Case Presentation 10

MULTIPLE CUTANEOUS ULCERS ASSOCIATED WITH BEVACIZUMAB THERAPY

Dermatopathology
Weill Cornell Medical College

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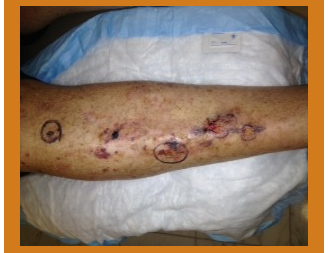

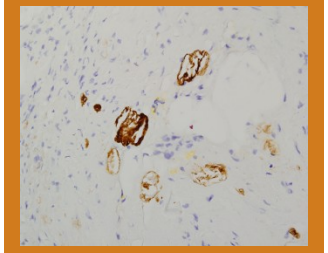

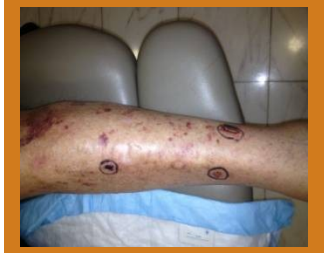

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Clinical History

The patient was a 74-year-old male who presented to the dermatologist with a several week history of asymptomatic crusted hemorrhagic ulcers on the lower legs (figure 1). The clinical impression by the dermatologist referring the patient to the plastic surgeon was one of multifocal squamous cell carcinoma. Due to the unusual clinical presentation, a biopsy was performed of one of the many rupioid appearing ulcers.

Light Microscope Findings

The biopsy showed an ulcer with supervening marked degenerative changes of the epidermis and within the dermis (figure 2). There was extensive necrosis of the eccrine coil. In the deeper seated vessels of the dermis and extending into the subcutaneous fat a striking pauci-inflammatory thrombogenic vasculopathy accompanied by intravascular papillary endothelial cell hyperplasia was observed (figure 3a, figure 3b). There was concomitant lipomembranous fat necrosis.

Phenotypic Profile

To better evaluate the nature of the thrombotic diathesis, a series of immunohistochemical stains were conducted. There was extensive vascular deposition of C3d, C4d, and C5b-9 (figure 4). The foci of lipomembranous fat necrosis were also highlighted by the C5b-9 stain (figure 5) .

Additional History

Given the presence of a thrombogenic vasculopathy as the etiologic basis of the ulcers, a more detailed history was obtained. The patient did not have any prior history to suggest a thrombophilic tendency state as revealed by the lack of any history of recurrent deep venous thromboembolic events, symptoms of pulmonary embolism (i.e. shortness of breath, chest pain and palpitations) and or strokes. His past medical history however was remarkable for an advanced lesion of glioblastoma multiforme treated with partial resection, radiation, temozolamide, and bevacizumab. The ulcers developed shortly following the initiation of bevacizumab.

Discussion

We have presented a case of a multifocal ulcerating pauci-inflammatory thrombogenic vasculopathy temporally associated with bevacizumab therapy. We postulate a role for the administration of bevacizumab in the pathogenesis of this multifocal ulcerative process. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is an angiogenesis inhibitor used to treat a variety of cancers, including lung, colon, and renal cancers as well as glioblastoma multiforme. Bevacizumab also falls under the trade name of Avastin.

This drug ranks as the first clinically available angiogenesis inhibitor in the United States. Given the dependency of certain tumors on angiogenesis, it would be most effective in those tumors that are highly dependent of an adequate vascular supply. Bevacizumab binds directly to vascular endothelial cell growth factor (VEGF) to form a protein complex which is incapable of further binding to VEGF receptor sites. Avastin/Bevacizumab improves response and survival in patients with recurrent glioblastoma and ovarian cancer in comparison to historical controls. That particular study also found that it may be useful in the treatment of radiation necrosis, since it reduces edema and mass effect and diminishes blood-brain-barrier leakage. Given the inhibitor effects on neovascularization, intraocular diseases associated with the formation of new vessels such as age-related macular degeneration and diabetic retinopathy may also benefit from bevacizumab intervention. There are additional VEGF inhibitors. For example, ranibizumab has a very short half- life which is in contradistinction to the 20 day half-life of bevacizumab. The long half-life of this drug may contribute to its main adverse vascular sequelae while the shorter half-life of the other VEGF inhibitor accounts for the lack of adverse side effects. Bevacizumab targets VEGF-A however there are other monoclonal antibodies that have been developed that target other related receptors and ligands of VEGF including VEGF-B. Therapies targeting other ligands in the VEGF pathway include ziv-aflibercept, VEGF receptors (eg, ramucirumab), and their tyrosine kinase signaling (ie, tyrosine kinase inhibitors).

While bevacizumab has a defined role in medical treatment, it is not without complications as is well exemplified by this case. Given the known inhibitor effects of the drug on the inhibition of neovascularization, it may impair wound healing, and worsen coronary artery and peripheral vascular disease. Other complications include a higher incidence of hypertension and bleeding complications. In addition an important adverse effect relates to thrombotic complications. Among the thrombotic complications associated with the use of this drug are nasal septal perforation, portal vein thrombosis, superior vena caval syndrome, internal jugular vein thrombosis, arterial thrombosis with resultant myocardial ischemia, hemolytic uremic syndrome (HUS) and perforation of viscera. An ulcerating thrombotic diathesis involving the skin is without precedent however dermatologists should be aware of this potential complication.

The mechanisms for thrombosis in the setting of bevacizumab therapy is multifactorial and may include direct endothelial cell injury, production of endothelial nitric oxide, increased platelet aggregation, and activation of the FcγRIIa platelet receptor. Perhaps one of the critical mechanisms however is one related to a lack of replenishment of endothelial cells given the critical role of vascular endothelial cell growth factor in the endothelial cell survival and growth. In particular any reduction in the potential pool of endothelial cells needed to replenish dying endothelial cells will result in a thrombotic diathesis and may also contribute to other forms of arteriopathy most notably the obliterative fibrointimal arteriopathy of lupus erythematosus and scleroderma . In essence the inhibition of VEGFR activation by anti-VEGF antibodies and by the inhibition of the VEGF intracellular signalling pathway would be highly deleterious to normal endothelial cell function, survival and replenishment. C5b-9 may be the effector mechanism of vascular thrombosis at least based on the extent of deposition in our index case and in kidney and skin biopsies procured from patients with HUS.

The differential diagnosis of a multifocal ulcerative process associated with a thrombogenic vasculopathy encompasses defects in anticoagulation, hyperviscosity states and endothelial cell dysfunction. The commonest defect in anticoagulation is a factor V Leiden which represents a mutant form of factor V resistant to degradation of the protein C/S thrombomodulin complex while a hyperviscosity state may be in the context of a cryopathy syndrome.

continued

Antiphospolipid antibodies and homocysteine likely induce thrombosis through endothelial injury. A summary of the various conditions associated with this combined clinical presentation and histology is summarized in table I. Drugs are rarely implicated as being causative of microvascular thrombosis. In addition to coumadin skin necrosis, the other well defined thrombotic diathesis directly associated with drug therapy is HUS defined by the triad of a renal thrombotic microangiopathy, hemolysis and thrombocytopenia. Chemotherapy drugs especially gemcitabine and beculizumab are among the drugs associated with HUS. A summary of the more common drugs associated with HUS is presented in table II.

TABLE I:
CLINICAL LAB EVALUATION FOR PATIENTS PRESENTING WITH A PAUCI-INFLAMMATORY THROMBOTIC DIATHESIS AFTER RULING OUT A DRUG BASED TRIGGER

Protein C and S
Prothrombin
Factor 5 Leiden
Beta 2 gylcoprotein
Lupus anticoagulant
Anticardiolipin antibodies
Reptilase time to rule out dysfibrinogenemia
Cryopathy screen
CBC
Homocysteine levels
Factor VIII
SPEP

TABLE II:
DRUGS ASSOCIATED WITH THE DEVELOPMENT OF HEMOLYTIC UREMIC SYNDROME

Acylovir
Bevacizumab
Gemcitabine
Oxaliplatin
Mitomycin—C
Sunitinib-
Docetaxel
Micafungin

Case References

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Figure Legend

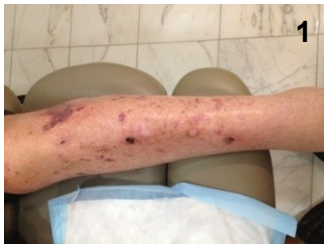


Figure 1 : The patient presents with multiple ulcers bilaterally involving the lower extremities. A biopsy of the lesions was performed.

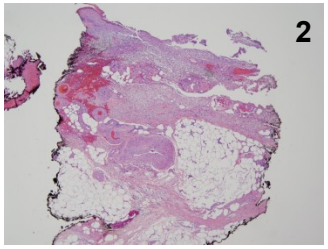
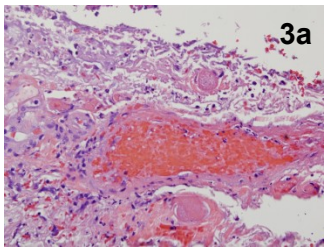
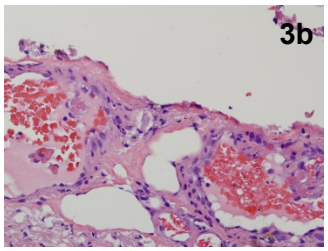


Figure 2 : A biopsy shows an area of epidermal and dermal necrosis associated with a thrombotic diathesis.





Figures 3a & 3b : Higher magnification shows a vessel occluded with thrombus accompanied by intravascular papillary endothelial cell hyperplasia. Macrophages contain imbibed fibrin. The process is pauci-inflammatory and therefore not truly vasculitic in nature.

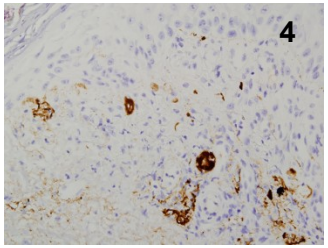


Figure 4 : This thrombotic diathesis is associated with extensive deposits of C5b-9. Other C5b-9 mediate microvascular injury syndromes include hemolytic uremic syndrome which is a known complication of bevacizumab therapy.

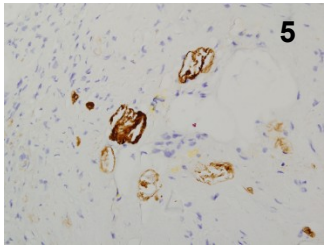


Figure 5: Lipomembranous fat necrosis may be a sign of dermal ischemia and can be highlighted by C5b-9 suggesting a potential role for ischemic driven complement activation within adipocytes.
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Under the direction of Dr. Cynthia M. Magro, the Weill Cornell 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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