January 6, 2011

This monograph began as a review for the journal EPlasty. The paper submitted for review was of a woman who had wound and necrosis complications following breast reconstruction. Post-mastectomy reconstruction was done with bilateral TRAM flaps which were themselves intrinsically healthy and trouble free. The reconstruction and eventual results were excellent, but the case was complicated in the post-operative period by multiple infarcts and wound dehiscence around the flaps and on the abdomen. The patient had had a trauma splenectomy 12 years prior. She had no overt sequelae of that, and her platelet count before the breast reconstruction was 350K. After surgery, as the skin and wound infarcts progressed, her platelet count rose and topped out at 1690K. The wound complications were attributed to "post-splenectomy thrombocytosis". While that might have been true, it was naive to assume that and pursue no other workup nor diagnosis, nor to try to manage and limit the infarcts. This monograph was an invited commentary that is pending publication as a separate paper. It is post here at Arimedica.com to accompany lectures and presentations based on this material.

Marc E. Gottlieb, MD, FACS
January 6, 2011

Commentary:

This is a case study of unexpected soft tissue infarction and ulceration following elective surgery. At face value, it illustrates how post-splenectomy secondary thrombocytosis might complicate surgery or trauma. Nominal thrombocytosis is defined by platelet counts over 400,000 or 600,000 or 1,000,000 (depending on type of problem, specific nomenclatures, and other circumstances). Thrombocytosis has two general categories, primary and secondary. Primary or essential thrombocytosis is one of the myeloproliferative disorders (along with chronic myelogenous leukemia, polycythemia vera, and myelofibrosis). It occurs due to pathological deregulation of platelet production. Secondary thrombocytosis is a reactive elevation of platelets due to some other primary pathology, the common causes being trauma and surgery, infection and inflammatory states, and cancer and various other diseases. Post-splenectomy thrombocytosis is common, with an incidence of transient, persistent, or incidental thrombocytosis as high as 80%. Thrombosis in conjunction with thrombocytosis is a well recognized phenomenon, but the incidence is not high. Thrombotic and embolic complications of post-splenectomy thrombocytosis are only about 5%. Even in myeloproliferative primary thrombocytosis, the disease is generally benign (with treatment), and the incidence of thrombosis or embolism is only about 10-15%. Platelet elevations also imply a spectrum of possible intrinsic and extrinsic types of platelet dysfunction, and hemorrhagic complications also have a small incidence.

While post-splenectomy thrombocytosis and thrombosis are basic textbook knowledge, a complication such as presented is unexpected. Given the statistics just mentioned, it is understandable that adverse risks and events might be underappreciated by a surgeon until it is "too late", after an event is initiated or minor damage progresses to major damage. That is especially true in this case, where pre-operative platelet counts were normal. However, “major damage” is avoidable, and some knowledge of these disorders can help avert or minimize thrombotic complications and sequelae. When unexpected wound and soft tissue necrosis occur after trauma and surgery, it is generally due to some well defined circumstances and pathologies. Understanding these predisposing conditions and risks starts with understanding the concept of pathergy.

“Pathergy” has the general meaning of an abnormal or exaggerated response to an injury or challenge. The term appeared in the early 20th century to describe rapid responses to allergens. In the 1930's, Behçet, in describing his eponymic syndrome, extended the concept to include an intense inflammatory and ulcerative response to minor trauma. It has since taken on a yet broader meaning, signifying any unexpected or disproportionate adverse response of wound or periwound to accident, disease, or deliberate injury (debridement and surgery). The injury-induced necrosis of pyoderma gangrenosum is a paradigm. In modern parlance, “pathergy” is synonymous with “unexpected acute wound failure”. It is a tokenized way to describe progressive inflammation, infarction, necrosis, tissue lysis, wound bursitis, dehiscence, and other undesirable wound complications that are not due to obvious causes such as infection, macrovascular ischemia, or excess mechanical load, especially if the problems are unanticipated, exaggerated, or a consequence of treatment or of injury-triggered flare-up of an underlying disease.

Wound pathergy is most prone to occur with any disorder that causes severe ischemia or severe inflammation. This includes (1) athero- and other macro-occlusive arterial diseases, traumatic devascularization, and other conditions of gross hypoperfusion or flow stasis (including “bad flaps”), (2) hypercoagulable, microthrombotic, formed-element hematopathologies, dysproteinemias, and other micro-occlusive disorders, and (3) autoimmune vasculitis and angiopathies, and the various active immunopathies, including connective tissue disorders, panniculopathies, inflammatory dermatoses, and any similar disease of immunity and inflammation. In these disorders, every surgical procedure, from simple debridements and biopsies, even just needle sticks (Behçet's "pathergy test"), through any major trauma, incision, and wound closure, is at risk for necrosis, lysis, dehiscence, and ulceration. The pathogenetic pathways to wound failure are mediated in many ways, including acute neutrophilic inflammation, complement and lymphocyte activation, abnormal cytokine profiles, protease activation, platelet-mediated thrombosis, and coagulation-mediated thrombosis, to name a few of these pathologies that are best understood. In sick hosts or wounds, these events lead to ischemic infarction, inflammatory tissue lysis, or both, i.e. necrosis and ulceration. It is crucial to understand the triad of injury-thrombosis-inflammation. This is the mutually interdependent non-linear controlled response to tissue damage that, while necessary to contain the damage and prepare for repair, is nonetheless inherently destructive. Robustly healthy wounds and hosts weather injury-thrombosis-inflammation as the acute events wax then wane. Sick wounds and hosts do not have sufficient degrees of freedom to accommodate the secondary injury created by this triad, and when the system is unbalanced, then secondary injury, i.e. necrosis and ulceration, can become quite significant.

One crucial point to understand is that this is a case of pathological wound complication, not just simple trauma, devascularization, and bad "flapology". What undoubtedly tweaked the attention of the authors is that the TRAM flaps themselves had no intrinsic complications. In looking at the photographs, we can see that they were inherently "good flaps", an otherwise beautiful reconstruction, around which the wounds and the donor site had all the problems. Pathological wounds are due to an underlying disease. Treating the disease and managing the wounds and necrosis depend on proper accurate diagnosis. What makes this case interesting is in understanding how to parse the pathophysiology of the events and make the correct diagnosis in support of proper treatment. In this case, the thrombocytosis may or may not have been the primary or only culprit that caused the necrosis. In analyzing this type of case, there are a few concepts about platelet function worth remembering:

- Platelets are not just dust and debris, but rather active elements with complex metabolic functions programmed to respond to acute events. Not only do platelets adhere and aggregate, but they trigger thrombosis, trigger inflammation, have various effects on vessels

themselves, and even have an important role in initiating wound repair. Their function is highly connected to various proteins which likewise have multimodal roles. These interactions can become complex to the point of confusion and incongruity. Consider: (1) von Willebrand disease, in which hypocoagulable-hemorrhagic events are due to a factor deficiency which affects both platelets and clotting proteins; (2) heparin induced thrombocytopenia (HIT) in which severe thromboembolism is concurrent with low platelets; (3) myelofibrosis, in which low platelet counts can be accompanied by both hyper- and hypocoagulable states. And remember, thrombosis, pathergy, infarcts, and ulceration also result from any number of other non-platelet-related states due to inflammatory, hematological, vascular, and metabolic pathologies. It is incorrect to think simplistically about thrombocytosis as a passive "log jam" of too many platelets and particulate sludge damming the small vessels.

- Platelets are not always “on” and active. They exist as a reserve in “standby” mode, awaiting an undesirable event. Normal healthy platelets require a trigger to do their business. Even if platelet counts are high, random adhesion-aggregation-thrombosis is unlikely, explaining the low thrombosis statistics mentioned above. However, this is true only during baseline "healthy" status, absent potent triggers such as trauma or inflammation. Nominal thrombocytosis may seem completely benign during non-morbid periods, but once a trigger occurs, acute platelet events are accelerated or amplified. Thus, abnormal high platelet counts become much more relevant during morbid states or when normal triggers occur (inflammation, trauma, surgery), even in patients who might have had benign thrombocytosis without incident for a long time.

- Thrombosis is not linearly related to platelet count. Thrombotic risk obviously has some general relationship with platelet load, but the physiology is so complex that a one-to-one graph of platelet counts versus secondary events cannot be made. Because platelets are not “on”, but on “standby”, face value numbers are irrelevant until a trigger occurs. Once a trigger does occur, acute platelet activation is a strongly non-linear self-amplifying process that rapidly begets more platelet thrombus and protein thrombus. (As those who have done any microvascular surgery can likely all attest, "white thrombus" due to abnormal platelet aggregation occurs unexpectedly, generally in patients with normal platelet counts, and once it starts, it is difficult to control.) An a priori high platelet count can unbalance this controlled system in ways which make the amplified response more rapid or exaggerated once a trigger occurs. Interestingly, it is also possible that high platelet counts per se can lower their own trigger threshold (increase sensitivity) via the concept of "quorum sensing". This dynamic, validated for situations such as infection and inflammation, most likely applies as a means by which platelets might "count" their own numbers, becoming overly aggressive or sensitive to triggers that initiate their aggregation or to conditions of stasis and accumulation.

- Surgery and trauma are immediate and complex platelet triggers. Remember, surgery and trauma not only trigger platelet activity, they also upregulate platelet production and release from the bone marrow (in principle to balance the consumption of circulating platelets). This complex integrated system also releases formed blood elements from reservoir or capacitance areas within the circulation, and it activates protein thrombosis (clotting). Thrombocytosis and thrombosis are not simply built into these events, they are the primary intent of these events, as long as they stay within numerical bounds and confined to the area of injury. But this is a complex non-linear multi-control self-amplifying process which can leach into the general circulation and trigger thrombosis in remote areas. Healthy patients with “healthy protoplasm” keep it all in proper balance, but in extreme circumstances or in a priori unhealthy patients, keeping these events regulated and confined within physiological limits is less certain.

Thrombocytosis raises risk in principle, but the likelihood of morbidity and complications can not be accurately based on platelet counts alone, especially with platelet counts less than 1 million. In the case presented, thrombocytosis could in fact have been a coincidence to the events, or else just one link in a chain of interrelated pre-conditions. However, even in someone who has had thrombocytosis without incident for a long time, a prior benign history is no guarantee of safety, and when the right trigger hits and the system cascades, the response can be dramatic. That is why a patient with thrombocytosis or the first signs of a related complication needs timely evaluation and treatment, to minimize subsequent damage.

So, what else could this case represent? What should be done the next time a surgeon encounters a situation of thrombocytosis, thrombosis, and infarction, either pre-operatively or after the wound pathergy and complications have occurred? Relevant items to be considered in evaluating such a patient or situation are (1) platelet count per se, (2) the cause of the thrombocytosis and associated pathologies, (3) presence or absence of triggers and acute disease, (4) intrinsic disorders of platelet dysfunction, and (5) the possibility of an unrelated or coincidental pro-thrombotic or micro-occlusive disorder. How is the differential diagnosis evaluated in such patients? In order of the five items just enumerated, here are issues to consider:

(1) Simple thrombocytosis: Remember the importance of the injury-thrombosis-inflammation triad. Surgery, which causes these events, or the vascular stasis that occurs at the margins of a new flap could ipso facto by themselves have caused the problems presented in this case. Such complications happen now and then to seemingly normal people and wounds (or are they really normal?), so in a patient with an otherwise benign thrombocytosis, there could certainly be an exaggerated response to these normal triggers. So yes, it is true, that this case could have been nothing more than one among that 5% of patients who gets thrombotic complications of post-splenectomy thrombocytosis, occurring in response to an appropriate physiological trigger (injury) or to the conditions of low flow and stasis that are inherent to fresh flaps. However, this possibility does not relieve the doctor from adequately evaluating the situation and making a discriminating diagnosis. And even if it is just simple benign thrombocytosis, the higher the platelet count, the more relevant it is to preemptively treat before surgery, especially when counts exceed the 1,000,000 level.

(2) Myeloproliferative disorder: In the case presented, the assumption is made that the thrombocytosis reflects benign hyposplenism, but it could have been an early or forme fruste myeloproliferative disorder. All of the myeloproliferative disorders, in fact any of the disorders of the formed elements of the blood are associated with the risk of wound pathergy and infarction, and also chronic skin ulceration (sickle cell ulcers are a paradigm that most physicians are probably aware of). Like any other disease, the myeloproliferative disorders have a gradient of severity. At one end, chronic essential thrombocytosis can be marginally certain if platelet counts hover around 600,000, and at the other end, the disease can progress to myelofibrosis or chronic myelogenous leukemia. In less severe forms, where platelets and megakaryocytes remain responsive to normal controls, normal triggers for reactive thrombocytosis can have an exaggerated response. Attributing transient thrombocytosis to impaired splenic clearance may miss an underlying disorder of greater significance.

(3) Concurrent acute illness and triggers: To reiterate, surgery and flow stasis initiate injury-thrombosis-inflammation, and a priori thrombocytosis could augment this in principle. Nonetheless, in patients with thrombocytosis, post-operative wound pathergy is the exception rather than the rule, so concurrent active illnesses, acting as sensitizers, must be considered. This includes: any acute inflammatory or thrombotic state due to pathogens, allergens and immunogens, or trauma; metabolic imbalances due to renal, hepatic, and endocrine disorders, or due to drug effects; hemo-pathological states due to blood, bone marrow, and reticuloendothelial disorders or due to cancer. It is worth mentioning Trousseau's syndrome, thrombotic complications associated with cancer. This tends to occur in late invasive or metastatic disease, and does not apply to the case presented (Stage IIa). Skin infarcts, chronic ulcers, wound pathergy, and thrombotic complications of surgery are very real issues in this syndrome, and sadly, recent onset leg ulcers or skin pathergy and necrosis after minor trauma can be the presenting symptom of late stage metastatic colon or pancreatic or other cancers.

(4) Intrinsic disorders of platelet function: As discussed above, high counts of otherwise normal platelets might or might not by themselves carry thrombotic risk. Intrinsic dysfunction of platelets also occurs, but the majority of disorders and syndromes that are commonly appreciated are those that cause hemorrhage (e.g., von Willebrand, hemophilia, Glanzmann, drug effects). Many nominally thrombopenic-hypoactive-hemorrhagic platelet deficiencies also have some thrombotic risk. However, in comparison to the hemorrhagic problems, the basic science and clinical knowledge of platelet hyperactivity syndromes is wanting. Either such diseases are few and infrequent, or we have yet to learn to recognize most of them. One such well defined condition, the "sticky platelet syndrome", is debated as to whether it is a distinct genomic or metabolic entity, versus a dynamical expression of weak platelet alterations coupled to acute triggers. Even absent robust knowledge or strict nomenclature, platelet functions and over-activity can be assessed in the laboratory. "Aggregation studies" depend on triggering platelet activation with chemical triggers such as epinephrine, ADP, or collagen, thereby mimicking normal in vivo events. Obviously, demonstrable alterations of function are more significant than a simple diagnostic moniker.

(5) Concurrent primary pro-thrombotic or micro-occlusive disorder: The acute illnesses mentioned above have a counterpart in chronic, oftentimes occult illnesses which create heightened inflammation and thrombotic risk. These are the hidden bogeymen of wound pathergy, lying in wait for unsuspecting trauma, surgery, and surgeons to unmask their nefarious effects. Most of them are either vascular and hematological, or else immune and inflammatory. They will all trigger the injury-thrombosis-inflammation triad unexpectedly or to excess, leading to tissue infarction (the vascular and micro-occlusive components) or tissue lysis and ulceration (the immune and inflammatory components). They include:

- Endovasculopathies: These are intrinsic and luminal vasculopathies in which blood vessels are abnormal. (Blood is normal, and coagulation is intrinsically normal, thrombosis occurring in response to blood stasis or thrombotic activation.) Atherosclerosis is the dominant pathology, but thromboangiitis and the arteritides may be included, and so too metabolic vasculopathies such as calciphylaxis-hyperparathyroidism. The effects of atherosclerosis to cause pathergy and undermine an otherwise good operation must be appreciated. All surgeons are familiar with the caveats of working on the ischemic leg. The same problems can happen around the pelvis and lower abdomen in patients with aorto-iliac occlusive disease, especially if they have clinical Leriche syndrome, and abdominal flaps and wounds gone bad can and do occur in certain atherosclerotic patients. The chance of complications is further heightened by a concurrent pro-thrombotic hemopathology, like the presence of thrombocytosis.

- Exovasculopathies: These are extrinsic and mural vasculopathies in which blood vessels likewise are abnormal, and blood and coagulation remain intrinsically normal. Unlike the endovasculopathies in which platelets are triggered by thrombogenic surfaces and flow turbulence or stasis, the exovasculopathies tend to be inflammatory or immune in origin, with inflammatory mediators also triggering thrombosis in passing blood. These disorders include the classic arteritides (polyarteritis nodosa, thromboangiitis obliterans, etc.), venous vasculitis, the classic connective tissue disorders, and other immunopathies. Acute neutrophilic leukocytoclastic vasculitis and polyarteritis nodosa are the must aggressive of these pathologies, but many chronic ulcers associated with these conditions will also have a chronic peri-arteritis. Spontaneous and trauma-induced infarcts and ulcers are common complications, and chronic and acute thrombosis are common findings in the debrided material.

- Non-hypercoagulable hemopathologies: These are various micro-occlusive disorders in which vessels are normal and the plasma protein coagulation system is intrinsically normal, but other elements of the blood are abnormal. The clotting system responds "correctly" to abnormal conditions of stasis or thrombotic activation. These include: (1) the hemoglobinopathies (e.g., sickle cell disease, thalassemias, other hemolytic anemias); (2) dys- and cryoproteinemias (e.g., cryoglobulinemia, cryfibrinogenemia,

macroglobulinemia, gammopathies & myeloma); (3) red cell & platelet abnormalities (e.g., hereditary spherocytosis, thrombotic thrombocytopenic purpura, myeloproliferative disorders, polycythemia rubra vera, leukemias). Thrombocytosis and platelet pathologies might be seen as straddling this category and the hypercoagulable states.

- Hypercoagulable hemopathologies: These are disorders in which vessels are normal and blood is normal (formed elements and serum), but the plasma based clotting system is abnormal. Abnormal inappropriate thrombosis is the primary event, and blood stasis and vascular occlusion are consequences. The hypercoagulable disorders can be intrinsic (the "pre-thrombotic" primary disorders of the coagulation system) or extrinsic due to metabolic or auto-immune alterations. Common intrinsic causes are gene mutations (e.g., factor 5 Leiden, prothrombin 20210G), coagulation protein alterations (e.g., proteins C & S, anti-thrombin-3, plasminogen, fibrinogen), and various other pathologies with a tie-in to the formation and metabolism of these factors (e.g. liver disease, estrogens and pregnancy, paroxysmal nocturnal hemoglobinuria, dicoumarol-derivative complications). The extrinsic causes include miscellaneous metabolic and pathological states (e.g. homocysteinemia and cancer-Trousseau), but they are dominated by the antiphospholipid antibody syndromes and other immune thrombogens and auto-immune states. Virtually all of the classic connective tissue or collagen-vascular diseases have a high incidence of hypercoagulopathy, and vice versa.

The auto-immune states and connective tissue disorders deserve special emphasis. Not only are they very strongly correlated with hypercoagulable states, but between the immune-inflammatory and thrombo-infarctive components of this duality, these disorders are one of the most significant causes of chronic ulceration and impaired wound healing, and one of the most under-appreciated causes of wound pathergy and surgical complications, much more so than any of the thrombocytoses. In evaluating any patient who has had a major complication of wound pathergy, it is essential to evaluate for connective tissue and hematological disorders. The following tetrad is virtually pathognomonic of pre-thrombotic hypercoagulable states: a personal or family history of (1) major thrombosis or embolism, (2) miscarriage, (3) chronic ulcers or wound pathergy, (4) an immune or connective tissue disorder. High risk autoimmune disorders include not only the full spectrum of the classic rheumatological or collagen-vascular diseases, but also the inflammatory dermatoses and panniculopathies (e.g., pyoderma gangrenosum, Weber-Christian, eosinophilic fasciitis, pemphigus), inflammatory bowel and hepato-biliary disease, immune pneumonitis and nephritis, multiple sclerosis and immune neuropathies, and various induced or toxic states (e.g. drug-induced lupus). Behçet's syndrome deserves mention again because, amongst the connective tissue disorders, not only is it one of the riskier diagnoses for hypercoagulability, pathergy, and wound morbidity, but it has a certain incidence of significant platelet elevations. Taking a perfunctory history related to these disorders can rapidly and reliably indicate a strong suspicion for something beyond a simple thrombocytosis.

Any patient who has had the complications described in this report warrants a thoughtful evaluation for all of these potential associated or underlying diagnoses. The majority of items can be ruled out by basic history and physical examination, and in fact many of these diagnoses can be made on positive criteria by history and physical alone. For confirmation, or to clarify the items that remain on a differential, laboratory evaluation usually resolves the diagnosis easily enough. Standard screens or panels for hematological, auto-immune, and coagulopathic disorders are important. If platelet problems are suspect, then platelet function assays are needed, i.e. platelet aggregometry. Even a simple bleeding time test can be very useful. Microvascular measures, such as transcutaneous pO_2, laser doppler, or multi-spectral reflectance imaging can confirm the presence of micro-occlusive states. Histology is of particular value in cases of trauma- or surgery-induced wound pathergy, revealing thrombosis, inflammatory profiles, vasculitis or vascular necrosis, immune complex fixation, and other relevant pathological alterations. Biopsies can come from the debrided infarcts, from the ulcers, from nearby skin and fascias, from other suspect tissues, and ultimately from the bone marrow for cases of thrombocytosis.

The spectrum of therapies needed for a case like the one presented are twofold: first, those relevant to the causes of the stasis and infarction, and second, those relevant to protecting and promoting survival of the affected tissues. Remember though that these events have a highly interconnected physiology. If platelet problems are the primary diagnosis, then controlling platelets means not just interfering with their own intrinsic function, but also blocking the secondary events that they initiate, such as plasma coagulation and inflammation. The physician's toolbox for these events includes: (1) antiplatelet therapies, including short acting inhibitors (aspirin, clopidogrel), long term suppressants (hydroxyurea, anagrilide), and immediate platelet clearing modalities (plasmapheresis); (2) anticoagulant therapies, including heparin (raw heparins and low molecular weight variants), dicoumarol derivatives (warfarin being the only one in modern use), and factor-specific inhibitors (fondaparinux, argatroban); (3) blood rheology therapies, including rheological drugs (lmw dextran, pentoxifylline) and viscosity lowering modalities (phlebotomy to reduce red cell mass, and plasmapheresis to remove proteins); (4) anti-inflammatory drugs, including non-steroidals (nsaid's) and high potency steroids (prednisone, methylprednisolone); (5) circulation restoring therapies, relevant to certain circumstances, including thrombolysis, procedural revascularization, and vasodilators and other vasoactive pharmaceuticals (sympatholytic and other autonomic agents, nitrates, prostanoids, calcium channel blockers, and numerous others); (6) tissue survival therapies, including hyperbaric oxygen to support basic tissue survival and metabolism in highly ischemic areas, and pharmaceuticals to protect against reperfusion injury (many putative agents, including mannitol, allopurinol, tocopherols and other anti-oxidants . . . and a long list of current interest drugs); (7) if there are wounds or if surgery has already or must been done, then proper topical care (hygiene plus silver or sulfa based topicals or permissible alternatives), and wound closure or protection with non-autogenous skin substitutes (alloplastic, semibiological, cadaveric, living). This is not an exhaustive list of treatment agents, and many pharmaceutical classes represented by the examples given have a variety of similar drugs from competing manufacturers. Plasmapheresis and hyperbaric oxygen might not be available in all

communities, but otherwise most of these items are easily prescribed and readily available. As a means to rapidly reduce platelet counts (along with hematocrit and blood viscosity if needed), the crucial role of plasmapheresis must be emphasized.

In wound pathergy cases there are also forbidden activities, mainly more surgery. Without proper preparation, more surgery means more thrombosis and inflammation, augmenting the adverse events already taking place. Most surgery is done with the implicit and naive faith that the incisions will heal. This is true the great majority of times, but when wound and soft tissue pathologies are present, the simple rules of "cut-and-sew" are invalidated. Further discussions about platelet and pathergy therapeutics might be best appreciated via a case example, specifically, a critique of certain items in the case presented:

- "On post-op day 18, the patient underwent operative debridement of her abdominal and chest wounds with primary closure of the breast wounds . . . over the next several weeks, the wounds deteriorated again . . ." The significance of wound and soft tissue pathergy cannot be overstated, especially when due to hematological, immune, and related micro-occlusive disorders. Dermatology residents are taught early never to let a surgeon see a case of pyoderma gangrenosum, and for good reason. Indiscriminate surgery will simply trigger more of the same events. "Forewarned is forearmed." "Fool me once, shame on you; fool me twice, shame on me." Such aphorisms are most apropos. This patient's wounds could have and should have been managed by basic wound hygiene, simple debridement of separating eschar, and judicious use of appropriate topical therapies, i.e. what she ultimately had, without the intermediate, irrelevant, ineffective return trip to the operating room. Re-operation is not categorically forbidden, but it cannot happen without proper preparation and peri-operative care. Anti-platelet drugs would have been appropriate (but carry bleeding risk for re-operation). Anti-coagulants would have been of value. Pre-operative knockdown of platelet counts by hydroxyurea or anagrilide would have been slow but reasonable and safe (good preparation for elective surgery, except for potential wound healing deficits due to hydroxyurea). The simplest, safest, fastest, and most effective means of pre-operative preparation, especially for urgent indications, would have been simple plasmapheresis, augmented with reasonable doses of aspirin and heparin or argatroban. That is the main point of this review, to recognize risks and pre-empt those risks by proper planning and treatment before the next operation.

- "Over the next 2 weeks, both the mastectomy and abdominal skin flaps underwent progressive necrosis as the platelet count rose to 1390 thou/cm . . . and aspirin therapy was instituted." Nowhere else in this report is any mention made of any workup or therapy for the thrombocytosis other than aspirin. Aspirin is indeed effective prophylaxis against platelet adhesion-aggregation-degranulation. Had the patient had nothing more than an incidental thrombocytosis without problems, then aspirin would have sufficed as good prophylaxis against platelet complications. But this patient had a significant complication for which repeat trouble can be expected. Aspirin was appropriate, but formal workup as detailed above should have been done, and other therapies initiated. Clopidogrel or ticlopidine could have been used for a more potent anti-platelet effect (subject to discussions of safety in the peri-operative period, but a trial could be justified based on the significance of the situation). And platelets per se are not the whole story. They directly trigger plasma coagulation, and then flow stasis results in further thrombosis elsewhere in the affected tissues, so anti-coagulation should have been started as well. The quintessentially important relationship between platelets, thrombosis, and inflammation must be kept in mind, and steroids would have been a good adjunct therapy. Hyperbaric oxygen would have been a potentially valuable therapy to try to minimize necrosis in the ischemic flaps and wounds, and various anti-oxidant and rheological pharmaceuticals could have been initiated in anticipation of physiological revascularization and reperfusion. Again, the utility of plasmapheresis for acute control of platelet counts (and viscosity and hematocrit) must be emphasized. (Hematocrit also deserves special mention. The normal "healthy" hematocrit is a baseline capacitance which serves as a life-saving hedge against injury and hemorrhage. For all of the many reasons already discussed, blood functions best during morbid conditions when hematocrits and blood viscosity are lower than "normal". This concept has been validated by encyclopedic amounts of surgical research done throughout the latter 20th century, including various studies of flap survival. Depending on the model used, "optimum hematocrit", where tissue oxygen delivery and consumption are maximized and cardiac work is minimized, is in the range of 20 - 35. Plasmapheresis is the handy one-stop shop for all of your viscosity reducing needs.) In other words, all of the strategies and methods ordinarily used to control platelets and to try to salvage critically ischemic tissues should have been considered, rather than passively capitulating to the disease.

- "Once both thrombocytosis and platelet activation occur, antiplatelet activation drugs are recommended [quote from a referenced article] . . . Should this patient ever require surgery in the future, a platelet activation profile study might be a valuable tool to assess the potential need for aggressive platelet therapy." No, the patient needs that evaluation and treatment planning now. This is precisely the type of morbid event, with life-and-limb threat, that mandates pre-emptive evaluation, diagnosis, and treatment planning, first to rule out a more significant underlying problem, and then, regardless of the specific diagnosis, to be prepared so that similar events can be prevented the next time the patient has surgery or trauma.

The majority of patients with thrombocytosis will not have thrombo-infarctive complications, and most will not need active treatment. With a benign history, prophylaxis is not mandatory, and the need for preventive or preparatory treatments must be evaluated individually for each patient. However, once an adverse event occurs, the rules change. The point of this review is that one cannot lightly assume that the problems here were due to simple secondary thrombocytosis. Assumptions of diagnosis are never correct, to the extent that current knowledge, art, and technologies permit an exacting diagnosis. Post-splenectomy thrombocytosis, while a real entity, is a diagnosis of exclusion – you cannot be explicitly certain that that is all it is until you have confirmed that it is not something else. Furthermore, correct diagnosis is only the first step in treatment planning so that immediate problems can be mitigated and future morbidity can be prevented. Even if this was simple reactive thrombocytosis, and other diagnoses had been ruled out, nonetheless this event was not "benign" for this patient, and passive non-peremptory management cannot be justified. In the

broad scope of medical practice, some patients are healthy or recovered and need no care. Other patients are actively or chronically sick and need ongoing care. And then other people have latent problems which become manifest only during certain circumstances, and these patients need a reserve plan of care to be implemented at those special times. That is the case for a patient with nominally "benign" thrombocytosis, especially one who has proven once already that this state is associated with latent major morbidity or complication.

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June 6, 2009

ILLUSTRATIONS

The following is a set of case studies meant to illuminate these points. This sampler was selected based on two simple criteria: the cases illustrate the points to be made about micro-occlusive disorders and wound pathergy, and I had sufficient photographs of them to illustrate those points. These are just a few among many with similar problems in a busy clinic dedicated to wounds and soft tissue pathology. The case mix has no other bias nor selection criteria, so it is notable (and probably statistically highly significant) for the number of deaths in this series. Deaths were due to the underlying diseases and their comorbidities. The disorders that cause vascular micro-occlusion carry severe risks beyond just wound pathergy. Post-splenectomy thrombocytosis is relatively benign, but when the rare complication occurs, it can be very serious for the affected patient.

As seen in these cases, it is a mistake to trivialize the significance of such events, and then to be complacent about the diagnosis so as to overlook something else of greater morbidity and risk. The important lessons are: (1) recognize and respect wound pathergy and cease any more surgery until the problem is worked up and treated; (2) respect and preemptively deal with baseline conditions of vascular, autoimmune, and hematological diseases and related complications.

Set 1: Ulcers due to thrombocytosis

Case #01. A case to illustrate the association of wound and soft tissue problems with thrombocytosis.
This 67 year old man had primary essential thrombocytosis. He was otherwise healthy, with a negative system review and risk profile for other thrombo-occlusive and ulcerogenic disorders. His platelet counts were maintained within normal ranges with hydroxyurea, but they would periodically rise and reach over 1 million, necessitating variable drug doses. Ulcers developed on the leg and ankle during an elevation of platelet counts above 800K. Basic topical wound care controlled gross inflammation and active ulceration, but a proliferative wound module failed to appear, even with platelet counts restored to normal, a failure attributed to the wound healing negative effect of hydroxyurea. Wound healing began after switching to anagrilide instead of hydroxyurea, and after starting wound stimulatory topical therapy with PDGF (platelet derived growth factor).

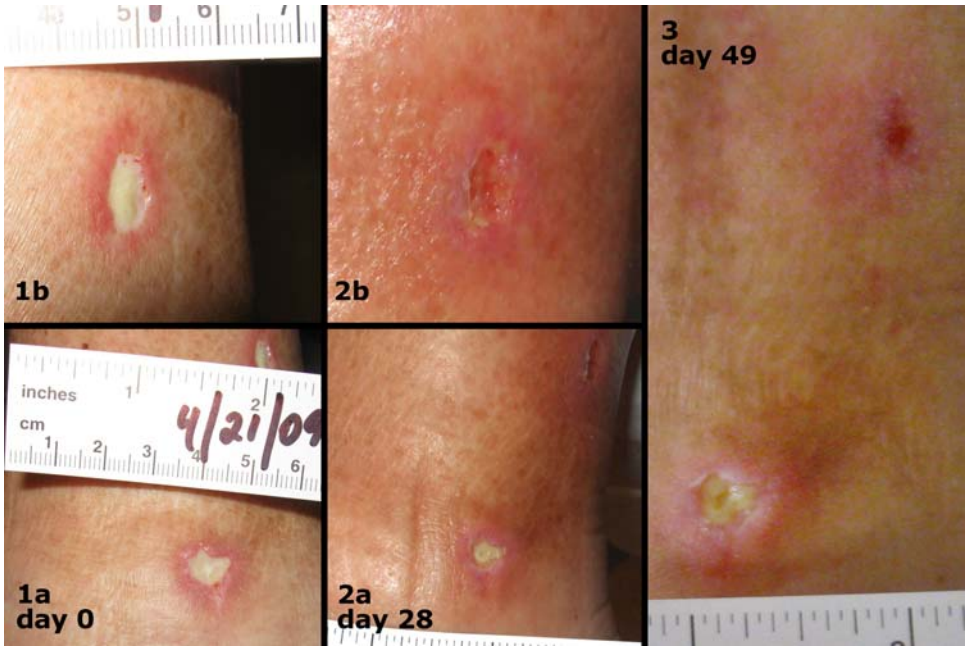
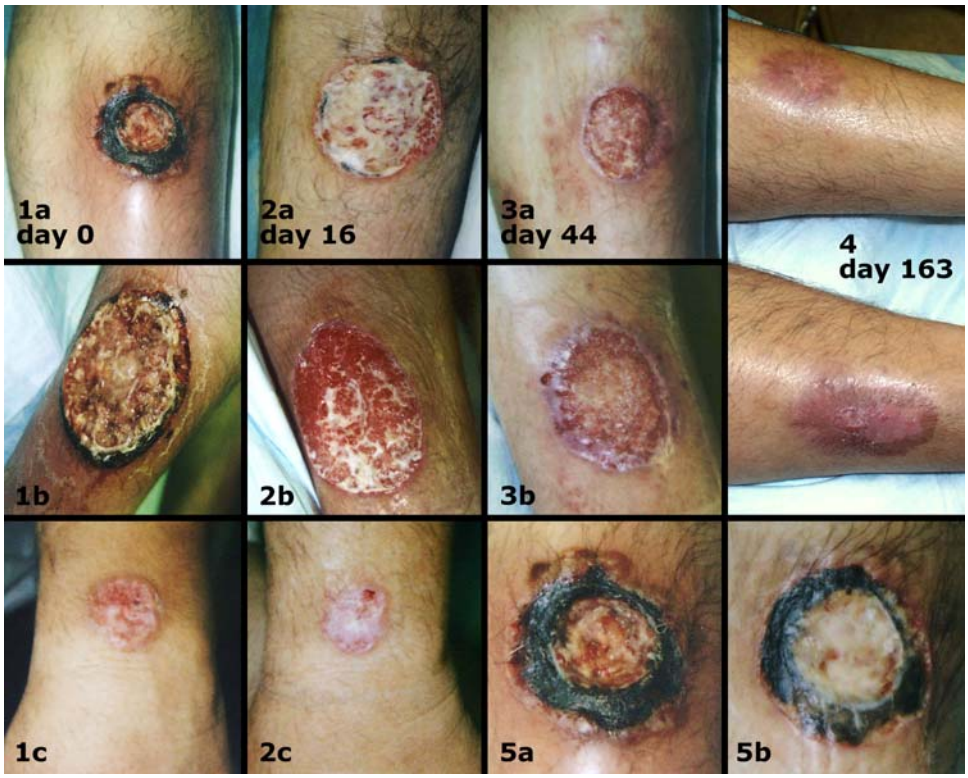


Figure 1a (day 0) shows two ulcers on the left lateral leg; the inferior one is over the malleolus; the superior one is shown closeup in **figure 1b**. They are shown a month after the thrombocythemic episode that caused them, after a month of hygienic wound care and stabilization of platelet counts. Inflammation and active ulceration have been controlled, but the ulcers remain wound healing incompetent. **Figures 2a, b** (day 28) are the same views one month later after the switch to anagrilide and PDGF (the two views are shown at the same scales as their counterparts in figure 1). The malleolar ulcer has contracted, and the upper ulcer has developed a complete wound module including epithelial ingrowth. **Figure 3** (day 49) shows that three weeks later the upper ulcer is nearly healed. Because the lower ulcer perforates into the malleolar bursa, it cannot close any more without other intervention, but it has remained stable and symptom free, along with platelet counts stable around 200K.

Set 2: Pathergy and pathological wound complications

Case #02. A case to illustrate the basic concept of wound pathergy.
This is a 45 year old man with recurrent and persistent multifocal ulcerations of leg, trunk, and upper extremity. The lesions have the typical stigmata of pyoderma gangrenosum, especially the involvement of skin per se, sparing the subcutaneous panniculus. Biopsy was also consistent, showing an intense neutrophilic infiltration. Acute disease was resolved with intralesional and oral steroids. The disease remained under control as the patient was transitioned off of steroids and onto sulfasalazine, and the wounds began normal proliferation. He was healed and stable 4 months after the start of proper treatment. The aforementioned biopsy was taken before consultation, "bare" without the protection of steroids, and the effects are seen in the photo as a ring of black eschar surrounding the initial debridement – paradigm wound pathergy.



Figures 1a, b, c (day 0) show lesions of left leg, right leg, and wrist at the time of consultation. Note the cutaneous eschar and preservation of viable adipose. **Figures 2a, b, c** (day 16) show the same lesions after initiating treatment. Disease has not progressed, eschar is now gone, and a wound module has appeared. **Figures 3a, b** (day 44) show the same leg lesions after several weeks. Wound healing, both contraction and epithelialization are active, and pathological changes are absent. **Figure 4** (day 163) shows the legs fully healed and maturing. In **figure 5a**, a close up of the original left leg lesion (day 0), note the edema and erythema around the wound, and the progressive necrosis at the superior margin, then note on **figure 5b** at 9 days, how these are resolved after starting treatment. Note too the ring of eschar on this lesion, progressive infarction after a smaller lesion had been excised or biopsied.

Case #03. A case to illustrate the risk and severity of wound pathergy.
This 80 year old man had recurrent skin infarcts for 5 years. These events, often accompanied by confusion and mental status changes, were usually heralded by an inflammatory or traumatic event, such as urinary infection, viral upper respiratory illness, and bruises or cuts. He had been treated with warfarin, with difficulty regulating the dosage. The terminal event, which followed a period of warfarin instability, began with the onset of mental status changes and new skin infarcts on the legs and feet, both more severe than usual. Large and central vessels were patent (including cerebral and coronary vessels). Head CT scan showed chronic cerebral atrophy with signs of prior vascular events. Acute oliguria and rise in creatinine also occurred, without overt cause. One of the leg lesions was excised for histology, promptly triggering extensive new periwound stasis and infarction. The histology confirmed acute and chronic thrombosis. Further workup revealed deficiencies of proteins C & S and antithrombin-3, with alterations of other thrombosis-related proteins. Total and gamma proteins were low, with high kappa and lambda light chains (the patient died before these results were available, thus urinary Bence-Jones proteins were not measured). The patient was started on heparin anticoagulation, and in spite of using a closely monitored and regulated protocol, he died from an event of acute back pain, hypotension, and anemia, presumed to be retroperitoneal hemorrhage. This case illustrates the complexity and multi-factorial risks of pathergy prone diagnoses: an a priori pre-thrombotic hypercoagulable state; thrombo-infarctive events associated with warfarin variations; known pathergy from trauma and inflammation; possible myeloma or light chain disease. This case also demonstrates that when the coagulation system and its many intricate physiological interconnects fall into a pathological attractor (i.e. become severely unbalanced), then hyper- and hypo-coagulable events can occur concurrently (see case #6).

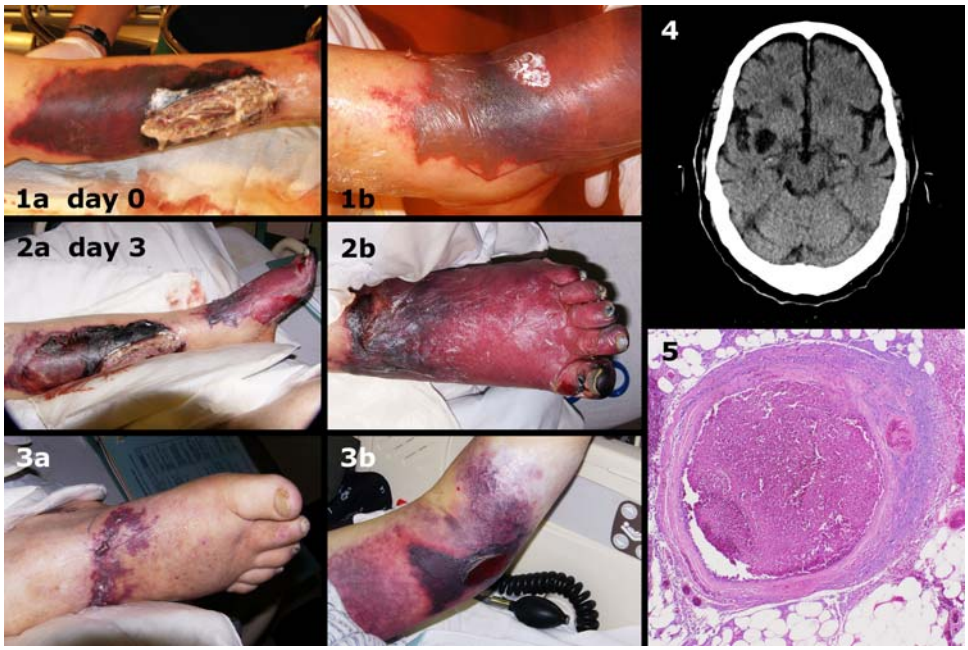
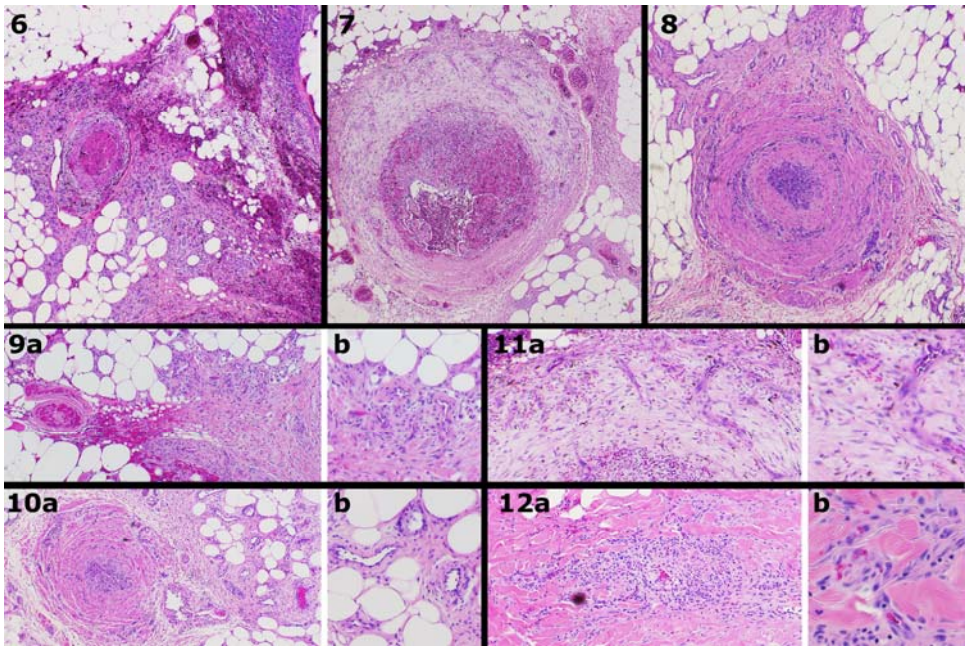


Figure 1a (day 0), the medial left leg shows the excision site of an initial smaller lesion. That excision triggered progressive infarcts with complete necrosis at the margins (the dark black areas), and a wider zone of vascular stasis (blistered areas) which might recover with treatment. Underlying muscles and neuromuscular function were normal. **Figure 1b** shows the ankle and dorsal foot with similar changes, mostly ischemic blisters. **Figures 2a, b** show the same lesions 3 days later, after therapy with anticoagulants, steroids, rheological agents, and hyperbaric oxygen. The leg lesion and toes have progressed to complete necrosis, but the foot is largely viable, anticipating a transmetatarsal amputation (but the patient died shortly after these images). **Figures 3a, b**, the right foot and left medial elbow show similar lesions with mixed patterns of progressive damage or recovery. **Figure 4** shows a defect in the basal ganglia, a consequence of prior vascular infarction. Compare these images to the complications of common atherosclerosis, carotid and ilio-femoral disease, in which total leg gangrene and hemispheric strokes are expected. In the coagulopathic disorders, dramatic acute events can also happen, but the problems tend to be smaller and multifocal, more insidious and chronic, damage often being prolonged and cumulative. **Figure 5**, from the excised specimen seen in figure 1a, shows acute thrombosis in a large subdermal vessel, including necrosis of the vessel itself. Histology revealed other features of this disease as seen in the addendum images below. They emphasize that insidious risks are the norm for many micro-occlusive disorders, a consequence of chronic recurrent subtle overlooked events. In cases of microthrombosis, wound pathergy, and other peculiar surgical complications, histologic examination of affected tissues often reveals the complexity of the problem, avoiding oversimplified nominal diagnoses such as “post-splenectomy thrombocytosis”. These and the other micrographs shown throughout this review are meant to emphasize that unanticipated surgical complications and pathological wound events are due to demonstrable anatomical disease. A surgeon ignores these diseases at the patient’s peril.



Addendum images: These additional histology pictures (also from the original excised leg specimen) show additional findings beyond just the thrombosis and necrosis seen in figure 5. **Figure 6** shows acute thrombosis and vascular stasis, with hemorrhage and necrosis in the adjacent tissues. What is peculiar is the degree of cellularity and hypertrophy in the surrounding septae of the hypodermis. As seen in the further pictures, this is angioid and fibrous stroma, not inflammation. (In thrombo-occlusive infarcts, inflammatory cells cannot be transported into the zone of injury thus acute inflammation is not seen.) **Figure 7** shows a large vessel in which chronic thrombosis and reorganization are accompanied by acute thrombosis in smaller surrounding vessels. Note the peculiar thickening and delamination of what should be the muscularis, and also the hypertrophy and fibrosis of surrounding septae. **Figure 8** is another large vessel having a dense infiltration of angioid cells within concentric layers of thrombosis and reorganization. Note too the high density of small vessels within the thickened stroma around the large vessel. **Figures 9, 10, 11, 12** are all accompanied by a closeup (**b**) to show what the cells look like, mainly to emphasize that there are no inflammatory cells. Instead, the cells are all regenerative mesenchyme or matured stroma. **Figure 9** shows acute thrombosis and necrosis in a smaller vessel. In adjacent areas of septal hyperplasia there is solid angioid tissue with a high density of organized capillaries, just as would be seen in normal proliferative wound healing (reparative or "granulation" tissue). **Figure 10** shows another large vessel with concentric layers of hyperplasia and organization. It is densely peppered with small new vessels, both within itself and outside in the surrounding hyperplastic septae. The hyperplastic areas are angioid and fibrous stroma without acute nor chronic inflammatory cells. **Figure 11** is a closeup of the vessel in figure 7, showing diffusely migratory spindle shaped angiocytes in ground substance matrix, with dense reorganization into mature vascular conduits. This is normal reactive (wound healing type) angiogenesis being overdriven. **Figure 12** shows the papillary-reticular boundary in healthy dermis outside the infarct zone. The sub-papillary vessels are not normal, with (1) diffuse cellular hyperplasia consistent with unregulated angiogenic stimulation, and (2) normal cell morphology consistent with reorganizing vessels in any wound. What all of these images show, in addition to the obvious thrombosis and necrosis, is that there is chronic diffuse angioid and stromal hyperplasia. This is probably the result of chronic "wound healing" proliferative activity which was stimulated by angiogenic cytokines, which were released by platelets or inflammation, which were induced by chronic persistent microvascular thrombosis. It all implies that during the several years of overt skin infarcts that this patient had, that there was also a background of low level subclinical events and pathological activity.

Case #04. A case to illustrate wound pathergy, Behçet's disease, and severe responses to even minor injury.
This case illustrates an even more unexpected and disproportionate tissue-destructive response to injury. This 43 year old woman was given a therapeutic injection near the hip (the drug was a common safe narcotic pain medicine). The injection site became ulcerated and widely bruised, with extensive fat necrosis deep to the skin. When seen in consultation, the diagnosis was made directly from a relevant history and physical. Of Lebanese origin, her intake inventory was positive for many signs and symptoms of an immunopathy, including oral and genital ulcers and ocular symptoms. This profile is not only pathognomonic of Behçet's syndrome, it is what defines the syndrome. Illustrated is the textbook Behçet's "pathergy test" in which the lateral thigh was given the most trivial of traumas, a single prick with an 18 gauge needle. At 12 hours after the needle, the surrounding skin appears widely bruised. The ability to do safe surgery without further pathergy depends on the use of corticosteroids. Under cover of intravenous methylprednisolone, oral prednisone, and intracutaneous triamcinolone, the patient had biopsy of the needlestick site and operative excision and repair of the hip wound. Histology confirmed that this was a complex inflammatory reaction, not just ecchymosis, with hemorrhage and mixed inflammation at the boundary between dermis and hypodermis. While there are some neutrophils, the reaction is predominantly mononuclear, with lymphocytes, plasma cells, and monocytes. Chronic peri-arteritis and unusual features such as membrano-cystic degeneration of the fat are not unique to Behçet's syndrome but nonetheless distinctive. With sustained anti-inflammatory therapies, all wounds healed without further complication. Had the original injection site reaction on the buttock been recognized for what it is and treated accordingly, the rest of this story would not have happened.

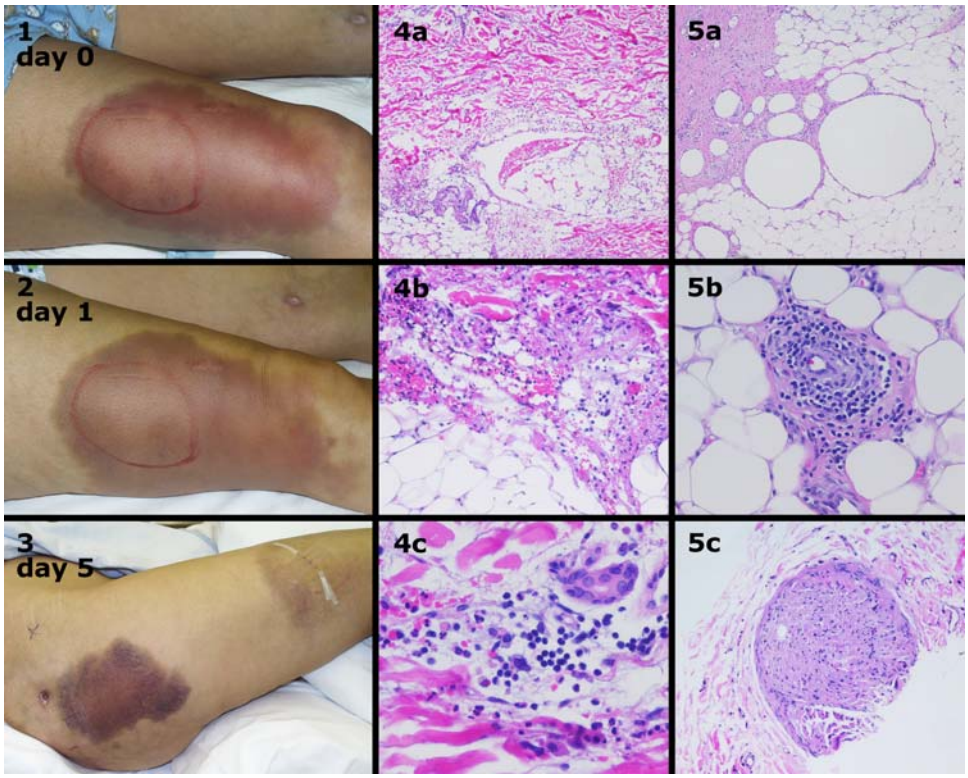


Figure 1 (day 0) shows the results of Behçet's pathergy test 24 hours after a needlestick in the center of the marked circle. **Figure 2** (day 1) is another 24 hours later, after starting high dose steroids. The "ecchymosis" has not enlarged, and edema and scarlet erythema in the lesion have waned. Note the scar on the opposite knee, typical of many she had from prior lesions. In **figure 3** (day 5), the thigh lesion is already resorbing the acute changes, and the biopsy done 4 days earlier has had no complications. On the buttock is the ulcerated original injection site injury and surrounding reaction, and they are benign, uninflammed, and beginning to heal (this photo was taken just prior to excision and closure of this wound). **Figure 4** shows the distinctive histologic features from the thigh 24 hours after the pathergy test needlestick: **(a)** mixed hemorrhage and inflammation at the dermal-hypodermal boundary, confirming that this is not simple ecchymosis, **(b)** a closer view showing plasma exudates and mixed cell infiltration, without suppuration or other generic acute inflammation spilling indiscriminately into the adjacent fascias, **(c)** a closer look at the cell mix, some neutrophils with many lymphocytes and monocytes. **Figure 5** shows distinctive histologic features in the original chronic hip ulcer: **(a)** membrano-cystic degeneration of the fat, seen with many immune panniculopathies, **(b)** chronic (non-neutrophilic) peri-arteritis, **(c)** chronic organization and fibrosis within a vessel, attesting to the thrombotic component of the pathology that caused the original ulceration.

Case #05. A case to illustrate wound pathergy, occult disease, and Trousseau's syndrome.
This 57 year old woman had diabetes mellitus. She presented with typical mal perforans ulcers under the metatarsal heads in conjunction with significant peripheral neuropathy and ankle equinus due to achilles shortening. She had good pedal pulses and triphasic dopplers. She gave no history nor symptoms of gastro-intestinal disorder. Debridement and arthrectomy were done, accompanied by simple achilles lengthening through short incisions on the calf. Ten days after surgery, the otherwise uncomplicated leg incisions and periwound became cyanotic. This progressed to infarction of the surrounding skin. Laboratory evaluation for micro-thrombotic disorders was initiated, but it was never completed, because a few days later she had a rectal bleed. This was her presenting event for liver-metastatic colon carcinoma, and she died within 2 months.

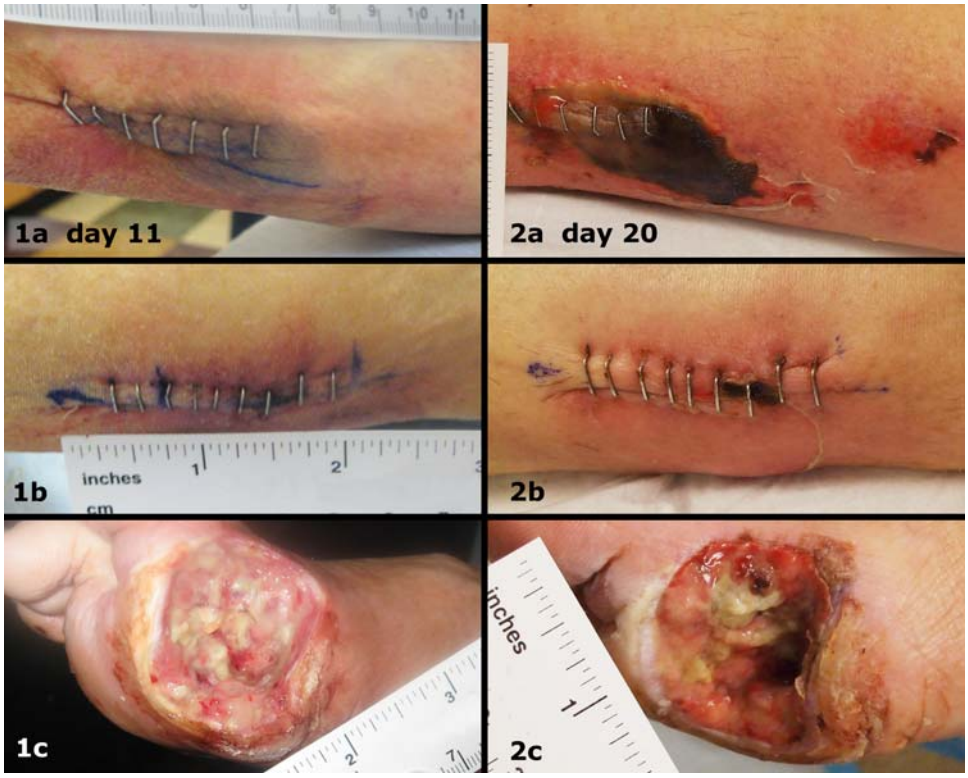


Figure 1 shows the posteromedial aspects of the right **(1a)** and left **(1b)** legs 11 days after simple achilles tendonotomy. Although the incisions looked normal and healthy for the first week after surgery, and although no complications would be expected, especially in a patient with normal pulses, nonetheless both incisions show signs of ischemia and vascular stasis. The debrided MP joint **(1c)** still looks healthy. At 20 days, **figure 2**, the left calf incision has recovered **(2b)**, but on the right **(2a)**, there is progressive ischemia and infarction. Small infarcts have also appeared in the metatarsal wound **(2c)**. This is the style of pathergy that can afflict innocent incisions, typical of pyoderma, Behçet's, arteriopathies, various formed-element hematopathologies, and paraproteinemias, including cancer-related Trousseau's syndrome.

Case #06. A case to illustrate wound pathergy and serious patient risk.
This 63 year old woman had decompressive laminectomy of the lumbar spine for complications of active rheumatoid arthritis. Over the first few days after surgery, the incision and periwound became cyanotic, then necrotic. The photos demonstrate extensive necrosis of muscles and fascias as well as the skin. This is wound pathergy. For an elective incision on the trunk to behave this way is extremely unlikely, and this is an alert to a pathological state. Note that the findings reflect a thrombo-occlusive state, rather than an inflammatory-lytic state, which implies something about the underlying diagnosis. The differential is limited to just a few types of pathology: this could theoretically have happened due to severe aortic occlusive disease with lumbar ischemia (atheromas or aneurysm), but this patient had no macro-vascular disease, leaving the auto-immune connective tissue disorders and the various micro-occlusive disorders as possibilities. In this case, a specific diagnosis was not made beyond the rheumatoid itself, but laboratory profile showed markers of a hypercoagulable disorder or thrombotic state (high protein C and fibrinogen). Operative debridement of the wound (including coverage with a pathergy-controlling semi-biological material) triggered a profound hypo-coagulopathy, and the patient died shortly afterward from uncontrollable diffuse hemorrhage.

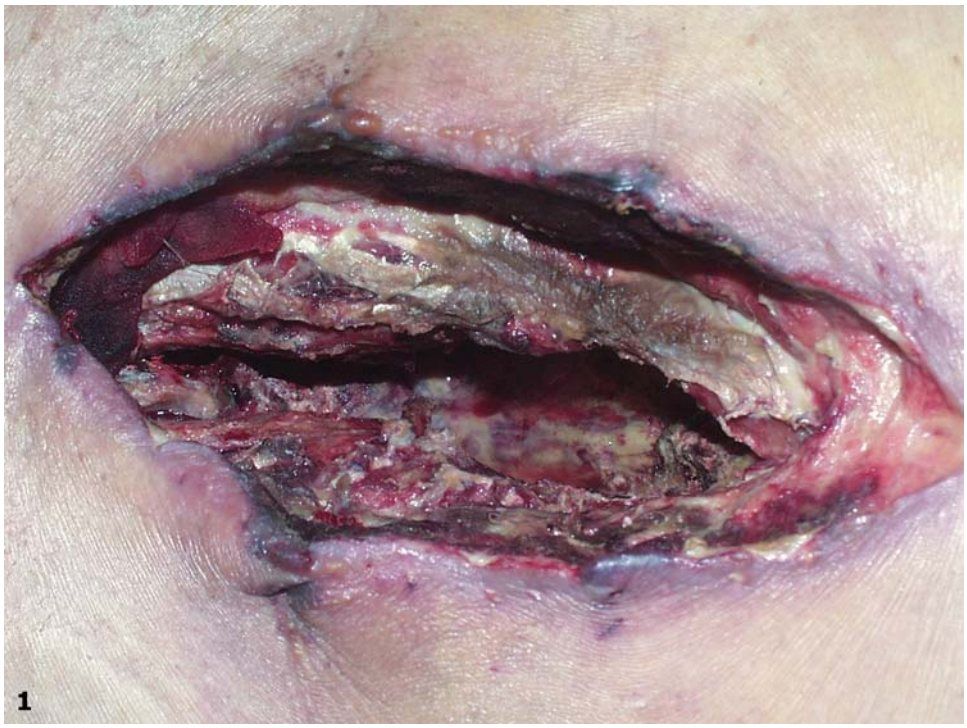
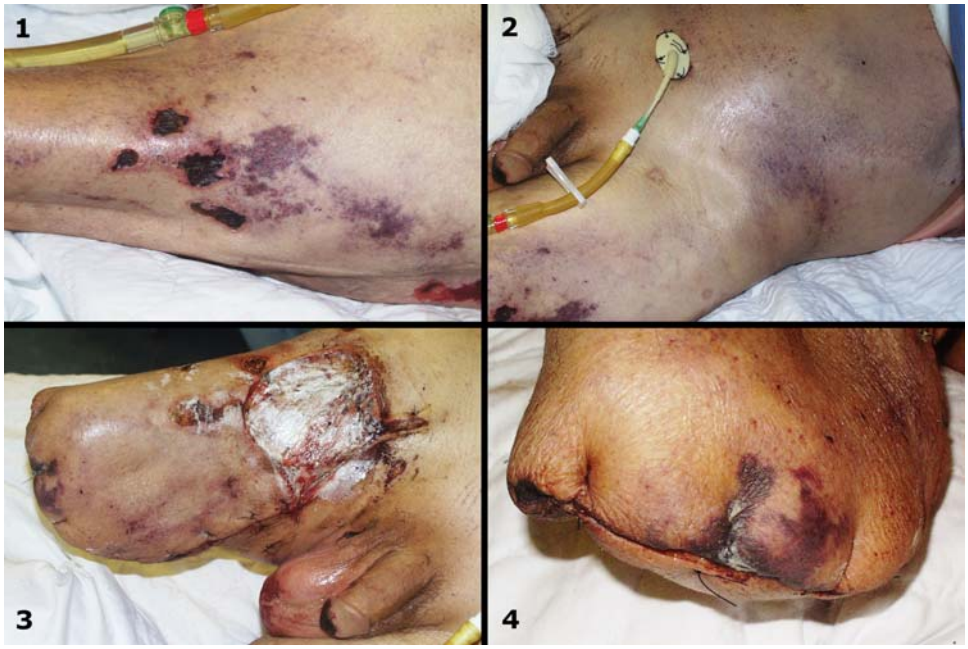


Figure 1 shows the midline lumbar wound as it appeared 1-2 weeks after surgery. The appearance is notable both for what is there, and what is not. What is not there: no gross inflammatory changes, no signs of suppuration nor suppurative necrosis, no significant edema and no scarlet erythema in the peri-wound. What is there: cyanotic vascular stasis and skin infarcts at the wound margins, and infarcted bones, muscles, and fascias. Note the piece of gelatin sponge (left edge) used to stop some troublesome bleeding. This case reiterates that when the complex coagulation system becomes acutely pathological and dynamically unbalanced, then hyper- and hypo-coagulable events can occur concurrently (see case #3).

Case #07. Another case to illustrate wound pathergy and serious patient risk.
This 58 year old man had coronary angioplasty, seemingly uncomplicated until a week or two after starting warfarin. Diffuse multifocal skin infarcts occurred involving many anatomical areas. The right lower extremity required amputation, which was complicated by skin infarcts along the edges of the incisions. Across his body, debridement, open wound management, and interim closure with semi-biological matrices were all complicated by progressive infarcts. While unusually severe, this was otherwise a typical case of warfarin necrosis. It generally occurs within the introductory few weeks of warfarin anticoagulation, attributed to ungoverned relative imbalances between the vitamin K dependent clotting factors as these proteins go from their normal to their therapeutic low levels. This complication is more apt to occur in someone whose coagulation system is already "untuned" due to a prethrombotic hypercoagulopathy, and for this patient, laboratory evaluation confirmed APC resistance (activated protein C), implying a factor V mutation. (For at-risk patients with an existing hypercoagulopathy, this complication can be prevented by concurrent treatment with heparins until warfarin effects are therapeutic.) The patient died from multi-system failure due to visceral infarcts. Wound pathergy can have a spectrum of severity, from self-limited and anatomically confined (such as a small lesion of pyoderma gangrenosum), through disastrous outcomes like this one. As a generic concept, its significance and risk to the patient cannot be trivialized.



Figures 1, 2 show the vascular stasis and multifocal infarcts on the trunk and extremities. Note the thrombo-infarctive appearance of the tissues, with stasis and cyanosis, and no edema nor other gross inflammatory changes. **Figure 3** shows the right thigh after amputation and debridement. The ilio-femoral and tibio-peroneal vessels were all patent at the time of amputation, consistent with the micro-occlusive nature of the problem. Necrosis is present at the margins of incisions and sutures – this is wound pathergy. **Figure 4** is a closeup of some of these pathergic changes. Plastic surgeons will all be familiar with these findings, common events along the margins of any incompletely vascularized flap. The principles of good "flapology" are meant to avoid, mitigate, or manage these problems. The situation illustrated was unexpected, and the underlying cause and its complications were fatal, but it is nonetheless identical to the ischemic flap, an issue of critical soft tissue hypoperfusion in which any further insult or injury can cause necrosis.

Set 3: Micro-occlusive and ulcerogenic disorders: Vasculopathies

Case #08. A case to illustrate wound pathergy due to atherosclerosis and arterial insufficiency.
This 78 year old man presented with skin infarcts and ulcers of the legs and ankles. He had ilio-femoral atherosclerosis associated with hypertension and hyperlipidemia. Although vascular reconstruction was attempted, arterial flows remained low. Histology of debrided material showed that atherosclerosis also involved small cutaneous vessels. Debridement was associated with progressive skin necrosis at wound margins. Leg amputation might have controlled symptoms but was also at high risk for wound pathergy and the need for high level or progressive amputation. Instead, the wounds and general functional status were maintained with hygienic topical care until the patient died from cardiovascular events unrelated to the leg.

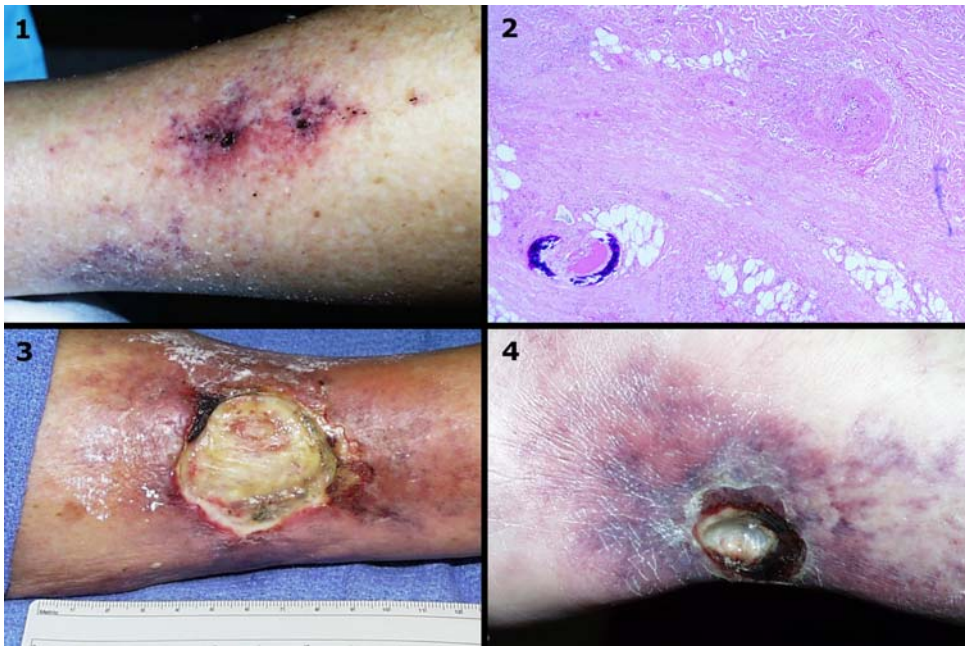


Figure 1 shows one of the several cutaneous infarcts that developed on the legs. **Figure 2** shows that dermal and hypodermal vessels are sclerotic and have reorganizing thrombus. Absent a risk profile nor laboratory markers of a hypercoagulable state, the thrombosis is due to low flows and thrombogenic vessels. The debridement which supplied the specimens was subject to pathergy, as seen in **figure 3** (above the malleolus) and **figure 4** (over the achilles), which demonstrate progressive vascular stasis and wound margin necrosis after incision and debridement.

Case #09. Another case to illustrate wound pathergy due to atherosclerosis and arterial insufficiency.
This 47 year old man had diabetes, end stage renal disease, and atherosclerosis with high grade tibio-peroneal occlusion. He presented with urinary sepsis and intercurrent complications. The original anterior ankle ulcer was pre-existing, probably from some mundane trauma, a small bruise or laceration, something presumably innocuous had it been in a normal person. As acute illness progressed, skin infarction and signs of profound arterial stasis ensued, progressing outward from the original ulcer. This is a dominant feature of ischemic wound pathergy, in which any focus of injured tissue, thrombosis, inflammation, or interrupted flow patterns, including surgical incisions, becomes the hub from which develops more of the same. Any number of hemodynamic, coagulopathic, and inflammatory events can trigger progression of the infarcts, and so too can treatment, including pressure from bandaging and any sort of further trauma such as biopsies, debridement, or any other surgery. (After transfer to another facility, the outcome of the patient is unknown.)

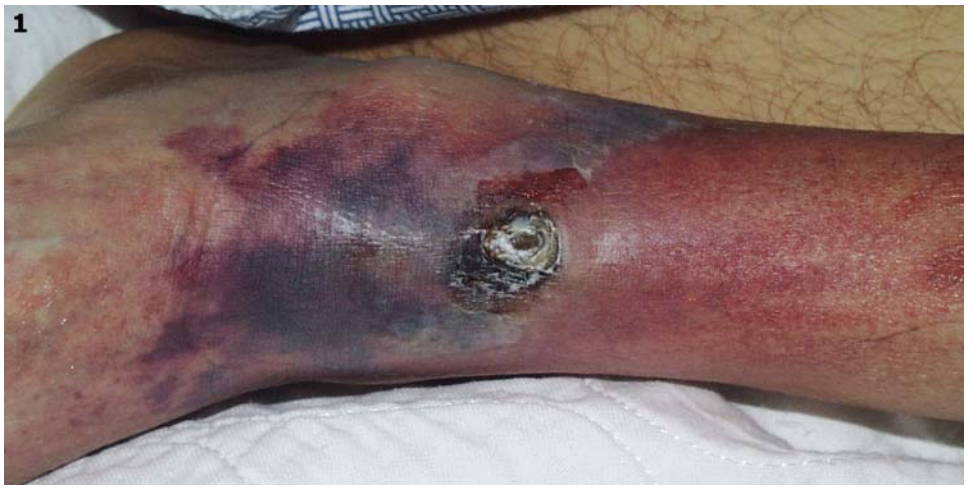


Figure 1 shows the prior ankle ulcer, now infarcted and escharotic after onset of generalized illness. This is apt to happen in a patient with vascular disease and low flows who then develops a state of injury-inflammation-thrombosis or hemodynamic alterations such as hypotension. The problem is exacerbated in a patient who has a pathergy prone hematopathology such as thrombocytosis. The magenta and violet discolored areas represent areas of extreme low flow and arterial stasis, leading to regional thrombosis and extension of the infarct. Any incision into these tissues will do more of the same. Unless the foot and leg can be revascularized, amputation is probably unavoidable. In the 1960's and 1970's, vascular surgeons taught us that arteriopathic legs need not be indiscriminately amputated, that revascularization will recover the situation. That concept of "limb salvage" is true, but not sufficient. Skin, wounds, and incisions must be managed as well. For discussion's sake, assume that this particular patient had good circulation at thigh level, and that although below-knee amputation might be of questionable outcome, an above-knee amputation would be certain to heal. Today's concepts and technologies mean that preemptive management of pathergy risks, utilizing the many applicable therapies in support of the "cut-and-sew" procedure, should allow for successful amputation at a level distal to the certain "no problem" level, making below-knee amputation feasible for this patient.

Case #10. A case to illustrate wound pathergy due to micro-arteriosclerosis.
This 51 year old woman, with diabetes and end stage renal disease, presented with painful infarcts of skin and subcutaneous fascias on the abdomen and breast. The presentation, history, and features of the lesions were pathognomonic of calciphylaxis, confirmed by histology (showing calcific micro-arteriosclerosis and micro-thrombosis), and further supported by high parathormone levels and low transcutaneous oxygen levels. Characteristically in this ischemic disorder, tissues tend to heal very slowly when treated by topical care in support of natural contraction. Skin grafts typically are uncertain, and direct repair and local flaps tend to fail. Likewise, simple debridements and biopsies also risk progression of the infarcts and wounds, just as for any micro-thrombotic or ischemic tissue. This patient had successful and rapid resolution of the lesions by using a pathergy-preventing protocol: complete excision, immediate closure with a semi-biological regenerative matrix (Integra™), and short term support of potential post-operative wound ischemia with hyperbaric oxygen.

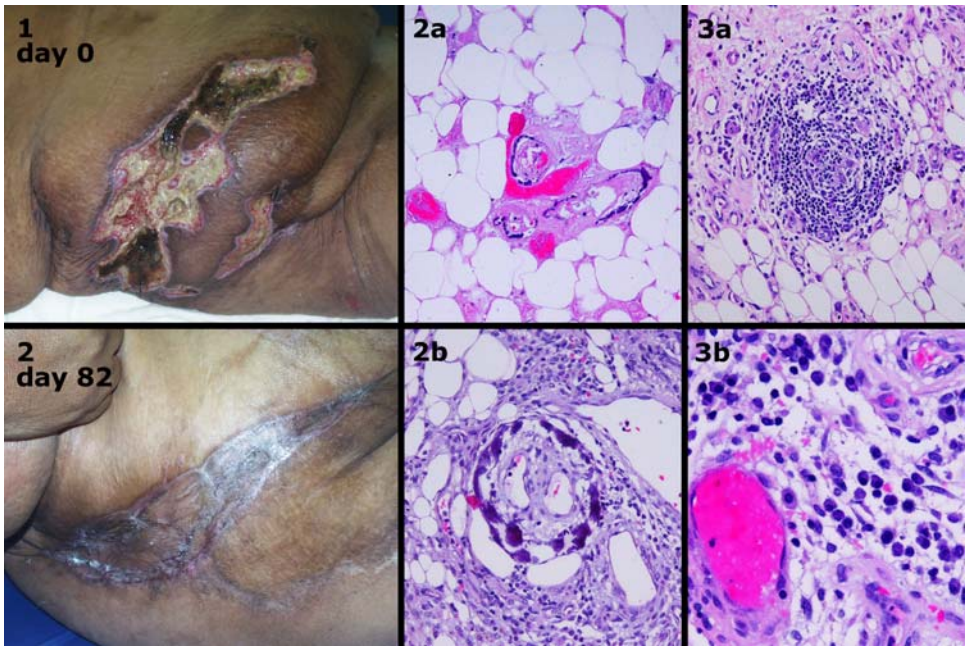


Figure 1 shows the skin and pannicular infarcts on the right flank and abdomen. Similar lesions were on the left side and on the breasts. **Figure 2** shows the completed reconstruction, completely healed and maturing 3 months later. The skin and pannicular lesions of hyperparathyroidism-calciphylaxis are often viewed as highly morbid and difficult to treat, but that perception is illusory. This is a benign form of micro-occlusion, without intrinsic or primary inflammatory events, and without intrinsic wound healing deficits (unlike the auto-immunopathies and connective tissue disorders in which wound healing is intrinsically damaged). If microperfusion and oxygenation can be maintained, and if peri-operative pathergy can be prevented, these lesions heal quite easily. **Figures 2a, b** show the primary pathology of this disorder, small vessel calcific arteriosclerosis. However, it is not the calcium deposits which kill tissue, it is the secondary thrombosis, seen here in later phases of organization and recanalization. **Figures 3a, b** show a chronic peri-arteritis around vessels which are occluded or congested. As in any chronic inflammation, lymphocytes and plasma cells predominate. Neutrophils and a generalized inflammatory process in surrounding tissues are absent. While hyperparathyroidism and calcific arteriopathy might be the nominal pathology of this disorder, the reality is that pathergy-prone disorders and soft tissue infarcts generally represent a complex interaction of injury-thrombosis-inflammation which can be triggered in many ways. Managing these risks and events leads to predictably good results.

Set 4: Micro-occlusive and ulcerogenic disorders: Hematopathologies

Case #11. A case to illustrate wounds and risks due to red blood cell disorders.
This 88 year old woman had multifocal ankle ulcers characteristic of immune and hematological diseases. There were no stigmata of venous disease, and arterial circulation was normal. She had hereditary spherocytosis (including chronic mild anemia and hyperbilirubinemia) not requiring therapy. She also had a history of rheumatoid arthritis, not currently active nor treated. Laboratory evaluation showed numerous direct and indirect markers of a hypercoagulable disorder, including high fibrinogen, high protein C, hyperhomocysteinemia, and an unmeasurably high anticardiolipin. All of the hemoglobinopathies and hemolytic anemias carry the risk of chronic ulceration, but in this case, spherocytosis by itself was certainly not the only cause of the ulcers. Many patients with pathological wounds, both acute pathergy and chronic ulceration, will have markers of mixed and concurrent immune and hematological diseases. It is important to understand that nominal diagnoses such as "spherocytosis" or "primary thrombocytosis" cannot be accepted at face value as the cause of severe wound and soft tissue complications. This patient healed with topical care and warfarin anticoagulation over a period of 6 months. Any attempt to solve the problem with basic wound repairs or local flaps would have simply made the problem worse.

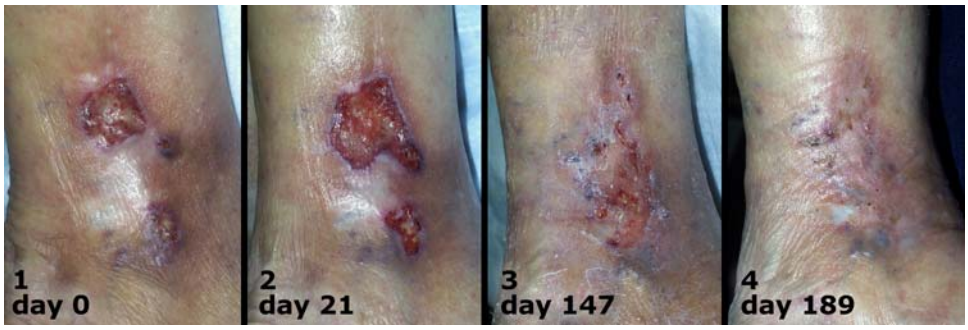


Figure 1 shows the left lateral malleolus and ankle at presentation. **Figure 2** (day 21) shows that the original foci enlarged and coalesced over 3 weeks. During that interval, the wounds were kept clean by basic care, but no diagnosis-specific therapy was started while awaiting the laboratory evaluation mentioned above. Warfarin therapy was then started, and the wounds began to heal. Epithelial growth was slow but consistent, and the wound was healed then stable 4-5 months later (**figures 3, 4**, day 147 & day 189).

Case #12. A case to illustrate wounds and risks due to hypercythemias and polycythemias.
This 72 year old woman had polycythemia vera. Her blood counts broke through therapy, and she developed multiple ankle ulcers. At the time of consultation, while otherwise healthy and non-acute, her red blood cells were normal, but white blood cells were 35K/mm3 and platelets were 760/mm3. Workup for associated disorders was significant for positive anti-nuclear antigens (1:160), elevated rheumatoid factor, low protein C, and high anticardiolipins. The patient was started on warfarin, the leg ulcers were prepared by basic topical care, and then skin reconstruction was started with Integra™ collagen-gag regenerative matrix. The reconstruction was never completed because the patient died from an acute cerebro-vascular event. The ulcers are prototypical pathological wounds due to immune or hematological disease. Such lesions on the distal leg and ankle can have several distinctive modes of onset: random panniculitis, dermatitis, or vasculitis; immune synovitis along tendons and bursas, or due to minor trauma (wound pathergy). Trauma-pathergy (starting as everyday bumps and dings on the ankle) and immune bursitis are the common modes for initiating malleolar ulcers. Note that although she had a nominal diagnosis of a myeloproliferative disorder, she had significant markers of immunopathy and coagulopathy, a very common association, illustrating again that a major wound complication cannot be blithely attributed solely to "benign thrombocytosis".

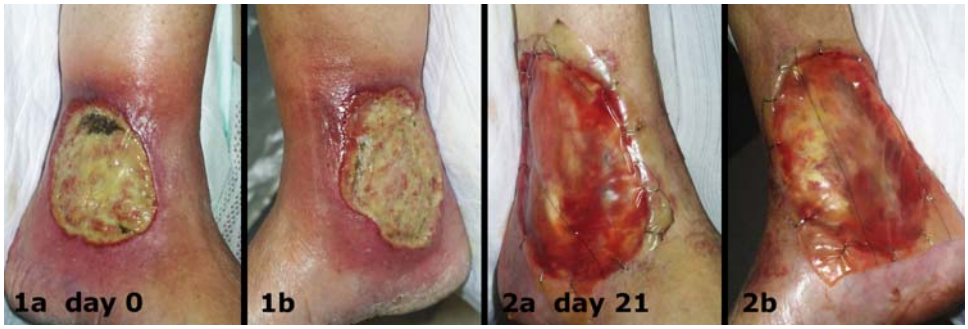


Figure 1 shows the right ankle and ulcers (**1a** is lateral, **1b** is medial). There is active necrosis and ulceration at the margins, and the periwound has vascular stasis and intense inflammation. The pattern is mainly inflammatory-lytic rather than thrombo-infarctive, consistent with auto-immunity rather than micro-occlusion being the primary pathology. This illustrates the principle that simple assumptions about diagnosis and pathogenesis, such as "sludging from high platelet counts", are naive and inconsistent with the information that can be gleaned from a proper history, exam, and laboratory investigation. **Figure 2** shows the same views 3 weeks later, after excising the wounds and closing them with Integra™ collagen-gag regenerative matrix. Note the complete control of periwound inflammation and active ulceration. In a patient like this, simple cut-and-sew surgery without regard to controlling pathergy will be subject to continued inflammation and wound failure.

Case #13. Another case to illustrate wounds and risks due to polycythemias and mixed hematological disease.
This 54 year old man had multifocal leg ulcers characteristic of immune and hematological diseases (with no signs of venous disease nor arterial insufficiency). He had polycythemia vera, counts well controlled with treatment, and a history of venous thrombosis and pulmonary embolism. Laboratory evaluation showed numerous direct and indirect markers of a hypercoagulable disorder, including high fibrinogen, low proteins C & S, hyperhomocysteinemia, a lupus anticoagulant, unmeasurably high anticardiolipins, elevated speckled anti-nuclear antibodies, and factor V Leiden heterozygote. Polycythemia vera is a nominal risk for leg ulceration, but as in many patients with pathological wounds, markers of immune, hematocellular, and hypercoagulable diseases occur concurrently, making the problem much more complex than just the index diagnosis. This is very similar to the previous cases, and once again it is important to understand that the "face value" diagnosis cannot be accepted blindly as the only cause of wound and soft tissue complications. This patient healed with topical care and warfarin over a period of months. Had wound repair surgery been attempted, it likely would have resulted in flap necrosis and wound failure.

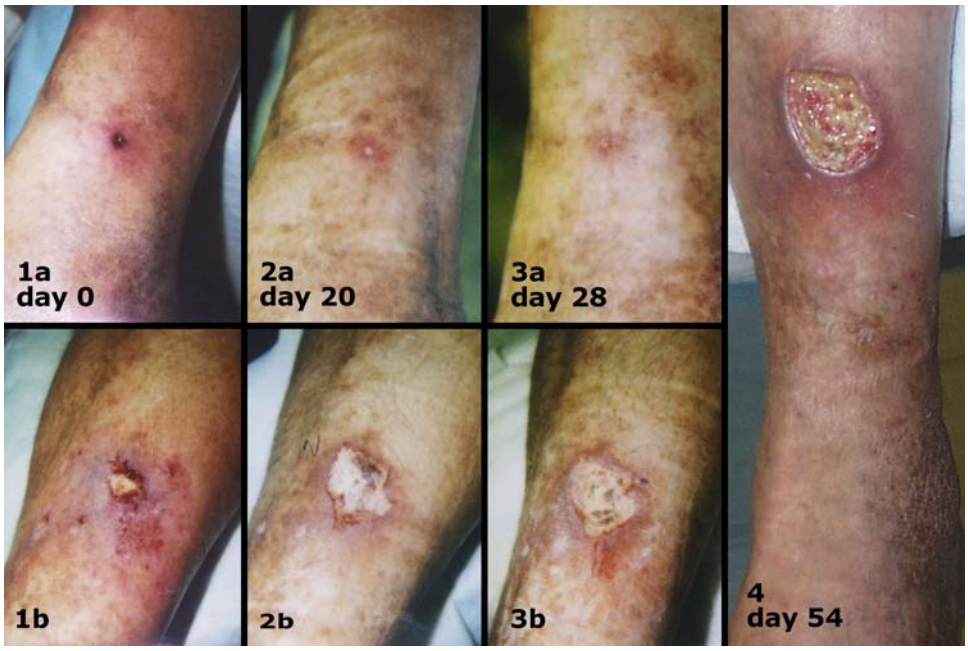


Figure 1a (day 0) shows a small skin infarct and ulcer just proximal to the left ankle; **figure 1b** is another infarct more proximal; similar lesions were also present on the medial side of the leg. **Figure 2** shows the same lesions at 20 days. The lesions have stabilized with treatment, and while the eschar has not all separated, there are no signs of active new necrosis at the wound margins. **Figure 3** (day 28) shows the small lesion almost healed, and the larger lesion showing signs of wound module proliferation. **Figure 4** (54 days) shows that minor lesions throughout the distal leg are healed, and edema and skin quality are generally improved. Wound healing kinetics of the large tibial ulcer are obviously delayed, but they are qualitatively correct, and this wound is expected to heal with topical care and wound stimulatory therapies. (The patient also had multi-pathology heart disease; shortly after this he had heart catheterization, and subsequent status is unknown.)

Set 5: Micro-occlusive and ulcerogenic disorders: Hypercoagulopathies

Case #14. A case to illustrate wounds and pathergy due to a hypercoagulable disorder.
This 69 year old woman had biopsy of a small lesion on the leg. She had no relevant medical history, and pulses were normal. The small sutured biopsy site promptly became ulcerated, and a proliferative wound module failed to appear after a period of basic topical care. Laboratory evaluation confirmed a hypercoagulopathic or micro-occlusive state from cryoglobulins and protein C deficiency. Warfarin was initiated, and then skin was successfully reconstructed with a pathergy preventing regenerative material (Integra™ collagen-gag matrix). Conventional cut-and-sew surgery, had it been attempted without prior anticoagulation, would have resulted in the same kind of pathergy and wound failure as accompanied the original biopsy, merely making the problem bigger (see case #24).

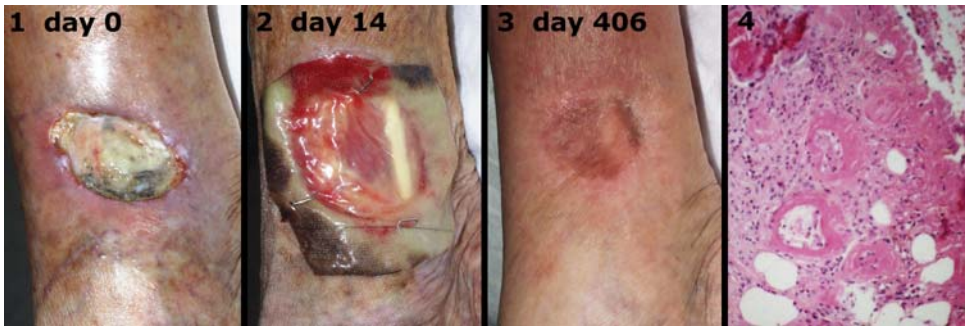


Figure 1 shows the ulcer on the right medial ankle. There is active ulceration at some of the margins, necrosis along the base of the wound, and absence of significant periwound inflammation, a pattern consistent with primary micro-thrombosis. **Figure 4** histology confirms the necrosis at the ulcer base, along with vascular thrombosis and necrosis of the vessels themselves, without dense or neutrophilic inflammation, a typical histology of hypercoagulable ulceration. **Figure 2** shows the wound after excision and closure with a pathergy controlling material. Wound colors are healthy, and there is no new necrosis. **Figure 3** is the healed and stable wound a year later. The ulcer itself was the pathergic response to excision of a small skin lesion, so any attempt to do further debridement or conventional surgery without controlling the response would simply have enlarged the entire problem.

Case #15. Another case to illustrate wounds and pathergy due to a hypercoagulable disorder.
This 72 year old woman had a minor household injury, bumping the leg against furniture, causing a small wound which became progressively and chronically ulcerated. The patient gave no history suggestive of immune or hematological disorders, and arterial exam was normal. Exposure of gliding muscle in the anterior compartment required a small flap for closure. Assuming this to be a benign wound due solely to trauma, closure was done with a local flap, and the flap donor site was closed with a skin graft. The flap appeared well vascularized in surgery, and it did survive and eventually heal. However, it went through a period of unexpected relative ischemia, and complete healing was delayed by recurrent areas of necrosis and ulceration at its margins The skin grafts placed on the flap donor site immediately became necrotic, but that site too healed eventually. Well after the primary reconstruction was healed, the thin split thickness skin graft donor site remained unhealed with signs of vascular stasis and recurrent small infarcts and ulcers. Curiosity about the cause of these variances from expected behavior prompted a laboratory screen for immune and coagulopathic disorders, and they were positive, a primary elevation of anticardiolipins with a reflex elevation of protein C. Anticoagulation was not started because by then everything was healed. Had the patient had a suggestive history before surgery, anticoagulation would have been started at the beginning, and the delayed healing would have been avoided. The history of unexpected ulceration after minor trauma, the failure of incisions and grafts, infarcts along incised edges, and delayed healing are all manifestations of wound pathergy and the underlying disease that caused it.

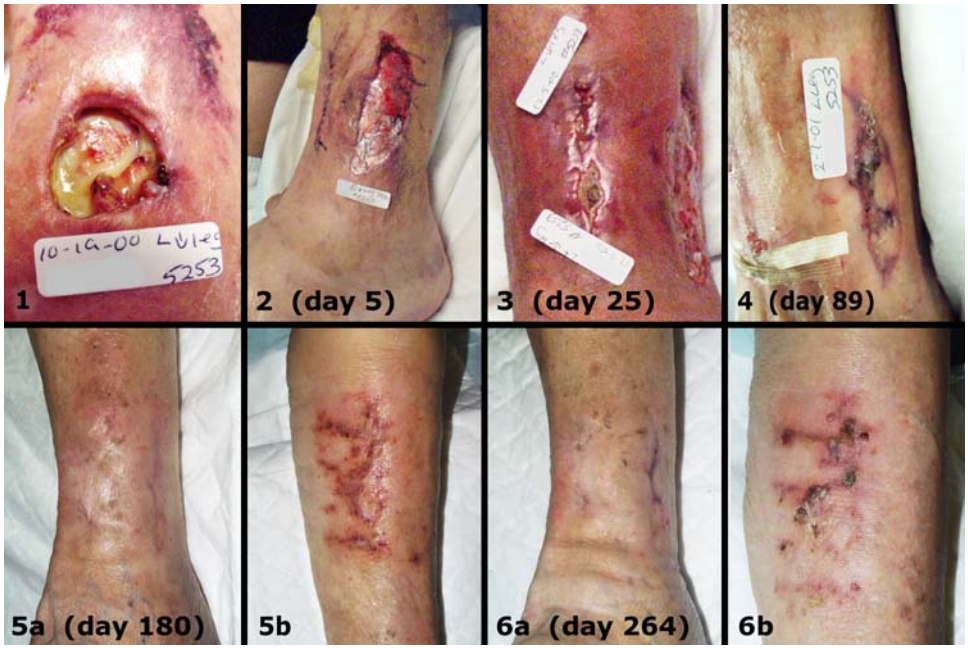


Figure 1 is the original ulcer of the anterior left leg prior to surgery. The skin margins and subcutaneous fascias have areas of active infarction and ulceration, a tipoff to active pathology. **Figure 2** is the reconstruction, a bipedicle flap, 5 days after surgery. While some ischemia could occur in a bipedicle flap, the area of cyanosis was inconsistent with the healthy appearance and bleeding during surgery. Note too the loss of the skin graft. The suture line, i.e. the coapted edges of the excised ulcer is healthy. **Figure 3** (25 days) shows small ulcers and eschar at the coapted edges, occurring on both the flap and the static margins (i.e. not just due to flap ischemia). At 3 months (**figure 4**) the reconstruction is still not fully healed. It is healed at 6 months (**figure 5a**), and remains so at 9 months (**figure 6a**). However, at the same times, the skin graft donor site has persistent vascular stasis with small infarcts and ulcers.

Set 6: Immune disorders and wound pathergy

Case #16. A case to illustrate common pyoderma gangrenosum.
This 50 year old healthy woman developed a lesion over the hip. It appeared spontaneously with no apparent instigation. It appeared as purpura with suppuration, eventually turning to dry eschar after treatment. The photos show that it was confined strictly to the dermis, sparing the adipose fascias underneath. This is paradigm pyoderma gangrenosum. The process was arrested with intra-lesional steroids, and it healed rapidly with basic topical care. Many pyoderma cases are small and innocuous like this one, but the disease can be fulminant and systemically toxic when it involves large areas (see case #22). This process is notoriously prone to wound pathergy, and the naive surgeon who debrides this without understanding the diagnosis nor without pretreating with steroids is virtually guaranteed to cause progression of the problem, with new infarcts occurring along any incised margin.

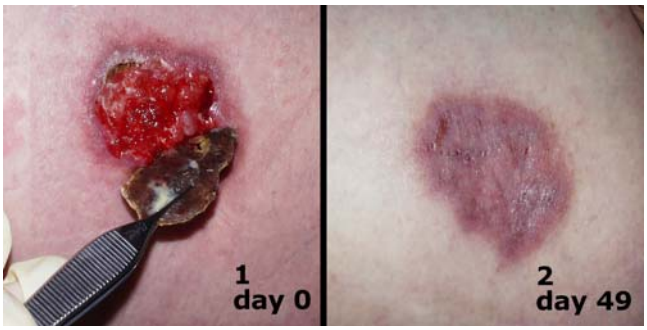


Figure 1 (day 0) shows distinctive features of the pyoderma lesion, about 3 weeks after onset of the lesion. Skin only is escharotic and is separating. The hypodermis is healthy and starting to heal. There is no peri-wound inflammation, and the disease itself has been quiet for 2 weeks. **Figure 2** (day 49) shows the wound completely reepithelialized. These images show that as long as the causative disease is arrested, the wound will behave as a normal wound, and eschar will eventually separate. There is no need for exogenous debridement which is a risky intervention for active pyoderma.

Case #17. A case to illustrate disease-associated pyoderma gangrenosum and the risk of wound pathergy.
This 26 year old woman had Hodgkin's lymphoma. Periodic disease recurrence prompted periodic retreatment, but she had stayed healthy and mostly disease free for several years. The current leg and foot ulcers occurred during one of her episodic recurrences and treatment cycles. Presenting as several purpuric lesions of the skin, an initial biopsy or debridement resulted in progression of the problem. When seen in consultation, the lesions were easily recognized as classic pyoderma gangrenosum. This case is nearly identical to the preceding (case #16), except that this one is associated with another disease (and one that explicitly involves the lymphoreticular system). Intralesional steroids were injected, and oral steroids were started. The disease was thereby arrested, then the eschar was debrided, and then the lesions all healed with basic topical care over 2 - 3 months (and the patient remains free of active Hodgkin's). There is a tendency for surgeons to want to excise or debride these lesions, but trauma must be avoided to prevent pathergic progression of the infarcts. The sooner that steroids are given, the sooner the problem extinguishes. While half of pyoderma is incidental in healthy people, its occurrence should prompt a history and system review to screen for immune and hematological diseases.

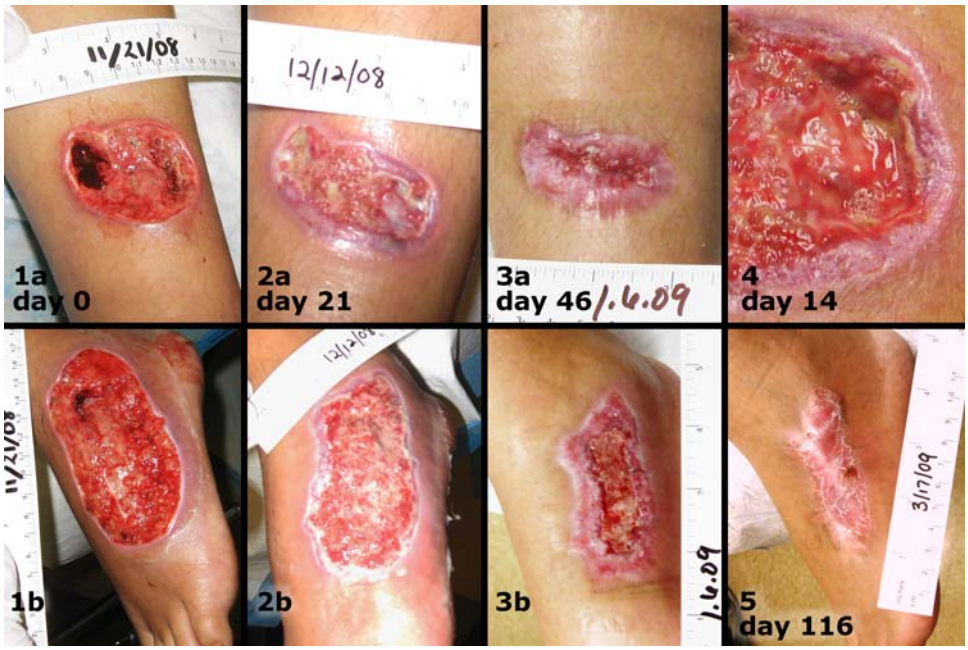


Figure 1 (day 0) shows the left anterior leg (**1a**) and dorsal foot (**1b**) about 2 weeks after the onset of the problem, and 1 week after intralesional steroids were given and oral steroids started. No images are available of the original skin infarcts, but a few remaining scraps of eschar are still visible. Note the preservation of the subcutaneous adipose, typical of pyoderma. **Figure 2** (day 21) and **figure 3** (day 46) show progressive healing with basic hygienic wound care, without any flareup of the primary pathology. **Figure 4** is a closeup of the leg lesion at day 14. There is a fully expressed wound module with significant epithelial ingrowth, confirming that wound healing kinetics are unhampered by pyoderma (once the disease is fully controlled). **Figure 5** shows the foot lesion at 4 months, healed and stable.

Case #18. A case to illustrate wound and soft tissue complications of auto-immunopathies and vasculitis.
This 85 year old woman presented with multifocal leg and ankle ulcers. They were prototypical immunopathic ulcers, with gross features of vasculitis, synovitis, and panniculitis. The patient gave no history of prior major illness, but review of systems was positive for a variety of immunopathic symptoms, and laboratory evaluation was positive for low level rheumatoid and lupus serologies. Histology showed a neutrophilic vasculitis and perivasculitis along with acute and chronic microthrombi, vascular necrosis, and microvascular fibrosis and stenosis, findings typical of leukocytoclastic vasculitis or especially polyarteritis nodosa (PAN). The wounds healed unexpectedly well with just steroids and topical care, but over the course of one year, there were several recurrences. The last flare up caused sufficiently large ulcers and tendon exposure that surgical coverage was planned, using a collagen-gag regenerative matrix so as to avoid the certain pathergy and wound problems that would complicate conventional cut-and-sew surgery. However, the patient became progressively ill and died before surgery could be done. The sudden appearance, severity, and recurrence of these lesions was typical of autoimmunopathy out of control. While most physicians might think of end stage lupus or rheumatoid (or Behçet's or Wegener's or PAN, etc.) as being characterized by intense arthritis, nephritis, pericarditis, pneumonitis, cerebritis, gastro-intestinal ulceration, opportunistic infections, or similar dramatic visceral events, there is a certain group for whom the terms "collagen vascular disease" and "connective tissue disorder" live up to their namesake, manifest most overtly by dermal vasculitis, synovitis, and panniculitis with resulting skin ulcers. The presenting profile of this patient is highly correlated with end stage autoimmunopathy and mortality.

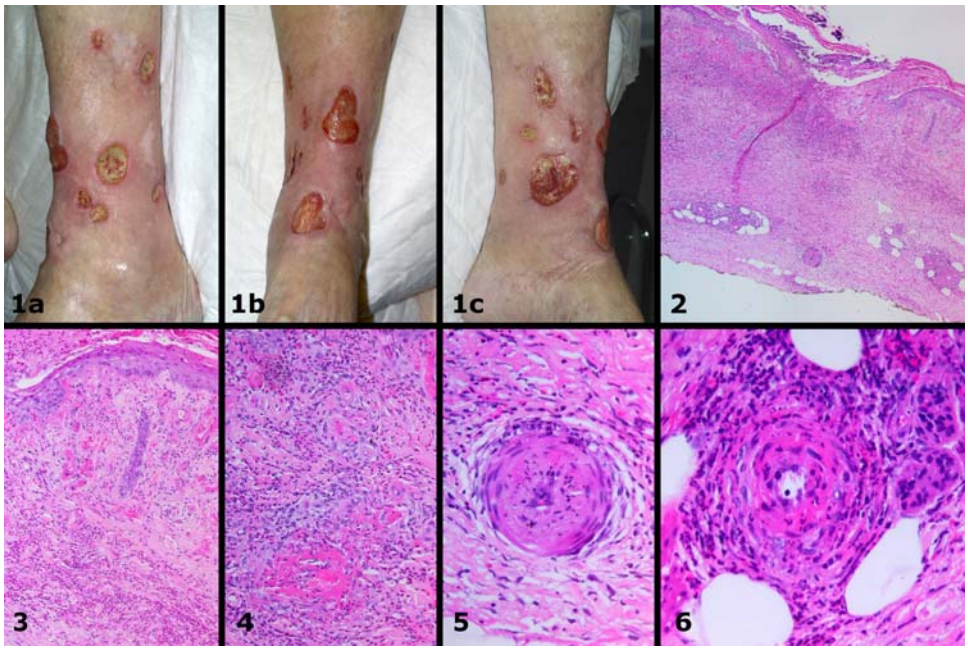


Figure 1 shows lateral, anterior, and medial views of the left ankle. The anterior ulcers (**b**) are along the tibialis tendon, consistent with a synovitis, whereas the others extend into the subcutaneous tissues due to vasculitis or subdermal panniculitis. The remaining figures show various histological features of these immunopathic wounds (from a biopsy of one of the lesions). Seen in overview in **figure 2**, there is skin ulceration over an area of concentrated acute inflammation, but it is the surrounding tissues which are more revealing. There is chronic wound healing and wound module at the margins of the ulcer, including epithelial migration. At the base of this activity is a lamina of acute inflammation, in what would be the subpapillary network in normal skin, or the inflammation-free fibroplastic layer in a normal wound. It is easy to see that the ulcer occurs in an area where this tangential inflammation has become more intense. Since the papillary dermis is merely the vessel-dense lamina propria for the epidermis, it is not surprising that vasculitis is active through this layer. Deep to this, in the reticular dermis, larger vessels have inflammatory infiltrates, without surrounding abscess or generalized fibrositis, characteristic of polyarteritis nodosa. **Figure 3** is a closeup of the wound module at the ulcer margin, with the inflammatory lamina below, a finding which would never be seen in a benign healthy post-traumatic wound. **Figure 4**, from the subpapillary or interlaminar zone shows intense perivascular inflammation with fibrinoid degeneration of vessels. **Figure 5** shows a larger dermal vessel with chronic thrombosis, inflammation, and fibrosis. **Figure 6** shows the acute primary vasculitis, with infiltration of the vessel wall, fibrinoid changes, and intense peri-arterial leukocytic inflammation. The cells are nearly all neutrophils, including a lot of "poly dust" (nuclear debris). As with the other micrographs shown in this review, chronic ulcers and pathological wounds, and the surgical risks that they carry, are due to demonstrable anatomical disease.

Case #19. Another case to illustrate wound and soft tissue complications of auto-immunopathies and vasculitis.
This 58 year old woman with scleroderma-crest developed an inflammatory ulcer of the finger and dry escharotic infarcts of the foot (She also had a more generalized lupus component of her disease, and she was already missing other fingers and toes). The referring physician's notes document "she received a paper cut [one month ago] to the middle phalanx of her left index finger and this has gone on to become a fairly large eschar involving the dorsal aspect of the proximal and middle phalanx." Those notes also described "ongoing skin slough involving the transtarsal amputation" (the amputation, performed four years earlier, was healed until these new acute events). Workup was done for relevant immune, vasculopathic, and hypercoagulable states. Arteriograms confirmed the presence of advanced "lupus angiopathy" and severe digital ischemia. For this patient, angiolysis and digital sympathectomy were done in foot and hand, with DIP amputation of the finger and skin grafts to the foot, supported with steroids and hyperbaric oxygen therapy, resulting in complete healing. The loss of a finger due to a simple paper cut is a paradigm example of wound pathergy. Pathergic complications are apt to occur in patients with vascular or other occlusive-ischemic disorders or else immune-inflammatory disorders, and obviously a patient with scleroderma-crest has both risks. Imagine that that paper cut had been an unwary operative incision, and it is now easy to understand why surgery done without disease management nor pre-operative preparation against pathergy will assure enlargement of the problem (see cases #26, #27, #29).

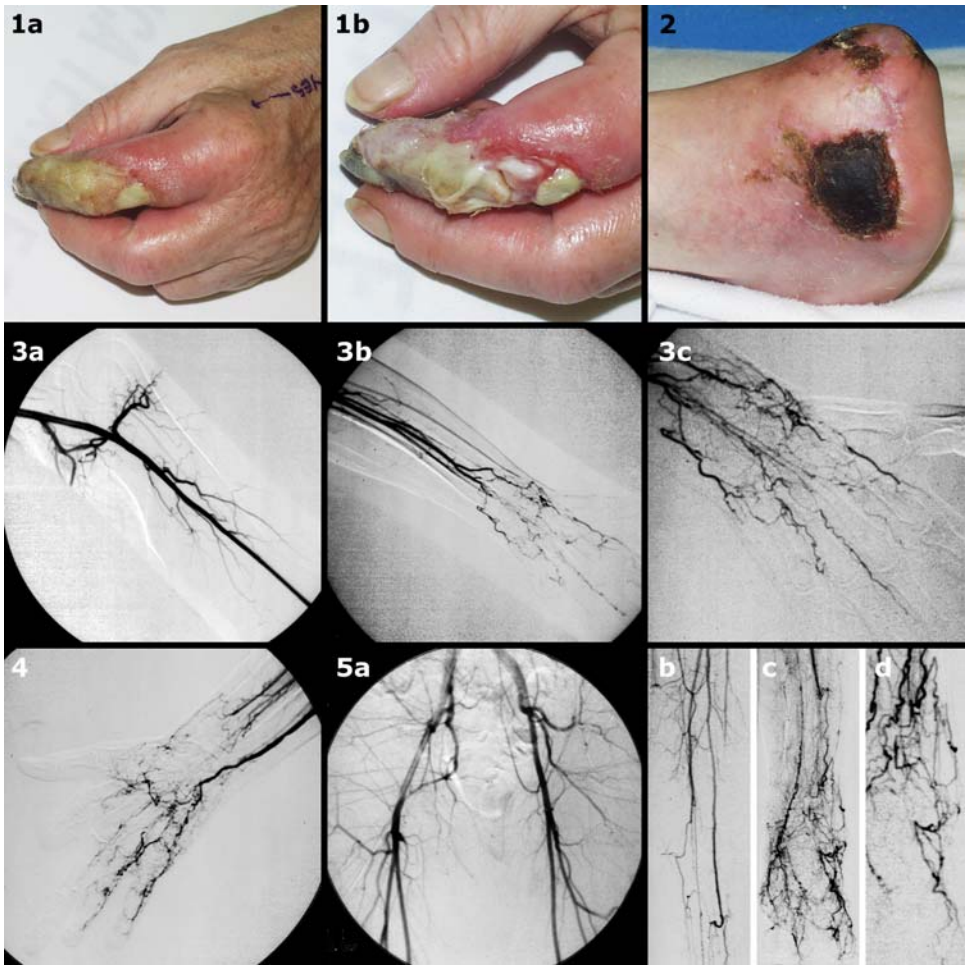
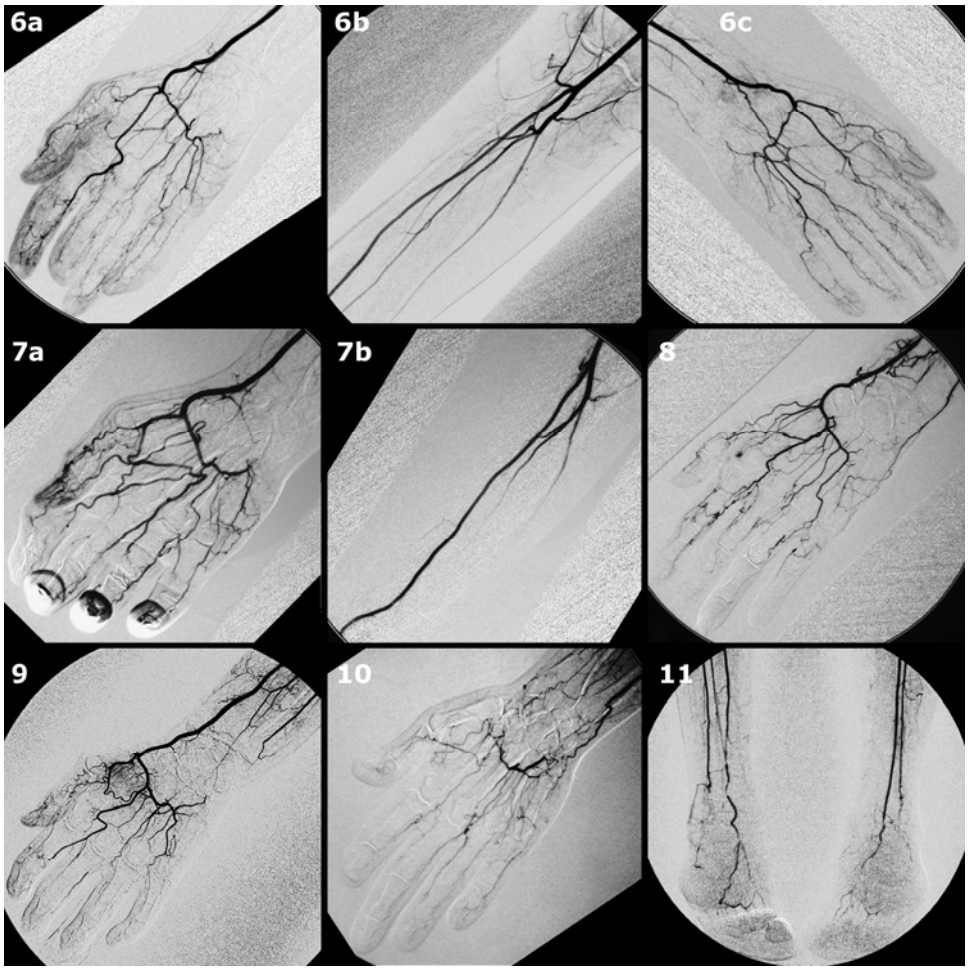


Figure 1a is the ulcerated index finger just prior to amputation. **Figure 1b** is a closer view, after removing some eschar, confirming destruction of the extensor mechanism and joint capsule. This is the result of a "paper cut" in an ischemic finger. **Figure 2** shows the foot with multiple areas of escharotic skin. The angiograms confirm the typical arteriopathy of scleroderma-crest (see addendum images below for more information). In **figure 3a**, the brachial artery and branches in the arm are normal. In the forearm, **figure 3b**, there is a transition from normal vessels proximal to pathological vessels at the wrist and into the hand (hand closeup in **figure 3c**). **Figure 4** shows comparable disease in the other hand. **Figure 5** shows the lower extremity. The ilio-femoral vessels are normal (**figure 5a**), but at mid leg, the tibial and peroneal vessels develop the same type of segmental stenoses and occlusions that are present in the hands (**figure 5b**). **Figure 5c** shows disease across the ankle, comparable to the disease at wrist and hand. Figure 5d is a closeup at the ankle showing more detail about the morphology of the affected vessels. Severe ischemia is obviously a consequence, putting the hand at risk for pathergy and necrosis in the event of any trauma or inflammation.



Addendum images: Observe in the patient's angiograms above that disease occurs only acrally, that vessels are normal proximal to elbow and knee. Observe that while the left wrist had advanced disease involving both major vessels, that disease is radial dominant on the right. Note the numerous segmental stenoses and occlusions, the corkscrew or "unwound" appearance of non-stenotic vessels, and the patchy obliteration of the palmar arches and digital vessels. These are the characteristic, actually pathognomonic changes of lupus or crest angiopathy. This is the non-atheromatous fibro-stenotic arteriopathy that results from long standing auto-immune vasculitis. It is typically most frequent and most dramatic in scleroderma-crest, but it will be found in any patient with lupus or any other collagen-vascular disease in which digital ischemia and ulceration are present. It is more prevalent in the upper rather than lower extremities. It centers on the wrist or ankle, advancing proximal and distal into forearm-leg and hand-foot as the disease progresses, but always remaining strictly and exclusively acral, distal to elbow or knee. It also tends to strongly affect one side or the other, ulnar or radial, more often ulnar, but both sides can become involved as disease progresses. Raynaud's vasospastic episodes, representing vascular reactivity when vessels are inflamed, are a prelude to more advanced histological disease. Vasospastic episodes still occur even when advanced long-segment stenosis is present. It is important to understand though that ulcers and infarcts do not occur until there is anatomical disease with sustained ischemia, and that once ulceration occurs, the problem is no longer simply "Raynaud's". Improved circulation with ulcer healing and relief of ischemic pain is reliably achieved by sympathetic blockade and angiolysis. Short term therapy and symptomatic relief can be done by local anesthetic blockade of the vessels in the wrist and hand (and or stellate ganglion blockade). More definitive therapy with sustained effects leading to healed wounds is done by "digital sympathectomy". This is a surgical adventitial stripping and fibro-myectomy of vessels in wrist (or ankle) and within the hand which eliminates the sympathetic nerves and the stenotic vascular segments. Botulinum toxin blockade of wrist and hand vessels, in lieu of operative angiolysis, can have the same effects and good results as operative angiolysis (the effects of botulinum blockade typically last 4 to 9 months). Because this pathology occurs in patients with connective tissue disorders, the possibility of a concomitant hypercoagulable state must always be considered and evaluated. Obviously, a hypercoagulable state in the presence of flow stasis and thrombogenic surfaces is a bad combination, and all components of the problem must be treated. In the following examples, none of these patients had diabetes nor any other form of calcific atherosclerosis, just lupus angiopathy. **Figure 6** shows disease from a patient with lupus and finger ulcers (48 year old woman). Vessels in the proximal forearm and above the elbow are normal (**figure 6b**). The characteristic changes described above are present throughout the wrists and hands (**figure 6a** is right, **figure 6c** is left). Note that disease is ulnar dominant on both sides. **Figure 7** shows the same changes in another patient with lupus (49 year old man). The hand has the same characteristic features with ulnar dominant disease and diffuse patchy obliteration of digital vessels (**figure 7a**). Disease starts at mid-forearm, with the antecubital vessels (and everything proximal) being normal (**figure 7b**). **Figure 8** is from a 62 year old woman with scleroderma-crest, with the same changes and ulnar dominant disease. **Figure 9** is similar, from a 62 year old woman with scleroderma-crest. **Figure 10** is also similar, from a 50 year old woman with scleroderma-crest, but with radial

dominant disease. **Figure 11**, from a 66 year old woman with scleroderma and lupus, protein S deficiency, and foot ulcers, shows similar disease starting just above the ankles (with otherwise clean vessels at all higher levels). Every one of these patients presented with severe ischemic changes and symptoms, with ulcers of fingers or ankle or toes. Every one had normal arteries proximal to elbow and knee. Everyone had active autoimmune disease. Everyone was healed after angiolysis along with miscellaneous other relevant care. All had had prolonged ineffective treatment with vasodilators or other naive therapies for "Raynaud's", treatments that cannot correct this advanced state of anatomical angiopathy. For the main patient of case #19, the acute problem was due to wound pathergy following trivial trauma. For some of these other patients, they too had some minor finger injury, whereas for others the problem began with spontaneous scleroderma ulceration. All were at risk for wound pathergy and complications if indiscriminate surgery would have been done without acknowledging the disease and peremptorily treating the risks before surgery. Yet all had successful uncomplicated surgery (digital sympathectomy) with healed wounds by a priori planning for these risks.

Case #20. A case to illustrate wound pathergy and surgical complications associated with a collagen-vascular disease.
This 67 year old woman had a 20 year history of active rheumatoid and crest, maintained with steroids. She had decompressive laminectomy and fusion for arthritis related problems. The back wound failed. The photos show necrosis at the skin margins and throughout the wound. She had a family history of venous thrombosis, and work up confirmed factor V Leiden heterozygote, plus high fibrinogen with reflex markers of a hypercoagulable state (protein C and plasminogen elevated). She was started on warfarin, the wounds were cleaned up by a period of topical care, and then surgery was done to close the wound (paraspinal muscle flaps and direct skin advancement).

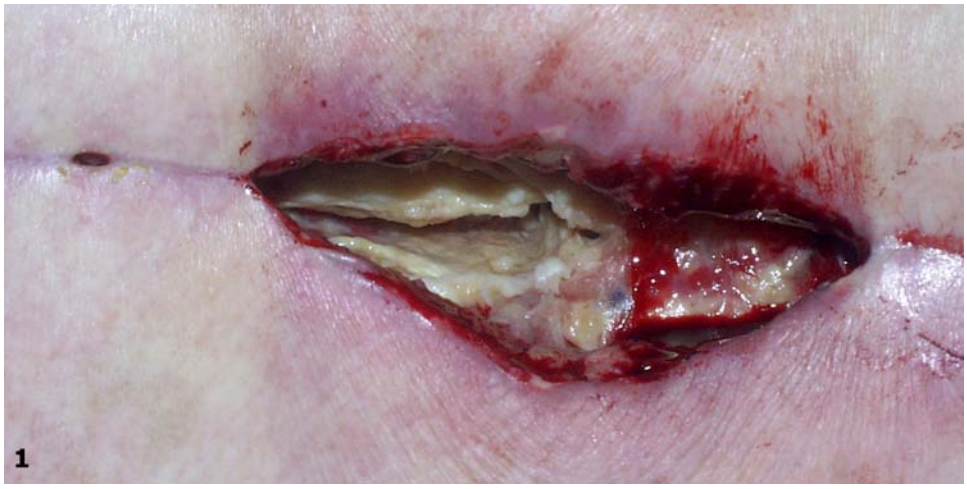


Figure 1 shows the lumbar back wound 5 weeks after surgery. Wound module proliferation has started in some of the tissues, but residual necrosis and eschar are present at wound margins and in musculoskeletal structures at the base. Had this surgery been done in an otherwise healthy patient for trauma or degenerative joint disease, this complication would have been unlikely to occur. If pathergy prone diagnoses are appreciated in advance, then problems like this can be oftentimes be avoided. This patient had no antecedent diagnosis of a hypercoagulable state (the diagnosis was made due to this event), but the rheumatoid history was clear, and that was enough of an alert to ask about all such potential problems in the patient interview and review of systems.

Case #21. A case to illustrate wound pathergy and surgical complications associated with an immune dermatosis.
This 41 year old woman had been treated for several years for pemphigus vulgaris. She took prednisone 180 mg daily, which resulted in lipomatous hypertrophy of various tissues. One such lipoma caused acute spinal cord compression and paraparesis which required emergency laminectomy and decompression. The back incision failed. The photos show multifocal infarcts and lysis at the wound margins. Her pemphigus lesions had been under control, so it is uncertain whether this was ulcerative wound pathergy due to an autoimmune flareup versus simple dehiscence due to steroid-induced wound healing insufficiency. Her coagulopathic workup was negative. (Much is talked about the wound healing negative effects of steroids. Steroids are generally benign for wounds, and in fact their ability to control disease is the cornerstone of good wound healing when underlying immunopathic and inflammatory disorders flare up and cause ulcers. The entity is real, but it happens under only a limited set of extreme circumstances, such as high load wounds, e.g. laparotomy in a patient with chronic steroid-dependent bronchitis, or with very high cumulative steroid doses, such as in this case.) The wounds nearly healed with vitamin A and topical care, and her paresis gradually started to recover, but this was interrupted when she died from flareup of an autoimmune state with multiple system failure.

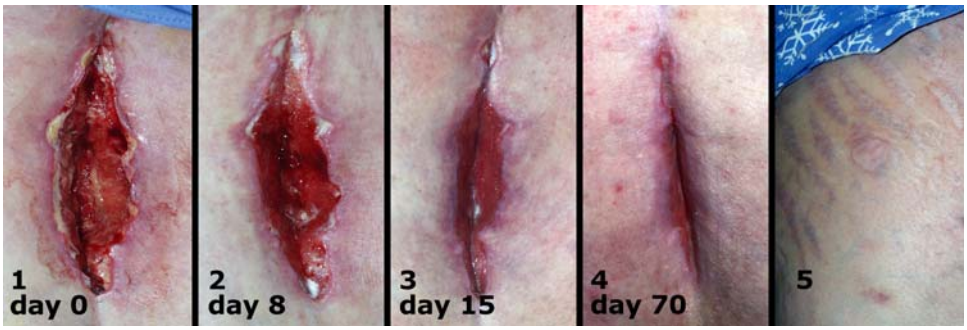
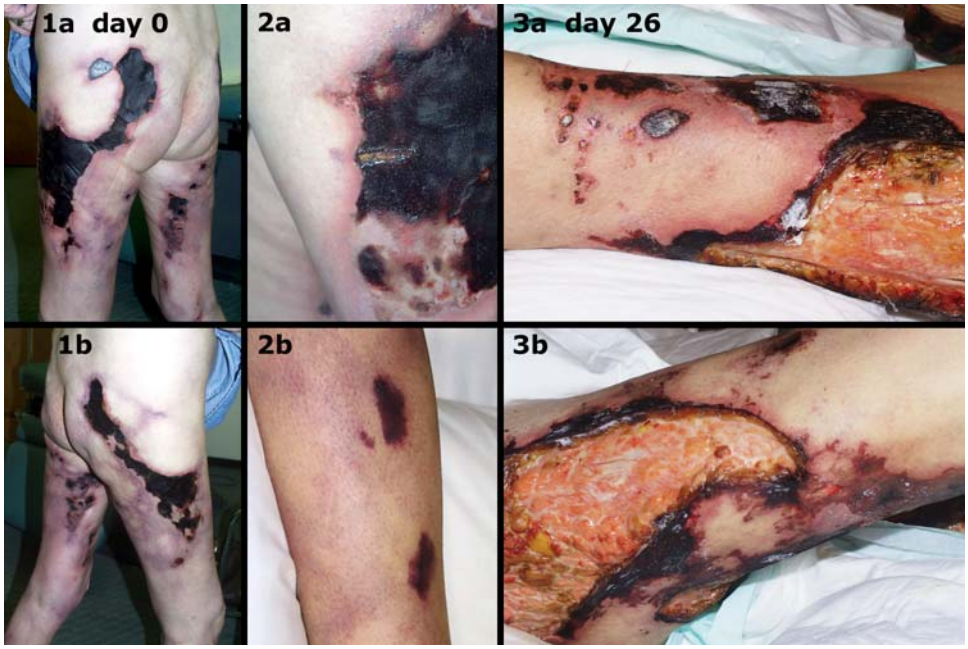


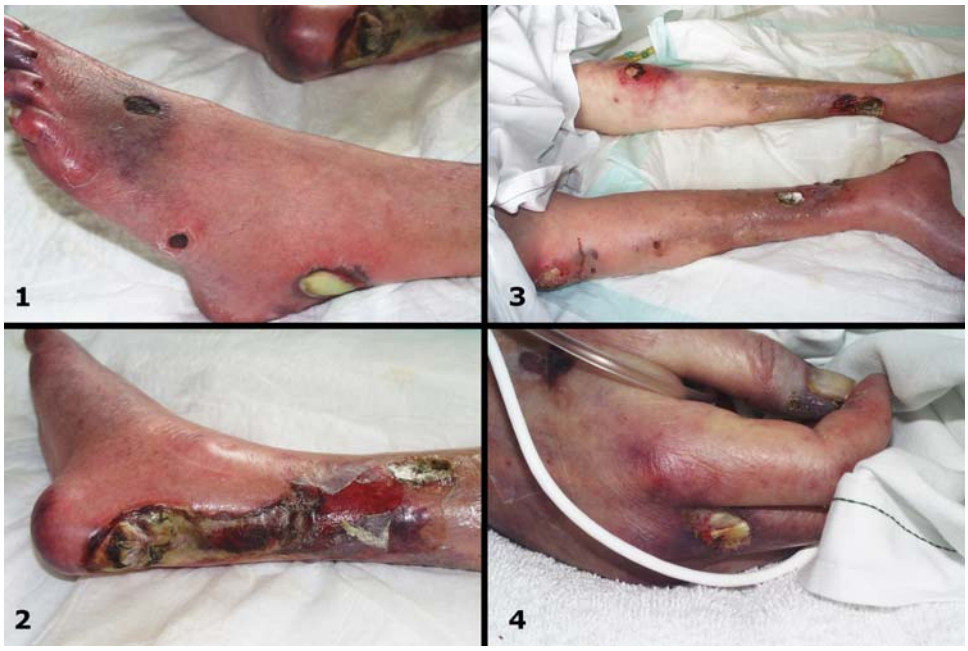
Figure 1 (day 0) is the wound on initial consultation, 4-5 weeks after lower thoracic laminectomy. Although acute events are subsided, residual infarcts and eschar are visible at skin margins and in the base of the wound. The wound surface has a red blush suggestive of wound angiogenesis (aka "granulation tissue"), but close examination shows that fat lobules and muscle and fascia bundles are still all visible, so wound proliferation and repair dynamics are significantly retarded. **Figure 2** (day 8) shows less eschar, with the onset of more normal proliferative angiogenesis and of wound contraction. These favorable behaviors seem to have accelerated toward normal after initiating pharmacological doses of vitamin A to counteract the wound-negative effects of the steroids (the steroids had already been lowered to low therapeutic doses). At day 15, **figure 3**, the wound is behaving normally, and by day 70, **figure 4**, it is nearly healed. **Figure 5** shows obesity and striae of the trunk due to the extraordinary corticosteroid doses she had been on (and she had various other Cushingoid features as well). This case is a reminder that both severe immunopathies and their various treatments can have active pathergic effects on wounds and also detrimental effects on wound healing. Common wound-healing adverse drugs include certain antimetabolites (e.g. cyclophosphamide, hydroxyurea) and TNF-a inhibitors.

Case #22. A case to illustrate skin and soft tissue infarcts due to acute immunopathic states.
This 35 year old woman developed acute lupus shortly after pregnancy and delivery. An extremely morbid event with severe liver and renal failure, she lived through it due general critical care and aggressive treatment of the primary disease. She developed large skin infarcts as part of the acute process, which had turned to dry black eschar by the time of consultation. The differential diagnosis includes a variety of immune and hematological ulcerogenic or necrotizing states, all related one way or another to lupus. Pyoderma gangrenosum is one likely state, and multifocal toxic pyoderma of the central body is an event that has happened to other post-partum patients. However, in this patient the necrosis involved subcutaneous fascias as well as skin, a distinctive difference from usual pyoderma. Fascial necrosis implies immune panniculitis or a non-immune micro-thrombotic disorder. Immune panniculopathies would include the classic connective tissue disorders (lupus, Behçet's, Sjögren's, etc.) plus the various primary panniculopathies such as eosinophilic fasciitis and necrobiosis lipoidica (Weber-Christian is perhaps the most prevalent of these panniculopathies, but it has an erythema nodosum type of presentation and histology and it is not likely to cause escharotic infarction of this variety). Absent biopsies during the acute phase, these pathologies could not be discriminated histologically. Workup for micro-thrombotic disorders showed that this patient had protein S deficiency accompanied by low transcutaneous oxygen pressures in the affected areas. The general appearance of the skin and wounds is more thrombo-occlusive than inflammatory-lytic, so a hypercoagulable state most likely contributed much to the mix that caused these infarcts. Her primary immune-inflammatory state was still active though, and conventional skin grafts or other surgical repair, which carry a very high risk of wound pathergy, were not even attempted. Instead, she was treated by a pathergy-controlling strategy of excision and closure with a collagen-gag matrix and hyperbaric oxygen support. The reconstruction was not completed because, following a dose of cyclophosphamide, she became severely neutropenic leading to mycotic brain abscess and death.



Figures 1a, 1b show the skin infarcts of the pelvis and lower extremities. **Figure 2a** is a closeup showing the boundary between eschar and living skin. **Figure 2b** is another closeup showing foci of intense vascular stasis which are not yet escharotic, but which will probably die. The absence of edema and other significant inflammatory changes, and the generalized skin purpura and cyanosis are characteristic of thrombo-infarctive pathologies rather than immune-inflammatory. In spite of the overt diagnosis of a collagen-vascular disease, workup must also look for hypercoagulable states which are likely to accompany the immune disorder. Shortly after these images, the large eschars were excised and the wounds covered with Integra™ collagen-gag matrix. **Figures 3a** (left thigh) and **3b** (right thigh) show the skin one month later, after disease flared up again, causing new infarcts. While the collagen-gag matrix is protective against acute wound pathergy when underlying disease has some degree of control, it cannot protect against flagrant active disease. Note especially the eschar along the borders of the excisions, characteristic behavior of pathergy prone disorders.

Case #23. Another case to illustrate skin and soft tissue infarcts due to acute immunopathic states.
This 47 year old woman was treated for several years for progressive neurological problems attributed to multiple sclerosis. At the time of these photographs, she had developed multiple acute morbidities, including a dense neurolepsy, respiratory failure, and multifocal skin infarcts on multiple areas of the body. History and physical confirmed a multitude of immunopathy related symptoms and signs, qualifying this as a lupus-like or mixed connective tissue disorder. Strong features included a history of uveitis and oral and genital ulcers, which in conjunction with the nature of the skin lesions made Behçet's syndrome the "best fit" diagnosis. Cerebral angiograms confirmed a diffuse angiopathy consistent with acute and chronic vasculitis. Given the dismal mortality statistics for untreated acute lupus and Behçet's, it is no surprise that the patient died. As seen in the photographs, not only were skin infarcts severe, but preliminary debridements simply resulted in more of the same, a prototypical example of Behçet's skin pathergy.



Figures 1, 2 are views of the feet and ankles showing multifocal infarcts in patterns consistent with small vessel and microvascular thrombosis, pressure injury (thresholds lowered by vascular insufficiency), and synovitis. Along with all of the new infarcts, areas of prior ulceration or debridement at the malleolus and calcaneus have a ring of black necrosis at the skin margins, the kind of pathergy which can affect surgical incisions in predisposed diseases such as Behçet's and pyoderma gangrenosum. **Figure 3** is another view of the lower extremities illustrating the extent of the problem. The same spectrum of problems also occurred elsewhere, including trunk, face, and upper extremities, as seen on the hand in **figure 4**.

Set 7: Proscription against surgery

Case #24. Wound pathergy due to a red blood cell disorder, the wound made worse by surgery.
This 33 year old woman with sickle disease had a chronic ulcer of the lateral ankle, unresponsive to a variety of therapies. An attempt was made to close the wound by some sort of local skin advancement. It did not heal – the wound failed – and what had been a small ulcer was now a large ulcer with the same problems along all of the incisions. Upon consultation, it was opted to reconstruct skin using one of the most dependable strategies there is for controlling wound pathergy and healing at-risk pathological wounds: preparatory wound care, then closure with a collagen-gag regenerative matrix (Integra™), supported by hyperbaric oxygen therapy (because of the severe reduction in local flow and transcutaneous oxygen tensions). This approach eliminated further complications, and the wound almost fully healed. However, the patient's life, including plans to touch up and conclude the reconstruction, was interrupted by numerous sickle crises and hospitalizations. The ulcer persisted, but with time, the patient accepted it as a chronic condition, and was able to keep it stable with good hygienic topical care. Had the original conventional cut-and-sew surgery not been done, the problem, even if it did not heal, would have remained small and easier to manage.

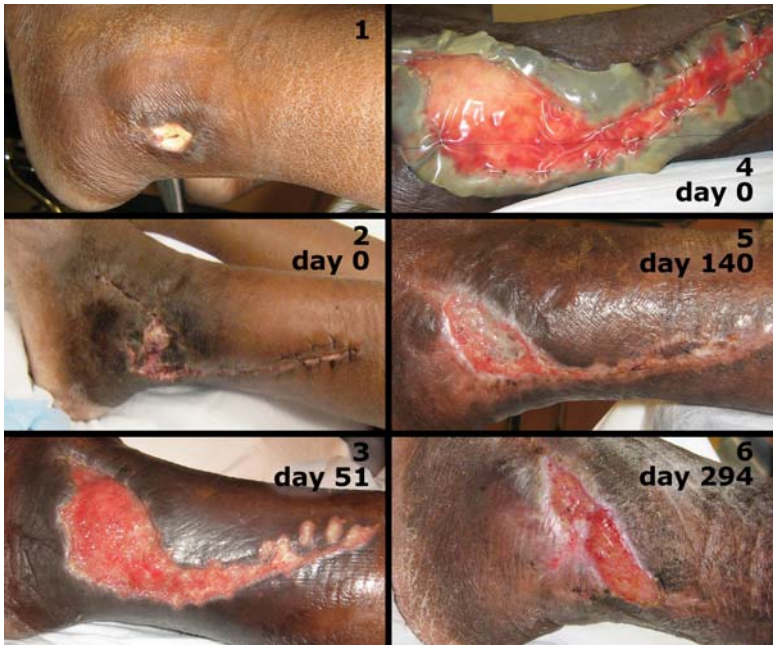


Figure 1 shows the original ulcer on the lateral left ankle. **Figure 2** (day 0) shows the ankle after attempted closure. Listed in the medical records as a "rotation flap", this improper design would not have covered the wound under the best of circumstances, and in this patient with a pathergy prone micro-occlusive disorder, flap necrosis and wound failure were predictable. **Figure 3** shows the ankle 51 days later after a return to basic topical care. The wound is clean, free of further injury, and proliferating. Nonetheless, as a pathological wound, wound module kinetics are impaired, and the wound failed to make any further improvements after 3 months of topical care. **Figure 4** (designated as a new day 0) shows the wound with Integra™ collagen-gag matrix in place, the start of a regenerative skin reconstruction using a pathergy-preventing matrix. **Figures 5, 6** show the reconstruction 140 and 294 days later. The remaining wound appears healthy, and in a healthy person it would easily epithelialize to complete closure. However, the patient's progress was interrupted by numerous sickle crises, and it got no better. For the sake of further management, the judicious and economically circumspect use of new layers of regenerative matrix or of topical stimulatory therapies are all worthy and justifiable, since they incur no further risk to the patient. Conventional therapies such as transfusion (erythrocyte exchange) and rheological drugs are always worth trying (although long term multi-transfusion has its own risks). Doing more conventional surgery with incisions and repairs would be improper and subject to the same complications.

Case #25. Wound pathergy due to macro-arterial disease, with preventable complications due to indiscriminate surgery. This case illustrates the one type of wound pathergy that most surgeons have at least some awareness of, progressive amputations due to arteriosclerotic peripheral occlusive disease. This 64 year old man with hypertension and atherosclerosis developed a small ulcer or infarct on the foot. Foot or toe amputation was followed by below-knee amputation and then above-knee amputation which likewise infarcted. The progressive amputations were obviously done because of necrosis and wound failure at each prior level. The patient was seen in consultation after having been threatened with hip disarticulation, which would also have died, inasmuch as the patient had Leriche syndrome and high grade aorto-iliac stenosis. The thigh-level infarct was resolved and healed by usual modalities (preparatory wound care, closure with Integra™ collagen-gag regenerative matrix, and hyperbaric oxygen support). Wound pathergy was due to severe ischemia. While a macro-vascular disease was the culprit here, the same risks accrue to any vaso-occlusive disorder. It is now 55 years from the first abdominal aortic replacement and femoral-popliteal bypass, 35 years since vascular surgeons clearly enunciated the principles of limb salvage, and 15 years since endo-technologies have made revascularization a reasonably dependable low morbidity affair available in most communities. Nonetheless, too many patients have indiscriminate surgery on ischemic limbs by unwary or uneducated surgeons resulting in completely preventable major morbidity and disability. For this patient, operative revascularization became impossible once the thigh amputation was done, but proper management from the beginning would have corrected the problem and preempted all subsequent issues. At any point along the way, prudent wound care and wound reconstruction would have solved the problem at a lower level. The indiscriminate use of surgery in patients with pathergy-producing risks is disallowed. Proper diagnosis and peremptory management before further surgery are mandatory.

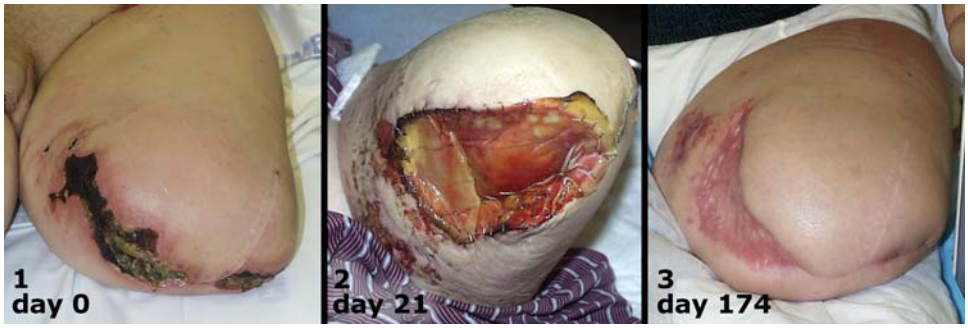


Figure 1 (day 0) shows the thigh following recent amputation, just prior to threatened hip disarticulation. Disarticulation could not have been condoned for any number of reasons, but even assuming that it had some theoretical legitimacy, it would have had the same pathergic necrosis of the incision, since the level of vascular occlusion was well above the blood supply to the hip. **Figure 2** (day 21) shows the thigh after excision and closure with pathergy-controlling Integra™ collagen-gag regenerative matrix. **Figure 3** (day 174) shows the thigh fully healed. By understanding the relevant pathologies, unexpected post-operative necrosis and complications can be anticipated. By using appropriate strategies and methods, wound necrosis can then be preempted. Had these principles been exercised when the problem was confined to the foot, significant amputation likely would not have been needed.

Case #26. Another wound pathergy due to arterial disease, with preventable complications due to indiscriminate surgery. Diabetes mellitus and its complications are epidemic among native peoples of the American southwest. Unlike other groups where atherosclerosis is associated with hypertension, smoking, hyperlipidemias, and other risk factors (including diabetes), the vascular disease in this population can result in severe distal occlusive disease of the upper extremity. This 51 year old man had a small injury or infarct of his fingertip. Attempts to debride it turned a small problem into a progressively bigger problem. As seen in the photos, at the time of consultation, the wound surfaces after recent debridement-amputation were all necrotic. Wound stability and the slow induction of a proliferative wound module were contingent on basic hygienic wound care, judicious piecemeal debridement of separating eschar, wound stimulatory therapies, and especially on doing no further surgery. Conventional surgery simply creates a new level of injury and pathergy through viable tissues, unnecessarily extending the wound. Partial finger amputation may have been unavoidable, but had any of the strategies for preventing pathergy been used, the problem would never have progressed proximal to the metacarpophalangeal joint. (The patient died from other complications of diabetes, renal, and vascular disease before his hand healed.)

Figure 1 (day 0) shows the dorsum of the left hand. The ring finger debridements progressed to the ray amputation seen here, and the resulting wound has necrosis of all exposed tissues. **Figure 2** (day 17) shows that although the wound is not yet healing, that necrosis has been arrested with proper care. **Figure 3** (day 90) shows that: there is no further necrosis; eschar is gone (other than tendons being preserved); a proliferative wound module has appeared; there is early epithelial growth at some of the margins. **Figure 4** (day 115) shows a healthy wound with progression of these positive changes, including wound contraction and significant epithelialization.

Case #27. Another wound pathergy due to arterial disease, with preventable complications due to indiscriminate surgery. This is very similar to the preceding case, a 42 year old woman, southwest native American with diabetes and upper extremity athero-occlusive disease. A small ulcer of the long fingertip, followed by overly ambitious attempts to cure it with surgery, resulted in progressive necrosis and amputation, resulting eventually in ray amputation and necrosis of the adjacent finger. Progressive surgery simply meant progressive displacement of the zone of active infarction to an ever more proximal position. At the time of consultation, active necrosis and progressive ulceration were arrested by basic pathergy-controlling modalities (hygienic topical care with silver sulfadiazine, judicious debridement of separating eschar, and eventual closure with Integra™ collagen-gag regenerative matrix). Had these modalities been initiated at the beginning in lieu of surgery, the rest of the story would never have happened.

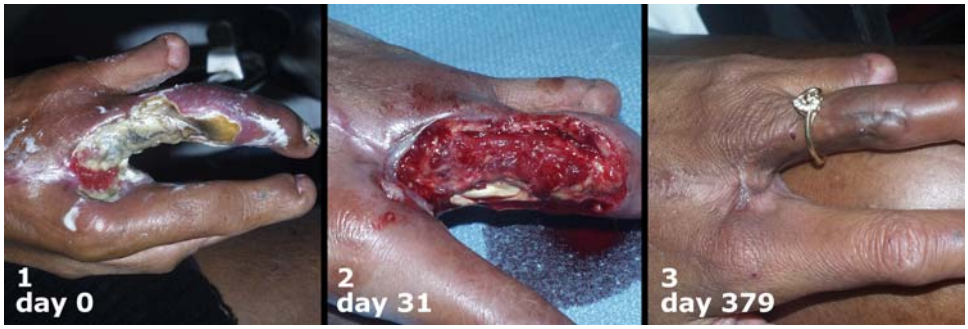
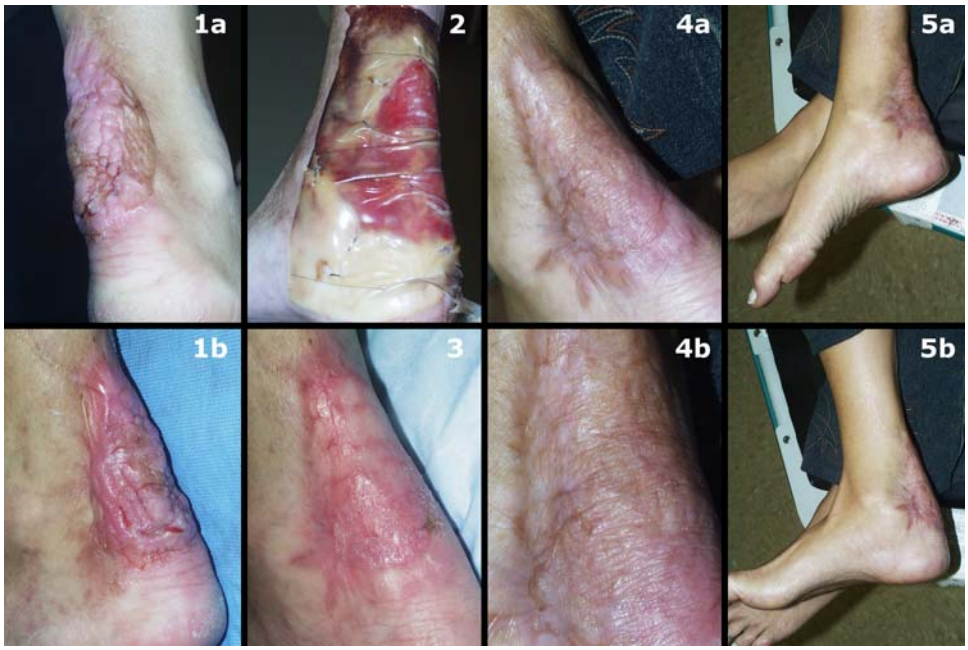


Figure 1 (day 0) shows the left hand after multiple failed attempts to cure ischemic ulceration with more surgery. At the time of presentation, the dorsum of the hand in the third ray was completely necrotic. A period of basic wound care (hygiene, silver sulfadiazine) arrested the infarcts and allowed the wound to start healing. The partially necrotic ring finger requires some sort of pathergy-safe closure. **Figure 2** (day 31) shows the ring finger at the time of debridement and closure with Integra™ collagen-gag regenerative matrix. **Figure 3** shows the hand healed at one year. Had these principles of care and pathergy avoidance been applied from the outset, the patient would have lost only a fingertip.

Case #28. Wound pathergy due to a micro-thrombotic disorder, with progressive ulceration due to repetitive surgery.
This 44 year old woman had an achilles tendon rupture during exercise. Attempted repair was complicated by necrosis of the overlying skin. Multiple repair attempts caused more necrosis. Eventually, the wound was covered with a rectus abdominis free flap which did heal, but the overlying skin grafts became chronically ulcerated and painful. Attempts to repair or revise them also resulted in skin necrosis and persistent ulceration. The patient's history was significant for blindness in one eye due to retinal artery thrombosis. This history is highly suggestive of a hypercoagulable disorder, and when seen in consultation, laboratory evaluation showed high anticardiolipins and fibrinogen, confirming an antiphospholipid antibody syndrome. Warfarin anticoagulation was started, and then the old dysplastic grafts and ulcers were excised, and skin was reconstructed with a pathergy-controlling collagen-gag regenerative matrix (Integra™). The ankle healed and matured without further problems. In an otherwise seemingly healthy patient without vascular disease, the multiple failed wounds after multiple operations were an obvious alert to a pathergy producing pathology. Had the significance of this been appreciated after just one or two procedures, most of the prolonged activities, morbidity, expense, and remote donor sites that she went through would have been avoided.



Figures 1a, 1b are lateral and medial views of the achilles as first seen on consultation. A small area of old skin graft is mature, but most of it has villous hypertrophy or overt inflammation, with multiple small ulcers which had persisted for months. Since no skin was lost due to the original tendon rupture, all of the missing native skin was a consequence of the repetitive failed cut-and-sew procedures. **Figure 2** shows the collagen-gag matrix in place after starting warfarin and then excising the old grafts and ulcers. This resurfacing was the only one of her many prior procedures which was not complicated by wound and skin necrosis or persistent ulceration. **Figure 3** shows the result at 7 months. The skin is still immature, and there remains a small unhealed area, but there are no pathological or aberrant scar changes. **Figure 4a** is the result at 15 months, fully healed and maturing. **Figure 4b** is a closeup showing how the regenerated skin is thin and compliant, with Langer's lines wrinkles and creases, and with none of the scar, hypertrophy, nor ulceration that was present before. **Figures 5a, 5b** confirm that ankle and skin mechanics are good. The patient has been restored to normal activities without symptoms nor further care (except for lifelong anticoagulation).

Case #29. Wound pathergy due to a micro-thrombotic disorder, with progressive infarcts due to repetitive surgery.
This 66 year old man had sigmoid resection for diverticular colo-vesical fistula. Anastomotic leak required drainage and colostomy, which was complicated by colonic necrosis. This was followed by colectomy and ileostomy, which resulted in small bowel infarction. With each procedure, there was progressive necrosis of the abdominal wall until most of the anterior muscles and fascias were dead. By the time of consultation, the patient was too damaged to recover. However, diagnosis of a pre-thrombotic hypercoagulable state could be established by history (history of venous thrombosis and pulmonary embolism, and also a finger amputation for necrosis following a minor fingertip injury), by histology (excised material showed primary small vessel thrombosis), and by laboratory (confirming activated protein C deficiency). While a simple anastomotic leak does not trigger any special diagnostic concerns, everything else in this history was an alert to a hypercoagulable or other micro-occlusive state. Unlike for skin complications, further surgery could not have been postponed in this case of peritonitis, but recognizing the problem and treating with anticoagulants would have prevented the progressive morbidity. Whenever unexpected infarcts and tissue complications occur – i.e. wound pathergy – that is the tipoff to the observant surgeon that some sort of workup and pretreatment is needed in advance of further surgery.

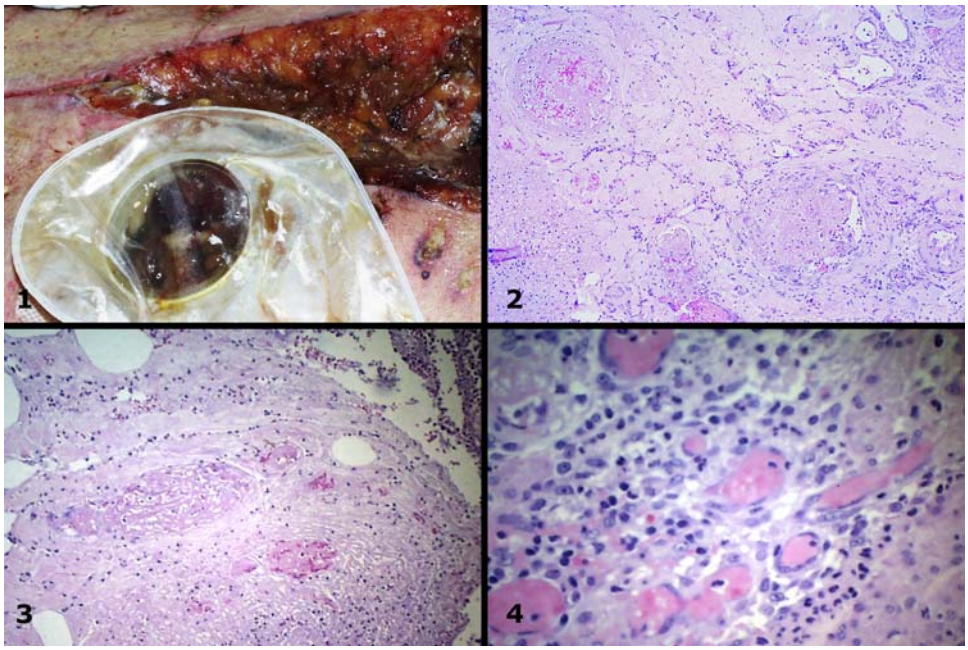


Figure 1 shows the abdomen after the multiple procedures described above. The deeper subcutaneous fascias are dead, and so are the muscles and muscular fascias. There are cutaneous infarcts around suture holes. The ileostomy is completely necrotic. **Figures 2, 3, 4** are specimens taken from the excised colon. There are thrombi with inflammatory infiltrates, areas of necrosis, and vascular stasis. The upper right corner in **figure 3** is the colonic lumen, ulcerated without any mucosa, with inflammatory exudates on the surface of submucosa or muscularis. The necrosis and relative low density of inflammatory cells within the tissues pegs this as a primary thrombotic event. Acute disseminated multi-tissue vascular infarcts have few causes other than the hypercoagulable disorders. In a hypercoagulable patient, once the injury-thrombosis-inflammation triad has been upregulated into an extreme pathological attractor, it does not take much additional provocation to cause catastrophic thrombosis. It is the “flip side” of disseminated intravascular coagulation (DIC), a similar pathogenesis resulting in vascular thrombosis and infarcts rather than factor consumption and hypocoagulability. Avoiding more trauma, and giving anticoagulants and steroids are the strategies to break the cycle.

Case #30. Wound pathergy due to an immune-coagulopathic disorder, with progressive complications of repetitive surgery. This 34 year old man was treated for several years for systemic lupus erythmatosus, controlled with steroids, but always having some level of active signs and symptoms. He sustained a small laceration on the dorsum of a finger. It did not heal after simple suturing. After other attempts at local repair, closure was tried with a full thickness graft from the groin. The groin donor wound dehisced and did not heal. An attempt was then made to close the groin wound with a fasciocutaneous flap from the adjacent lower abdomen, which likewise fell apart. The patient also had a chronic leg ulcer due to a similar minor injury over the tibia. When the first few repairs on his finger failed, especially in an area that should normally heal without problems, all in a patient with lupus, those were sufficient reasons to do no more surgery until the problems were diagnosed. When seen in consultation, the lupus was already being treated and under reasonable control. Workup was done for hypercoagulable disorders. The patient had high anticardiolipins, i.e. an antiphospholipid antibody syndrome. Warfarin anticoagulation was started, and his wounds then healed promptly by natural contraction and epithelialization supported by basic topical care. Sadly, the story does not end there. Several years later, while traveling out of town, he was in an automobile accident and required emergency laparotomy and splenectomy. Not only did his abdominal wall dehisce and fail to heal, but his transverse colon necrosed resulting in a defacto colostomy in the middle of the abdominal wound. When seen again in consultation after returning home, warfarin was restarted, along with basic wound care, and the wounds re-epithelialized. The plan was to allow the healed wounds 12-24 months to mature before taking him back to surgery for bowel and abdominal wall reconstruction. Half way into that waiting period, and no longer anti-coagulated, the patient tripped and fell at home. He “hurt his back”. He had no immediate neurological deficits, but he became paretic over the next 24-48 hours. Imaging showed no evidence of fracture, herniation, hematoma, nor other signs of cord compression. While the diagnosis could not be directly proven, it appeared that local inflammation and thrombosis in the zone of some otherwise minor musculoskeletal sprain or fracture triggered a wider zone of thrombosis that directly affected the spinal cord – an extreme but not surprising complication of the hypercoagulopathies (the same disorders that cause Budd-Chiari liver thrombosis, Paget-Schroeder subclavian thrombosis, Sheehan’s pituitary apoplexy, retinal artery thrombosis, and any of the other not-so-common major thrombo-occlusive catastrophes). Anticoagulation and hyperbaric oxygen therapy were initiated, to try to minimize necrosis and salvage some function, but given the multitude of problems that the patient faced, the family and patient opted out of further significant care, and the patient eventually died. The abdominal and spinal cord events – bizarre and unanticipated post-traumatic thrombosis and necrosis – as well as the many original skin and fascia complications, all are just another manifestation of wound pathergy.

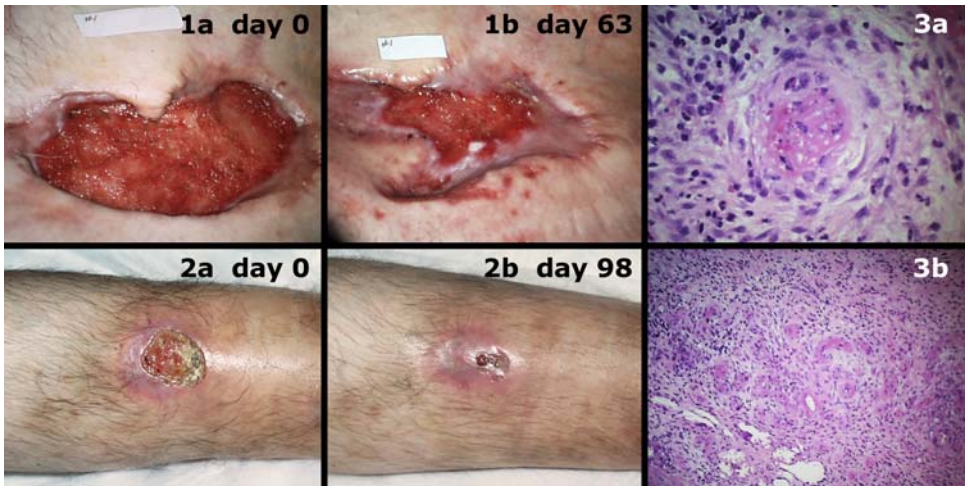


Figure 1a shows the groin and lower abdominal wound not long after consultation and the initiation of workup and care. It had become chronic with failed contraction and epithelialization. After diagnosis of an antiphospholipid antibody state, warfarin was started, and wound kinetics became more normal. **Figure 1b** two months later shows the response, and the wound healed entirely by continued contraction. **Figure 2a** is the tibial ulcer. It too healed readily after warfarin started, **figure 2b**. The ulceration of the finger and tibial wounds, and the necrosis and ulceration of the various flaps and grafts are all variations of post-traumatic wound pathergy. **Figure 3a** shows intravascular thrombus from a biopsy of the wound margins, consistent with the hypercoagulable disorder. **Figure 3b** shows another feature of chronic pathological ulcers typically seen in those of immunopathic and hematological origin, that of fibrinoid vessel degeneration and perivascular fibrin cuffs against a background of chronic inflammation.

To repeat, the important lessons of this review are: (1) recognize and respect wound pathergy and cease any more surgery until the problem is worked up and treated; (2) respect and preemptively deal with baseline conditions of vascular, autoimmune, and hematological diseases and related complications.

END