

Seventy-four-year-old woman with myelodysplastic syndrome and splenomegaly

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ABSTRACT

We present a 74-year-old woman with a recent diagnosis of myelodysplastic syndrome who presented with left upper quadrant abdominal pain and fatigue with significant splenomegaly, anemia, and thrombocytopenia. She underwent splenectomy and bone marrow biopsy. Pathology of both spleen and bone marrow revealed an unusual diagnosis. A review of the differential diagnosis, laboratory tests, nature of the underlying disease, and treatment are provided.

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Key words: D816V, hematologic non-mast cell lineage disease, hypersplenism, mast cells, mastocytosis, myelodysplastic syndrome, splenomegaly, systemic mastocytosis with associated clonal, urticaria pigmentosa

CASE PRESENTATION

Chief Complaint

Left upper quadrant abdominal pain.

History of Present Illness

A 74-year-old woman with gastroesophageal reflux disorder, hypothyroidism, osteoporosis, history of breast cancer currently in remission, and recent diagnosis of myelodysplastic syndrome (MDS) presented with progressively worsening left upper quadrant abdominal pain for 4 months. The patient was diagnosed with refractory cytopenia with multilineage dysplasia, a category of MDS, just over a year before presentation. Report of a bone marrow biopsy done at the time showed dysplastic changes in the megakaryocytes and in the myeloid precursors and a cytogenetic analysis showed a 20q deletion. She had received erythropoietin injections for her anemia at an outside facility but this was refractory to treatment and she required several transfusions.

The patient first developed the left upper quadrant abdominal pain 4 months before presentation. She described it as a chronic “tight” discomfort with acute

episodes of sharp pain. She also noted a fullness and then a bulge in the area. Eventually, she was able to feel a mass in her upper abdomen that was painful and very tender to touch. The pain did not radiate and was worsened by movement, cough, and deep breathing. She denied any nausea/vomiting, hematochezia, or melena as well as any skin complaints. At the same time these symptoms developed, the patient noted that she would tire easily. She was found to be anemic, and it became necessary to give her red blood cell transfusions. Serial transfusions were necessary and increased in frequency from every 3 weeks to every 2 weeks. A CT scan at the time revealed a splenic hematoma. There was no history of trauma to her abdomen. She was transfused at that time without surgical intervention.

Her abdominal pain continued to increase in frequency and severity. Repeat CT scan done 1 month before presentation showed increased spleen size of 13.5 cm in anteroposterior diameter with subcapsular splenic hemorrhage without active bleeding. She was seen by her primary care physician and was found to be profoundly anemic with a hemoglobin of 6.6 g/dL in the clinic and was admitted to the hospital for further workup.

The patient's medical history is positive for hypothyroidism, currently euthyroid, osteoporosis, gastroesophageal reflux disorder stable on esomeprazole, MDS, and history of breast cancer over 15 years ago s/p modified radical mastectomy with cancer in remission. Her medications include sucralfate, esomeprazole, and triamterene-hydrochlorothiazide as well as thyroid replacement. Her family history is significant for a brother who died at age 18 years from Hodgkin's lymphoma and a sister who also has MDS. Her mother

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is deceased and had diabetes mellitus and breast cancer. Her father is also deceased because of heart problems. Her social history is significant for a remote history of smoking (quit in 1967).

She is a social drinker. Current review of systems is notable for fatigue, left upper quadrant (LUQ) abdominal pain, daily night sweats, and mild dyspnea on exertion. She denied any cardiac, skin, or neurological problems.

Physical Examination

Vital signs included a temperature of 38°C, a respiratory rate of 20, and elevated blood pressure of 132/70 with tachycardia to 105. Oxygen saturation on room air was 96%. General examination revealed an age appropriate woman, alert and oriented in mild distress.

Head, eyes, ears, nose, and throat examination was significant for mild scleral icterus and pale conjunctivae, and neck exam showed no significant lymphadenopathy or jugular venous distention. Examination of the chest showed clear lung fields and the right breast was reconstructed with a well-healed scar. Cardiac examination was positive for tachycardia but without murmurs. Abdominal exam elicited tenderness in the LUQ with palpable splenic margin. Liver span was normal. Neurological exam was normal and the skin showed no rashes or lesions.

Laboratory and Imaging

Initial admission laboratory values are outlined in Table 1. Notable values include hemoglobin and hematocrit of 7.0 g/dL and 24.2%, respectively, with a normal mean corpuscular volume. Platelets were also low at $57 \times 10^3/\mu\text{L}$. Chemistry labs were most significant for a lipase of 324 U/L and bilirubin of 2.4 mg/dL with conjugated bilirubin 0 and direct Coombs negative. Further workup showed an elevated lactate dehydrogenase (LDH) of 1236, normal haptoglobin, and hepatitis A antibody positive; however, hepatitis B and C studies were negative. CT of the abdomen showed increasing size of the spleen to 17.1 cm in greatest anteroposterior dimension (Fig. 1), previously measuring 15.3 cm 1 month prior. The spleen appeared heterogeneous with a hyperdense rim, suggestive of recent hemorrhage. There was also a right lower pulmonary nodule that was stable and a new nodule in the right middle lobe, as well as interim development of bilateral pleural effusion. Lymph nodes were not enlarged.

Clinical Course

The patient continued to require significant transfusions; thus, splenectomy was performed. The spleen weighed 1440 g, which is approximately 7–10 times larger than normal. She tolerated the procedure well and her postoperative course was uneventful. Pneumococcal, meningococcal, and *Haemophilus influenza*

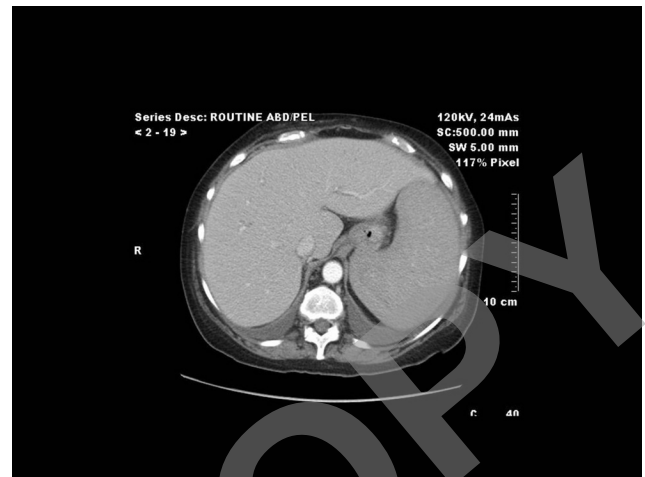


Figure 1. CT scan of the abdomen shows enlargement of the spleen, measuring 17.1 cm in greatest anteroposterior dimension. The spleen is heterogeneous with a hyperdense rim suggestive of new blood.

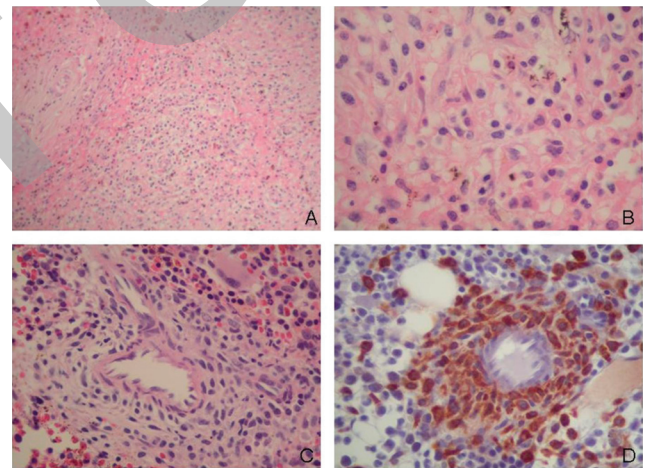


Figure 2. (A) (Spleen hematoxylin and eosin (H&E) stain 100×) Loss of normal architecture of the spleen. (B) (Spleen H&E 500×) Infiltration of the spleen by >15 cells with abundant cytoplasm in aggregates. (C) (Bone marrow H&E 500×) Cells with clear cytoplasm surrounding blood vessels and trabeculae. (D) (Bone marrow tryptase 500×): The cells stain positive for tryptase indicating mast cells.

immunizations were administered before discharge from the hospital. The need for red blood cell transfusions ceased immediately after the surgery, and the platelet count very quickly returned to normal. Hemoglobin was stable at 10.8 g/dL, and platelets were $510 \times 10^3/\mu\text{L}$. Pathology reports of the spleen revealed significant mast cell infiltration, extramedullary hematopoiesis, and hemorrhage (Fig. 2). The spleen was stained for CD117 and the vast majority of cells stained positive. Bone marrow examination showed morphological evidence of trilineage dysplasia in >10% of erythroid, granulocytic, and megakaryocytic cell lines with <5% blasts. These findings confirmed the pre-

Table 1 Initial laboratory data

Laboratory	Value (Reference Range)
White blood cell $\times 10^3$	8.4 (4.0–10.0/mm ³)
Red blood cell $\times 10^6$	2.64 L (3.90–5.30/mm ³)
Hemoglobin	7.8 L (11.5–15.5 g/dL)
Hematocrit	24.2 L (34.0–45.0%)
Mean corpuscular volume	91.7 (80.0–96.0 fL)
Mean corpuscular hemoglobin	29.5 (27.0–32.0 pg)
Mean corpuscular hemoglobin concentration	32.2 (31.0–37.0%)
Red blood cell distribution width	19.0 H (11.6–14.0%)
Platelets $\times 10^3$	57 L (150–400/mm ³)
Mean platelet volume	11.1 (8.0–12.0 fL)
Nucleated red blood cells/100 white blood cells	Occasional
Peripheral Smear	Polychromasia 2+
	Elliptocytes/ovalocytes 2+
	Schistocytes 1+
	Basophilic stippling present
Gran (%)	58.1 (40.0–73.0%)
Lymph (%)	28.3 (18.0–53.0%)
Mono (%)	13.2 H (4.0–12.0%)
Reticulocyte (%) and absolute	Reticulocyte % 6.43 H
	Reticulocyte absolute
	0.284 $\times 106/\mu\text{L}$ H (0.03–0.09)
Direct antiglobulin test	Negative
Prothrombin time/Activated partial thromboplastin time	Within normal limits
Chem 7	Normal except for glucose
	201 H (70–110 mg/dL)
Calcium	8.0 L (8.6–10.6 mg/dL)
Magnesium	1.7 (1.7–2.4 mg/dL)
Total bilirubin	2.4 H (0.1–1.1 mg/dL)
Conjugated bilirubin	0
Unconjugated bilirubin	2.4 H (0.1–1.1 mg/dL)
Hepatitis A Ab	Positive
Hepatitis B surface Ag and Ab	Negative
Hepatitis C Ab	Negative
T Protein	6.5 (6.3–8.2 g/dL)
Albumin	3.4 L (3.5–5.0 g/dL)
Alk Phosph	133 H (34–122 U/L)
Alanine transaminase (serum glutamic pyruvic transaminase)	21 (9–51 U/L)
Aspartate transaminase (serum glutamic oxaloacetic transaminase)	43 H (13–40 U/L)
Lipase	324 H (0–220 U/L)

vious diagnosis of refractory cytopenia with multilineage dysplasia. In addition, the bone marrow biopsy showed >15 perivascular mast cell aggregates with >25% spindling (Fig. 2). Tryptase level was subsequently ordered and found to be markedly elevated at 302 $\mu\text{g/L}$ (reference range, 0.4–10.9 $\mu\text{g/L}$).

QUESTIONS

What Is the Differential Diagnosis?

Splenomegaly has numerous etiologies, including infectious (*e.g.*, viral hepatitis, Epstein-Barr virus, and

tuberculosis), inflammatory disorders (*e.g.*, Felty's syndrome and systemic lupus erythematosus), congestive splenomegaly usually caused by liver cirrhosis, hematologic disorders (*e.g.*, hemolysis and malignancy, particularly, myeloproliferative disorders), storage diseases, and miscellaneous causes such as amyloidosis, cysts, and mastocytosis.¹ Hypersplenism is characterized by splenomegaly, cytopenia, and normal or hyperplastic cellularity of bone marrow, with evidence of increased cell turnover such as reticulocytosis.¹ The cytopenia resolves with splenectomy. Hypersplenism

Table 2 World Health Organization criteria for the diagnosis of systemic mastocytosis

Major	Multifocal dense infiltrates of mast cells in (≥ 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)*
Minor	a. Mast cells in bone marrow or other extracutaneous organs show an abnormal (spindling) morphology ($>25\%$)* b. c-kit mutation D816V or other activating mutation of codon 816 in extracutaneous organs* c. Mast cells in the bone marrow or extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers* d. Serum tryptase >20 ng/mL (does not count in patients who have an associated clonal myeloid disorder)

*Fulfillment of criterion by patient.

Diagnosis criteria fulfilled if one major and one minor or three minor criteria were met.³

can be primary or secondary. Common secondary causes are infectious, inflammatory processes such as systemic lupus erythematosus, congestive splenomegaly, storage disorders, malignancy, chronic hemolytic disorders, myeloproliferative disorders, and splenic malformations. Hypersplenism is not a typical feature of MDS and thus its presence arose suspicion of another pathological process underlying the splenomegaly.

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

In a patient presenting with MDS, splenic hemorrhage, splenomegaly, and cytopenia, additional studies should include hepatitis A, B, and C serologies and antinuclear antibody as well as workup for hemolysis, such as a peripheral blood smear, LDH, Coombs, and haptoglobin. The peripheral smear showed polychromasia, elliptocytes, and ovalocytes and basophilic stippling as well as rare schistocytes. The polychromasia was a reflection of the increased reticulocyte count. Reticulocytes appear as polychromatophilic cells on the routine blood smear. The elevated reticulocyte count resulted from the extensive hemorrhage into the spleen. Basophilic stippling is sometimes seen in the presence of massive bleeding into tissues. The presence of ovalocytes or schistocytes may possibly be explained by some red cells that might have been fragmented while passing through the spleen engorged with massive numbers of red cells. LDH was elevated; however, Coombs was negative and haptoglobin was normal; thus, an immunologic hemolytic process was less likely. Our patient's hepatitis A serology was positive, likely indicating vaccination or prior infection. Her hepatitis B and C serology and antinuclear antibody were negative. Ultimately, the final diagnosis was made with the pathological examination of the splenectomy and bone marrow specimens that revealed aggregates of mast cells, consistent with the diagnosis of systemic mastocytosis (SM).

DISCUSSION

Mastocytosis is a heterogeneous entity characterized by the abnormal growth and accumulation of mast cells in one or more organ systems. The clinical manifestations of mastocytosis typically include skin symptoms such as flushing and pruritus, gastrointestinal (GI) symptoms, syncope, anaphylaxis, osteoporosis, organomegaly, and/or cytopenia.² The most common skin lesions are those of urticaria pigmentosa, which typically present with fixed red-brown maculopapular lesions that intensify with rubbing, the so-called "Darier's sign." Our patient had no cutaneous symptoms although she did have some GI complaints along with the splenomegaly and cytopenia. She also had osteoporosis, which would not be unexpected given her age. It is estimated that $\sim 80\%$ of all mastocytosis patients have skin involvement; however, in SM, skin lesions occur in $\sim 50\%$ and more often are observed in those with an indolent course.³ As a general rule, in the evaluation of patients with SM, the lack of skin lesions should arouse suspicion for an aggressive mast cell disorder, although there are certainly subvariants without skin lesions that are more benign.⁴

The World Health Organization has devised diagnostic criteria for mastocytosis (Table 2).³ The diagnosis is established if one major plus one minor or three minor criteria are met. The major criterion involves identification of at least 15 aggregating mast cells (MC) in biopsy from the bone marrow or other extracutaneous sites.

Mediators such as tryptase may be measured in the serum as surrogate markers, which may aid in the diagnosis of mastocytosis. A serum tryptase of >20 ng/mL is a minor criterion for diagnosis, although this does not apply in patients with systemic disease with associated clonal hematologic non-MC lineage disease. Elevated tryptase levels may also be observed in MDS, hypereosinophilic syndrome, and myeloid malignancies, as well as renal failure.⁵ CD25 and CD2 are markers of aberrant mast cells found commonly in SM and also qualify as a minor criterion. Other minor criteria

include atypical morphology of mast cells as well as demonstration of mutation at codon 816 of c-kit.³

The World Health Organization has also devised a classification schema for mastocytosis to include variants and subvariants: (1) cutaneous mastocytosis (CM), which includes urticaria pigmentosa, diffuse CM, mastocytoma of skin, and telangiectasia macularis eruptiva perstans; (2) indolent SM, which includes smoldering SM and isolated bone marrow mastocytosis; (3) SM with an associated clonal hematologic non-MC lineage disease (SM-AHNMD); (4) aggressive mastocytosis, which includes lymphadenopathic mastocytosis with eosinophilia; (5) mast cell leukemia; (6) mast cell sarcoma; and (7) extracutaneous mastocytoma.³ CM limited to the skin is often diagnosed in children but is uncommon in adults, who tend to have more systemic disease.⁴ Thus, children with isolated urticaria pigmentosa without hepatosplenomegaly, lymphadenopathy, or cytopenia need not undergo bone marrow biopsy, although it is recommended that adults with skin lesions should undergo bone marrow evaluation.⁵ The bone marrow is the most commonly involved extracutaneous site but the GI tract, lymph nodes, liver, and spleen may also be affected.⁶ Our patient had a concurrent hematologic disease (*i.e.*, MDS) which places her into the category of SM-AHNMD. The more common hematologic disorders associated with mastocytosis include chronic myelomonocytic leukemia, acute myelogenous leukemia, and myeloproliferative disease as well as MDS.^{7,8} Mast cell leukemia is defined by the presence of >20% mast cells in bone marrow as well as ≥10% of mast cells in the peripheral white blood differential and is associated with a poor prognosis.^{4,6,9}

Systemic mastocytosis may be further classified based on the presence of B and C findings. B findings suggest a high MC burden but without organ dysfunction. These include (1) infiltration of MC in bone marrow of >30% on histology and/or tryptase of >200 ng/mL; (2) hypercellular bone marrow with dysmyelopoiesis without cytopenias, MDS, or acute myeloproliferative disorders; and (3) organomegaly such as palpable hepatomegaly, splenomegaly, or lymphadenopathy without impaired organ function. C findings, on the other hand, characterize aggressive mastocytosis and indicate impaired organ function: (1) cytopenia; (2) hepatomegaly with impaired liver function, ascites, and/or portal hypertension; (3) osteolyses and/or severe osteoporosis causing pathological fractures; (4) palpable splenomegaly with hypersplenism; and (5) malabsorption with weight loss.³ B findings without C findings are suggestive of indolent SM; however, the presence of C findings indicate aggressive mastocytosis.¹⁰

In most patients with SM, the mutation is in the c-kit gene. The c-kit proto-oncogene encodes the tyrosine kinase-type receptor, which interacts with the cytokine stem cell factor to promote proliferation and differentiation of mast cells from progenitors.^{11,12} The most com-

mon mutation identified in 95% or more of adults with SM is a substitution of valine for aspartic acid (D816V), which is a gain of function mutation.^{3,11} Interestingly, most patients with the mutation have indolent disease; thus, it has been suggested that the mutation by itself is insufficient to cause oncogenic transformation.¹³ Patients with SM-AHNMD may also have other genetic defects, such as RUNX1-RUNX1T fusion gene in SM associated with acute myelogenous leukemia, and JAK2 V617F in SM associated with myeloproliferative neoplasms.³

Patients with clinical manifestations of mastocytosis with eosinophilia, which this patient did not have, may have mutations in the platelet-derived growth factor receptor α (FIP1L1-PDGFR α).⁵ This was not pursued as this mutation without eosinophilia is highly unlikely (Todd Wilson, D.O., Staff Clinician, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, personal communication). It has been shown that the D816V SM with eosinophilia is a clinically distinct entity from FIP1L1-PDGFR α hypereosinophilic syndrome¹³ and these latter patients should be classified as having a myeloid neoplasm with eosinophilia and rearrangement of PDGFR α .³

There are currently no curative treatments for mastocytosis; thus, management consists of alleviation of symptoms caused by mediator release. Commonly used strategies use H₁- and H₂-histamine receptor blockers, leukotriene antagonists, cromolyn sodium, topical as well as systemic steroids, treatment of osteoporosis including bisphosphonates, and epinephrine for anaphylaxis.⁹ Avoidance of triggering stimuli that may lead to mediator release of mast cells and subsequent anaphylaxis should be emphasized, which may include temperature extremes, heat, physical and emotional stress, alcohol, insect venoms, and certain medications such as nonsteroidal anti-inflammatory drugs and opioids as well as contrast dyes.^{5,8} Methoxypsoralen and ultraviolet A may be helpful in those with skin lesions.⁵ The D816V mutation is resistant to imatinib, in contrast to the FIP1L1-PDGFR α mutation, which tends to be responsive.^{3,11} This is thought to be caused by the inability of imatinib to bind the activation loop of KIT, which is the structure that is altered in the mutation of the former.⁵ Patients who are negative for the D816V mutation, however, may show benefit from imatinib.¹⁴ SM with an associated hematologic disorder is treated separately as two issues, *i.e.*, treat the hematologic disorder as if the mastocytosis was not present, and treat the mastocytosis as if the hematologic disorder was not present.¹²

In patients with aggressive forms of mastocytosis, cytoreductive medications such as interferon α and cladribine (2-CdA) are first-line and second-line treatment options.^{3,5,8} Interferon α has had equivocal results and is currently recommended in patients with slowly progressing aggressive SM or smoldering SM with a high mast cell burden.⁶ It has been most helpful in decreasing mast

cell burden in the bone marrow, cytopenias, and osteoporosis and alleviating ascites.⁸ Its use is limited by its side effects such as fatigue, bone pain, anorexia, and depression.⁶ Cladribine is a nucleoside analog that has been found to be an effective treatment; however, response has been transient and incomplete.^{5,6,15} Bone marrow transplantation has been performed in patients with aggressive disease with variable results.^{5,6} Second-generation tyrosine kinase inhibitors such as PKC412 have had variable results,⁵ although another tyrosine kinase inhibitor dasatinib was recently found to have efficacy along with chemotherapy in a case report of a patient with SM and acute myeloid leukemia.¹⁶ Finally, splenectomy is occasionally required in aggressive mastocytosis and SM-AHNMD, particularly if there is massive splenomegaly associated with hypersplenism or portal hypertension.⁶

Prognosis is considerably variable. Children with CM have a favorable outcome and their disease may regress spontaneously before or during puberty.³ Cutaneous lesions in adults, however, do not tend to regress. Patients with indolent disease may have a normal life expectancy, but patients with aggressive disease may survive only a few months to years. Indicators of a poorer prognosis include late onset of symptoms, absence of cutaneous lesions, cytopenia, hepatosplenomegaly, bone marrow hypercellularity, and elevated LDH and alkaline phosphatase.³ The clinical course of patients with an associated hematologic malignancy is typically dictated by the hematologic malignancy.

The patient has continued to feel well postoperatively. Her cell counts have been stable and there have been no mast cells detected in her peripheral blood. She was subsequently evaluated at the National Institutes of Health and underwent repeat bone marrow biopsy, which showed >50% of the marrow replaced by CD2-, CD25-, and CD117-positive mast cells. Mutational analysis was negative for the D816V c-kit mutation; however, it was positive for the D816A KIT mutation.

Repeat tryptase was increased to 762 ng/mL (reference range, <11.5 ng/mL). She also showed increased numbers of monocytes in the peripheral blood ($3.22 \times 10^3/\mu\text{L}$) and bone marrow, and this finding along with increased bone marrow blasts were suggestive of progression to chronic myelomonocytic leukemia. The bone marrow cytogenetic study also reconfirmed a 20q deletion in 10–20 metaphases, with an extra copy of chromosome X noted in two of the metaphases. BCR-ABL was negative. Because her cell counts are otherwise stable, she will be closely monitored for progression of her MDS to chronic myelomonocytic leukemia. She is also being managed with symptomatic treatment for her mastocytosis. Because the D816A mutation is also resistant to imatinib, this is not a viable option for her.

Final Diagnosis

SM-AHNMD.

CONCLUSION

SM-AHNMD may present with hypersplenism without significant cutaneous or GI symptoms. There should be a high index of suspicion of aggressive disease in those patients without skin lesions.

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