it has been noted that EH often occurs concurrently with secondary S. aureus skin infection in patients with AD [43].

Eczema herpeticum is a severe and potentially life-threatening complication of atopic dermatitis. It should be treated promptly with systemic acyclovir or valacyclovir to minimize the risk of complications and prevent progression to severe disease. Early antiviral treatment can shorten the duration of mild illness and prevent morbidity and mortality in severe cases [39].

Human papillomavirus (HPV)

It is well established that the human papillomavirus (HPV) is responsible for causing many epithelial lesions and cancers. It can manifest itself as cutaneous and anogenital warts, which, depending on the subtype, can lead to cancer [50]. People with atopic dermatitis (AD) have defects in the skin barrier, which is associated with increased susceptibility to infections, including viral infections [12,20]. Therefore, it has been observed that patients with AD have a higher incidence of skin warts and recurrent genital warts caused by HPV [16,44,45]. Studies show that childhood atopic dermatitis may also increase the risk of cervical cancer. A retrospective case-control study of index cervical cytology with documented hrHPV testing and at least 2 years of clinical follow-up noted that atopic dermatitis was more common in hrHPV-positive cases compared to HPV-negative controls. It was concluded that atopic dermatitis is associated with cervical hrHPV infection in adult women [46]. It can be assumed that in this group of patients, cervical cancer prevention actions, such as cervical cancer screening and HPV vaccination, are particularly important.

CONCLUSION

Individuals with atopic dermatitis have an increased risk of developing cutaneous infections. By far, they are the most common complication of AD. Due to the varying impact on health and life, it is important to recognize and start treating skin infections early in people with AD. In addition, it is significant to adequately treat AD to improve the skin barrier as a preventive step against the development of infections and related complications. In this group of patients, it seems important to educate patients about their disease and risk factors for exacerbation.

Receiving funding: No funding was received.

Funding statement: No financial support was received.

Conflict of Interest Statement: We declare that there is no conflict of interests which could have influenced impartiality and reliability of the paper entitled "Cutaneous infections in Atopic Dermatitis (AD) – a literature review."

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