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## CLINICAL VIGNETTE

# Drug-Induced Lupus Secondary to Escitalopram

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A 42-year-old female with a history of breast cancer (treated with bilateral mastectomy and chemotherapy) and hypothyroidism presents with arthralgias and a facial rash. The most affected joints are bilateral hands, wrists, and knees. Her symptoms began gradually six weeks ago and increased in severity over time. The arthralgias primarily involve bilateral hands, wrists, and knees. She tried various over-the-counter NSAID's with mild relief of symptoms. She also tried various over-the-counter products for the facial rash without success. Current medications include levothyroxine 75 mcg daily and escitalopram 10 mg daily. The escitalopram was started three months ago. She does not take supplements and reports allergy to penicillin.

Physical Examination: Blood pressure is 104/66, pulse 52, temperature 98.4 Fahrenheit, height 5 feet 2, 109.0 pounds. The patient is comfortable in no apparent distress. Her physical exam was remarkable for an erythematous malar rash. Oral mucosa and conjunctiva were unremarkable and the remainder of her skin exam was within normal limits. Joints exam was remarkable for mild swelling with limited range of motion of bilateral hands DIP, PIPs, wrists, and knees.

Her labs revealed normal CBC, chem 14, TSH, and urinalysis. Her ANA was positive at 1:640 with positive anti-histone and negative anti-dsDNA antibody levels.

### **General Discussion, Epidemiology, and Etiology**

Drug-induced lupus erythematosus (DILE) is an autoimmune variant of systemic lupus erythematosus triggered by the acute or chronic use of a medication.<sup>1</sup> Affected patients often have no prior history of autoimmune disorders.<sup>1</sup> Signs and symptoms can arise days, months, or even years after initiation of the offending agent.<sup>2</sup> Many medications have been linked to DILE, but some of the more commonly reported medications include isoniazid, diltiazem, griseofulvin, atenolol, cefepime, bupropion, cimetidine, penicillamine, lithium, glyburide, omeprazole, esomeprazole, minoxidil, atorvastatin, simvastatin, minocycline, carbamazepine, procainamide, quinidine, hydralazine, HCTZ, amiodarone, nitrofurantoin, sulfasalazine, phenytoin, oral contraceptives, and terbinafine.<sup>2</sup> There may be a genetic predisposition, as some cases have been linked to the HLA-DR4 antigen.<sup>3</sup> Medications appear to trigger an autoimmune response with an elevation in blood levels of ANA, Rheumatoid Factor, ESR, and CRP.<sup>3</sup> Many DILE cases are without clinically apparent disease.<sup>3</sup> In symptomatic cases, signs and symptoms usually resolve relatively quickly with removal of the

offending medication.<sup>4</sup> The epidemiology of DILE differs from typical SLE cases. DILE patients usually present between the ages of 50-70, while SLE patients typically present between the ages of 20-40. DILE affects males equally as often as females, while SLE has a 9:1 predilection for females over males.<sup>1</sup> Anti-histone antibodies are positive in nearly all DILE cases, while they are positive in about half of SLE cases.<sup>5</sup> Anti-ds DNA levels are usually positive in SLE cases, while they are usually negative in DILE cases.<sup>5</sup> Complement levels (C3 and C4) are usually reduced in SLE, while they are usually normal in DILE.<sup>5</sup> ANA levels are usually elevated in both SLE and DILE cases.<sup>5</sup> About 5-10% of cases of lupus erythematosus are drug-induced.<sup>2</sup> There are approximately 20,000 cases of DILE per year in the United States.<sup>6</sup>

### **Pathophysiology**

It is believed that the SLE and DILE have different pathophysiological mechanisms.<sup>7</sup> The pathophysiologic mechanism of SLE appears to be related to molecular mimicry where the immune system generates antibodies against foreign antigens and these antigens attack the body's own cells.<sup>7</sup> There are many theories for the pathophysiology of DILE.<sup>7</sup> One theory is that the offending drug or its metabolites are oxidized and eventually alter lymphocyte activity in the thymus.<sup>7</sup> This theory may explain cases where the patient is on the medication for months or years prior to the development of symptoms.<sup>7</sup> A second theory is a dysfunctional P450 system related to genetically determined differences in acetylator status leading to the generation of toxic metabolites and the production of autoantibodies.<sup>8</sup> A third theory is that the offending medication causes decreased T-cell methylation and overexpression of the LFA-1 antigen resulting in auto-antibody production.<sup>7</sup> Irrespective of the mechanism of DILE, the end-result is end-organ damage and autoimmune overactivity.<sup>7</sup>

Genetic factors appear to play a role in DILE as patients have an increased incidence of HLA-DR2, HLA-DR4, HLA-DQB1, and the C4 null allele.<sup>9</sup> Slow acetylation rate is also a risk factor for DILE, although it is not a risk factor for SLE.<sup>10</sup>

Autoantibodies in DILE patients differ from those with SLE.<sup>1</sup> Nearly all DILE patients are positive for anti-histone antibodies and ANA, but other autoantibodies are usually absent.<sup>1</sup> Patients with SLE can be positive for other autoantibodies including anti-dsDNA, anti-RNP, anti-Ro, and anti-Sm.<sup>9</sup>

## Clinical Features

The most common clinical features of DILE are arthralgias, myalgias, lymphadenopathy, fever, fatigue, and serositis.<sup>1</sup> Patients can have dermatologic findings of a scaly, erythematous, photosensitive rash.<sup>1</sup> DILE symptoms tend to be less severe than SLE symptoms unless the offending agent is continued for an extended period of time.<sup>1</sup> Onset of disease is different for DILE vs. SLE with SLE usually having a gradual onset, while DILE usually having an abrupt onset.<sup>9</sup> The most common clinical feature of DILE is arthralgias which is present in nearly all cases.<sup>2</sup> Most DILE cases present from 1-24 months after starting the offending medication.<sup>9</sup> Serologic findings can, however, take months to years to resolve after stopping the medication although symptoms usually resolve within days to weeks.<sup>1</sup> Renal, cardiac, and central nervous system findings are almost never seen in DILE except for specific situations such as hydralazine-related glomerulonephritis or penicillamine-related renal disease.<sup>11</sup> Findings on physical examination can include hepatomegaly and splenomegaly, while alopecia, mucosal ulcers, and discoid plaques are not usually seen.<sup>1</sup> Cases of hepatic necrosis has been reported in DILE related to certain medications such as minocycline.<sup>1</sup> DILE patients can also occasionally have erythematous papules, erythema nodosum, and Raynaud's.<sup>11</sup>

## Diagnosis and Testing

DILE patients usually test positive for ANA with a homogenous pattern, test negative for anti-dsDNA, have normal complement levels, and test negative for anti-Sm, anti-Ro, and anti-RNP.<sup>9</sup> Anti-histone antibodies are usually positive in DILE, but are often negative in SLE.<sup>9</sup> SLE patients usually test positive for anti-dsDNA in contrast to DILE patients who usually test negative.<sup>9</sup> The work-up for DILE should include a CBC (to assess for anemia or leukopenia), chemistry panel (to assess for renal or hepatic involvement), and urinalysis (to check for hematuria or proteinuria).<sup>5</sup> A skin (or other organ) biopsy may be needed in certain cases to clarify the diagnosis.<sup>5</sup> Histologic findings often include perivascular lymphohistiocytic infiltration, epidermal atrophy, and basal vacuolization.<sup>5</sup>

## Treatment

The treatment for DILE is primarily focused on stopping the offending agent.<sup>4</sup> NSAID'S or a short course of corticosteroids (topical or systemic) are sometimes used to help with dermatologic or rheumatologic symptoms.<sup>1</sup> NSAID's can also be useful in cases of pleurisy or pericarditis.<sup>4</sup> Abnormal findings, if present, can be monitored to resolution.<sup>4</sup> More severe cases may require anti-malarials (such as hydroxychloroquine) to control cutaneous and musculoskeletal symptoms.<sup>1</sup>

## Prognosis

The prognosis for DILE is excellent so long as diagnosis is promptly made and the offending medication is discontinued within a short period of time.<sup>1,12</sup> The longer the delay in diagnosis, the greater the chance for longer term issues that could involve end organs.<sup>13,14</sup>

## Clinical Course and Follow-Up

The patient saw her primary care provider for follow-up. The SSRI was slowly tapered off over the next 4 weeks. The ANA and anti-histone antibody levels were monitored over time and gradually diminished over the next six months. The patient's symptoms resolved four weeks after the medication was fully discontinued.

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