

No. 36 in a series providing the latest information for patients, caregivers and healthcare professionals

Highlights

- Mastocytosis is a rare condition. It is a type of cancer in which an abnormally large number of mast cells accumulate in the body's tissues and organs.
- The main types are cutaneous mastocytosis (involves only the skin) and systemic mastocytosis (involves other parts of the body, most often the bone marrow, liver, spleen, and gastrointestinal tract). Subtypes within each of these two main types include forms of the disease that vary in severity and rarity.
- Mastocytosis is typically associated with a mutation in the *KIT* D816V gene. This mutation causes the overproduction of activated mast cells which release substances, such as histamine, leading to signs and/or symptoms.
- It is important for patients to avoid anything that triggers an allergic reaction. Patients with a history of having had a severe allergic reaction should carry an EpiPen® (injectable epinephrine) because another such reaction could bring on anaphylactic shock (a potentially life-threatening allergic reaction).
- There are a variety of treatments available depending on the form of the disease.

Introduction

“Mastocytosis” is the name of a group of disorders that are caused by an excess number of mast cells in the body. Mast cells are a type of white blood cell, originally produced in the bone marrow, that can move into the body's tissues and organs. They are part of the immune system and help protect the body from infection. Mast cells are also involved in other bodily functions such as bone growth, blood vessel formation, and wound healing.

Mastocytosis is a rare condition and a type of cancer. Mastocytosis is often associated with a mutation in the *KIT* D816V gene. This mutation makes a protein that results in continuous growth and activation of mast cells. Activated mast cells cause the release of an excess of chemicals called “mast cell mediators.” Histamine is the most significant mediator and is involved with allergic reactions, such as itching, sneezing and watery eyes.

Mastocytosis classification is based on the location of the mast cells, the signs and/or symptoms, the clinical presentation, and the pathology results (description of the cells or tissues based on microscopic evidence). Knowing the type and/or subtype of mastocytosis determines the treatment and the prognosis.

Types of mastocytosis include:

Cutaneous Mastocytosis. This type affects the skin, often causing reddish-brown lesions that itch. Cutaneous mastocytosis is more common in children. Subtypes include:

- Urticaria pigmentosa, also known as “maculopapular cutaneous mastocytosis” (rash of raised reddish-brown lesions that itch or sting with contact)
 - Monomorphic (multiple small, roundish skin lesions)
 - Polymorphic (larger lesions of variable size)
- Diffuse cutaneous mastocytosis (found in infants and manifesting as swelling and thickening of the skin)
- Cutaneous mastocytoma
 - Isolated mastocytoma (typically a solitary nodule of mast cells 2 to 5 centimeters in diameter)
 - Multilocalized mastocytoma (2 or 3 lesions)

Systemic Mastocytosis. This type affects internal organs (eg, enlarged lymph nodes and liver) and occurs mainly in adults. Systemic mastocytosis is considered a type of blood cancer. Patients may have significant signs and/or symptoms and blood abnormalities. Skin lesions are quite common in most forms of systemic mastocytosis, although in some subsets of advanced diseases (eg, mast cell leukemia), it is less common. The main subtypes of systemic mastocytosis are:

- Bone marrow mastocytosis (bone marrow involvement and the absence of skin lesions)
- Indolent (slower growing) systemic mastocytosis
- Smoldering (slow to progress) systemic mastocytosis
- Aggressive (fast growing) systemic mastocytosis
- Systemic mastocytosis with an associated hematologic neoplasm (blood-related abnormal growth of cells or tissue)
- Mast cell leukemia is an extremely rare and aggressive form of systemic mastocytosis. In this disease, mast cells buildup in the bone marrow and other tissues, leading to organ damage.

Note: Well-differentiated systemic mastocytosis (WDSM) is a variant that may occur in any systemic mastocytosis type or subtype, including mast cell leukemia. It is distinguished by round, granular mast cells heavily invading the bone marrow.

Mast Cell Sarcoma. Mast cell sarcoma is a very rare cancerous form of mastocytosis. This disease is diagnosed by the presence of a solid tumor, made of atypical mast cells, in bones or soft tissues.

Signs and/or Symptoms

A “sign” is a change in the body that the doctor sees in an examination or a test result. A “symptom” is a change in the body that a patient can see and/or feel. The signs and/or symptoms of mastocytosis may include:

- Anaphylaxis (a severe and potentially life-threatening allergic reaction to an antigen, such as a bee sting. The blood pressure drops suddenly and airways narrow, blocking breathing.)
- Itching, flushing, hives, swelling
- Red or brown blotches or blisters on the skin
- Wheezing or shortness of breath
- Blood pressure changes, dizziness, fainting
- Nausea, diarrhea, vomiting, stomach pain
- Anemia or bleeding disorders
- Muscle and joint pain, osteoporosis
- Enlarged liver, spleen, or lymph nodes
- Mood changes, headache, brain fog
- Fatigue and lack of energy

Diagnosis of Mastocytosis

Your healthcare provider will take a medical history and conduct a physical examination, including careful inspection of the skin. A variety of tests may be ordered depending on your form of the disease.

The diagnosis of mastocytosis is made according to criteria published by the World Health Organization (WHO).

For cutaneous mastocytosis, diagnosis is based on the appearance of skin lesions (growths), a skin biopsy showing an abnormal number of mast cells, and the results of certain laboratory tests. Bone marrow biopsy and ultrasound may also be recommended depending on the patient’s signs and/or symptoms.

For systemic mastocytosis, diagnosis is typically based on the results of a bone marrow biopsy, genetic testing for the *KIT* D816V mutation, and select laboratory tests. According to WHO, the major feature is the presence of clusters of mast cells in the bone marrow or other organs. Minor diagnostic criteria include high serum tryptase level (a protein in the mast cells indicating increased mast cell activity), abnormal expression of surface markers on the mast cells (such as CD25 and/or CD2), and presence of the *KIT* D816V mutation. (The *KIT* D816V mutation can cause the mast cells to grow out of control and accumulate in one or more of the body’s organs.) About 95% of adult patients have the mutation called *KIT* D816V. The presence of one major and one minor criteria, or three minor criteria, is required for diagnosis.

Common tests are:

- **Blood tests**—to check blood counts and tryptase levels (tryptase is a protein released by mast cells)
- **Urine test**—to look for the presence of histamine (a chemical released in response to allergens)
- **Imaging tests such as ultrasound, MRI (magnetic resonance imaging) scan, or CT (computed tomography) scan**—to check for an enlarged liver or spleen
- **Biopsy, such as a skin biopsy, bone marrow biopsy, or gastrointestinal biopsy**—to obtain a sample of skin or cells for study
- **Skeletal or bone survey**—x-rays of the bones in the body to see if there are lytic lesions (holes) in the bones
- **DEXA or DXA (dual energy x-ray absorptiometry) scan**—to check bone density
- **Liver function tests**—to measure substances made by the liver
- **Genetic tests, such as high-sensitivity *KIT* D816V testing**—to look for a mutation of the *KIT* D816V gene

Visit www.LLS.org/booklets to view *Understanding Lab and Imaging Tests* and *Understanding Genetics* for more information.

Treatment

There is no single treatment for mastocytosis. Your healthcare provider will discuss your treatment options, including possible participation in clinical trials. It is important to see a hematologist-oncologist (a doctor who specializes in treating cancers of the blood) who has experience treating mastocytosis. Another option is going to a hematologist-oncologist who consults with a mastocytosis expert at a major cancer center.

People with mastocytosis have an increased risk of developing a severe allergic reaction. Therefore it is important for patients to avoid anything that might trigger an allergic reaction, such as allergens (like pollen, pet dander and dust mites); sudden temperature changes; stress; spicy foods, alcohol or drugs; insect bites. Allergens for each patient tend to be individual and unique.

Medications. There are a variety of treatments to help you manage mastocytosis. For example:

- For the signs and symptoms of an allergic reaction, such as itchy skin lesions, treatments include antihistamines (eg, **cetirizine [Zyrtec®]**, **famotidine [Pepcid®]**, **diphenhydramine [Benadryl®]**, emollients, and corticosteroid creams. Some patients should carry an **EpiPen® (injectable epinephrine)** in case of anaphylactic shock, which is a severe and potentially life-threatening allergic reaction.
- To reduce mast cell activation, a drug called “**cromolyn sodium**” (various brands)
- To strengthen weak bones, treatment may include **bisphosphonates** (various brands)
- To reduce flushing, a leukotriene-inhibitor like **montelukast (Singulair®)**
- To relieve bone pain, a nonsteroidal anti-inflammatory drug like **aspirin** may be offered.
- In some patients, corticosteroids like **prednisone** (various brands) can be an option.

Treatment for Systemic Mastocytosis. The main treatments for systemic mastocytosis are targeted therapy, chemotherapy, immunotherapy and a clinical trial.

Targeted therapy is the administration of drugs or substances that block the growth and spread of cancer by interfering with specific molecules such as enzymes and proteins. Targeted therapy generally causes less harm to normal cells and may have fewer side effects.

The types of targeted treatments that are approved for mastocytosis are called “kinase inhibitors.” They block the action of enzymes called “kinases.” Kinases are a part of many cell functions, including cell signaling, growth, and division.

Indolent Systemic Mastocytosis. When treating indolent (slower growing) systemic mastocytosis, the healthcare team will focus on preventing anaphylactic reactions and identifying and avoiding symptom triggers. There are medications that can be used to help with symptom

triggers. **Avapritinib (Ayvakit®)**, approved by the Food and Drug Administration (FDA), is an oral medication that targets the mutated KIT D816V gene. This drug is indicated for the treatment of adult patients with indolent systemic mastocytosis.

Advanced Systemic Mastocytosis. Advanced systemic mastocytosis includes three different types: aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm (blood cancer), and mast cell leukemia. There are three treatments available.

- **Avapritinib (Ayvakit®)**, approved by the FDA, is an oral medication that targets the mutated KIT D816V gene. This drug is indicated for all three types of advanced systemic mastocytosis.
- **Imatinib mesylate (Gleevec®)**, approved by the FDA, is an oral medication only indicated for a small subset of advanced systemic mastocytosis patients without a mutation in the *KIT* D816V gene or whose mutational status is unknown.
- **Midostaurin (Rydapt®)**, approved by the FDA, is an oral medication that either slows or stops the growth of abnormal mast cells. This drug is indicated for all three types of advanced systemic mastocytosis.

Chemotherapy—This type of treatment damages the DNA (deoxyribonucleic acid) or RNA (ribonucleic acid) in cancer cells and interferes with their ability to grow or multiply. **Cladribine (Leustatin®)** is administered by intravenous infusion and stops the growth of cancer cells.

Immunotherapy—This treatment consists of encouraging the immune system to do its job more effectively.

Interferon alfa (Intron A®) is given by injection and interferes with cancer cells’ ability to divide. It may be administered with oral prednisone (a corticosteroid).

Participation in a Clinical Trial. Taking part in a research study is an appropriate treatment choice for many patients. Discuss this option with your healthcare provider or contact an LLS Information Specialist for more information.

Allogeneic Hematopoietic Stem Cell Transplant. Stem cell transplantation, sometimes referred to as a “bone marrow transplant,” is a procedure in which a patient receives healthy stem cells to replace damaged stem cells.

Visit www.LLS.org/booklets to view *Blood and Marrow Stem Cell Transplantation* for more information.

Treatment Side Effects

Side effects depend on many factors, including the type of treatment and dosage, and the patient's age and coexisting medical conditions. Therapy may cause fever or chills, fatigue, nausea, loss of appetite, mouth sores, peripheral neuropathy (tingling, burning, numbness or pain in the hands and/or feet), changes in blood cell counts, infection, rash, vomiting, diarrhea, shortness of breath, swelling, temporary loss of hair and other side effects.

Side-effect management is important. If you have any concerns about potential side effects, talk to the members of your healthcare team to get help. Most side effects can be managed without compromising the effectiveness of your treatment. In fact, talking to your healthcare team about your side effects often leads to better treatment outcomes. Most side effects are temporary and resolve when treatment is completed. However, other long-term side effects may appear years after the treatment has been completed. Late side effects may include development of another type of cancer, heart disease, low levels of thyroid hormones (hypothyroidism), and loss of fertility.

Visit www.LLS.org/booklets and Filter by Topic (Side Effect Management) for more information.

Clinical Trials for Blood Cancers

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called “clinical trials” and they are used to find better ways to care for and treat people who have cancer.

In the United States, the FDA requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer. Researchers use cancer clinical trials to study new ways to

- Treat cancer using
 - A new drug
 - A drug that has been approved, but to treat a different kind of cancer
 - A new combination of drugs
 - A new way of giving a drug— by mouth, intravenously (IV), etc
 - Manage cancer signs and/or symptoms and ease treatment side effects
 - Find and diagnose cancer
 - Keep cancer from coming back (recurring) after treatment
 - Manage long-term side effects
- By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to
- Have a list of questions to ask about the risks and benefits of each trial (visit www.LLS.org/WhatToAsk for lists of suggested questions).
 - Ask a family member or friend to go with you when you see your doctor—both for support and to take notes.
- Clinical trials can be difficult to understand and to navigate, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find potential clinical trials, overcome the barriers to enrollment and provide support throughout the entire clinical-trial process. Our Clinical Trial Nurse Navigators are registered nurses who are experts in blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will
- Talk with you about your treatment goals
 - Help you understand the clinical-trial process, including your rights as a patient
 - Ask you for details about your diagnosis (such as past treatments, treatment responses, and your cancer genetic profile), your current health, and your medical history, because these might impact whether you can take part in certain clinical trials
 - Help you understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials
 - Guide and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
 - Help deal with any problems you might have as you enroll in a trial
 - Support you throughout the clinical-trial process

Please call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Also, visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers*.

Outcomes

The prognosis for patients with mastocytosis depends on disease type, patient age, rate of disease progression, and response to therapy. In children with cutaneous mastocytosis, the signs and/or symptoms often resolve over time. Adults with indolent systemic mastocytosis tend to have a low mast cell burden, mediator-related symptoms (eg, itching, flushing, hives, blood pressure changes, stomach issues), a normal life expectancy, and low risk of progression to more serious disease.

Adult patients with advanced systemic mastocytosis will have significant and persistent signs and/or symptoms and may experience organ dysfunction and low blood counts. Patients with another blood cancer such as myeloproliferative neoplasm (MPN), myelodysplastic syndromes (MDS), or chronic myelomonocytic leukemia (CMML) may experience additional complications.

Incidence, Causes and Risk Factors

Mastocytosis is estimated to occur in 1 per 10,000 to 20,000 people worldwide. The disease may begin in childhood or adulthood. It affects men and women equally.

Most pediatric cases are diagnosed within the first year of life and typically involve the skin. The disease often resolves during puberty.

Adults, typically, have the indolent systemic form of the disease rather than the cutaneous form.

While research is ongoing to understand possible causes of mastocytosis, it is often associated with a mutation in the *KIT* D816V gene. Why this mutation occurs is unknown. The mutation in the *KIT* D816V gene produces a protein causing the excessive growth and accumulation of mast cells in the body's organs or tissues. These mast cells release an abnormal amount of chemicals, called "mast cell mediators." Examples of mast cell mediators are histamine, tryptase, leukotrienes, and prostaglandins. These mediators can cause an allergic response.

Very rarely does the *KIT* D816V mutation appear to be inherited. In most cases the mutation is a random occurrence that occurs after conception.

While there is no way to prevent mastocytosis, patients can take steps to minimize the signs and/or symptoms by avoiding the situations that trigger an allergic reaction.

Related Diseases

Mast Cell Activation Syndrome is a condition, not a cancer, where mast cells frequently release chemicals resulting in recurrent and severe allergic reactions. Patients typically experience signs and/or symptoms in two or more organ systems. Patients may have high levels in their blood of

- Tryptase—a protein stored in mast cells
- Histamine—a chemical released by cells in response to allergens
- Prostaglandins—a hormone-like substance involved in many bodily functions such as blood pressure and inflammation
- Leukotrienes—inflammatory chemicals that the body releases after coming into contact with an allergen

Signs and symptoms may ease up or resolve with the use of antihistamines or other drugs. Patients need to avoid allergens that are triggers and use medications to block the chemicals released during severe allergic reactions.

Hereditary Alpha-Trypsinemia is an autosomal dominant genetic trait caused by multiple copies of the alpha tryptase gene (*TPSAB1*), leading to increased levels of the tryptase protein made by mast cells. The increased levels of the tryptase protein are often associated with the release of histamine. Therefore, treatment with antihistamines may be helpful.

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our website at www.LLS.org/ChapterFind or contact an Information Specialist at (800) 955-4572.

LLS offers free information and services for patients and families affected by blood cancers. This section lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

For Help and Information

Consult with an Information Specialist. Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date information about disease, treatment and support. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 am to 9 pm ET)
- Email and Live chat: www.LLS.org/InformationSpecialists

Clinical Trials (Research Studies). Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical-trial process. Please visit www.LLS.org/CTSC for more information.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian with experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management, and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition for more information.

Free Information Booklets. LLS offers free education and support booklets that can either be read online or ordered. Please visit www.LLS.org/booklets for more information.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.

Financial Assistance. LLS offers financial support, including insurance premium and medication co-pay assistance, to eligible individuals with blood cancer. For more information, please:

- Call: (877) 557-2672
- Visit: www.LLS.org/finances

LLS Health Manager™ App. This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format and share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Please visit www.LLS.org/HealthManager to download for free.

LLS Coloring for Kids™. This free coloring app allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. The app includes blank canvases, general coloring pages and pages from LLS coloring books. This app can be used anywhere and may help pass time in waiting rooms or during treatment. Please visit www.LLS.org/ColoringApp to learn more and download.

Podcast. *The Bloodline* with LLS is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Please visit www.LLS.org/TheBloodline for more information and to subscribe.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Please visit www.LLS.org/SuggestedReading to find out more.

Community Resources and Networking

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Please visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients reach out and share information. Please visit www.LLS.org/chat for more information.

LLS Chapters. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection® Program* (a peer-to-peer support program), local support groups and other great resources. For more information about these programs or to contact your chapter, please:

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to view the directory.

Advocacy. The LLS Office of Public Policy (OPP) enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

Additional Help for Specific Populations

Información en Español (LLS information in Spanish). Please visit www.LLS.org/espanol for more information.

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please

- Call: the VA (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

World Trade Center Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help from the World Trade Center (WTC) Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a 2-week period. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov and enter “depression” in the search box

Other Resources

National Cancer Institute (NCI)

www.cancer.gov
(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health (NIH), is a national resource center for information and education about all forms of cancer.

National Organization for Rare Disorders (NORD)

www.rarediseases.org
(800) 999-6673 / (203) 744-0100

The National Organization for Rare Disorders is a unique federation of voluntary health organizations dedicated to helping people with rare “orphan” diseases and assisting the organizations that serve them. It is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and service.

The Mast Cell Disease Society

<https://tmsforacure.org/>

The Mast Cell Disease Society is a nonprofit organization dedicated to providing multi-faceted support to patients, families and medical professionals in our community and to leading the advancement of knowledge and research in mast cell diseases through education, advocacy and collaboration.

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Information Specialist: **800.955.4572**

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