Amoxicillin - Induced Systemic Lupus Erythematosus (SLE)

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Abstract: Autoantibodies and, less commonly, systemic rheumatic symptoms are associated with treatment with numerous medications and other types of ingested compounds, based on clinical and laboratory features, as well as exposure history. Drug-induced lupus has been reported as a side-effect of long-term therapy with over 40 medications. It's clinical and laboratory features are similar to systemic lupus erythematosus, except that patients fully recover after the offending medication is discontinued. This syndrome differs from typical drug hypersensitivity reactions in that drug-specific T-cells or antibodies are not involved in induction of autoimmunity, it usually requires many months to years of drug exposure.

Keywords: Amoxicillin, Induced Systemic Lupus Erythematosus, Drug-induced

1. Case Presentation

23 - years old female from Yamen visited our hospital complaining of joint pain since one year.

Pain was started in the small joints of both hands with swelling and hotness with morning stiffness of at least one hour daily. By time, other joints have been involved asymmetrically and in additive way along with fatigue, these symptoms limited her daily activities.

- She described also malar rash and recurrent painful mouth ulceration.
- No other mucocutaneous lesions and there was no muscle weakness.
- She denied having dysuria or vaginal discharge prior to her symptoms.
- She has good appetite, no marked weight loss and no fever.
- Patient is complaining of recurrent pharyngitis in which she is taking Amoxicillin tablet for 3 to 4 days duration almost every 10 days and she used to do so in the last 8 years. She is married, house wife and has no children.
- No family history of rheumatological diseases.
- By examination, she is young female with average body built and normal vital signs.
- There was malar rash sparing the nasolabial fold.
- No signs of active arthritis and unremarkable physical examination.
- Laboratory reports showed normal CBC and electrolytes,
- Positive ANA with titer of 1:160
- Positive Anti histone Antibodies.
- Reumatoid factor was negative
- Anti ccp was negative

She had been instructed to stop Amoxicillin, and her symptoms improved about 50% after 3 months of follow up. 6 months later, symptoms were totally resolved.

2. Literature Review

Patient diagnosed to have Amoxicillin induced lupus and certain drugs may trigger an autoimmune response; most often, these drugs induce autoantibodies, which may occur in a significant number of patients, but most of these patients do not develop signs of an autoantibody -associated disease. In some patients, a clinical syndrome with features similar to systemic lupus erythematosus (SLE) may develop, which is termed drug-induced lupus.(1)

Although there are currently no formal classification criteria for the diagnosis of DILE, it is widely accepted that DILE is defined as the development of lupus-like symptoms (commonly fever, musculoskeletal involvement and serositis) that is temporally related to continuous drug exposure (1 month) which resolves with cessation of the offending drug.(2)

It is usually accompanied by serologic findings of a positive antinuclear antibody (ANA) as well as anti-histone antibodies.

Autoantibodies — An important immunologic characteristic of drug-induced lupus is the presence of autoantibodies. The autoantibodies or patterns of autoantibodies that are seen largely depend upon the inciting agent. As examples , in disease related to certain drugs, there are antinuclear antibodies that have specificity for histone proteins, while, with disease due to other agents, antibodies that are more often associated with idiopathic SLE (e.g., anti-double stranded DNA antibodies) or with systemic vasculitis (e.g., antineutrophil cytoplasmic antibodies) may be present

The ANA pattern is consistently homogenous as the autoantibodies target nuclear histone proteins.
Anti-histone antibodies are positive in up to 95% of DILE while anti-dsDNA antibodies are rare; in contrast to idiopathic SLE.

Longitudinal studies have shown that the ANA and anti-histone titers gradually decline with the resolution of DILE. It has been demonstrated that various subnucleosomes with peptide in the histone-DNA complex in the cell nucleus, having varying antigenicity across different drugs in DILE.

For example the (H2A-H2B)-DNA complex is the predominant antigenic particle in procainamide-induced LE. Anti-double stranded DNA antibodies — they are typically absent in drug-induced lupus due to procainamide, hydralazine, and isoniazid, but these antibodies are associated with drug-induced disease with other agents, particularly with interferon-alfa and anti-tumor necrosis factor (TNF) agents. With the latter class of anticytokine therapies, although the majority of patients may eventually develop antinuclear antibodies and other autoantibodies, including anti-dsDNA antibodies, relatively few patients with any of these antibodies develop clinical manifestations of drug-induced lupus.

- Antineutrophil cytoplasmic antibodies (ANCA) — Drug-induced ANCA are sometimes associated with necrotizing vasculitis.
- The age of onset of DILE is generally older; with an equal female to male distribution.
- An estimated incidence of 15,000–20,000 cases per year. Whites may be affected up to six times more frequently than blacks and may have more severe manifestations. The time between drug exposure to onset of symptoms varies from one month to as long as over a decade after initiation of the drug treatment. However, onset is generally insidious.

Patients commonly present with fever, arthralgia (90%) or arthritis, myalgia (50%) and serositis. These symptoms are usually mild although life-threatening cases have been reported.

The classic malar or discoid rash, oral ulcers and major organ involvement (renal and neurologic) seen in idiopathic SLE are notably seen rarely.

The pathomechanisms in drug-induced lupus is unlike classical drug hypersensitivity reactions for several reasons:

1) It lacks drug-specific T-cells or antibodies and the target autoantigens are not directly affected by the offending drug.
2) Course for the development of DILE tends to be much slower than that of classic drug hypersensitivity.
3) Reintroduction with a lupus-inducing drug is not associated with memory of prior exposure if systemic autoimmunity had normalized.
4) Idiopathic SLE also form a variety of other autoantibodies, including those directed against DNA and small ribonucleo proteins, which are less common in drug-induced lupus.
5) The duration of exposure and drug dose affects the likelihood of development of DILE.
6) Another distinguishing feature of ANA in DILE is that these antibodies are not complement fixing, unlike those in SLE.

Many mechanisms of pathogenesis have been hypothesized in the literature to date: (7,8)

a) Hapten hypothesis

Either the drug or its metabolite binds to protein(hapten), thus making it ‘foreign’ and incites an immune response against the hapten or it possibly self-antigens by virtue of molecular mimicry or antigen processing resulting in presentation of cryptic antigens.

b) Direct cytotoxicity hypothesis

Certain reactive drug metabolites may directly cause cell death via a non-immune mediated process. This has been demonstrated a wide variety of lupus inducing drugs in vitro. However, this process cannot entirely explain the immune perturbations in DILE. Hence, it has been postulated with a paucity of evidence that drug metabolites also alter degradation and clearance of apoptotic cells which eventually leads to the loss of tolerance to self-antigens.

c) Lymphocyte activation hypothesis

Murine splenocytes exposed to procainamide or hydralazine in vitro demonstrated an increased proliferative response to autologous antigen-presenting cells without the need for cognate antigen and promoted B cell differentiation in antibody-secretory cells. Adoptive transfer of such cells induced a lupus-like syndrome in mice.

d)Disruption of central immune tolerance

Murine models have shown that intra-thymic injections of lupus-inducing drugs resulted in a delayed but sustained production of anti-chromatin antibodies. It was subsequently demonstrated that these drugs interfered with the establishment of tolerance to endogenous self-antigen that are normally presented by the MHC to thymocytes. Hence mature T-cells are capable of undergoing spontaneous activation when encountering similar self-antigens in the periphery.

Acetylator status — Drug-induced lupus is more likely to develop and develops sooner with certain drugs metabolized by acetylation in those patients who are slow acetylators, ie, those in whom there is a genetically-mediated decrease in the hepatic synthesis of N-acetyltransferase. Examples of such drugs include procainamide and hydralazine.

In contrast to the high degree of risk for drug-induced lupus with procainamide, particularly in slow acetylators, there is little or no antinuclear antibodies (ANA) formation or symptomatic lupus following the administration of N-acetylprocainamide (NAPA), the major active metabolite of procainamide. Furthermore, remission of procainamide-induced lupus can be achieved by switching to NAPA. These observations suggest an important pathogenic role for the aromatic amino group on procainamide.
Immunogenetics: Possible genetic risk factors include human leukocyte antigen (HLA)-DR4, HLA-DR0301, and the complement C4 null allele. These factors vary between different agents. As examples:

- Risk factors for procainamide-induced lupus, may include HLA-DR6Y, but not DR4 or DR3 (13).
- Risk factors for hydralazine-induced lupus include female sex; the HLA-DR4 genotype; and the null gene for the fourth component of complement, C4. In one study, lupus developed in 19 percent of women taking 200 mg of hydralazine daily, compared with 13 of 13 women who also had the HLA-DR4 genotype. These factors may interact; it is possible that slow acetylation increases free drug levels, while low levels of C4 might prevent clearance of any immune complexes that are formed.(14)
- Patients with HLA-DQB1 and either HLA-DR2 or HLA-DR4 may be at increased risk of developing minocycline-induced lupus(15)

DILE can be divided into three main groups according to the likelihood of causing DILE based on the level of evidence available in the literature (2):
- Group I: Definite association based on controlled studies confirming its pathogenic role in inducing DILE.
- Group II: Probable association based on large series or cohorts consistently reported.
- Group III: Possible association with a few case reports.

### Table 2: Drugs implicated in the development of DILE

<table>
<thead>
<tr>
<th>Definite</th>
<th>Probable</th>
<th>Possible</th>
<th>Recent case reports</th>
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<tbody>
<tr>
<td>Hydralazine</td>
<td>Sulphasalazine</td>
<td>Antibiotics</td>
<td>Infliximab</td>
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<tr>
<td>Procainamide</td>
<td>Anticonvulsants</td>
<td>Non-steroidal anti-inflammatory agents</td>
<td>Etanercept</td>
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<td>Isoniazid</td>
<td>Anti-thyroid</td>
<td>Antihypertensives</td>
<td>Interleukin-2</td>
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<td>Methyldopa</td>
<td>Statins</td>
<td>Lithium</td>
<td>Zafirlukast</td>
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<td>Tinidine</td>
<td>Terbutaline</td>
<td>Interferons</td>
<td>Clofazimine</td>
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<td>Minocycline</td>
<td>Penicillamine</td>
<td>Gold salts</td>
<td>Tocainide</td>
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<td>Chlorpromazine</td>
<td>Fluorouracil</td>
<td>Lisinopril</td>
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**PROGNOSIS:** The prognosis of drug-induced lupus is generally quite favorable in most case series and in our experience, with disease typically resolving after drug withdrawal, even though treatment may be needed for up to several months in some patients. Occasional patients require glucocorticoid therapy, but life-threatening disease is infrequent (16).

**TREATMENT:** There have been no randomized trials that have examined the optimal treatment approach to drug-induced lupus.

The initial step in treatment is to stop the offending medication. Specific manifestations should then be treated temporarily until they resolve using the same approaches used in patients with idiopathic systemic lupus erythematosus. Treatment is based upon the observations of the authors and other experts that symptoms gradually resolve after drug discontinuation in most patients and that medications that are effective in idiopathic SLE and subacute cutaneous lupus (S克莱) are also effective in patients with drug-induced illness. As examples, we treat arthralgia, arthritis, and serositis initially with nonsteroidal anti-inflammatory drugs (NSAIDs),

- In patients with more resistant disease, antimalarials (e.g., hydroxychloroquine) can be temporarily used if constitutional, cutaneous, and musculoskeletal symptoms do not clear within four to eight weeks. Systemic (e.g., orally administered) glucocorticoids are infrequently required, but may benefit patients with more severe pleurisy or pericarditis, for which they can usually induce quick resolution.(17)

### References


