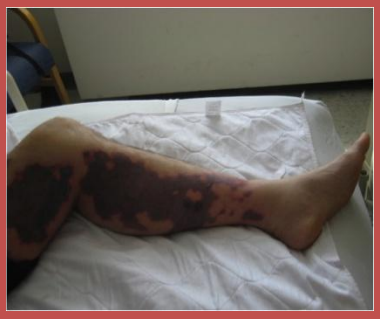
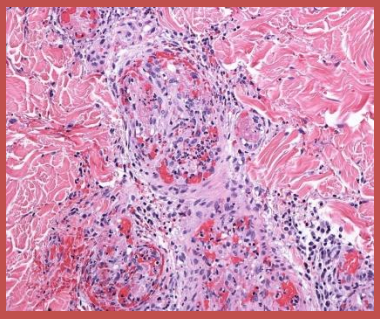
Dermatopathology

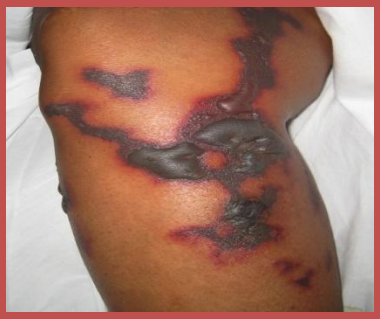
Weill Cornell Medical College

Case Presentation 7

COCAINE ASSOCIATED RETIFORM PURPURA







This educational series for physicians is presented by the Weill Cornell Comprehensive Dermatopathology Service

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Clinical History

A 53-year-old female presented to the emergency department with a chief complaint of a non-painful purpuric rash for three days accompanied by nausea and vomiting of dark colored fluid. The rash started on her legs and spread upward to involve the rest of her body. She also had non-painful oral lesions. She had similar rashes in the past, once that started in her breasts and then spread to her legs, and another occasion the rash was strictly on her legs (figure 1). She admitted to regularly snorting cocaine every Friday, and it was the day after her last use that the lesions appeared. She felt otherwise well.

On exam, she had purpuric plaques with sharp irregular borders and a necrotic central crust on all four extremities, buttocks, and ears. Despite the impressive appearance of the rash, it was nontender. The remainder of her physical exam was unremarkable.
The patient was admitted for further evaluation and given the degree of skin involvement and necrosis, she was sent to the burn unit. Her laboratory studies were significant for positive ANCAs with myeloperoxidase and proteinase 3 specificities along with positive anti-cardiolipin antibodies (IgM 54). Her hospital course was complicated by a hemoglobin drop to 5.8 g/dL requiring transfusion. She required several visits to the operating room for wound debridement and split thickness skin allografts throughout her body.

Two biopsies were performed both showing a very striking thrombotic diathesis involving capillaries, venules, and arterioles throughout the dermis and subcutaneous tissue (figure 2,3). In addition to these aforesaid changes, there was evidence of a true necrotizing vasculitis over and above the aforesaid thrombotic vascular changes. Immunofluorescent and immunohistochemical studies showed very extensive granular deposition of C3d and C5b-9 within the endothelium, vessel wall, and thrombus (figure 4). The ICAM-1/ CD54 stain showed extensive staining of endothelium, vessel wall and perivascular inflammatory cells in all biopsies (figure 6).There was cytoplasmic expression of caspase 3 within the endothelium of many vessels in all biopsies examined (figure 5).

Discussion

The case represents a classic example of cocaine induced retiform purpura. This condition is a recently described entity characterized by very striking hemorrhagic necrosis involving areas of skin including the cheek and ears temporally associated with the administration of cocaine, being first reported in 2010(1). The usual route of administration is in the context of intranasal and/or inhalational cocaine. There is likely a direct role for both cocaine and levamisole, an adulterant in cocaine, in its pathogenesis(2,3).

The exact mechanism by which cocaine with or without levamisole induces the distinctive cutaneous vascular changes has not been fully elucidated in the skin. The initial description of this distinctive syndromic complex reported two patients who developed agranulocytosis and purpuric eruptions in association with lupus anticoagulant positivity and/or c- or p-ANCA positivity in the setting of intranasal cocaine use(4,5). It has been suggested that levamisole may be the main causative agent given the striking similitude of the clinical lesions and serologic findings with levamisole associated purpura in children receiving this agent for nephrotic syndrome . The most common antiphospholipid antibody reported with this syndrome is anticardiolipin antibody, although it is not clear based on these previously published studies if other antiphospholipids such as those directed toward cytoplasmic membrane based phospholipids were specifically assessed. The ANCA subtype can be quite variable in this disorder comprising antibodies with specificity to myeloperoxidase, proteinase 3, cathespin, and neutrophilic elastase(4).

The histomorphologic changes in cocaine associated retiform purpura ranges from a pauci-inflammatory thrombogenic vasculopathy to one of a cell rich thrombogenic necrotizing leukocytoclastic vasculitis producing a morphologic semblance to septic vasculitis. In addition, prominent deposits of C5b-9 are present within the cutaneous vasculature, a finding we have found in this and other cases of cocaine induced retiform purpura. Our caspase 3 studies indicate a state of enhanced endothelial cell apoptosis while enhanced ICAM-1 expression likely contributes to the efflux of inflammatory cells(6). Hence, cocaine associated retiform purpura represents an acute C5b-9 mediated thrombotic angiopathy syndrome associated with a state of enhanced endothelial cell apoptosis and secondary formation of proapoptotic antibodies. These direct effects of cocaine are further compounded by

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similar proapoptotic and inflammatory effects of levamisole. It is likely that the incipient lesion in cocaine associated retiform purpura is a thrombotic one with intraluminal macrophage accumulation, extensive C5b-9 deposition and enhanced apoptosis without true necrotizing vasculitic changes. The later stage lesions could be truly vasculitic, reflecting the effects of ANCA as well as enhanced ICAM-1 expression on the promotion of leukocyte influx. Understanding the pathophysiologic basis of cocaine associated retiform purpura will allow more effective therapies to be established including the potential of use of drugs such as Eculizumab. Inhibition of C5b-9 formation through Eculizumab administration has halted the acute thrombotic diathesis observed in other settings including acute catastrophic thrombotic syndromes such as antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome. The exact mechanism by which blocking the formation of the terminal complement cascade abrogates acute intravascular thrombosis is not entirely known.

Table 1: CLINICAL AND PATHOLOGICAL HALLMARKS OF COCAINE RETIFORM PURPURA

- STRIKING SYMMETRICAL RETIFORM PURPURA WITH CHARACTERISTIC EAR INVOLVEMENT
- DIRECT TEMPORAL ASSOCIATION BETWEEN THE ONSET OF THE PURPURIC RASH AND THE USE OF INTRANASAL COCAINE
- OTHERWISE LARGELY ASYMPTOMATIC WITHOUT FEATURES OF A SYSTEMIC VASCULITIC SYNDROME
- POSITIVE ANTICARDIOLIPIN ANTIBODIES
- POSITIVE ANCA WITH NEUTROPHIL ELASTASE SPECIFICITY
- THROMBOSIS AND NEUTROPHIL RICH VASCULITIS MIMICKING SEPTIC VASCULITIS
- ENHANCED ENDOTHELIAL CELL APOPTOSIS WITH PROMINENT VASCULAR DEPOSITS OF C5B-9
- BOTH COCAINE AND LEVAMISOLE ACTIVATE COMPLEMENT, ENHANCE APOPTOSIS AND UPREGULATE ICAM-1 EXPRESSION

Case References

1. Waller JM, Feramisco JD, Alberta-Wszolek L, McCalmont TH, Fox LP. Cocaine-associated retiform purpura and neutropenia: is levamisole the culprit? JAm Acad Dermatol. 2010 Sep;63(3):530-5.

2. Walsh NM, Green PJ, Burlingame RW, Pasternak S, Hanly JG. Cocaine-related retiform purpura: evidence to incriminate the adulterant, levamisole. J Cutan Pathol. 2010 Dec;37(12):1212-9. doi: 10.1111/j.1600-0560.2010.01613.x. Epub 2010 Aug 25. PubMed PMID: 20738457

3. Yachoui R, Kolasinski SL, Eid H. Limited cutaneous vasculitis associated with levamisole-adulterated cocaine. J Clin Med Res. 2012 Oct;4(5):358-9.

4. Gulati S, Donato AA. Lupus anticoagulant and ANCA associated thrombotic vasculopathy due to cocaine contaminated with levamisole: a case report and review of the literature. J Thromb Thrombolysis. 2012 Jul;34(1):7-10

5. Graf J. Rheumatic manifestations of cocaine use. Curr Opin Rheumatol. 2013 Jan;25(1):50-5

6. Magro CM, Wang X. Cocaine-Associated Retiform Purpura: A C5b-9-Mediated Microangiopathy Syndrome Associated With Enhanced Apoptosis and High Levels of Intercellular Adhesion Molecule-1 Expression. Am J Dermatopathol. 2013 Feb 7.

Figure Legend

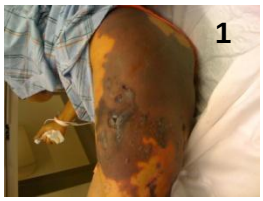

Figure 1 : The patient presented with large hemorrhagic bullous lesions involving the extremities. This dramatic clinical presentation is characteristic of retiform purpura associated with cocaine exposure and reflects the occlusive thrombotic diathesis.

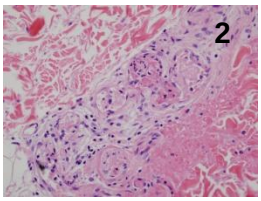

Figure 2 : The biopsy shows a Pauci-inflammatory thrombogenic vasculopathy, a finding seen in most biopsies of cocaine associated retiform purpura.

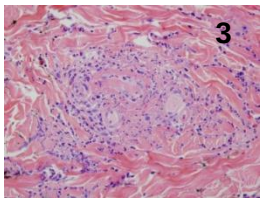

Figure 3: In this photomicrograph one observes both a necrotizing vasculitis as well as intraluminal thrombosis. Other conditions that combine features of a necrotizing leukocytoclastic vasculitis with prominent vascular thrombosis include mixed cryoglobulinemia and septic vasculitis.

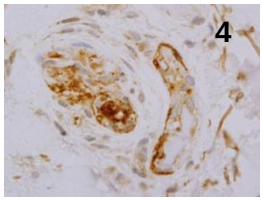

Figure 4: There is extensive deposition of C5b-9 within and around blood vessels of the dermis.

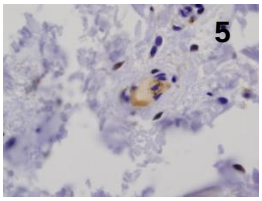

Figure 5: There is prominent nuclear staining of endothelial cells for caspase 3.

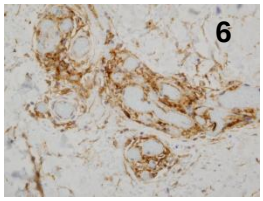

Figure 6: There is prominent staining of ICAM-1/CD54 within the cutaneous vasculature.

Under the direction of Dr. Cynthia M. Magro, the Weill Cornell Comprehensive Dermatopathology Service is a leading edge consultation service and CAP-accredited laboratory for dermatologists, plastic and general surgeons and other dermatopathologists. Dr. Magro is an internationally renowned dermatopathologist, educator and author. She is a Professor of Pathology and Laboratory Medicine at the Weill Cornell Medical College in Manhattan, and is board certified in anatomic pathology, dermatopathology and cytopathology. Dr. Magro is an expert in the diagnosis of complex inflammatory skin diseases. Her areas of expertise include cutaneous manifestations of auto-immune disease, systemic viral disease and vasculitis, atypical drug reactions, benign, atypical and overtly malignant lymphocytic infiltrates of the skin, and diagnostically difficult melanocytic proliferations.The award-winning author of *The Melanocytic Proliferation: A Comprehensive Textbook of Pigmented Lesions*, Dr. Magro has recently completed her second book, *The Cutaneous Lymphoid Proliferation, a comprehensive textbook on benign and malignant lymphocytic infiltrates*. She has co-authored over 250 peer reviewed papers and several textbook chapters. Dr. Magro frequently presents courses on inflammatory skin pathology and difficult melanocytic proliferations to the American Academy of Dermatology, the United States and Canadian Academy of Pathology, and the American Society of Clinical Pathology. Dr Magro has consistently been recognized in Who's Who in America®, Castle Connolly's renowned America's Top Doctors – New York Metro Area® edition and in the Super Doctors® list published in The New York Times Magazine.

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