Surgical Management of Levamisole-Adulterated Cocaine Induced Soft Tissue Necrosis: Case Study and Treatment Algorithm

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Levamisole is an increasingly common cocaine adulterant that can cause severe and rapid onset cutaneous vasculitis in humans. While most cases may be managed conservatively, we describe a series of patients in whom the extent of skin and soft tissue necrosis mandated surgical intervention. A retrospective review of all patients admitted to one of two regional burn centers between 2006 and 2016 for soft tissue necrosis after exposure to levamisole-adulterated cocaine was included in our study. Ten patients, majority female (9/10) with an average age of 43.4 years (range 31–57), were included. Cocaine usage before presentation averaged 6 days (range 1–14). Presenting complaints consisted of arthralgia (5/10), fever (7/10), and purpuric lesions (10/10). Average TBSA involvement was 23.5% (range 4–70). Immunological testing revealed perinuclear antineutrophil cytoplasmic antibody (pANCA+) in 8 of 10 and cytoplasmic antineutrophil cytoplasmic antibody (cANCA+) in 4 of 8 patients. Operative intervention occurred by postadmission day 11.6 (range 3–30). The mean number of operations required was 3 (range 2–6); length of stay averaged 46.8 days (range 14–120); and survival to discharge was 100% (10/10). To our knowledge, this is the largest case study detailing the surgical management of levamisole-associated skin necrosis. Additionally, we describe the most extensive case of this disease process at 70% TBSA involvement. Based on our experience, we recommend waiting for purpuric rash resolution and soft tissue necrosis to be fully demarcated before fascial debridement and then staged skin grafting with allograft followed by autograft. (J Burn Care Res 2017;38:e638–e646)

Levamisole is a synthetic imidazothiazole with immunomodulatory effects previously used in humans for the treatment of colon cancer, rheumatoid arthritis, and pediatric nephrotic syndrome.[1,2] In 1999, it was withdrawn from usage in humans due to concerns over profound neutropenia, but still remains available for veterinary use as an anthelmintic agent.[3–5] Recently, levamisole has emerged as an increasingly common adulterant of cocaine by drug cartels.[6,7] Cocaine is often adulterated with cheaper bulking agents as well as pharmacologically active drugs to enhance the effect. The exact reason for the emergence of levamisole as a favored adulterant is unclear, but several hypotheses have been proposed based on its complex and not fully elucidated mechanism of action.[8] These theories include the mood-enhancing activity of levamisole via norepinephrine reuptake inhibition, the cocaine's potentiating effect of levamisole on nicotinic receptors, and finally a possible direct effect of levamisole on the brain reward pathway via dopamine.[8] Cocaine was first documented as being adulterated with levamisole in 2003, and reports from 2007 to 2010 show the percentage of cocaine samples seized at the U.S. border containing levamisole increased from 10 to 77%.[9,10] The result is levamisole-adulterated cocaine users increasingly presenting with a characteristic combination of hematologic and dermatological findings as a result of the exposure. The cutaneous side effects of levamisole are the most striking feature and may include nonspecific eruptions, fixed drug eruptions, and classically an ecchymotic or purpuric rash that develops

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with a predilection for the ear lobes and dependent regions, although it can involve any part of the ear, cheeks, face, buttocks, legs, thighs, and arms.[3,4,9] Furthermore, these dermatological findings have been shown to reoccur with increasing severity upon reexposure to the levamisole-adulterated cocaine.[8] If levamisole exposure is suspected, tests for levamisole in urine or blood should be performed within 48 hours of cocaine use due to the short half-life of levamisole, which is between 5 and 6 hours.[11] Patients often present well after this 48-hour window, however, resulting in failure to detect levamisole after exposure. Laboratory studies of these patients typically demonstrate neutropenia in addition to varying degrees of elevated perinuclear antineutrophil cytoplasmic antibody (pANCA), cytoplasmic antineutrophil cytoplasmic antibody (cANCA), antinuclear antibody, C-reactive protein, and antiphospholipid antibody levels.[3,4,9,12] Immunologically, levamisole has been strongly associated with drug-induced antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and agranulocytosis.[10] Histopathological findings include involvement of small to medium vessels with a mixed pattern of leukocytoclastic vasculitis and microvascular thrombosis, although this can range to a vascular occlusive disease without evidence of vasculitis. The rapid onset of skin necrosis sometimes observed, is believed to be due to this autoimmune phenomenon occuring in the skin and soft tissue vasculature. Diagnosis and medical management of levamisole-induced skin necrosis are well documented,[4,9,13–17] but only several case reports describe the surgical management of large TBSA levamisole-induced skin necrosis.[3,11,12] Medical management primarily consists of halting the offending agent, high-dose steroids, and supportive care.[9,12–16] Many of these patient's skin lesions resolve or improve with medical management alone, but in rare instances the degree of involvement may be extensive enough to require surgical debridement and skin grafting.[3,12] Currently, there is no consensus for operative management of patients who present with large surface area involvement of skin necrosis secondary to levamisole-induced vasculitis. Here, we present 10 cases of cocaine-associated soft tissue necrosis likely secondary to levamisole exposure and describe our algorithm for surgical management.

METHODS

After the approval by the institutional research ethics board, a retrospective chart review was performed using inpatient data stored in our respective institutions' burn center database. All patients admitted to regional burn referral centers in Toronto and Winnipeg from June 2006 to April 2016 with a diagnosis of levamisole-induced skin necrosis were included in the study. A chart review was performed to collect demographic data, medical history, hospital course, laboratory data, and surgical intervention information. ANCAs were detected using indirect immunofluorescence, and levamisole testing was done via urine toxicology screening. Data collected were analyzed using Microsoft Excel for Mac version 15.2 (Microsoft Corporation, Redmond, Washington, 2016). Three representative cases were then selected for in-depth review.

RESULTS

Case study patient characteristics, serology markers, biopsy results, and management are shown in Table 1. Ten patients, the majority female (9/10) with an average age of age 43.4 years (range 31–57), met inclusion criteria. Medical history was significant for hepatitis C+ (7/10), hepatitis B+ (5/10), and current smoker (5/10).

Exposure

Timing of adulterated cocaine usage before presentation averaged 6 days (range 1–14). The route of exposure in descending order was inhalational (7/10), intravenous (2/10), and nasal (1/10). The majority of patients (7/10) had previous levamisole-related skin complications occurring on average of 2 years (range 1–4 years) before the most recent admission.

Clinical Presentation

Presenting complaints consisted of arthralgia (5/10), fever (7/10), and purpuric lesions (10/10). Areas of involved skin were as follows: lower extremities (10/10), upper extremities (6/10), hands (4/10), face (4/10), buttocks (3/10), and torso (3/10). Average TBSA involvement was 23.5% (range 4–70).

Laboratory Findings

Levamisole was found via urine toxicology in 6 of 10 patients. White blood cell (WBC) levels were depressed to a neutropenic level in 6 of 10 patients. Immunological testing revealed pANCA+ in 8 of 8 patients, cANCA+ in 4 of 8 patients, and C-reactive protein was elevated in 5 of 10 patients. Pathology results were obtained for 5 of 10 patients, and of these 5 of 5 reported

Table 1. Case study clinical characteristics, serology markers, biopsy results, and management

No.	Age, Sex	Prior Skin Findings	Cocaine Use, Timing	Skin Areas Involved	TBSA (%)	Leukopenia or Neutropenia	Serology	Path	Management
1	37, M	Yes, 4 yr	Intranasal, 7 days	Ears, chest, back, legs, arms	70	Neutropenia (0.73)	pANCA+, cANCA–	Small-vessel vasculitis, multiple intravascular thrombi	Wound excision, staged skin grafting, starting PAD 7
2	57, F	Yes, 2 yr	IV, unknown	Legs	4	Normal	pANCA+, cANCA+	No biopsy	Wound excision, staged skin grafting, starting PAD 21
3	35, F	No	Inhalation, 5 days	Legs	14.5	Neutropenia (0.5)	pANCA+, cANCA–, ↑CRP	Thrombotic vasculopathy without vasculitis	Wound excision, staged skin grafting, bilateral AKA, starting PAD 12
4	52, F	No	Inhalation, 7 days	Legs	18	Neutropenia (1.3)	pANCA+, cANCA Agranulocytosis, ↑CRP	No biopsy	Wound excision, staged skin grafting, starting PAD 30
5	32, F	No	Inhalation, 14 days	Legs	14	Normal	pANCA+, cANCA–	No biopsy	Wound excision, staged skin grafting, starting PAD 12
6	47, F	Yes, 1 yr	Inhalation, 10 days	Legs, arms, nose, cheeks, ear, chin	40	Agranulocytosis (0.3)	pANCA+, cANCA+, ↑CRP	Thrombotic vasculopathy with vasculitis	Wound excision, staged skin grafting, bilateral AKA, starting PAD 10
7	48, F	Yes, 2 yr	Inhalation, 1 day	Legs, arms	20	Neutropenia (0.7)	pANCA+, cANCA–, ↑CRP	Thrombotic vasculopathy with vasculitis	Wound excision and staged skin grafting, starting PAD 3
8	31, F	Yes, 3 yr	Inhalation, unknown	Face, abdomen, buttocks, legs, hands	27	Normal	↑CRP	No biopsy	Wound excision and staged skin grafting, starting PAD 15
9	46, F	Yes, 1 yr	Inhalation, 4 days	Buttocks, arms, thighs	9.5	Neutropenia (1.4)	↑CRP	No biopsy	Wound excision and staged skin grafting, starting PAD 3
10	49, F	Yes, 1 yr	IV, 1 day	Face, chest, buttocks, thighs, legs, left arm	18	Normal	pANCA+, cANCA+, ↑CRP	Thrombotic vasculopathy with vasculitis	Wound excision and staged skin grafting, starting PAD 3

AKA, above knee amputation; *cANCA*, cytoplasmic antineutrophil cytoplasmic antibody; *CRP*, C-reactive protein; *PAD*, post admission day; *pANCA*, perinuclear antineutrophil cytoplasmic antibody.

occlusive vasculopathy with vasculitis being present in the dermal vasculature.

Management

Operative excision and skin grafting occurred on postadmission day 11.6 (range 3–30). The mean number of operations required was 3 (range 2–6), and average length of stay was 46.8 days (range 14–120). There were no mortalities in our study so survival to discharge was 100% (10/10). Case study descriptive data are summarized in Table 2.

REPRESENTATIVE CASES

Case 1

This report presents the case of a 37-year-old male with 1-week history of fever, arthralgia, and purpuric rash after inhalation of two lines of cocaine. Medical history was significant for hypertension, gastroesophageal reflux disease, sleep apnea, biliary colic, and type II diabetes. Four years before, the patient had developed a similar purpuric rash on the ears after exposure to levamisole-adulterated crack cocaine that resulted in admission for membranous nephropathy, which resolved with medical management only. This time, the purpuric rash began on the left ear and progressed to involve the chest, back, and all extremities (Figure 1). At the time of presentation, the patient was in profound shock requiring emergent intubation and subsequent intensive care unit care. His medical issues included primary metabolic acidosis, renal failure, and decreased level of consciousness, with associated diffuse purpuric rash associated with bullae and foul discharge covering all extremities. Urine toxicology screen was positive for levamisole; further immunological testing revealed pANCA-myeloperoxidase (MPO+) (97, normal 0–20), cACNA-proteinase 3– (12, normal 0–20). The patient's WBC count was elevated initially, but after admission he developed profound neutropenia. The areas of purpura subsequently progressed to full-thickness skin necrosis in all affected areas. The final TBSA involvement was 70% when all areas of skin necrosis had fully demarcated by admission day 7. The patient was then taken to the operating room for debridement down to muscular fascia in most areas. These areas were then autografted followed by allografting of the chest, extremities, back, and face (Figure 2). Tissue biopsies obtained intraoperatively showed evidence of isolated thrombotic vasculopathy. Direct immunofluorescence findings were negative for IgG, and positive for IgA, IgM, and C3 localizing to the lumen and walls of the superficial and deep dermal blood vessels. The total number of operations required for debridement and grafting of all affected areas was six. The grafts achieved 100% incorporation throughout with a good result, and the patient was discharged to a rehabilitation facility. The length of hospital admission was 120 days.

Case 6

The patient was a 47-year-old woman who presented to an outside facility with febrile neutropenia and purpuric lesions over scattered areas of her bilateral arms, legs, ears, and entire nose comprising about 10% TBSA. Her medical history was significant for hepatitis B, hepatitis C, anemia of chronic disease, and chronic obstructive pulmonary disease. She also

Table 2. Comparison of previously published surgical management strategies for levamisole-associated skin necrosis

	Early Excision and Grafting (Miner et al[12])	Late Excision and Grafting (Ching et al[3])
Rationale	Treat as burn wound: early excision and grafting	Allow necrotic area to fully demarcate prior to intervention
Operative indication	Full-thickness dermal wound	Full-thickness dermal wound
Time to wound excision	10 days after admission (13 days after exposure)	36 days after admission (38 days after exposure)
Basis for intervention	Clinical exam	Clinical exam
	Histopathological confirmation	pANCA antibody levels
Advantage	Fewer infectious complications	Allow vasculitic process to resolve
	Decreased length of stay	Prevention of unnecessary graft loss
	Less limb loss reported	
	Improved cosmesis fewer reported number of operations (2)	
Disadvantage	Vasculitic process potentially still ongoing	Antibodies may remain elevated for up to 14 mo
	Higher chance of graft loss	Greater reported number of operations (18)
	Increased number of operations	
Evidence for recommendation	Review of literature	Review of literature
	Case report: 34-year-old female, 49% TBSA	Case report: 52-year-old male, 52% TBSA
	Level V	Level V

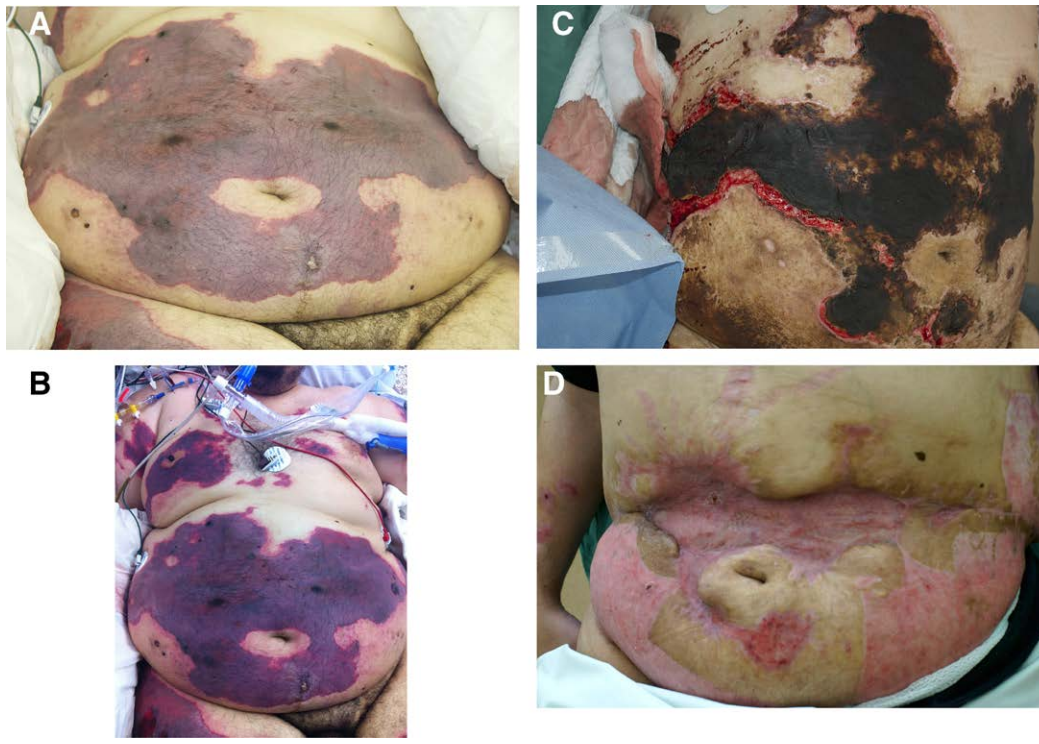

Figure 1. A 37-year-old male with 70% TBSA as a result of levamisole exposure. Purpuric lesions on abdomen at initial presentation (A). Progressing purpura to fully necrotic wounds that easily lifts off the underlying tissue (B, C). Result at 4 months after excision and skin grafting (D).

Figure 2. Same patient from Figure 1 showing purpuric skin lesions (A) that progress to necrotic wounds (B) with an easily removable eschar (C). After initial excision, allograft was placed to prepare wound bed for autografting (D).

reported a long history of crack cocaine and IV drug abuse. Her skin lesions had slowly progressed since, approximately 7 to 10 days before her admission after smoking crack cocaine. The patient was initially managed with supportive care, silver sulfadiazine dressings, and high-dose steroids. Laboratory testing was positive for hepatitis B, hepatitis C, and positive antinuclear antibody (antinuclear antibody +1:320). Further hematologic and rheumatologic workup was negative for dsDNA, extractable nuclear antigens, Echo G1LV, cANCA, IgM anticardiolipin, and hemolytic anemia markers. The pANCA antibody was positive. Her wounds were allowed to demarcate and resulted in full-thickness necrosis of 20% TBSA. On postadmission day 10, she underwent tangential wound excision followed by allograft application. Postoperatively steroids were tapered, and immediately the purpuric areas began to spread down the arms and legs to involve the dorsum of both the hands and feet, in addition to involving the bilateral cheeks. This resulted in an increase of 40% TBSA involvement (Figure 3). Reintroduction of the steroids appeared to halt this secondary progression. On postadmission day 15, the patient returned to the operating room for additional debridement and intraoperatively was found to have significant necrotic muscle and exposed tibia bilaterally that subsequently required bilateral below-knee amputations. The remaining soft tissue defects required three subsequent operations for staged excision and skin graft coverage. The grafts achieved 95 to 100% incorporation throughout with a good result, and the patient was discharged to a rehabilitation facility.

Case 7

This case report describes a 48-year-old female who presented with generalized muscle pains, fever, and purpuric skin lesions on the bilateral buttocks, arms, legs, ears, and back. These lesions slowly progressed

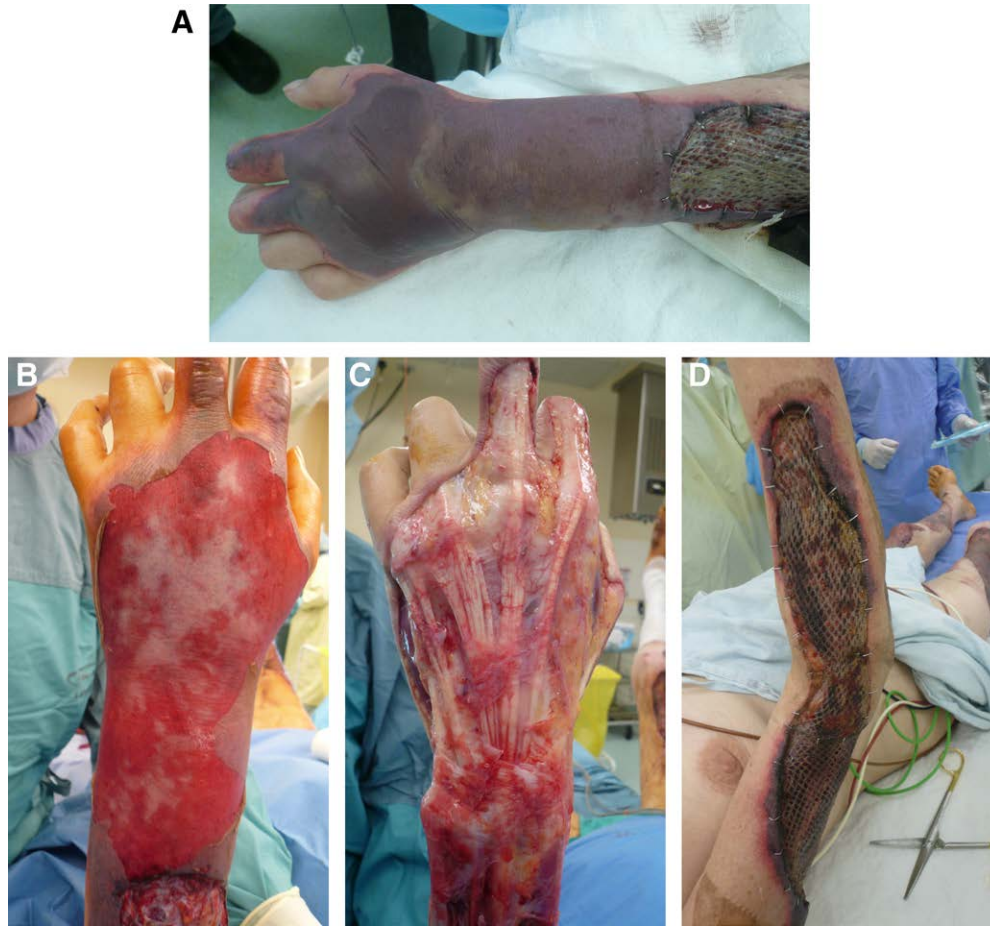

Figure 3. A 47-year-old female with 40% TBSA full-thickness skin necrosis after levamisole exposure. Patient's left hand is shown with purpuric lesions that developed after debridement and allografting in areas of skin previously unaffected (A, B, C), this required fascial debridement down to viable tissue that appeared unaffected by the vasculitic process. The same process occurred with less severity on the patient's right arm as well (D).

to full-thickness areas of skin necrosis over 4 days. Medical history included depression, anxiety, hepatitis C, peptic ulcer disease, and chronic anemia. Social history was significant for smoking, alcohol, and regular crack cocaine usage for the past 15 years. Her last crack cocaine usage was the day before her admission. The patient was initially managed with silver sulfadiazine wound dressings, supportive care, and high-dose steroids until the wounds had fully demarcated. The final wounds involved 15% TBSA full-thickness skin necrosis to the bilateral thighs. Three operations were then required for staged fascial excision and skin grafting. Postoperatively, steroids were weaned, and the patient was discharged home with routine skin graft care. One year later, the patient presented with a similar clinical picture. She had been free of crack cocaine use for several months but had begun to use heavily in the weeks leading up to her admission. Blood markers for pANCA were positive and for cANCA were negative. WBC count on admission revealed agranulocytosis (WBC 0.7). Her wounds were treated with daily silver sulfadiazine until necrosis was fully demarcated at 20% TBSA. Again the wounds required fascial excision to a viable wound bed and staged skin grafting with allograft as a primer before final autografting. The grafts achieved 95 to 100% incorporation throughout with a good result, and the patient was discharged to a rehabilitation facility after a 16-day admission.

DISCUSSION

Complications arising from levamisole-adulterated cocaine use were first reported in 2009, and there is a growing body of literature, which continues to describe this phenomenon.[7] In the majority of cases, cutaneous complications arising from levamisole-adulterated cocaine use may be managed conservatively, but our focus was on those cases, which progress to full-thickness necrosis requiring surgical debridement.[9] Systematic reviews have demonstrated these severe cases to be characterized by strong female predominance, autoantibody production, leukopenia and/or neutropenia, retiform purpuric rash, which progresses to necrosis with a predilection for the lower extremities, and high recurrence rates with future cocaine use.[8,13] In our case study, patients were mostly female (90%), pANCA+ (70%) with neutropenia (60%), purpuric rash (100%), predilection for lower extremities (100%), and high recurrence after exposure (70%). Pathological confirmation of small-vessel thrombosis and vasculitis was seen in 5 of 5 patient samples taken. Five patients had no pathological data in the database, and we have since standardized our protocol to ensure that a skin biopsy of all patients suspected of levamisole-associated skin necrosis was sent for pathological confirmation. In a related finding in our study, 60% of patients tested positive in urine toxicology screen. This is higher than numbers previously reported of 28%[8] likely due to our low threshold for ordering levamisole screens on patients presenting with purpuric rash. One patient presented in our case study had wounds involving 70% of his TBSA. To our knowledge and based on our review of the existing literature, this is the most extensive and severe presentation of levamisole-induced vasculitis described to date. It is also exceedingly rare to see the degree of shock associated with this condition, as seen in this case. Interestingly, before his second admission, this patient suffered from nephrotic syndrome, which is another extremely rare complication of levamisole.[2] In our review, we found that 70% of patients had previous skin changes related to levamisole usage. This finding agrees with previous studies reporting high reuse rates of levamisole-adulterated cocaine in this patient population.[13,16,18,19] As in other delayed hypersensitivity phenomena, there is a rapid progression of symptoms on rechallenge with levamisole. In our review, the comparison between those with previous skin changes and those without is difficult due to small sample size. The average TBSA difference of those with previous levamisole exposure (26% TBSA) compared to those without (15% TBSA) did not reach statistical significance ($P = 0.4$). We hypothesize that those with previous levamisole exposure and sensitization would have a more severe and rapid course of skin necrosis on subsequent exposures.

Differing surgical management strategies for levamisole-induced soft tissue necrosis have previously been published based on single patient experience and review of the literature[3,12] (Table 2). Miner et al[12] describe a 34-year-old female with 49% TBSA injury who underwent early excision and grafting, while Ching et al[3] describe a 52-year-old male with 52% TBSA injury who underwent late excision and grafting, after immunological factors had stabilized, and the wound had fully demarcated. The rationale for early excision and grafting is consistent with that currently recommended for full-thickness burns, which itself is based on a large volume of scientific literature. For Miner et al[12], the decision to operate was made clinically by experienced evaluation of the wounds and confirmatory histopathological findings of full-thickness injury. Ching et al[3] also used clinical evaluation as a guide with the addition of pANCA antibody levels to determine ongoing

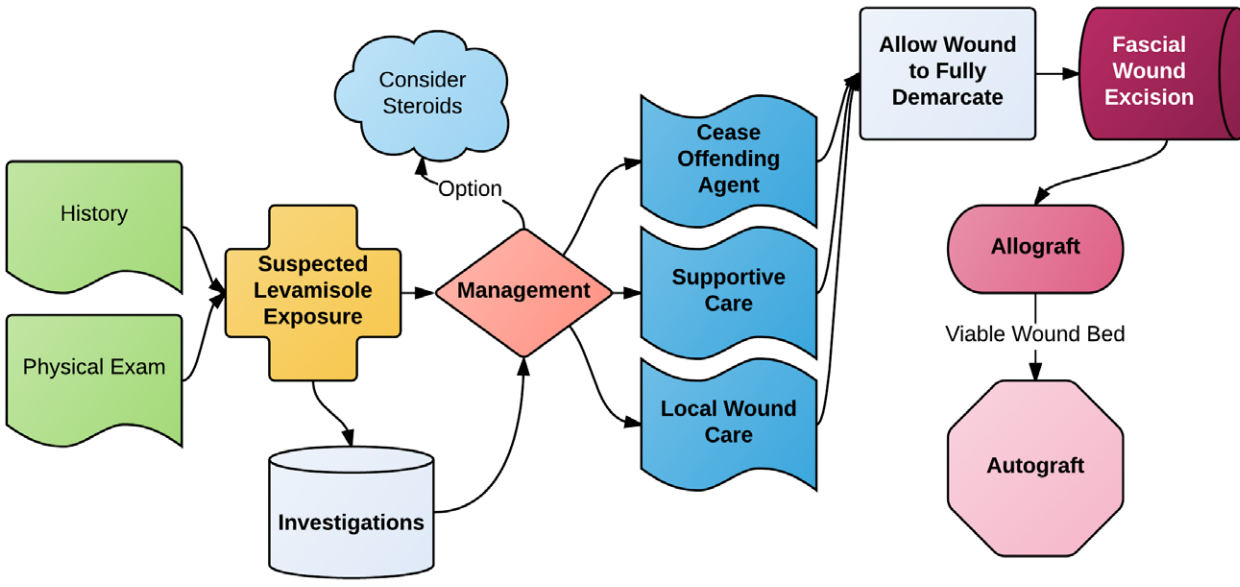

Figure 4. Levamisole-associated skin necrosis surgical management algorithm.

necrosis for timing of excision and staged grafting. Time to wound excision in our review averaged 11 days with a range of 3 to 30 days. This compares with that in the study by Miner et al[12] in which excision was performed at day 10 of admission, whereas it was performed at day 36 by Ching et al[3]. Many variables make direct comparison difficult, but the time to excision is illustrative of the differing approaches these two authors had. All patients went on to survive their injuries, although the patient in Ching et al[3] reports required bilateral above-knee amputations. The difference in outcomes is likely attributable to the fact that the response to levamisole in the skin is currently still under investigation, and the depth of injury may be related to the amount and timing of exposure in these patients, which was not measured.

Our surgical management algorithm for levamisole-associated skin vasculitis is based on the experience with 10 patients as well as review of the literature (Figure 4). We first allow wounds to fully demarcate to a dry eschar with no ongoing purpuric rash before wound excision and debridement. Determining when a wound is ready for excision is based on the clinical judgment of surgeon experienced with full thickness dermal injury. When we operated earlier on wounds with ongoing purpura, this seemed to lead to injury progression and increase of the affected wound areas as described in case 3. We believe this may be due to the pro-inflammatory effects of the surgery acting as a secondary insult. It is our recommendation that the initial debridement should be a fascial excision. In our experience, using tangential excision, as we would in burn wounds, is inadequate, and there seems to be ongoing fat necrosis secondary to the vasculitis, which will require additional operative intervention. The indication for earlier intervention would be the presence of wound sepsis. Due to the nature of being a specialized care center, most patients have been treated at outside facilities before transfer, and they arrive with wounds that are colonized or infected, thus necessitating staged grafting with allograft to test the wound bed. Regardless of the presence of infection, we believe that these wounds need to be have allograft applied to determine wound bed viability, as the underlying process is a vasculitis with thrombosis of small vessels.

LIMITATIONS

Our current recommendation is limited to a small case study of patients. We tried to address this by collaborating with another burn referral center in order to present the largest case study in the literature to date. A second limitation is not all patients in our study were treated in a uniform fashion in terms of diagnostic studies and surgical management. This was due to the often complex presentation of these patients, the involvement of two burn centers, and the evolution in our surgical management of this disease. Our relatively large levamisole experience has now led to the standardization in workup and surgical management of those patients suspected of levamisole-associated soft tissue necrosis.

CONCLUSION

The increasing prevalence of levamisole-adulterated cocaine raises significant concerns about the complications that may result from its use. Levamisole exposure should be suspected in patients with a history of cocaine use, characteristic purpuric skin rash, and febrile neutropenia. In the majority of cases, treatment is supportive. In a small subset of patients, levamisole has the ability to cause extensive soft tissue thickness loss requiring specialized surgical management. Based on our experience, we recommend waiting for purpuric rash resolution and soft tissue necrosis to be fully demarcated before fascial debridement. This should be followed with staged skin grafting of allograft followed by autograft.

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