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Literature review

## **Risks for children diagnosed with mastocytosis, in the event of monkeypox infection**

Risks for the child diagnosed with mastocytosis in the face of monkeypox  
infection

Risks for children with a diagnosis of mastocytosis due to simic variola  
infection

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### **SUMMARY**

**Introduction:**Monkeypox is a zoonotic disease caused by the monkeypox virus. Since June 2022, the World Health Organization has warned of an increase in cases in non-endemic countries, with cutaneous manifestations predominating. Cases that progress to the complicated form of the disease are those with associated comorbidities, such as mastocytosis, which is characterized by an altered immune response.

**Aim:**Compile information on the main risks for children diagnosed with mastocytosis, in the face of monkeypox infection.



**Methods:**The literature available in Scopus, SciELO, PubMed Central, MedlinePlus, ClinicalKey, LILACS, WHO, PAHO, and INFOMED was reviewed. The descriptors used were medical genetics, genetic dermatological diseases, mastocytosis, monkeypox, and zoonoses.

**Analysis and synthesis of information:**Based on the etiopathogenesis and clinical manifestations of mastocytosis and monkeypox, the main risks for children diagnosed with mastocytosis upon monkeypox infection are outlined, including urticarial manifestations, anaphylaxis, and mast cell activation syndrome, which can lead to severe illness. Considerations for treating these patients are also discussed.

**Conclusions:**Infants diagnosed with mastocytosis are at risk of developing complications from monkeypox infection, which may include anaphylaxis, systemic damage, and death; recognizing the clinical manifestations allows for improved care of these patients and contributes to their prevention.

**Keywords:**Genodermatosis; Mastocytosis; Monkeypox; Zoonoses.

## ABSTRACT

**Introduction:**Monkeypox is a zoonosis caused by the monkeypox virus. Since June 2022, the World Health Organization has warned about the increase in cases in non-endemic countries, with a predominance of cutaneous manifestations. Cases that progress to the complicated form of the disease are those presenting associated comorbidities, as occurs in mastocytosis, which is characterized by an altered immune response.

**Objective:**To compile information on the main risks for children diagnosed with mastocytosis in the face of monkeypox infection.

**Methods:**The available literature was reviewed in Scopus, SciELO, PubMed Central, MedlinePlus, ClinicalKey, LILACS, WHO, PAHO, and INFOMED. The descriptors used were medical genetics, genetic dermatological diseases, mastocytosis, monkeypox, and zoonosis.

**Analysis and synthesis of information:**Based on the etiopathogenesis and clinical manifestations of mastocytosis and monkeypox, the main risks for children diagnosed



with mastocytosis in the context of monkeypox infection are described, such as urticarial manifestations, anaphylaxis, and mast cell activation syndrome, which can lead the child to develop severe conditions. Key elements for the management of these patients are discussed.

**Conclusions:**Children diagnosed with mastocytosis are at risk of developing complications from monkeypox infection, which may include anaphylaxis, systemic damage, and death. Recognizing the clinical manifestations allows for better management of these patients and contributes to prevention.

**Keywords:**Genodermatoses; Mastocytosis; Monkeypox; Zoonosis.

## SUMMARY

**Introduction:**Simian variola is a zoonose caused by the monkeypox virus. Since June 2022, the World Health Organization has been alerted about an increase in two cases in non-endemic countries, with skin manifestations predominating. The cases that evolve into a complicated form of the disease are only those that present associated comorbidities, such as mastocyte disease, characterized by an altered immune response.

**Aim:**compile information on the main risks for children with the diagnosis of mastocyte disease due to simic variola infection.

**Methods:**The literature available in the databases Scopus, SciElo, PubMed Central, MedlinePlus, ClinicalKey, LILACS, WHO, OPAS and INFOMED was reviewed. The descriptors used for medical genetics, genetic dermatological diseases, mastocytosis, monkey variola and zoonose.

**Analyze and synthesize the information:**Based on the etiopathogenesis and the clinical manifestations of mastocyte disease and monkeypox, the main risks are presented for children with the diagnosis of mastocyte disease in the face of infection by monkeypox, such as urticarial manifestations, anaphylaxis and mast cell activation syndrome, which can be caused by development of serious conditions. Only elements indicated should be considered in the treatment of patients.



**Conclusions:** In children with a diagnosis of mast cell disease, there are risks of developing complications resulting from simic variola infection, which can include anaphylaxis, systemic damage and death. The reconfirmation of clinical manifestations allows better care of patients and contributes to their prevention.

**Key words:** Genodermatoses; Mastocytosis; Simian variola; Zoonose.

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## Introduction

The term mastocytosis (ORPHA)[98292](#), OMIM[154800](#) Mast cell carcinoma refers to a heterogeneous group of disorders characterized by the proliferation and accumulation of mast cells in tissues of various organs, especially the skin and hematopoietic organs. (1,2) It has a prevalence of 13:100,000, and is more frequent in pediatric ages. (3)

The authors did not find any population studies showing the prevalence of the disease in Cuba; however, in Las Tunas, an eastern Cuban province, Velázquez et al., in a 30-year study of genodermatoses, reported that mastocytosis represents 5.17% of cases, (4) with a prevalence rate of 2.4 per 100,000. (5) This allows us to infer that, although there are no precise databases on this disease, its presence in the Cuban population is demonstrated.

Mast cells play a key role in the inflammatory response of the immune system to pathogens (parasites, viruses, fungi, and some bacteria). They are cells that originate in the bone marrow and are part of the immune system. They are abundant in the skin, lungs, and mucous membranes of the airways and digestive tract. (6) Infections represent a significant risk factor that predisposes patients with mastocytosis to developing complications such as mast cell activation syndrome, which in more severe cases can lead to anaphylaxis.



Monkeypox is a viral zoonosis. The monkeypox virus is a deoxyribonucleic acid (DNA) virus of the family Poxviridae, genus Orthopoxvirus, to which the smallpox virus also belongs. It was first detected in 1958 in African monkeys, although the largest reservoir is found in rodents. (7)

It was first detected in humans in 1970, specifically in a 9-month-old child in the Democratic Republic of Congo, and since then most cases have been reported in Central and West Africa. There are two known strains of the SV virus: the West African strain and the Congo Basin (CB) strain. Historically, the CB strain appears to be more virulent, with a case fatality rate (CFR) ranging from 1% to 10%, while the West African strain is associated with a lower overall CFR of <3%. The latest data for the latter show a CFR of 1.4%. (8)

Since June 6, 2022, the World Health Organization (WHO) has been notified of more than 1,000 laboratory-confirmed cases of monkeypox in 29 non-endemic countries, in Europe and North America, across four WHO regions, although no deaths have been reported. (9) Its incidence and geographic reach have increased, reaching 89,596 laboratory-confirmed cases and 157 deaths reported up to 2023, even in non-endemic countries. (10) By 2024, given the resurgence of cases in the Democratic Republic of the Congo and in a growing number of African countries, it constituted a Public Health Emergency of International Concern. (11) As of June of that year, the most affected regions were Africa, with 1,854 reported cases and 13 deaths, the Americas with 1,812 cases and 3 deaths, and Europe with 826 cases and 3 deaths. (12)

In the Americas, the countries most affected between 2023 and 2024 were Argentina, Bahamas, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Ecuador, the United States of America, Guatemala, Honduras, Mexico, Panama, Paraguay, and Peru. (13) Two imported cases have been reported in Cuba. (14)

Due to the epidemiological alert issued by the WHO, given the increase in the incidence of this zoonosis, it was decided to carry out the work with the objective of compiling information on the main risks for the child diagnosed with mastocytosis, in the face of monkeypox infection.

## Methods

A qualitative, descriptive analysis was conducted of studies published in Spanish or English, prioritizing original articles and systematic reviews. The literature available in Scopus, SciELO, PubMed Central, MedlinePlus, ClinicalKey, LILACS, WHO, PAHO, and INFOMED was reviewed. The search terms used were medical genetics, genetic dermatological diseases, mastocytosis, monkeypox, and zoonoses. Duplicates, articles without full-text access, and those not relevant to the study's purpose were removed. The information obtained was organized by topic: mastocytosis, monkeypox, risks to patients diagnosed with mastocytosis upon monkeypox infection, and the diagnosis and treatment of patients with mastocytosis upon monkeypox infection, as well as aspects related to treatment. During the review process, a total of 28 bibliographic references were cited, with a high update rate of 75%.

### Analysis and synthesis of information

**Mastocytosis**(ORPHA[98292](#), OMIM[154800](#)).

The term mastocytosis encompasses a group of disorders characterized by hyperplasia of functionally normal mast cells that infiltrate various tissues. (15) It is considered an autosomal dominant genodermatosis, and its pathogenesis centers on alterations in the structure and activity of tyrosine kinase (KIT), a transmembrane receptor expressed on the surface of mast cells, whose activation induces their growth and prevents cell apoptosis. Somatic mutations in the gene encoding KIT are thought to produce constitutive activation of this receptor, with consequent mast cell hyperplasia. Many of these mutations are located at codon D816 of the KIT gene. (16,17) Mast cell degranulation can be triggered by physical agents (surgery, heat, sun exposure), psychological factors (stress), chemical agents (histamine-releasing substances), and biological agents (infections). (18)

The first bibliographic reference to these processes dates from 1869, by Nettleship and Tay, cited by Tamayo K, et al, (19) who described in a child the presence of brown skin lesions that developed edema and inflammation when scratched. Paul Ehrlich in 1878, cited by Cantero, (3) described mast cells in connective tissue and correctly postulated that these cells could be related to tissue inflammation, blood vessels, nerves, and neoplastic foci. In 1949, Ellis, cited by Cantero, (3) demonstrated, for the first time, the systemic involvement of mastocytosis. (3)

The different clinical forms are classified according to the WHO as follows:

- Cutaneous mastocytosis: mastocytosis aculopapular (urticaria pigmentosa), solitary cutaneous mastocytoma, diffuse cutaneous mastocytosis and telangiectasia macularis eruptiva perstans.
- Systemic mastocytosis: indolent mastocytosis, aggressive mastocytosis associated with another monoclonal hematopathy, mast cell leukemia, mast cell sarcoma, and extracutaneous mastocytoma. (20)

Cutaneous mastocytosis can appear during the neonatal period, childhood, or adolescence, although 60 to 80% of patients develop the disease before one year of age. (18) Urticaria pigmentosa is sporadic, characterized by macules, papules, or nodules, rarely associated with systemic disease, and typically clearing by puberty. The pathognomonic sign on dermatological examination is Darier's sign, which consists of the formation of a wheal when the macular lesion is rubbed. (2,18)

A solitary mastocytoma can occur in childhood with a tendency to spontaneous involution, as a single, small, raised, yellowish-brown papule, plaque, or nodule that is slightly infiltrated to the touch and can appear in any location. (21)

Diffuse cutaneous mastocytosis is the least common but most severe form of cutaneous mastocytosis, present from birth. There is diffuse infiltration of mast cells in the dermis. Clinically, it presents as progressive thickening of the skin, pruritus, and systemic involvement due to mast cell degranulation. (22)

The Telangiectasia macularis eruptiva perstans is almost exclusively seen in adolescents and adults, and presents with erythema, papules, telangiectasias, and brown macules, accompanied by pruritus and dermographism. (19)

Systemic mastocytosis is characterized by vascular instability, increased vascular permeability, fibrosis, eosinophilia, lymphocytic infiltration, local anticoagulation, mast cell hyperplasia, and cachexia. It manifests with urticarial rashes and pruritus in the skin, gastric hypersecretion and abdominal pain in the gastrointestinal tract, bronchoconstriction, secretions, and pulmonary edema in the respiratory system, and bone remodeling and osteoporosis in the skeletal system. (17)

### **monkeypox**

Monkeypox virus is transmitted from infected animals to humans through direct or indirect contact. Transmission can occur through bites or scratches, or during activities such as hunting, skinning, or consuming animal meat. (23)

Person-to-person transmission can occur through direct contact with infectious skin or mucocutaneous lesions, and via respiratory droplets (possibly short-range aerosols requiring prolonged close contact). The virus enters the body through broken skin, mucous membranes (e.g., oral, pharyngeal, ocular, and genital), or the respiratory tract. The infectious period can vary, but generally, patients are considered infectious until the scab has fallen off and new skin has formed underneath. Transmission can also occur from the environment to individuals via contaminated clothing or bedding containing infectious skin particles (also known as fomite transmission). Smallpox surrogate virus has been found to persist in the environment and on various surfaces for 1 to 56 days, depending on ambient temperature and humidity. However, current data on transmission via contaminated surfaces or fomites, other than contaminated bed linens, are limited. Smallpox viruses are generally more resistant to environmental conditions and exhibit high environmental stability. (23,24) Intrauterine transmission of the SV virus has been demonstrated, as has mother-to-child transmission by direct contact. (7)



The incubation period for monkeypox is usually 6 to 13 days after exposure, but can range from 5 to 21 days. Although most people recover within a few weeks, serious complications and sequelae have been observed to be more common among people who have not been vaccinated against smallpox compared to those who have (74% vs. 39.5%). (9) It is unclear whether there is a decline in the immune response over time in people who received the smallpox vaccine; however, studies suggest that the smallpox vaccine is approximately 85% effective in preventing monkeypox. To date, most reported deaths have occurred in young children and immunocompromised individuals. (24)

Monkeypox can cause a range of clinical signs and symptoms. Typically, the initial phase of clinical illness lasts 1 to 5 days, during which patients may experience fever, headache, backache, muscle aches, fatigue, and lymphadenopathy (a hallmark of this disease). This is followed by a second phase, which usually begins 1–3 days after the fever subsides with the appearance of a rash. The rash progresses in sequential stages (macules, papules, vesicles, pustules, umbilication before crusting and desquamation over a period of 2–3 weeks). (7)

The main characteristics of monkeypox lesions are fluid-filled, purulent, and umbilicated lesions. The size of the lesions ranges from 0.5 cm to 1 cm in diameter, and the number of lesions varies from a few to several thousand. The rash tends to be centrifugal, starting on the face and spreading to the palms of the hands and soles of the feet. The oral mucosa, conjunctiva, cornea, or genitals may also be affected. Inflammation of the pharyngeal, conjunctival, and genital mucosa may also occur. (7)

Although uncommon, patients with monkeypox can experience serious and life-threatening complications. This is more frequent in patients with risk factors such as those at the extremes of age (childhood and old age), pregnant women, and patients with immune-debilitating diseases. Complications include cellulitis, abscesses or necrotizing soft tissue infections, and exfoliation, which can require surgical debridement and skin grafting in some areas of the skin. Less frequent complications include severe pneumonia and respiratory distress, corneal infection that can cause

vision loss, loss of appetite, vomiting and diarrhea that can lead to severe dehydration, electrolyte imbalances and collapse, cervical lymphadenopathy that can cause a retropharyngeal abscess or respiratory distress, sepsis, septic shock, encephalitis, and death. (7)

Some small studies observing analytical alterations in patients with monkeypox indicate that leukocytosis, elevated transaminase levels, low blood urea nitrogen levels, and hypoalbuminemia are common during the disease, and that lymphocytosis and thrombocytopenia were observed in more than a third of the patients evaluated. (24)

The skin eruption present in monkeypox may resemble, and must be differentiated from, diseases such as: herpes simplex, syphilis, Chlamydia trachomatis, nodular scabies, molluscum contagiosum, varicella, disseminated herpetic infection, folliculitis, prurigo, disseminated gonococcemia, impetigo contagiosa, contact eczema, hand-foot-and-mouth disease, bullous distal dactylitis, vasculitis, exanthematous pustulosis, pemphigoid, erythema multiforme, herpes zoster, fixed drug eruption, pyoderma gangrenosum, lymphogranuloma venereum, COVID-19, measles, exanthematous rickettsiosis, chikungunya, Zika virus, dengue, and other bacterial infections of the skin and soft tissues. (25)

### **Risks for patients diagnosed with mastocytosis from monkeypox infection**

Given the pathogenesis of their disease, patients with mastocytosis, if faced with infectious foci such as monkeypox. Children with mastocytosis experience increased release of mast cells into the skin, with a higher risk of developing urticarial and anaphylactic skin lesions. Diffuse cutaneous forms and systemic mastocytosis can develop mast cell activation syndrome. This term refers to systemic manifestations secondary to a release of mediators, which may or may not have a known etiology, frequently associated with increased IgE antibodies and elevated tryptase enzyme concentrations. These include moderate symptoms such as intense itching, and in severe cases, gastrointestinal complications (abdominal pain, diarrhea), cognitive

symptoms, and anaphylaxis. (6) This leads to the child with mastocytosis experiencing severe symptoms. serious cases of monkeypox infection.

### **Diagnosis and treatment of a patient with mastocytosis in the face of monkeypox infection**

The diagnosis is confirmed by viral culture or molecular detection by polymerase chain reaction in skin lesions or pharyngeal exudate. (7,9)

The care of patients with suspected or confirmed simian poxvirus infection requires: early detection of suspected cases; rapid application of appropriate PCI measures; testing for likely pathogens to confirm the diagnosis; treatment of symptoms in patients with mild or uncomplicated simian pox; and monitoring and treatment of life-threatening complications and conditions, such as extreme dehydration, severe pneumonia, and sepsis. (7)

In 2022, the European Medicines Agency (EMA) authorized tecovirimat, an antiviral that inhibits the VP37 viral envelope protein. Brincidofovir is authorized by the EMA and the US Food and Drug Administration (FDA) for the treatment of smallpox and has demonstrated antiviral activity against double-stranded DNA viruses, including poxviruses. Cidofovir is authorized by the US FDA for the treatment of cytomegalovirus. It inhibits SVV replication by inhibiting DNA polymerases and is administered by intravenous infusion. NIOCH-14 is a chemically synthesized compound developed by the State Research Center for Virology and Biotechnology Vector since 2001. NIOCH-14 is a tecovirimat analogue with comparable activity against orthopoxviruses. (26, 27)

The immunoglobulin vaccine (IGV) contains antibodies from people inoculated with the smallpox vaccine. The benefits of IGV in people exposed to monkeypox or who have a severe infection are unknown (if used, it should be within the framework of a clinical investigation and with prospective data collection). (7)

In the care of a patient with mastocytosis, in any of its forms, it is essential to educate the patient on the importance of avoiding factors that can induce the release of mast cell mediators, such as physical agents (heat, cold, skin pressure, scratching), emotional

factors (anxiety, stressful situations), drugs or medications (acetylsalicylic acid, antitussives, alcohol, muscle relaxants, anesthetics, poisons), and pathogens. (28) It is important to monitor for signs of anaphylaxis. Non-sedating H1 antihistamines are used to improve pruritus, flushing, edema, malaise, abdominal pain, and blistering. Cimetidine or ranitidine are useful in cases of gastrointestinal symptoms. Transient therapy with systemic corticosteroids is indicated in patients with aggressive forms of mastocytosis or symptoms of malabsorption, usually prednisone at 1-2 mg/kg daily. A recent study demonstrates the usefulness of cyclosporine combined with low-dose methylprednisolone for controlling aggressive forms of systemic mastocytosis. Interferon alpha 2b has also been used in systemic mastocytosis. (28)

### CONCLUSIONS

Monkeypox has increased in incidence and spread to countries near Cuba, posing a risk of infection with this zoonosis within the country. Individuals with compromised immune systems, such as those with mastocytosis, are particularly vulnerable. Infants diagnosed with mastocytosis are at risk of developing complications from monkeypox infection, including anaphylaxis, systemic damage, and death. Recognizing the clinical manifestations allows for improved care for these patients and contributes to prevention efforts.

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### **Conflict of interest**

The authors declare that there is no conflict of interest.

### **Authorship contribution**

Yordania Velázquez Avila: Literature review, design and writing of the article. Approval of the final version.

Odalenis Vargas Alarcón Literature review, article design and writing. Approval of the final version.

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