

IMMUNE RESPONSE IN A CUTANEOUS ALLERGIC DRUG REACTION SECONDARY TO IMIDAPRIL, BENAZAPRIL AND METFORMINAna Maria Abreu Velez¹, Isabel Cristina Avila², Michael S. Howard¹¹Georgia Dermatopathology Associates, Atlanta, Georgia, USA²Ph.D. Candidate, University of Antioquia, Medellin, Colombia, SA.**Source of Support:**
Georgia Dermatopathology
Associates, Atlanta, Georgia, USA
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None**Corresponding author:** Ana Maria Abreu Velez, MD PhDabreuvelez@yahoo.com

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Abstract**Introduction:** Cutaneous drug reactions may be classified with regard to pathogenesis and clinical morphology. They may be mediated by both immunologic and non-immunologic mechanisms.**Case report:** A 56 year old female presented with widespread patches and macules, concentrated on her face, trunk and extremities. The lesions were pruritic, and temporally associated with intake of benzapril hydrochloride, imidapril and metformin.**Methods:** Biopsies for hematoxylin and eosin (H&E) examination, as well as for immunohistochemistry (IHC) and direct immunofluorescence (DIF) analysis were performed for diagnostic purposes, and also to evaluate the lesional immune response.**Results:** Hematoxylin and eosin staining demonstrated a histologically unremarkable epidermis. Within the dermis, a moderately florid, superficial and deep, perivascular infiltrate of lymphocytes, plasmacytoid lymphocytes, histiocytes and rare eosinophils was identified, consistent with an allergic drug reaction. DIF demonstrated deposits of IgE, Complement/C3 and fibrinogen around dermal blood vessels. IHC demonstrated positive staining with HAM-56 and myeloid/histoid antigen in the cell infiltrate around the upper dermal blood vessels. HLA-ABC was overexpressed around those vessels, as well as around dermal sweat glands. COX-2 demonstrated positive staining in both the epidermis and upper dermis.**Conclusion:** Drug reactions are significant causes of skin rashes. In the current case, we were able to identify multiple antigen presenting cells in the area of the main inflammatory process. The immunologic case findings suggest that allergic drug eruptions may represent complex processes. An allergic drug reaction should be suspected whenever dermal, perivascular deposits of fibrinogen, Complement/C3 and other markers such as IgE are identified via DIF.**Key words:** HLA-ABC; biomarkers; myeloid-histoid antigen; HAM-56; GFAP; COX-2**Abbreviations and acronyms:** Immunohistochemistry (IHC), hematoxylin and eosin (H&E), direct immunofluorescence (DIF)**Cite this article:**Ana Maria Abreu Velez, Isabel Cristina Avila, Michael S. Howard: Immune response in a cutaneous allergic drug reaction secondary to imidapril, benazapril and metformin. *Our Dermatol Online*. 2013; 4(2): 192-195**Introduction**

Cutaneous drug reactions may be classified with respect to pathogenesis and clinical morphology [1-6]. They may be mediated by immunologic and non-immunologic mechanisms. Immunologic reactions involve the host immune response and may be mediated by IgE-dependent, immune complex-initiated, cytotoxic, or cellular immune mechanisms [1,2]. Non-immunologic reactions may occur via activation of effector pathways, overdoses, cumulative toxicity, side effects, interactions with other drugs, metabolic alterations or exacerbation of pre-existing dermatologic conditions [1-6]. Certain cutaneous clinical lesional

patterns may be associated with cutaneous drug reactions. These include urticaria, photosensitive eruptions, erythema multiforme, disturbance of pigmentation, morbilliform reactions, fixed drug reactions, erythema nodosum, toxic epidermal necrolysis, vasculitides and bullous reactions [1-7]. In addition, certain drugs cause defined cutaneous syndromes. These include iodides and bromides, hydantoins, corticosteroids, antimalarial agents, gold, cancer chemotherapeutic agents, tetracyclines, thiazides and sulfonamides, nonsteroidal anti-inflammatory agents and coumarin.

Case Report

A 56 year old Caucasian female was evaluated after presenting suddenly with erythematous macules and patches following a one week regimen of imidapril, 5mg once a day with concurrent benzapril and metformin. These medications were prescribed for treatment of her hypertension and Type II diabetes mellitus.

Methods

Our histopathologic studies and hematoxylin and eosin staining were performed as previously described [3-8].

Direct immunofluorescence (DIF) and immunohistochemistry (IHC):

In brief, DIF skin cryosections were prepared, and incubated with multiple fluorochromes as previously reported [3-8]. We utilized a normal skin negative control, obtained from

patients undergoing aesthetic plastic surgery. To test the local immune response in lesional skin, we utilized the following markers: antibodies to immunoglobulins A, E, G, and M; Complement/C1q and C3; kappa and lambda light chains, and albumin and fibrinogen. All of these antibodies were either fluorescein isothiocyanate (FITC) or Texas red conjugated for the DIF testing, and obtained from Dako (Carpinteria, California, USA). We also utilized Cy3 conjugated monoclonal anti-glial fibrillary acidic protein (GFAP) antibody from Sigma (Saint Louis, Missouri, USA). We studied the following markers via immunohistochemistry: Complement/C5b-9/MAC, HLA-ABC, monoclonal mouse anti-human myeloid/histiocyte antigen and COX-2, all also from Dako; and HAM-56 antibody from Cell Marque Corporation (Rocklin, California, USA). Our IHC studies were performed as previously described [3-8]. The IRB consent was obtained.

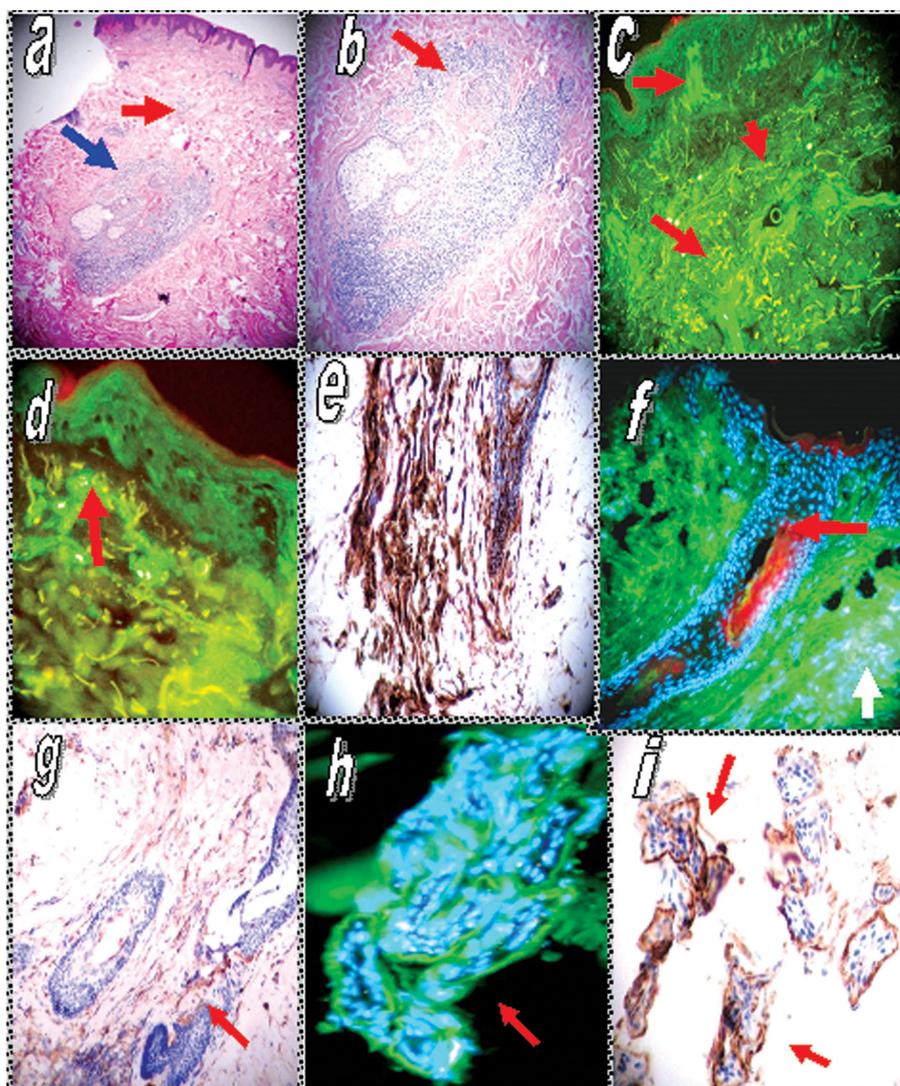


Figure 1. **a** and **b.** H&E staining at 100X and 200X respectively, showing a mixed inflammatory infiltrate along the upper and intermediate neurovascular plexuses of the skin (red arrows), as well as a strong infiltrate of lymphocytes, plasmacytoid lymphocytes, histiocytes and eosinophils near dermal hair follicles and sebaceous glands (blue arrow). **c** and **d.** At 100X and 400X magnification, respectively. DIF demonstrating positive staining with FITC conjugated IgE in the upper and intermediate neurovascular plexuses of the dermis (green staining; red arrows). **e.** HLA-ABC positive IHC staining around the hair follicular unit and blood vessels around this structure. **f.** DIF, demonstrating anti-human FITC conjugated kappa light chain antibody with positive staining around hair follicle areas (green staining; white arrow). Also note positive Texas red conjugated Complement/C3 staining inside the hair follicle (red staining; red arrow). **g.** Complement C5b-9/MAC positive IHC staining around the hair follicles and sweat glands (brown staining; red arrow). **h.** FITC conjugated Complement/C5b-9/MAC positive DIF staining around the hair follicles and eccrine glands (green staining; red arrow) **i.** IHC, demonstrating anti-human kappa light chain positive staining around dermal sweat glands (green staining; red arrows).

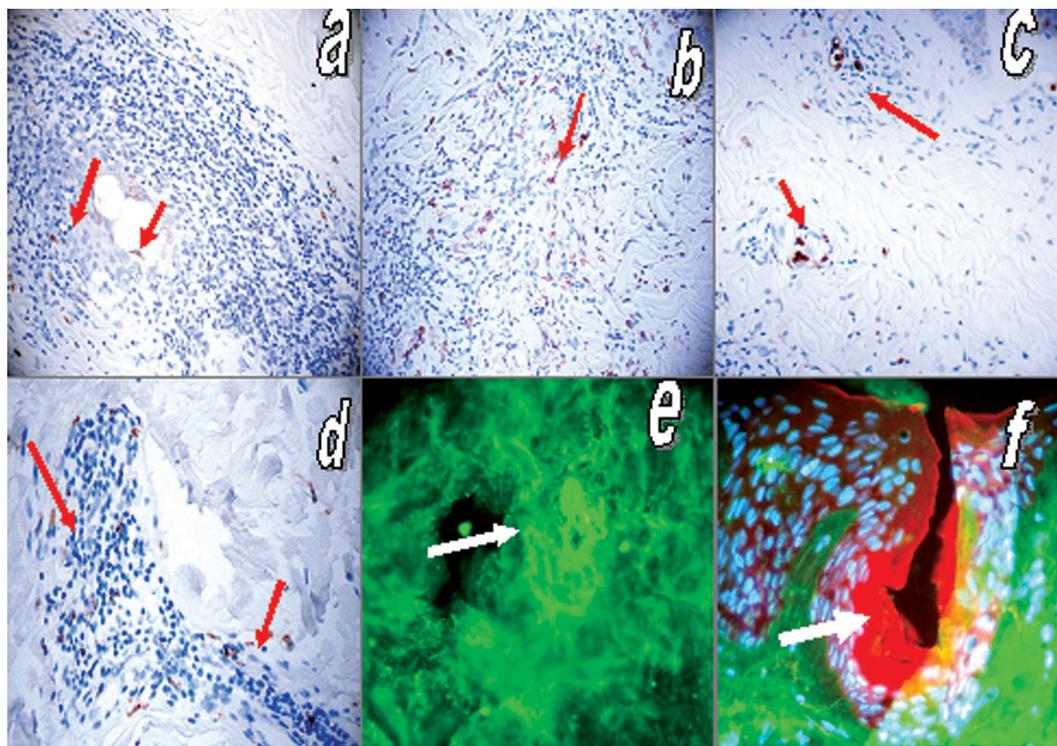


Figure 2. **a and b.** Positive IHC staining in the cell infiltrate with myeloid/histiocyte antigen (brown staining; red arrows). **c and d.** Positive IHC staining with HAM-56 (brown staining; red arrows). **e.** Positive DIF staining with FITC conjugated Complement/C3 to dermal blood vessels (green staining; white arrow). **f.** Positive Texas red conjugated Complement/C3 DIF staining in the isthmus of the hair follicle (red staining; white arrow).

Results

Examination of the H&E tissue sections demonstrated a histologically unremarkable epidermis. Within the dermis, a moderately florid, superficial and deep, perivascular infiltrate of lymphocytes, plasmacytoid lymphocytes and histiocytes was identified. Neutrophils and eosinophils were rare. Mild, deep dermal eccrine gland inflammation was also noted (Fig. 1). No dermal mucin deposition was seen. On DIF review, FITC conjugated anti-human IgE and Complement/C3 antibodies were positive around dermal blood vessels, especially those within the upper and intermediate dermal plexuses. Anti-human kappa light chain, Complement/C3, C1q and fibrinogen FITC conjugated antibody staining was positive within dermal eccrine sweat glands (Fig. 1, 2). On IHC review, the Complement/C5b-9/MAC complex antibody stained positive around dermal blood vessels, hair follicles and eccrine sweat glands (Fig. 1, 2). IHC also demonstrated positive staining via HAM-56 and myeloid/histoid antibodies in the cell infiltrate around the upper dermal blood vessels. HLA-ABC was overexpressed around those vessels, as well as around dermal sweat glands. COX-2 was positive in both the epidermis and upper dermis.

Discussion

Allergic reactions include 1) mild clinical events such as pruritus; 2) moderate events, including generalized skin eruptions and gastrointestinal and respiratory symptoms, and 3) severe reactions such as anaphylaxis with cardiovascular complications; these reactions represent common clinical challenges [1-6]. Allergic reactions may develop to inhaled substances, food and food additives, and foreign substances

(blood, latex, etc.). Many medications are documented causes of anaphylactic reactions, asthma, and generalized urticaria or angioedema [1-6]. Moreover, multiple skin reactions are induced by drugs via immune complexes, complement mediated reactions, direct histamine liberation and modulators of arachidonic acid metabolism. Notably, we found strong expression of COX-2 in both the epidermis and upper dermis. Finally, insect venom allergies may manifest with pain, disseminated exanthems and angioedema [1-9]. The discovery of new associations between drug toxicities and specific HLA alleles has been facilitated by the use of DNA-based molecular techniques and the introduction of high-resolution HLA typing, which have replaced serologic typing in this field of study [10,11]. Drug toxicity/HLA associations have been best documented for immunologically mediated reactions, such as drug hypersensitivity reactions associated with the use of abacavir, and severe cutaneous adverse drug reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis induced by carbamazepine and allopurinol use, respectively. The testing of HLA-ABC screening for the early diagnoses of potential drug reactions may thus be of interest in dermatologic practice for selected patients [10,11].

In our results, we found multiple antigen presenting cells present within the inflammatory reaction around dermal blood vessels, hair follicles and sweat glands. Other authors have reported similar findings [11]. Other authors also reported that following neurotoxicity screening, a gliosis reaction represents a hallmark of many types of nervous system injury [12].

Using a battery of neurotoxic agents, the authors showed that overexpression of the astroglial protein glial fibrillary acidic protein (GFAP) [12], could represent a skin biomarker of drug neurotoxicity. Qualitative and quantitative analysis of GFAP has shown this biomarker to be a sensitive and specific indicator of neurotoxic conditions. In our study, we found that GFAP was overexpressed and seemed to be associated with the hair follicular isthmus.

In summary, we conclude that the in situ immune response to our selected drug eruption is complex; more cases are needed to understand its pathogenesis. Given the aging of the population in some countries, older patients are often prescribed multiple medications for multiple clinical issues. The vendors of metformin clearly state that either the doctors and/or the pharmacist should avoid using metformin simultaneously with nonprescription medications such as vitamins, nutritional supplements, and herbal products. They also recommend avoiding the following medications:

- 1) acetazolamide (Diamox);
- 2) amiloride (Midamor, in Moduretic);
- 3) angiotensin-converting enzyme (ACE) inhibitors such as benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), lisinopril (Prinivil, Zestril), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace), and trandolapril (Mavik);
- 4) beta-blockers such as atenolol (Tenormin), labetalol (Normodyne), metoprolol (Lopressor, Toprol XL), nadolol (Corgard), and propranolol (Inderal);
- 5) calcium channel blockers such as amlodipine (Norvasc), diltiazem (Cardizem, Dilacor, Tiazac, others), felodipine (Plendil), isradipine (DynaCirc), nifedipine (Cardene), nifedipine (Adalat, Procardia), nimodipine (Nimotop), nisoldipine (Sular), and verapamil (Calan, Isoptin, Verelan);
- 6) cimetidine (Tagamet);
- 7) digoxin (Lanoxin);
- 8) other diuretics, including furosemide (Lasix);
- 9) androgen and estrogen hormone replacement therapy;
- 10) insulin and other medications for diabetes;
- 11) isoniazid;
- 12) medications for asthma and colds;
- 13) medications for mental illness and nausea;
- 14) medications for thyroid disease;
- 15) morphine (MS Contin, others);
- 16) niacin;
- 17) oral contraceptives;
- 18) other oral steroids such as dexamethasone (Decadron, Dexone), methylprednisolone (Medrol), and prednisone (Deltasone);

- 19) phenytoin (Dilantin, Phenytek);
- 20) procainamide (Procanbid);
- 21) quinidine;
- 22) quinine;
- 23) ranitidine (Zantac);
- 24) topiramate (Topamax);
- 25) triamterene (Dyazide, Maxzide, others);
- 26) trimethoprim (Primsol);
- 27) vancomycin (Vancocin);
- 28) zonisamide (Zonegran) [13].

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