June 2013 Critical Care Case of the Month: Scratch Where It Itches

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History of Present Illness

The patient is a 64 year old man who had suffered a non-orthostatic syncopal episode at home, shortly after the onset of lightheadedness. The patient was transported to an outlying hospital where he was described to be confused, wheezing, and in respiratory distress. He was said to be hypotensive (but no blood pressures were recorded in the transfer medical record). He was resuscitated with intravenous saline and underwent endotracheal intubation.

Past Medical History

On arrival at our hospital, further history revealed that the patient had a truncal rash for more than 20 years. He had two previous syncopal episodes associated with delirium, hypotension and respiratory failure. None of these episodes had any clear precipitating event. After the first event, two years previously, a cardiac evaluation resulted in coronary artery bypass surgery. He also had a history of type 2 diabetes mellitus and was taking glipizide and metformin. There was a history of glaucoma and he was receiving timolol.

Physical Exam

Vital Signs: blood pressure 111/60 mm Hg, RR 16 breaths/min, HR 72 beats/min, temperature 37.5° C.
HEENT: epistaxis and an oral endotracheal tube. The ETT tube had bloody pulmonary secretions.
Heart and lung: examination was unrevealing.
Skin: venous and arterial puncture sites were oozing blood. An erythematous and tan maculopapular rash covered his trunk (shown in figure 1).

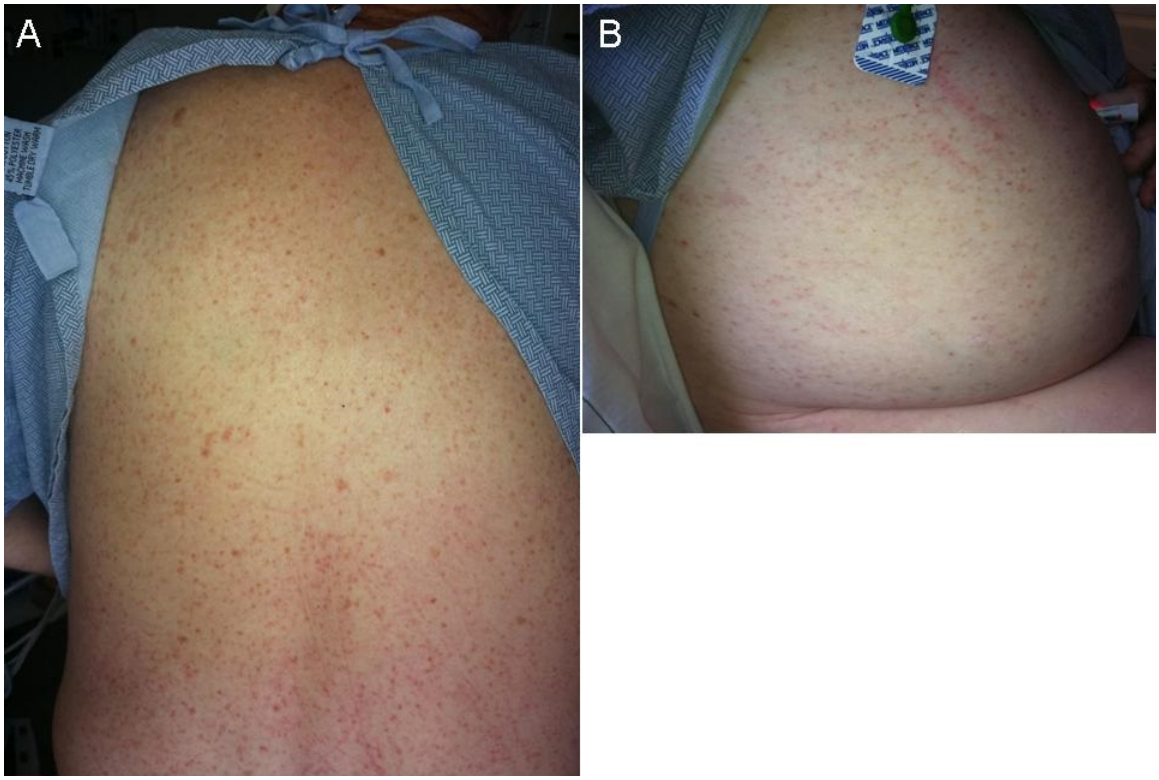

Figure 1. Tan maculopapular rash on patient's back (Panel A) and abdomen (Panel B)

Laboratory

Glucose 50 mg/dL (normal 70-100 mg/dL).
Activated partial thromboplastin time (aPTT) > 200 sec (normal < 30 seconds), prothrombin time (PT) > 120 secs (normal <30 seconds), and a fibrinogen of 39 mg/dL (normal 200-400 mg/dL), D-dimer 2.1 mcg/mL (normal <0.5 mcg/mL), haptoglobin <10 mg/dL (normal 41 - 165 mg/dL), LDH 508 U/L (normal 140-280 U/L), hemoglobin 9 gms/dL (normal 13-17 gms/dL), platelet count 274,000 cells/mcL (normal 150,000-450,000 cells/mcL).

Which of the following is (are) ***true***?

1. The glucose of 50 is just below the normal range and does not need treatment
2. The patient's elevated D-dimer is diagnostic of a pulmonary embolism
3. The patients abnormal coagulation panel is most consistent with a history of taking anticoagulants
4. The coagulation panel is consistent with disseminated intravascular coagulation
5. All of the above

Correct!
4. The coagulation panel is consistent with disseminated intravascular coagulation

It has become increasingly apparent that even mild hypoglycemia can produce adverse consequences in patients and should be treated, especially since the patient's confusion might well be secondary to hypoglycemia. Administration of 50 grams of glucose raised his blood sugar but did nothing for his confusion.

The abnormal coagulation panel is most consistent with disseminated intravascular coagulation (DIC). An older name for DIC was consumptive coagulopathy which is descriptive of its pathogenesis. DIC occurs when the formation of small blood clots inside the blood vessels throughout the body consumes coagulation proteins and platelets, normal coagulation is disrupted and abnormal bleeding can occur from a variety of sites including the skin (e.g. from venipuncture sites), the gastrointestinal tract, the respiratory tract and surgical wounds. The small clots also disrupt normal blood flow to organs, and multisystem organ failure is often a consequence. This patient's platelet count is higher than expected but this can occur, especially with chronic DIC, when platelet production is able to match platelet consumption. Haptoglobin is a protein that binds free hemoglobin which can be released from damage done to red blood cells by the intravascular clots. The D-dimer is one of the fibrin degradation products and nonspecifically indicates that blood clots are being degraded by fibrinolysis.

In this patient a wheal formed when the skin was stroked. Which of the following is/are ***true***?

1. Wheal formation from stroking the skin is known as Darier's sign
2. Wheal formation from stroking the skin is known as Derriere's sign
3. This patient's skin disease is consistent with urticaria pigmentosa which is associated with wheal formation
4. 1 and 3
5. None of the above

Correct!
4. 1 and 3

We suspected the patient's attacks represented acute degranulation events associated with systemic mastocytosis (SM). Systemic mastocytosis, as the name implies, occurs when dysregulated proliferation of mast cells leads to systemic symptoms. Our patient had urticaria pigmentosa which is characterized by red or brown papules that represent aggregates of mast cells in the skin. The mast cells, when irritated (e.g. by rubbing the skin, heat exposure), degranulate releasing histamine, leukotrienes, and other mediators, triggering an urticarial skin reaction sometimes referred to as Darier's sign. In Figure 1 note the erythematous wheals on upper abdomen elicited by stroking skin. Derriere is French for buttocks.

Which of the following would ***support*** a diagnosis of systemic mastocytosis?

1. An elevated tryptase level
2. Increased mast cells in the bone marrow and/or skin
3. Increased expression of CD25 on the mast cells
4. The D816/KIT mutation of the stem cell factor receptor
5. All of the above

Correct!
5. All of the above

The abundance of mast cells producing histamine, tryptase and a variety of other substances lead to the symptoms of SM. The symptoms are similar to anaphylaxis since the pathophysiology is similar. However, in contrast to anaphylaxis, tryptase levels remain elevated after resolution of the acute event. Our patient's tryptase level after his recovery was > 200 ng/mL (normal 1-10 ng/mL). CD25 is a portion of an interleukin-2 receptor expressed on the surface of mast cells in the bone marrow of patients with SM. This interleukin-2 receptor is involved in inflammatory or cell-mediated immune responses and not seen on resting mast cells. D816V/KIT is a mutation of the stem cell receptor CD117 commonly associated with SM and its presence leads to overstimulation of the receptor resulting in overgrowth of mast cells. A reference laboratory later confirmed the presence of D816V/KIT mutation in our patient.

The patient had previously had a skin biopsy which showed an abundance of mast cells consistent with SM. A bone marrow biopsy was performed which demonstrated multiple large aggregates of spindle-shaped mast cells that were CD25+ consistent with the diagnosis of systemic mastocytosis (Figure 2).

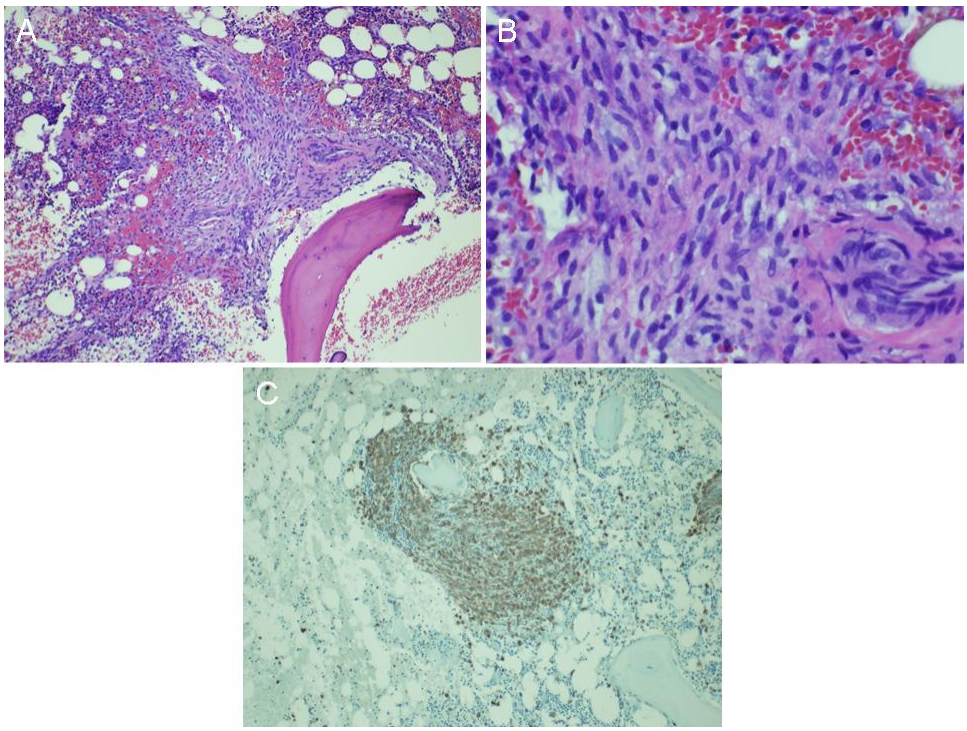

Figure 2. Bone marrow biopsy showing a low power view (Panel A) and a high power view (Panel B) of the typical spindle-shaped mast cells in the bone marrow. The cells were CD25 + on monoclonal antibody peroxidase staining (Panel C).

Which of the following are used for ***treatment of SM***?

1. Epinephrine
2. Antihistamines
3. H2 blockers
4. Mast cell stabilizers
5. All of the above

Correct!
5. All of the above

The treatment is similar to treating anaphylaxis. He had been given epinephrine earlier at his referring hospital. He was given famotidine, montelukast, cromolyn, and a short course of corticosteroids. His clinical condition rapidly improved over 48 hours, including the severe coagulopathy.

Systemic mastocytosis may present with urticarial pigmentosa, or with symptoms related to organ infiltration by mast cells (e.g. hepatosplenomegaly), but it is most likely to present in the ICU with a syndrome caused by acute mast cell degranulation. These events are closely related to anaphylaxis, but may occur without cross-binding IgA by an allergan. Degranulation of mast cells releasing histamine, leukotrienes, prostaglandins, cytokines cause an inflammatory cascade that results in increased vascular permeability, vasodilatation, and bronchospasm. Clinically, the patients suffer an acute onset of flushing, pruritis, urticaria, angioedema, syncope, hypotension, abdominal pain, nausea, vomiting, and diarrhea. Degranulation events can be precipitated by a wide range of triggers that include medications (narcotics, vancomycin, radiocontrast media, etc.), surgical procedures, alcohol ingestion, hymenoptera envenomation, and even ingestion of spicy foods and emotional turmoil. Heparin and platelet-activating factor can also be released, and in rare cases have caused severe coagulopathy resulting in life-threatening bleeding.

The intensivist should consider the possibility of systemic mastocystosis in any patient presenting with an acute anaphylactic-like syndrome. The history of recurrent anaphylactic episodes in a patient with urticaria pigmentosa - such as in this case - is highly suggestive of systemic mastocytosis. Urticaria pigmentosa is not likely to be readily recognized by a non-dermatologist, but Darier's sign (the rapid development of localized wheal when the skin is stroked) can be suggestive.

Confirmation of the diagnosis of SM typically requires bone marrow biopsy. Most patients will benefit from chronic inhibition of mediator release (which can otherwise cause osteopenia) with H1 and H2 histamine blockers, and leukotriene antagonists. Triggering events should be elucidated if possible and avoided. Patients should consider the diagnosis as a most important part of their medical history, since preparation with corticosteroids and mediator-release antagonists can prevent potentially fatal degranulation events that can be triggered by medical procedures – particularly surgery. Patients with SM should be referred to an expert in this disease for ongoing care.

References

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