Clinical Pharmacology & Toxicology Pearl of the Week

~ Drug-induced Lupus ~

- ✓ **Definition:** Drug induced lupus occurs in individuals after exposure to the causative drug for a few weeks to more than a year. It most commonly occurs in older patients (> 50 years), Caucasians, and equally in males and females.

- ✓ **Pathophysiology:**
  - Genetics – slow acetylator status; certain HLA subtypes (HLA-DR4, HLA- DR0301 and Complement C4 null allele)
  - Epigenetics – procainamide and hydralazine can decrease T cell DNA methylation leading to over-expression of LFA-1 causing immune dysregulation.
  - Biotransformation – procainamide and hydralazine can serve as substrate for methyl peroxidase in activated neutrophils. The reactive metabolite, procainamide hydroxylamine can affect the immune system.
  - Drugs may also function as haptens or agonists for drug specific T cells.

- ✓ **Manifestations (typically come on abruptly):**
  - Fever and/or other constitutional symptoms (50%)
  - Arthritis and arthralgias (80-95%)
  - Myalgias
  - Serositis (50% with procainamide, 25% with quinidine)
  - Hepatomegaly (5-25%)
  - Erythematous papular rashes (20%) (most commonly occurring with hydralazine)
  - Discoid lesions or malar erythema (2%)
  - Pulmonary infiltrate (especially with procainamide)
  - Severe manifestations of SLE, such as cytopenia, nephritis, and CNS involvement are exceedingly rare in drug induced lupus, as is the presence of dsDNA and hypocomplementemia.

- ✓ **Autoantibodies most seen in Drug induced lupus**
  - **ANA –** virtually all patients have positive ANA.
  - **Anti-histone antibodies –** Most patients (95%) with symptomatic drug induced disease due to procainamide, hydralazine, chlorpromazine, and quinidine demonstrate elevated levels of IgG Anti-histone antibodies.
  - dsDNA is rarely found in drug induced lupus.
  - Antibodies to Sm, RNP, Ro/SS-A, LA/SS-B are common in idiopathic SLE but are unusual or unlikely to persist in drug induced lupus.
  - APLA: can be seen in both DIL and idiopathic SLE.

- ✓ **Top 10 drugs associated with Drug-Induced Lupus**
  - Procainamide
  - Hydralazine
  - Quinidine
  - D-Penicillamine
  - Isoniazid
  - Methyldopa
  - Chlorpromazine
  - Minocycline (5/10,000 patients)
  - Anti-TNF Agents (2/1000 patients)
  - Terbinafine

- ✓ **List of other drugs implicated in drug induced lupus**

✓ **Definite**	✓ **Probable**	✓ **Possible**
✓ Procainamide ✓ Hydralazine ✓ Penicillamine ✓ Quinidine ✓ Isoniazid ✓ Minocycline ✓ Diltiazem (subacute cutaneous lupus) ✓ Anti-TNF agents ✓ Interferon-alpha ✓ Methyldopa ✓ Chlorpromazine ✓ Practolol	✓ Anti-convulsant agents (mephenytoin, phenytoin, carbamazepine, others) ✓ Propylthiouracil ✓ B- adrenergic blocking agents ✓ Sulfasalazine ✓ Anti-microbials (sulfonamides, nitrofurantoin) ✓ Lithium ✓ Captopril ✓ Docetaxel ✓ Hydrochlorothiazide ✓ Glyburide ✓ Amiodarone	✓ Statins ✓ Valproate ✓ Gemfibrozil ✓ Griseofulvin

Drug-induced Lupus versus SLE

@Lupusreference

		SLE		Drug-induced lupus (DIL)
Epidemiology	Prevalence Age F:M sex-ratio	10-180/100 000 Typically 20-40 9:1		≈10% of all lupus cases drug-dependent 4:1 to 1:1
Clinical manifestations		Malar rash Photosensitivity Alopecia, oral ulcers Lupus nephritis NPSLE	If present, are evocative of SLE versus DIL	Constitutional symptoms Arthritis, myalgia, serositis Kidney & NPSLE rare Malar rash is rare in DIL SCLE-DIL (terbinafine, thiazidic, PPI, ACE, calcium-b)
Laboratory Manifestations	CRP Cytopenia	Usually normal (except with serositis) Common		Usually normal (except with serositis) Less common (drug-dependent)
Immunological workup	ANA Anti-ENA Anti-dsDNA Anti-histone Low complement pANCA anti-MPO	>95% Positive in up to 30% Positive in 60-80% of cases Positive in 60-80% 50-60% Negative		>95% (IgG anti-chromatin) Rare (SSA+ for cutaneous DIL), anti-Sm rare Rarely positive (common with anti-TNF) Positive in >90% Rare (<5%) Seen with PTU (50%) and minocycline (65-100%)
Prognosis		Minor to life-threatening		Usually mild forms with constitutional symptoms
Treatment		Usual therapeutic management of SLE		Discontinuation of causal drug +++ Hydroxychloroquine csDMARDs and/or bDMARDs (rare) Topics for cutaneous-DIL
Evolution		Chronic disease		Disappearance of manifestations (weeks to months) and of autoantibodies (months to years)

✓ **Treatment of Drug induced Lupus**

- Discontinue the offending agent! The disease typically resolves after the drug has been discontinued within a few weeks of medication discontinuation.
- NSAIDs will help control the symptoms of arthralgias.
- Patients with severe symptoms, such as pericarditis or pleuritis, often require a short course of corticosteroids to control their disease.
- In more prolonged cases, anti-malarials (hydroxychloroquine) can be used.
- Further immunosuppression with azathioprine and cyclophosphamide is almost never required.

References:

Solhjoo M, Goyal A, Chauhan K. Drug-Induced Lupus Erythematosus. [Updated 2023 Apr 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441889/

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

Created: September 17, 2024

Reviewed: March 14, 2025