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Original Article

Cutaneous mastocytosis: A self-limiting benign disease in a series of 45 cases

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Abstract

Background Cutaneous mastocytosis is a rare disease. It results from a hyperplastic response of mast cells to abnormal stimuli due of activating c-KIT mutations.

Objective To collect all cases of cutaneous mastocytosis and evaluate them clinically and histopathologically.

Methods This is a case series descriptive study where cutaneous mastocytosis cases were collected during the period from 2017-2021. Full history and clinical evaluation were carried out. Skin biopsies were processed and stained with Giemsa stain and CD117 IHC marker to evaluate histopathological changes. Therapeutic trial using antihistamine and corticosteroids were conducted.

Results Analysis of forty five cases with the classical cutaneous mastocytosis was carried out involving 26 males (57.77%) and19 females (42.22%). Their ages ranged from 1-15 years with a mean±SD of 3.5±3.7 years while the age of onset was mostly after the age of one year. All patients had itching with variable severity. Forty-two (93.3%) patients had a generalized rash while 3(6.7%) cases had localized lesions. The rash was dark brown maculopapular rash in 35 (77.77%), bullous in 4(8.88%), plaque in 3 (6.66%), nodular in 2 (4.44%), and xanthogranuloma like in 1(2.22%) case. The Disease was slow and regressing apart from bullous variant which run aggressive course. Histopathology showed mast cells proliferation in the superficial and deep dermis and sub-epidermal blisters in four patients. All patients fulfilled the diagnostic criteria of cutaneous mastocytosis. All patients responded to therapy and their rash and symptoms were relieved.

Conclusion Cutaneous mastocytosis is a disease of children that runs a benign course and then regresses spontaneously. They all needed symptomatic treatment until they had a full remission.

Key words
Mastocytosis, Darier's sign, xanthogranuloma, mastocytosis.

Introduction

Mastocytosis is a rare disease characterized by accumulation and clonal proliferation of mast cells in the skin and/ or other organs. Mastocytosis is classified into two major forms: cutaneous mastocytosis (CM) and systemic mastocytosis (SM).[1] In 1869, Nettleship and Tay firstly describe mastocytosis and in 1878 Sangster called the cutaneous form urticaria pigmentosa (UP).[2,3]

The latest classification of mastocytosis was issued by the WHO in 2019 which included:

1- Cutaneous mastocytosis which includes the following forms:

- Urticaria pigmentosa (UP).
- Diffuse cutaneous mastocytosis.
- Mastocytoma.

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2- Systemic mastocytosis, usually associated with hematological neoplasm and includes the following forms:

1. Indolent systemic mastocytosis.
2. Smoldering systemic mastocytosis
3. Mast cell sarcoma.
4. Mast cell leukemia
5. Extracutaneous mastocytoma.[4-6]

Epidemiology Cutaneous mastocytosis most common in children, representing 90% of all cases in this age group.[7] The maculopapular variant represents the most common cutaneous form and includes urticaria pigmentosa and other nodular-plaque forms.

Pathogenesis The pathogenesis of CM in children is still unclear. Tyrosine kinase receptor (c-KIT), is expressed in the surface membrane of mast cells and needs SCF ligand to be activated. Mast cells originate in the bone marrow, and they migrate in a precursor state to connective tissue, in which they exert many different functions. Mast cell precursors mature through activation of the receptor CD117, also known as C- KIT receptor.[8] The c-KIT mutation is seen among 90% of patients with adult mastocytosis While pediatric patients can be found in varying ratios.[9]

Clinical feature Cutaneous mastocytosis is the most common form characterized by a well-demarcated maculopapular rash of variable sizes (1–2 cm). The color varies from red-brown to yellow and distributed on the trunk scalp, face, and extremities.[10,11] Usually, these lesions are itchy. [12] Many Trigger factors, such as cold water, hot baths, or exercise, may lead to erythema and wheal and formation of what is called Darier's sign which is an important sign in the diagnosis of CM.[13] Mastocytoma constitutes about 10–35% of CM and presents as single or multiple brown nodules. Sometimes, these lesions may vesiculate and blister. Diffuse cutaneous mastocytosis (DCM) is a rare variant and forms about 1-3% of CM. They present as subcutaneous nodules or diffuse bullae, yellow-orange in color, and may involve the whole skin. The skin shows a leathery and doughy appearance. It is sometimes associated with systemic symptoms, like anemia, diarrhea and other GIT symptoms, and this occurs due to an increased number of mast cell mediators released and absorbed locally and systemically.[10,14]

Telangiectasia macularis eruptive perstants (TMEP) is a very rare variant and consists of red, telangiectatic macules in a brown background and usually seen in adults.[10,15]

Diagnostic criteria for mastocytosis For each type of mastocytosis, there are diagnostic criteria.

Table 1 Criteria for diagnosis cutaneous mastocytosis.

Major criteria	Must have the signature or typical skin lesions.
Minor criteria	1. (monomorphic mast cell infiltration with aggregates exceeding 15 mast cells per cluster or distributed mast cells exceeding 20 per high microscopic power field 400 HPF). 2. Molecular criteria (detection of a c-KIT mutation at codon 816 in the affected skin.

*1 major and 1 minor criterion are required for diagnosis of CM.

Table 2 Criteria for diagnosis systemic mastocytosis.

Major criteria	Having multifocal, dense mast cell infiltrations in the bone marrow or extracutaneous tissues.
Minor criteria	1- More than 25% of mast cells are spindle-shaped or otherwise atypical in bone marrow samples or extracutaneous tissues. 2-Expression of CD25 and/or CD2 by extracutaneous mast Cells. 3-Presence of KIT codon 816 mutation occurring in blood, bone marrow, or extracutaneous tissues. 4-Serum total tryptase level exceeding 20 ng/ml.

* 1 major and 1 minor criterion or 3 minor criteria are required for diagnosis.

Histopathology The epidermis is normal apart from an increase in melanin, especially in the basal layer. There is an increase in the number of dermal mast cells which are oval or spindle shaped cells distributed around the blood vessels and papillary dermis in addition to other types of inflammatory cells such as eosinophils, lymphocytes. Also, edema of the papillary dermis could be observed. Subepidermal blister formation can be seen in bullous variants. Histiocytes and Touton giant cells are observed in XG variants.

Prognosis of cutaneous mastocytosis Around 50% of children with MC clear at adolescence while most of the mastocytomas in childhood have a spontaneous resolution but in adults only occurs in 10% of cases. In general, CM carries a good prognosis but in advanced cases of mastocytosis that is associated with a blood disorder, theprognosis depends on the hematological abnormalities and the management that is given.[16] Also, patients with large skin lesions (more than 1 cm) compared with those with small lesions (less than 1cm) have a more favourable prognosis suggesting that the size of cutaneous lesions is considered a prognostic parameter in childhood-onset CM.[17]

Management

Unfortunately, there is no curative treatment for mastocytosis butthe current management includes:

1- Avoidance of triggers for mast cell degranulation.
2- Symptomatic relief.
3- Detection of any significant systemic disease.

In general, oral H1 antihistamines are used to control itching and flushing while H2 antihistamines may help, especially with the presence of gastrointestinal symptoms such as abdominal pain, cramping, and diarrhea.[18] Topical and systemic steroids can be used for control of symptoms. Many other treatments such as cromolyn sodium, PUVA, Omalizumab, Ketotifen, and C-KIT inhibiter like Imatinib can be used accordingly.

The objective of the present work is to do a full clinical evaluation in a series of 45 cases of cutaneous mastocytosis. Also, the histopathological assessment will be carried out and a therapeutic trial will be tried.

Patients and methods

This is a case series descriptive study where all cases with well-documented cutaneous mastocytosis (CM) were included during the period from 2017 to 2021. All demographic and clinical features like age, age of onset, sex, clinical picture, progression, and course of the disease were recorded and analyzed. Darier's sign was done by strocking an existing lesion with a wooden tongue depressor and within a few minutes, a swollen red weal will be seen. All provoking factors for the disease like heat, exercise, shower, certain foods, drugs were assessed. Skin biopsies were obtained from 10 patients and in many of the others, biopsies were refused by their parents. Histopathological assessment with H&E and Giemsa stain was done. Immunohistochemical testing using CD 117 marker that was used to delineate the presence of mast cells was carried out. General investigations like CBC, USG, RFT and LFT were done in a selected number of patients and when it is necessarily needed.

All patients were treated with oral antihistamines (loratadine syrup; Claritin-BAYER Global) 5mg/ 5ml twice daily for children more than 2 years, Dimethindene maleate 1mg/ 1m (Finistil -SDI) drops 5 drops x3 times daily for a child less than 2 years and

loratadine tab (Claritin) 10 mg twice daily for adolescent for 1-month duration. Potent topical steroid, clobetasol propionate (Dermovate 0.05%-SDI) used twice daily for 1-month duration as topical treatment with prednisolone syrup (PREDNICORT–Pioneer) 5mg/ 5ml twice daily for 10 days duration. The treatment tapered gradually and stopped and could be repeated when it was needed.

Formal consent was taken from the patient or parent after a full explanation about the nature of the disease, investigations needed, treatment, and prognosis. All patients agreed to share their photos in the present work. This study was approved by the Scientific Ethical Committee of Dermatology, Iraqi Board for Medical Specialization.

Statistical Analysis

Microsoft Word Excel 2013 was used for data input and analysis. Quantitative data were presented as mean±SD (standard deviation) and categorical variables were presented with numbers, frequency, and percentages. A *P* value of <0.05 was considered significant.

Results

Analysis of a total of 45 patients was carried out including 26 (57.77%) males and 19 (42.22%) females with a male to female ratio (1.4:1). Patients ages at the time of examination ranged from 1-15 years with a mean±SD (3.5±3.7) years while the age of onset was mostly after the age of one year apart from three patients who had their disease around 15 years. Males age at time of presentation ranged from 1-15 years with a mean±SD (4.3±4.4) while females age ranged from 1-11 years with a mean±SD (2.5±2.2) years. The duration of CM ranged from 1 to >24 months with mean±SD (5.3±5.9); 35 (77.8%) of patients had CM duration of 1-12 months while10 (22.2%) of them had 13 to >24 months. History and examination of all patients showed itching with variable severity in all cases and it was mild in 10 (22.2%), moderate in 33 (73.3%), and severe in 2(4.4%). Forty-two (93.3%) patients had generalized rash while 3 (6.7%) cases had localized lesions. The type of rash was dark brown maculopapular rash in 35 (77.77%) patients, bullous in 4 (8.88%), plaque in 3 (6.66%), nodules in 2 (4.44%), and xanthogranuloma like in 1 (2.22%) case **(Figures 1-4)**.

In maculopapular variants, patients presented with multiple red-brown macules and papules of

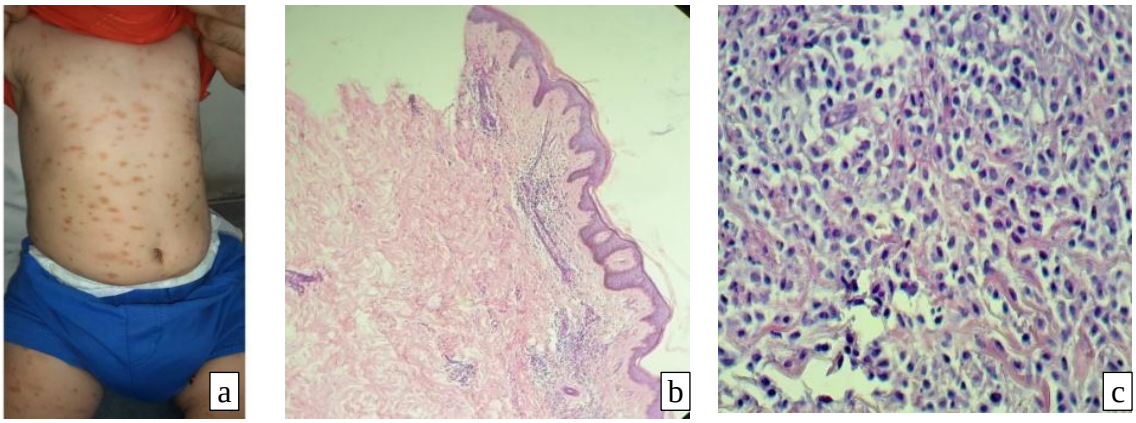
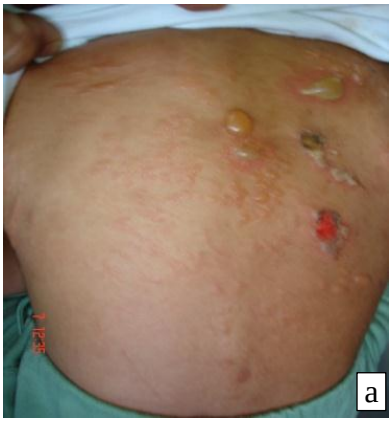


Figure 1 A two years old male patient .(a) clinical picture of mastocytosis.(b) histopathology showing basal layer hyperpigmentation (100 HPF). (c) perivascular infiltrate(400 HPF)



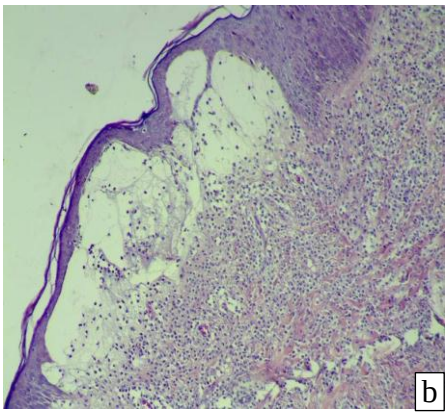


Figure 2 (a) A 3- year- old male child with multiple bullous and erosion involving the trunk. (b) histopathology showing subepidermal blister with mast cells infiltration.

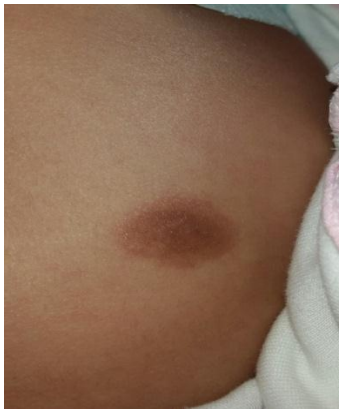
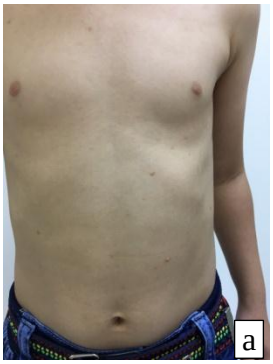
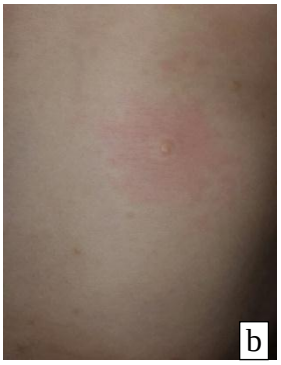
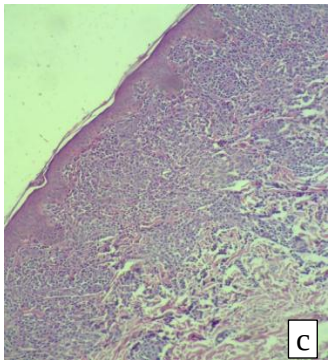


Figure 3 A 2- year- old female patient with nodular variant of cutaneous mastocytosis.







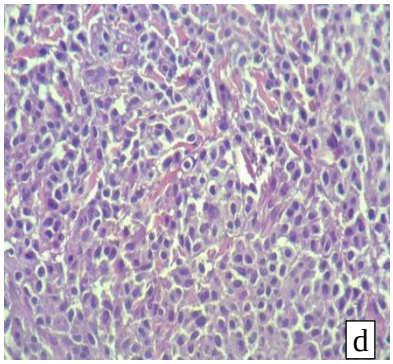


Figure 4 (a) A 6-year-old male child with xanthogranuloma variant,(b) positive Darier's sign. (c and d) histopathology showing basal layer hyperpigmentation and massive mast cells infiltration (H&E100x-400x/HPF).

variable size usually >1 cm apart from those occurring in patients around 15 years who had lesions <1 cm. They are distributed all over the body especially the trunk. The lesion was itchy with a positive Darier's sign.

In bullous variants 4 patients were presented with numerous pruritic bullae distributed over the trunk and started as itching followed by the appearance of erythematous macules and bullae at the site of itching; some areas of erosion were observed. Darier's sign was positive.

Three patients (6.66%) presented with red-brown plaques that were found in the lower part of the abdomen and thigh as single or few lesions. They were itchy with positive Darier's sign. Nodular variants were seen in 2 patients (4.44%) as a small nodule in lower extremities and were itchy with urtication upon stroking with a tongue depressor.

Xanthogranulomatous variant of cutaneous mastocytosis was found in 6 years old male child presented with an itchy rash on the trunk for 5 months duration. On examination, the lesion appeared as small yellowish papules distributed only on the trunk and the first impression was Xanthogranuloma but Darier's sign was positive and the result of the biopsy showed a typical picture of mastocytosis.

In 27 (60%) of cases, the skin lesions are distributed to involve most parts of the body including trunk, extremities, face, palm, and sole, while14 (31.1%) cases involved the trunk only, in 4 (8.9%) cases, the rash affecting just the lower extremities. Regarding the size of the

lesions, 40 (88.9%) patients had lesions ≥1 cm while in 5 (11.11%) cases, the size was <1 cm. Ten cases (22.2%) showed aggravation of the rash when exposed to a hot bath while 5 (11.11%) cases were aggravated by eating spicy food. Darier's sign was positive in all cases but after therapy the test became negative. Regarding family history, past medical and drug history were negative in all patients. The course, severity and the activity of the disease, it was slow and regressing over years apart from bullous variety ran an aggressive course.

Histopathological evaluation revealed normal epidermis apart from five cases that showed acanthotic epidermis while hyperpigmentation of the basal layer was detected in all patients. The dermis showed superficial and deep perivascular inflammatory infiltrate of mast cells, eosinophils, plasma cells, and lymphocytes. Mast cells that were seen by H&E and Giemsa stain were found in all biopsies as they were seen as round or spindle-shaped with abundant eosinophilic cytoplasm with distinct borders and often contained small granules, **Figure (4 c,d)**. These mast cells were concentrated in the upper dermis and around the blood vessels.

One to three readings of mast cells were carried out for each biopsy and the mean number of dermal mast cells using H&E and Giemsa stain varied from patient to patient, 6 (60%) biopsies had around 20 cells/ 400HPF while 4 (40%) had more than 20 cells/ 400HPF. Those patients having polymorphic variant rash (variable size) showed higher mast cell numbers when compared with patients with monomorphic rash. Sub-epidermal blisters were observed in 4 (40%) that had a bullous variant of CM. Xanthogranuloma like mastocytosis showed normal epidermis, hyperpigmentation of basal layer, perivascular inflammatory infiltration of mast cells and histiocyte without evidence of Touton giant cell. Immunohistochemical staining with CD117 marker was positive in all cases with CM.

All patients fulfilled the criteria for diagnosis cutaneous mastocytosis

One case with CM that born at 39 weeks and was delivered by normal vaginal delivery to 27 years old mother with unremarkable pregnancy. The neonate was noted to have skin lesions distributed throughout the body as multiple macular lesions without evidence of any systemic involvements by examination and investigations. He responded well to treatment and the follow-up was similar to other patients.

Treatment of these patients induced disease remission, then therapy was tapered gradually but was repeated when needed until full recovery and remission.

Discussion

Cutaneous mastocytosis is a group of disorders characterized by mast cell accumulation in the skin and/or internal organs, presented as solitary or wide spread itchy, red-brown skin lesions that appear in childhood or adulthood.[16]

Cutaneous mastocytosis is considered a rare disease while in Iraq it seems to be not a rare problem. It presents in multiple distinct forms, maculopapular is the mostcommon clinical presentation so-called urticaria pigmentosa (UP) and occurs in children and represents 70%-90% of the cases[19,] while plaque type is typically seen in pediatric age and have a generally good prognosis, large nodular lesions usually single or multiple commonly called mastocytoma.

Darier's sign is a wheal that is produced by stroking or rubbing skin lesions and confirms the diagnosis of cutaneous mastocytosis.[20,21]It results from the release of mast cell mediators

which can lead to the systemic effects that may arise after the lesion has been stroked and this is more common in children than adults.

To the best of our knowledge, this is the first study that was carried out in the Iraqi populations. In the present study, we found that the age of onset of CM was mostly after the age of one year, as in 66.7% of patients, the age was between 0-3 years and in 24.4% between the age of 3-6 years which is not comparable to Singalavanija *et al.* study who found that most of the cases (94%) appeared within the first year of life[22]. While M:F ratio in the present work was 1.4:1, it is comparable to other studies showing no much variations between males and females.[17]

The present study showed that the type of rash was generalized in 42 (93.3%) of patients while in 3 (6.66%) cases had localized lesions. The maculopapular rash was observed in 77.7% of cases which is approximately comparable with Gürkanetal and Lange *et al.* in which maculopapular rash appeared in 61% and 89.22% of patients respectively.[23,24]

Mastocytoma was seen in 4.4% of patients and all were females with age less than three years. This finding was not comparable with Hannaford *et al.* who recorded mastocytoma in 51% of patients with CM while Cohen *et al.* reported mastocytoma among 8 males and 6 females with ages more than 16 years. Bullous mastocytosis was detected in 8.88% of the present work in contrast to 23% of patients in Hannaford *et al.* study.[25,26]

Xanthogranuloma variant of CM which is a rare type which was reported in two patients in the literature, one adult male[27] and one in 5 months female.[28] The present study had also documented a 6 years old male patients presented with yellowish papules similar to xanthogranuloma lesions; it showed a positive Darier's sign and the histopathology confirmeda cutaneous mastocytosis.[29]

Huang *et al.* reported a case of a 37-week-old male, born by a cesarean section, had hepatosplenomegaly and ascites and diagnosed in utero. He had cutaneous and systemic manifestations of mastocytosis at birth and died at 10th weeks. It is incomparable to our case who born at 39 weeks by normal vaginal delivery to a 27 years old mother with uneventful pregnancy. The neonate was noted to have skin lesions distributed throughout the body as multiple macular lesions without evidence of any systemic involvements by examination and investigations. He responded well to treatment and the follow-up was unremarkable.[30]

Darier's sign, in the present work, was positive in all cases which is dissimilar to Macias *et al.* and Sinha *et al.* which showed negative Darier's sign in both maculopapular and XG variants respectively.[31,32] Darier's sign became negative after treatment and was considered a marker of remission in the present study.

There is no evidence of anaphylaxis or eye involvements observed in the present work and in contrast to what were reported in Brockow *et al.* & AlGhamedi *et al.* respectively.[33,34]

While Family history was negative in the present work, a positive family history was reported in Hannaford *R et al.* study.[26]

Diagnosis of CM in the present study was well documented by clinical and histopathological H&E, Giemsa stain, and CD117 marker which were positive for mastocytosis. Also, according to WHO score[35] all patients had positive major and minor criteria for diagnosis of CM.

Histopathological findings of the present work

were similar to other studies. The most important mast cell antigens used for diagnosis were tryptase and CD117 marker. In normal and reactive states, all mast cells express tryptase and CD117, but tryptase may be decreased or lost in rare cases of mastocytosis. So CD117 are important immunophenotype to confirm the diagnosis of cutaneous mastocytosis. In the present study, all cases were positive for CD117 marker.

Regarding therapy of these patients, as the disease run a benign self limiting course, hence there was no need for aggressive therapy, only supportive symptomatic treatment like oral antihistamine, topical and oral corticosteroids were given. This therapeutic trial had been similarly indicated by other workers.[36]

The prognosis of CM seems to be good and in favor of a self limiting course especially among infants and children.[37] During 2 years follow up, most patients had almost free of signs and symptoms apart from mild exacerbation. This was similarly reported as about 50% of children with CM clear at adolescence and most of the mastocytomas resolve in childhood but the spontaneous resolution of CM in adults occurs in 10% of cases. So in general, CM carries a good prognosis but in advanced cases of mastocytosis that is associated with a blood disorder, it depends on the hematological abnormalities and the management that is given.[38]

Conclusion

This is the first study that was carried out in the Iraqi population and showed that cutaneous mastocytosis is a disease of infants and children with full positive clinical and histopathological and histochemical scoring but this disease can have late-onset in early adolescent life. Cutaneous mastocytosis runs a benign course for several years and then regresses spontaneously as it is very rarely seen in adult ages but bullous type might have an aggressive picture. The present study and from the daily clinical observation have clarified that this disease is not rare among Iraqi people. They all needed symptomatic treatment until had full remission.

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