Oklahoma State University Medical Center/ Family Medicine Department

Anticonvulsant Hypersensitivity Syndrome (AHS)

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Overview of AHS

Anticonvulsant Hypersensitivity Syndrome is a rare, drug induced, multiorgan syndrome characterized by fever, rash, eosinophilia, and other multiorgan abnormalities.[1] This syndrome is most commonly associated with aromatic antiepileptic drugs such as phenytoin, phenobarbital, and carbamazepine.[2]

Case Report

Chief Complaint
Pruritic Rash

History of Present Illness
81 year-old female presented with pruritic rash onset 2 weeks ago. The rash spread from neck distally (Figure 1 and Figure 2). She was treated at Urgent Care 3 days prior to arrival who suggested hyperglycemia was the etiology of her rash, and increased her dose of Metformin. Her rash acutely worsened after the dose increase.

Past Medical History
Type 2 Diabetes Mellitus

Past Surgical History
Cranial tumor resection in 1993

Home Medications
Metformin 500mg PO QD
Phenytoin 100mg PO TID

Physical Exam
Vitals: 184/93, HR 124 bpm, T 36.8C, RR 18, O2 sat 99% on room air.
Skin: Diffuse, pruritic, confluent, maculopapular rash with leather-like texture changes involving the entire body including palms and soles. No mucosal involvement. Negative Nikolsky sign.

Hospital Course Timeline

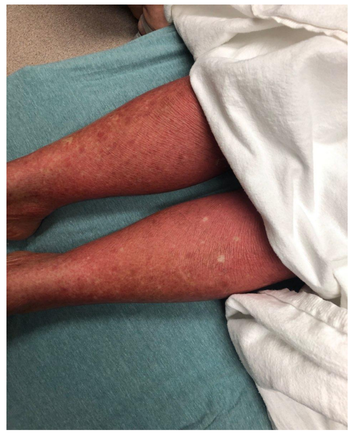
Admission
- Admitted to general medical floor in stable condition
- All home medications held

Day 1
- 1mg/kg prednisone PO initiated
- Punch biopsy obtained of right thigh

Day 2
- Additional punch biopsy of right deltoid obtained
- Rash 25% improved

Hospital Follow Up (Day 4)
- Pathology report reviewed confirming AHS
- Pathology reports confirmed Anticonvulsant Hypersensitivity Syndrome

RESULTS



Figures 1 and 2: Maculopapular rash with desquamation; Day 1

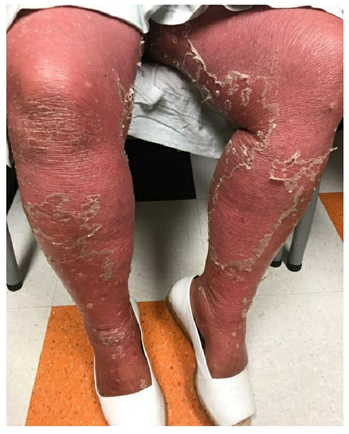


Figure 3: Outpatient clinic follow up appointment; Day 4

Laboratory Studies

WBC	8.2	ESR	13 (L)	Urine Clean Catch	
RBC	4.53	CRP	4.97 (H)	Urine Color	Yellow
Hgb	14.2	Na	135	Urine pH	6.0
Hct	42.2	K	4.1	Spec Gravity	1.010
MCV	93.2	Cl	97 (L)	Ur Protein	NEGATIVE
MCH	31.3	Bicarb	25	Ur Glucose	NEGATIVE
MCHC	33.6	AG	13	Ur Ketones	NEGATIVE
RDW	11.2	BUN	13	Ur Blood	NEGATIVE
Plt	197.	Cr	0.73	Ur Nitrite	NEGATIVE
MPV	7.1 (L)	GFR	76	Ur Bili	NEGATIVE
Neut %	77.0	Glucose	125 (H)	Ur Urobili	NEGATIVE
Lymph %	15.0	Ca	9.4	Ur Leuk Est	TRACE (H)
Mono %	6.0	T Bili	0.5	Ur RBC	NONE SEEN
Eos %	2.0	AST	20	Ur WBC	0-2
Baso %	0.0	ALT	22	Ur Squa Ep	0-2
Neut #	6.3	Alk Phos	128	Ur Bacteria	RARE
Lymph #	1.2	Total Protein	7.0	Ur Cx	Mixed Flora
Mono #	0.5	Albumin	3.9	Blood Cx x2	NEGATIVE
Eos #	0.2	PT	14.2		
Baso #	0.0	INR	1.1		

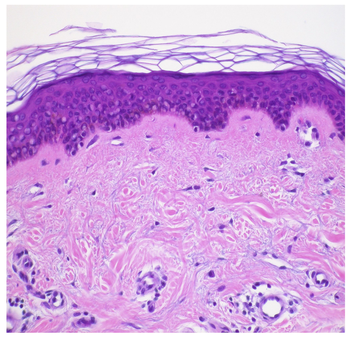
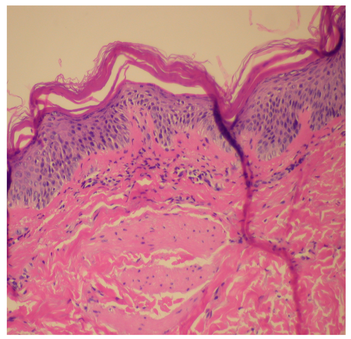
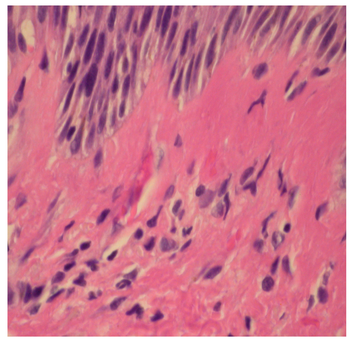


Figure 4: Normal skin biopsy.





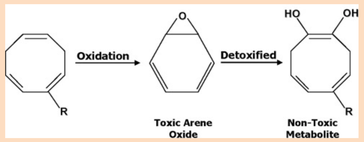
Figures 5, and 6: Patient's skin biopsy showing Drug Induced Hypersensitivity Reaction.

Discussion

Pathology confirmed this patient's rash was due to anticonvulsant hypersensitivity syndrome. A rare finding with a prevalence of 1 in 1,000 to 10,000 exposures.[3] This syndrome usually occurs 1-4 weeks after exposure to one of the aforementioned aromatic antiepileptic drugs.[4] What makes our case so unique is the 26 year latent period between administration and reaction. It is hypothesized this disorder is related to an autosomal dominant deficiency of epoxide hydrolase.[5] Aromatic anticonvulsants, such as phenytoin, are metabolized by the P450 system.[3] This can yield a toxic intermediate, which can result in cellular apoptosis or mutations - leading to an immunologic response. One possible explanation is as our patient aged, her ability to metabolize Phenytoin decreased, leading to a buildup of the toxic arene oxide intermediate. Phenytoin has been shown to have decreased hepatic clearance in aging adults.[7] This highlights the need for continued awareness of potential need for antiepileptic dose monitoring in the elderly.

Due to the acute decompensation of patient's condition and skin condition with unknown etiology, patient was admitted for continued observation in stable condition. Two punch biopsies were performed, one from her left deltoid and another from her right thigh for confirmation of suspected drug-induced skin changes. These were interpreted by Pathology as "The perivascular lymphocytic infiltrate and inflammatory changes are suggestive of an erythema multiforme-like eruption/Stevens Johnson syndrome. There is a long-term history of the patient taking Dilantin. The findings are consistent with Dilantin hypersensitivity syndrome. Shared decision making resulted in patient discontinuing all prescribed medications. She was empirically treated for a drug induced hypersensitivity reaction with 60mg of Prednisone daily and discharged in stable condition with close outpatient follow-up

Mechanism of Action



Proposed mechanism of action of aromatic anticonvulsant metabolism and production of toxic arene oxide metabolites.[6] Individuals susceptible to anticonvulsant hypersensitivity syndrome may have decreased levels of epoxide hydrolase, the enzyme required for detoxification.[3] Modified from Knowles et al.

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