Sakura's Sticky Situation

A case report of successful open wound management utilizing manuka honey and delayed surgical closure

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Introduction

Sakura Wally was hospitalized with Mississippi State College of Veterinary Medicine for 10 days, after she spontaneously developed a large necrotic wound over her dorsal lumbar region. She received extensive open wound management daily bandage changes, topical manuka honey, and targeted antibiotic therapy. Once the wound was deemed healthy, it was followed by delayed surgical closure and subsequent discharge for at-home care. Despite being managed at a specialty hospital because of an unusual set of comorbidities on presentation, the wound management in her case is still within the scope of a general practitioner. This case report describes extensive wound management methods incorporating manuka honey, that could easily be applied at a general practice clinic.

History and Presentation

Sakura Wally is a 6-year-old female spayed Shih Tzu with a history of epileptic seizures since the age of 2 years. Her seizures are managed at home with phenobarbital 2 mg/kg in the morning and 3 mg/kg in the evening, and KBr 35 mg/kg once daily. She has skin allergies which are controlled with daily Apoquel (oclacitinib) and twice daily diphenhydramine (unspecified dosages).

One week before presentation to MSU-CVM, Sakura ingested the liquid from a nicotine vape cartridge. Shortly after ingestion, she became lethargic, vomited, and had three consecutive seizures. Her seizures were treated by her owners with three additional doses of phenobarbital, and she was taken to her veterinarian. Sakura's primary care veterinarian provided symptomatic supportive care over the next two days, including maropitant, intravenous fluid support, and enrofloxacin. During the days following her discharge, Sakura's appetite and attitude declined, and she was taken to a local animal emergency clinic. During her stay, a large area of necrosis developed spontaneously over her dorsal lumbar region, and she was referred to MSU-CVM for continued wound care.

On presentation, Sakura was pyrexic, (103.9 F) and had a large, (~17.5 x 6cm) irregularly shaped necrotic area of skin over the dorsal lumbar area which was symmetrical across the spine. There were 3-4 small weeping open sores along the periphery of the main necrotic patch of skin. The wound was very well demarcated with a hyperemic rim. The site of her previous IV catheter in her left cephalic vein was also erythematous and painful on palpation. She was reported to drink large amounts of water and then regurgitate. The remainder of her physical exam was unremarkable.

Diagnostic Approach

Complete blood count (CBC) on presentation showed a general leukopenia characterized by a low white blood cell count at 4.33 $x10^3$/µl (normal 5.00 - 14.20 $x10^3$/µl), and a regenerative left shift. A mild anemia was also present. Blood chemistry showed a mild-to-moderate azotemia, elevated ALP (alkaline phosphatase) at 405 U/L (normal 11 – 140 U/L), and mildly elevated total bilirubin at 0.8 mg/dl (normal 0.2 - 0.6 mg/dl). Platelets were slightly low, confirmed by a manual count. SNAP 4Dx was negative for all (*D. immitis, Erlichia, Anaplasma*, and Lyme). Thoracic and abdominal radiographs were normal with the exception of a generalized mild hepatomegaly.

Sakura was placed on IV Plasmalyte at 1.5x maintenance, and broad-spectrum intravenous antibiotics Baytril (enrofloxacin) at 10 mg/kg IV once daily and Unasyn (ampicillin and sulbactam) at 30 mg/kg IV every 8 hours. She was kept on phenobarbital at 2 mg/kg orally every 24 hours, with midazolam 0.3 mg/kg rescue doses available in case of seizure. Methadone at 0.1 mg/kg IV every 4 hours was added for pain, and pentoxifylline at 30 mg/kg orally every 12 hours was included to attempt to improve blood flow to the remaining healthy tissues around the wound area and manage vasculitis.

Upon transfer to the internal medicine service, a biopsy was taken of the necrotic area, which revealed dermatitis, panniculitis and myositis, suppurative and necrotizing, subacute, diffuse, and severe, associated with fibrinoid vasculitis and thrombus formation.[1] Culture and sensitivity of the

wound eventually returned moderate growth Escherichia coli and *Enterobacter cloacae.* The sensitivity panel indicated marked resistance, with both organisms susceptible only to amikacin, imipenem, and gentamicin. With amikacin and gentamicin associated with renal toxicity, and azotemia already on the problem list, meropenem became the new antibiotic of choice for single-agent therapy, at 7.8 mg/kg IV every 8 hours.

Subsequent diagnostics included only recheck blood chemistry panels, which showed improved hepatic enzyme levels, and resolved azotemia. Mild hypoalbuminemia developed 2 days into her stay at 1.8 L g/dl (normal 2.5 - 3.9 g/dl) which was unsurprising with such a large weeping wound. No clinical signs associated with hypoalbuminemia were noted, and it improved on the following chemistry panels (2.0 g/dL, then 2.4 g/dL at discharge).

Differential Diagnoses

Because the necrotic wound appeared so soon after Sakura ingested the nicotine liquid from the vape cartridge, it is natural to assume causation. However, the cause of Sakura's wound could not be definitively linked to the nicotine ingestion, and a cause was never established. Biopsy results described dermatitis, panniculitis and myositis, with vasculitis and thrombus formation. No bacterial component was recognized within the inflammatory centers or the thrombi, but bacteria were present in small numbers in the more superficial layers. The top differentials included an arthropod bite, an atypical cutaneous drug reaction to phenobarbital and/or KBr, or a septic or nicotine related thromboembolic disease of the cutaneous vessels.

Venomous spider bites can cause necrotic wounds in dogs, but usually appear as a large round/ovoid area of hot, erythematous skin, progressing to central necrosis and a smaller weeping wound. Sakura's wound was well demarcated and sloughed the entire area nearly simultaneously, rather than only opening in the center, based on photographs provided by Mrs. Wally on the day of it's

appearance. Additionally, the almost perfectly symmetrical nature of Sakura's wound would imply a bite very near midline on her dorsum, which seems unlikely, but cannot be ruled out with certainty.

Cutaneous drug reactions are documented after anti-epileptic drug administration in dogs, including KBr and phenobarbital, and are generally associated with long-term use.[2] These reactions are usually considered a form of hepato-cutaneous syndrome.[3] Most reports describe either hyperkeratosis and splitting of paw pads, pustular dermatitis around the mouth, eyes and nose, or pruritic, crusting breakouts of haired skin.[2,3] No reports uncovered during the research of this paper described well-demarcated spontaneous dermal necrosis, although Sakura's wound could have been a markedly atypical presentation of this phenomenon.

Smoking and vaping nicotine is associated with increased coagulability.[4] Thrombosis of a cutaneous artery leading to a large area of dermal necrosis is not impossible, however, one would not expect a wound symmetrical around midline, as the vessels that supply the skin originate ventrally on each side of the body and converge near midline. An identical thrombus would need to form on both sides of the lateral body simultaneously in order to form a wound on the dorsum that is symmetrical about midline, based on a map of the direct cutaneous vessels in a dog.[5]

The pathologist who reviewed the biopsy results also suggested an underlying sepsis could have precipitated the thromboembolic dermal disease.[1] The Shwartzman phenomenon[18] describes a local or systemic vasculitis following exposure to bacterial endotoxin. A sensitization exposure to endotoxin causes intravascular fibrin thrombi. Reticuloendothelial blockade upon re-exposure to endotoxin prevents clearance of these thrombi.[18] Prior to developing the wound, Sakura displayed nonspecific signs of illness (lethargy, vomiting, diarrhea, inappetence, pyrexia) that could be attributed to sepsis. The site of her previous IV catheter was red and painful on presentation, likely representing phlebitis, which could have seeded a low-grade systemic sepsis. She was pyrexic on presentation to MSU-CVM, by

which time she had already developed the necrotic wound, so it is difficult to determine the initial cause of her fever. Differentials for Sakura's fever included the massive inflammatory response to the large necrotic wound, with or without contribution of local infection, or sepsis, or phlebitis from the previous IV catheter site. With the diagnostic results we now have, her fever on presentation most likely resulted from the infected necrotic wound.

The wound spread very little after the necrosis appeared, only sloughing all skin layers down to the underlying muscle. No cause was determined, and no skin necrosis developed anywhere else, so Sakura's care was exclusively supportive wound management.

Pathophysiology

No definitive cause was ever identified for the necrosis that started on Sakura's dorsal lumbar region. Biopsy indicated thrombotic disease with a vasculitis component. The four well known overlapping stages of wound healing include hemostasis, the inflammatory phase, the proliferative phase, and the maturation phase. In necrotic wounds, like Sakura's, that result from disruption of blood supply, the process effectively begins with the inflammatory phase.

Destruction of blood vessels eliminates blood supply to the dermis and underlying muscle, leading to ischemic death of tissues, and concurrent inflammatory infiltration. First, neutrophils predominate, which begin to be replaced by macrophages after approximately 24 hours.[6] Debridement by inflammatory cells removes dead tissue and debris, but can also damage surrounding healthy tissues. Plasma proteins and fluid are leaked into the wound area, which helps support physiologic inflammation, but in some large wound cases, may lead to systemic hypoproteinemia.

During the proliferative stage of healing, fibroblasts proliferate and secrete collagen. Angiogenesis begins simultaneously. The combination of fibroplasia and angiogenesis creates granulation tissue, through and upon which keratinocytes migrate, leading to epithelialization.

Myofibroblasts put tension on wound edges, drawing them towards each other and effectively decreasing the wound area necessary for re-epithelialization. Wound retraction begins around 5-9 days,[7] independently of re-epithelization, and continues until wound edges meet, or in the case of large wounds, tension on the skin exceeds pulling force by the myofibroblasts. Proliferative phase collagen (type III) is disorganized and bulky. As epithelialization completes, type III collagen is converted to type I collagen which is more organized, stronger, and less bulky. This maturation phase can continue for years after the initial wound occurs, creating a mature connective tissue scar.[6,8]

Treatment and Management

On presentation, a bandage was applied and was changed every 24 hours as the wound was allowed to declare itself. Once necrosis stopped progressing, mechanical debridement with dry-to-dry bandaging promoted healthy granulation tissue until the wound was deemed ready for surgical closure. The management in Sakura's case is well within the scope of a non-specialty clinic.

Each bandage change was performed with sterile gloves and instruments. The contact layer of the bandage was either sterile 4x4 gauze squares with topical manuka honey ointment, or sterile manuka honey and calcium alginate dressing pads (depending on availability.) The absorbent layer consisted of sterile lap sponges. Bandaging cotton (cast padding) was applied, held in place with conforming stretch gauze, and covered with self-adherent elastic wrap.

Once daily, using sterile surgical gloves and instruments, the old bandaging material was removed, creating gentle debridement of devitalized tissue and debris. Remaining debris was gently debrided with sterile gauze. Mechanical debridement supplements the debridement performed by inflammatory cells. Removing excess debris means fewer inflammatory cells are needed to clean the area, and helps diminish an over-exuberant inflammatory response that could damage healthy tissues.[8] Both mechanical and autolytic debridement were used in Sakura's care. In some cases, surgical

debridement may be necessary to remove large amounts of devitalized tissue. Small wounds may even be removed by complete excision ("en-bloc"). Enzymes like collagenases can be added to digest debris, but may put healthy tissues at risk. Biosurgical debridement with maggots is sometimes used in areas where appropriate dressings may not be realistically applied (e.g. perianal).[9]

Sakura's wound was lavaged with warm sterile saline at each bandage change. The cap of a 1 liter bottle of sterile saline was punctured 5 times with an 18g needle, and the bottle was squeezed to rinse the wound. Recommendations for wound lavage with sterile saline or a balanced electrolyte fluid range from about 4-15 PSI. This pressure removes debris and bacteria, without damaging tissues or driving fluid to accumulate in dead spaces.[10] 35-60cc syringes fitted with 18g needles can achieve about 7-8 PSI.[7] The punctured saline bottle provides roughly the same pressure. Lavage and debridement prevent build up of necrotic debris, and remove bacteria, to help provide a good environment for the wound healing process to continue. Leukocytes migrate best in moist environments free of necrotic debris.[8]

The previously described occlusive dry-to-dry bandage with honey was applied following debridement and lavage. A controlled moist environment is optimal for wound healing.[7,8] Occlusive bandages prevent drying, and lower O2 saturation at the surface of the wound. Leukocytes migrate better under moist conditions, and low O2 can stimulate macrophage activity.[8] Additionally, systemic antibiotics may accumulate in wound fluid, exerting action at the very surface of the wound.[8] Warmth and moisture stimulate autolytic debridement.[7,8] Very tight bandages should be avoided, since they diminish blood flow and circulated oxygen supply, which is critical for fibroplasia and angiogenesis.[8]

Sakura's wound was treated with medical grade sterile manuka honey. Depending on product availability, either a honey-impregnated sterile alginate dressing was used, or a manuka honey gel product was applied under sterile gauze. Manuka honey is produced by bees that exclusively pollinate

the *leptospermum scoparium* (tea tree) bush in New Zealand and Australia. Manuka honey has been shown to improve wound healing by several interacting mechanisms. Infected and necrotic wounds benefit from application of osmotic agents, which draw excess fluid and edema away from the wound bed, without drying the wound.[11] The high sugar content of any honey provides excellent osmotic action.[15,17] Sugar may also help support the metabolic component of healing,[13] even in topical application, and seems to promote autolytic debridement.[13,14,17] Low pH may also prevent bacterial colonization and support debridement.[15] Two of the active ingredients specific to manuka honey are leptosperin and methylglyoxal.[11] Leptosperin inhibits myeloperoxidases, which catalyze the production of tissue damaging reactive oxidants in inflammatory cells. Methylglyoxal demonstrates antimicrobial actions against *E. coli, S. aureus* and *P. aeruginosa*, via poorly understood mechanisms.[11,12] Manuka honey has shown antimicrobial action against some 20+ bacterial agents, including *Enterobacter and E. Coli* species, which were the agents cultured from Sakura's wound. Manuka honey also appears to show synergy with some systemic antimicrobials.[11,12] Manuka honey can reduce virulence factors, and reduce biofilm, protease, and DNAase production by some bacteria.[12] In general, wounds treated with manuka honey show faster healing times, reduced inflammation, and better epithelialization, than wounds not treated with manuka honey.[14,16]

When the wound had completely declared itself, all the macroscopic necrotic tissue had been debrided, and healthy granulation tissue was present over the entire open wound area, surgical closure was performed. In surgery, the granulation bed of the wound was debrided both with dry gauze and with a scalpel blade, and lavaged with sterile saline. The irregular skin at the edges of the wound was incised away cleanly with a scalpel until healthy skin and straight edges appropriate for apposition surrounded the wound bed. The skin around the wound was undermined using sharp and blunt dissection with Metzenbaum scissors. Walking sutures of 2-0 PDS were placed in the dead space around the wound to draw the skin closer to apposition, and to take some of the strain off the wound edges. A

continuous subcutaneous and subcuticular pattern of 3-0 Monocryl was applied. The skin edges were apposed using 3-0 nylon suture in a cruciate pattern, with scattered simple interrupted sutures in areas of high tension. Monofilament nonabsorbable suture on a reverse cutting needle provides the best healing for sutured skin incisions.[8] Interrupted sutures cause less edema and improved microcirculation, leading to higher initial tensile strength. Interrupted sutures also put less suture material in the skin, leading to less damaging inflammation.[8] The goal when closing skin incisions is to only just bring the edges into apposition. Looser apposed incisions are stronger in the first 21 days than tightly apposed incisions.[8]

Sakura remained hospitalized overnight and was transitioned to oral gabapentin at 10.5 mg/kg following day. Throughout her hospitalization, Sakura rarely exhibited signs of pain. Tylenol 4 (acetaminophen with codeine) would likely have been the oral pain medication of choice for most patients, but with azotemia, and increased ALP and TBili, gabapentin was preferred. Her pain appeared well managed on oral gabapentin. She was discharged on oral gabapentin 10.5 mg/kg to be given every 8-12 hours as needed for pain, injectable meropenem at approximately 7.7 mg/kg subcutaneously every 12 hours for 10 days, and pentoxifylline at 30 mg/kg orally every 12 hours to manage residual vasculitis.

Skin circulation is known to deteriorate for approximately 5 days after surgery.[8] Nonviable skin is usually visibly recognizable. Special stains are available to identify nonviable skin, but rarely outperform visual inspection.[8] The day of discharge (one day after surgical closure), two small (≤ 2 cm) areas of suspected nonviable skin were visible along the suture line. These areas may have resulted from damage to cutaneous supply vessels during undermining of the dorsal skin, or due to inflammatory damage of the surrounding skin.[7] Revision of the wound closure would further delay healing and put other healthy skin at risk of devitalization. Sakura was discharged with instructions for careful monitoring of the suture line. Her owner was able and willing to provide us with near daily photographs, as the devitalized tissue

began to slough. Both areas (and a few small additional sites) of devitalized tissue gradually necrosed and became large scabs. Still, the skin edges along the rest of the incision remained viable and apposed, so recommendations were made to patiently monitor without attempting revision. A few additional sutures were placed by Sakura's primary veterinarian, without revision of the previous surgical closure. At her 2-week recheck, the large scar was healing very well, and all sutures were removed. The large scabs eventually fell off completely within a month of discharge, with healthy scar tissue beneath. At this time, Sakura was allowed to gradually return to normal activity levels, as well as regular bathing and grooming.

Expected Outcome/Prognosis

Prognosis for healing of large full thickness wounds is variable and difficult to quantify. Wounds with compromised vascular supply can be expected to have a worse outcome than wounds with healthy blood supply. Wounds that undergo delayed closure are inherently riskier than clean, primarily closed surgical wounds of comparable size. Large, sutured wounds are more difficult to heal without complication than smaller ones, because of tension against the apposing edges. Wound location also plays a part:[18] wounds on extremities often lack the available skin for closure, resulting in high tension/risk of dehiscence, and wounds in areas of high motion and/or friction more frequently experience dehiscence. Infection delays and confounds healing in wounds of any size, and threatens systemic complications.

Sakura's wound was quite large compared to her body size. It is possible that with long term open wound management, it could have healed by second intention, but would have been at extremely high risk of complication. Fortunately, the wound was over her dorsal lumbar spine, with a relatively large amount of skin available to undermine for closure. Still, after closure, there was considerable tension on the wound edges. Some small areas of necrosis developed after closure, leading us to worry

that it would dehisce. However, small wounds have a good prognosis for healing by second intention, and revising the entire wound closure would put even more areas at risk, so the areas of post-closure necrosis were allowed to heal by second intention. The only drawback was poorer cosmetic appearance of the healed wound area, but that was not a concern in this patient.

Infection is a very important factor in considering wound healing prognosis. Sakura's wound had to be allowed to declare itself before surgical closure could be considered, meaning the wound was managed open for many days. In a hospital setting, this put Sakura at great risk of acquiring a resistant nosocomial infection. The bacteria cultured from Sakura's wound did exhibit a fairly impressive resistance panel, and meropenem was the antibiotic of choice in her case. One of the most important steps in preventing superinfection with new bacterial agents was to discharge Sakura from the hospital as soon as safely possible. Unfortunately, meropenem is only available as an injectable formula, since it is poorly absorbed enterally, and generally not stable in oral formulations.[19] Luckily, our client is skilled in nursing and was comfortable diluting, safely storing, and properly administering meropenem subcutaneously at home, which allowed us to continue to treat Sakura's infection without hospitalization.

As she healed at home, the tension of the wound and the adhesions associated with the extensive undermining of skin on her dorsum left Sakura moderately painful for several weeks. She was less active and would show signs of pain with exertion. She was managed on a steadily decreasing dose of oral pain medication provided by her primary care veterinarian and was eventually able to be weaned off completely.

As of today, it has been about 15 months since her initial presentation, and she is fully healed! A long scar remains across her dorsum, which is surprisingly subtle beneath her fur. She is pain-free and living a normal life today. Sakura still receives Apoquel, diphenhydramine, phenobarbital, and KBr at the

same doses she was on at presentation over a year ago. She has not had any seizures since eating the vape cartridge, only exhibiting rare tremor episodes which are managed with diazepam as needed.

Conclusion:

It is easy to be apprehensive when asked to manage a large open wound, but careful sterile procedure and carefully chosen bandaging materials with frequent changes can be promising for successful wound management. Manuka honey is widely available for general practice use, and has been shown hugely beneficial for use in wound management through many mechanisms. Although large wound management cases can be intimidating, it is not always necessary to refer such cases to a specialty clinic, especially when client finances are a concern. Managing large open wounds is often well within the scope of a general practitioner. With motivated clients, frequent (daily) bandage changes can be achieved without hospitalization. Depending on the susceptibility of any infectious organisms present, it may be possible to treat infections with oral medications without hospitalization.

Despite no cause ever being identified for Sakura's spontaneous dermal necrosis, her large open wound was managed successfully with daily wet-to-wet bandage changes incorporating manuka honey. Delayed surgical closure and subsequent discharge led her to complete healing and few complications.

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