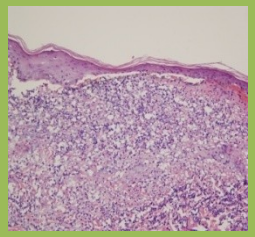
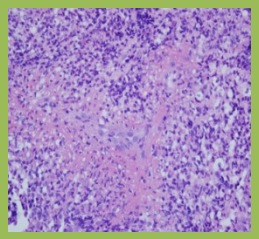
Dermatopathology

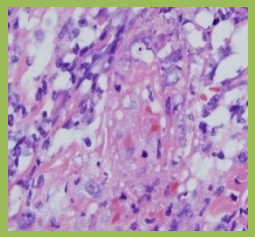
Weill Cornell Medical College

Case Presentation 8

HYDRALAZINE ASSOCIATED ANCA POSITIVE VASCULITIS PRESENTING WITH INTRAORAL, LARNYGEAL, AND INTRAESOPHAGEAL ULCERS AND AN EMBOLIC-LIKE ACRAL CUTANEOUS VASCULITIS







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

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Clinical History

The patient was a 71-year-old female nursing home resident with a past medical history remarkable for end-stage renal disease on hemodialysis, hypertension, diabetes mellitus, and coronary artery disease. She also had a remote history of breast carcinoma and anemia, the latter resulting in a few bone marrow biopsies without any conclusive evidence regarding an underlying hematologic dyscrasia.

From January 22, 2013 to February 13, 2013 the patient was hospitalized for respiratory insufficiency requiring intubation and pressor support. Approximately one month later on March 17, 2013 the patient developed difficulty swallowing and breathing although the shortness of breath was more due to upper airway abnormalities, at least according to the patient. She found it difficult to swallow solids with the symptoms of odynophagia becoming progressively worse over the ensuing days. She also complained of generalized weakness, fatigue, and lightheadedness when standing. Over the past two days prior to admission to the hospital she had a decreased appetite. Almost concurrent with the sore throat was the onset of a very distinctive skin rash which she described as otherwise asymptomatic.

At the time of admission the patient was evaluated by ENT in the emergency room whereby a flexible laryngoscopy demonstrated ulcerations involving the epiglottis, aryepiglottic folds, and arytenoids. She also had a skin biopsy. Endoscopy of the esophagus and stomach showed intraoral ulcerations along with a small ulcerative nodule involving the gastroesophageal junction. The patient was placed in the intensive care unit and intubated due to difficulty breathing associated with laryngeal edema and ulcerations. The patient had been on various long term medications including hydralazine (three 100 mg tablets per day) for treatment of hypertension.

On physical examination the patient showed left eyelid swelling with conjunctival injection in the lateral aspect. There were ulcerations of the lips and mucous membranes; the rest of the oral mucosa could not be visualized. Cutaneous examination revealed multiple lesions including hemorrhagic bullae scattered on the upper and lower extremities as well as palms and plantar surfaces of the foot and forehead(figures 1 and 2).

Laboratory studies revealed a white blood cell count of 6.3, hemoglobin of 9.7, hematocrit 28.6, and platelet count of 218. Blood cultures were negative. Viral serologies were also negative. A repeat bone marrow biopsy showed an increase in erythropoiesis and decreased granulopoiesis whereby a low grade myelodysplastic syndrome could not be excluded. The patient had a positive antineutrophilic cytoplasmic antibody assay showing a characteristic perinuclear staining pattern while ELISA studies demonstrated markedly elevated antibodies to myeloperoxidase . The patient was suspected of having a primary ANCA positive vasculitic syndrome such as microscopic polyarteritis. Skin and esophageal biopsies were performed to better elucidate the nature of the vasculitic process.

Pathology

Skin

A skin biopsy was performed, demonstrating a very striking necrotizing vascular reaction characterized by mural and luminal fibrin deposition involving capillaries and venules of the superficial and deep dermis(figure 3a and b). The vessel walls were infiltrated by neutrophils with concomitant leukocytoclasia(figure 4). Vessels in the mid dermis were occluded by acellular fibrin thrombi. Emanating from the zones of necrotizing leukocytoclastic vasculitis were marked extravascular neutrophilic infiltrates assuming a sheet-like pattern within the dermis albeit without frank dermolysis(figures 3a-b,4) Foci of neutrophilic interface dermatitis with subepidermal bulla formation were observed(figure 5). While neutrophils were present along the dermal-epidermal junction, frank intraepidermal pustulation was not discernible. Special stains to evaluate for microbial pathogens were negative.

Direct immunofluorescent studies were obtained showing +3/3 granular staining of blood vessels throughout the dermis for IgM, C5-9 and C3 compatible with a microvascular injury syndrome (figure 6).

Esophagus

An esophageal nodule showed a morphology that essentially mirrored that noted in the skin biopsy being that of a necrotizing leukocytoclastic vasculitis with accompanying extravascular neutrophilia.

Discussion

We have presented a patient who developed a very distinctive vasculitic syndromic complex associated with positive antineutrophilic cytoplasmic antibodies in the setting of long-term ingestion of the drug hydralazine. The patient was an older female who was on hydralazine in excess of 250 mg a day for several years before developing a distinctive cutaneous and extracutaneous vasculitis. The cutaneous lesions differed from classic palpable purpura due to their bullous hemorrhagic nodular quality in concert with their acral localization, resulting in a clinical morphologic semblance to a septic embolic event. In addition, also unusual in the realm of cutaneous vasculitis including drug induced vasculitis was the involvement of the oral cavity with extension to include the esophagus as well as lesions affecting the epiglottis and aryepiglottic fold bilaterally. Overall the findings were consistent with hydralazine induced ANCA positive vasculitis based on the similarity of this case to other cases reported in the literature. As with many other drug induced autoimmune syndromic complexes, oftentimes the implicated drug has been ingested for a long period of time before the patient develops autoimmune sequelae.

The first reported series of hydralazine associated vasculitis described two patients who developed a necrotizing leukocytoclastic vasculitis associated with high doses of hydralazine over several years were presented whereby in both cases cessation of the drug eventually led to resolution of their vasculitic syndrome(Finley et al 1980). One of the two patients had lesions localized to the dorsum of the feet similar to our patient. Since that first paper, other anecdotal case reports have been published(Norris et al Bernstein et al 1980; Peackock, Weatherell; Reynolds et al; Sangala et al 2010). The patients are typically older females who have been on higher doses of the drugs for years. The hemorrhagic blistering nature of the eruption with lower extremity involvemen is also characteristic (Sangala et al 2010.) The most recent reported cases manifests a striking similarity to our case. In particular, Keasberry and coworkers described a patient with bullous hemorrhagic features involving the dorsum of the feet accompanied by night sweats, lethargy, and weight loss in the setting of hydralazine therapy for three years prior to her presentation. Investigations revealed a high antinuclear antibody, antidouble stranded DNA antibody, and antimyeloperoxidase antibody. As with our patient the rash was bullous and hemorrhagic in quality. She also had a concomitant sore throat, mouth ulcers, and otalgia (Keasberry et al 2013).

continued

A characteristic feature of our case and potentially one other reported case is involvement of the epiglottis and aryepiglottic folds. Weiser et al described ulcerative lesions involving the epiglottis and arytenoepiglottic folds in the setting of hydralazine used for six months (Weiser et al 1984) .The epiglottic lesion had a pseudotumorous morphology very similar to the esophageal lesions identified in our patient.

In the early 1990s it became apparent that the hydralazine induced a lupus-like syndrome as well as hydralazine associated vasculitis was associated with very specific antibodies including lactoferrin and antineutrophilic cytoplasm antibodies. In 1994 Nasberger et al reported that antilactoferrin antibodies of IgG and IgM iotype were identified in 5% and 10% of systemic lupus erythematosus patients, respectively, while all patients with hydralazine induced systemic lupus erythematosus had antibodies of both isotypes with a rapid decrement in the antibody levels following drug withdrawal. In this regard they suggested that antilactoferrin antibodies were clearly able to discriminate between hydralazine induced systemic lupus erythematosus and true endogenous lupus erythematosus (Nasberger L et al 2013). According to Cambridge and coworkers, the presence of antineutrophilic cytoplasmic antibodies was very distinctive for drug induced lupus like reactions (Cambridge et al 1994). They showed that patients with endogenous lupus did not have high titers of anti-MPO antibodies but invariably contained antinuclear antibodies while anti-MPO antibodies of IgG and IgM iostype were observed in patients with both drug induced nephritis as well as drug induced systemic lupus erythematosus. The exact pathogenetic basis by which hydralazine evokes antibodies to myeloperoxidase remains hypothetical.

There may be several different mechanisms by which drugs induce autoantibody formation. Neutrophil mediated metabolism of drugs may occur. Procainamide and hydralazine are both metabolized by MPO released from activated neutrophils to form reactive intermediate compounds. Such metabolites may be directly cytotoxic, leading to cell death and abnormal degradation of chromatin whereby in a susceptible individual an autoimmune response directed against histone DNA complexes may occur. Alternatively, the reactive metabolites may act as a hapten for myeloperoxidase and result in antimyeloperoxidase antibody formation (Cambridge et al 1994). In the report by Short and Lockwood the authors felt that the combined pattern of antibodies to myeloperoxidase and lactoferrin were very characteristic and almost diagnostic of hydralazine induced vasculitis (Short et al 1995). Hydralazine and procainamide have been shown to inhibit T cell DNA methylase, leading to a reduced amount of 5-methylcytosine in the genome and to induce autoreactivity in cloned CD4 positive T cells. This decrease in T cell DNA methylation may provide a link between drug therapy and autoreactivity.

In summation, hydralazine associated ANCA positive vasculitis is a very distinctive syndromic complex characterized by bullous hemorrhagic lesions with a predilection to involve the dorsal surfaces of the feet oftentimes with a distinctive pattern of upper aerodigestive and intraoral ulceration with a predilection to involve the larynx.

Case References

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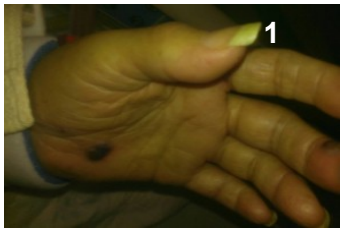
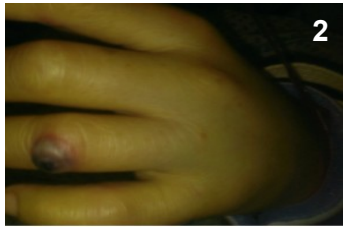
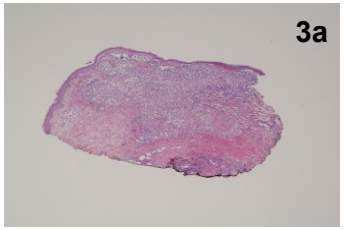
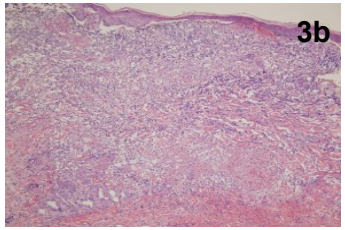
Figure Legend





Figures 1 & 2 : Cutaneous examination revealed multiple lesions including hemorrhagic bullae exhibiting prominent acral involvement.





Figures 3a & 3b : A skin biopsy shows a very striking necrotizing vascular reaction characterized by mural and luminal fibrin deposition involving capillaries and venules of the superficial and deep dermis. Emanating from the zones of necrotizing leukocytoclastic vasculitis are marked extravascular neutrophilic infiltrates assuming a sheet-like pattern within the dermis.

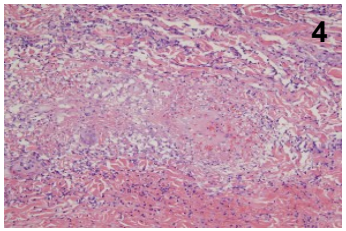


Figure 4 : The vessel walls are infiltrated by neutrophils with concomitant leukocytoclasia. There is extensive mural and luminal fibrin deposition.

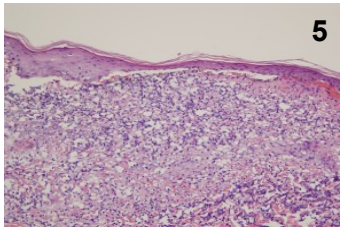


Figure 5: Foci of neutrophilic interface dermatitis with subepidermal bulla formation are noted,.

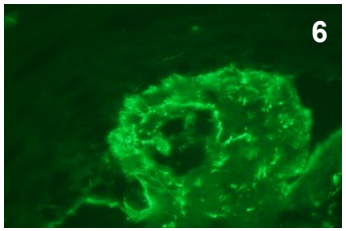


Figure 6 : IgM demonstrated a continuous band of +3/3 granular staining along the dermal-epidermal junction. In addition, there was +3/3 granular staining of blood vessels.

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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