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A short overview on systemic drug induced lupus erythematosus

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Abstract:

Drug-induced lupus erythematosus (DILE) arises after exposure to certain drugs for a period of time that induces a lupus like syndrome, which resolves after the offending drugs are stopped. As of now there are still no specific diagnostic criteria for DILE and its pathogenesis is still not clear. Like idiopathic lupus erythematosus, DILE can be divided into systemic (SLE), sub-acute cutaneous (SCLE) and chronic cutaneous lupus (CCLE). This review focuses on systemic DILE. Common findings in systemic DILE include skin signs, arthritis and serositis and a typical laboratory profile include positivity for anti-nuclear and anti-histone antibodies while double stranded (ds) DNA and extractable nuclear antigens (ENAs) are rare. Common drugs frequently involve are hydralazine, procainamide and isoniazid. The latest class of medications being associated with DILE is treatment with anti-TNFa. Anti-TNFa DILE is quite different from classic DILE in many ways. Rashes and renal involvement are reported in many cases of anti-TNFa DILE while they are rare in classic DILE. The laboratory profile of anti-TNFa DILE also differs from classic DILE and are anti-ENAs and anti-dsDNA antibodies and also low serum complement levels which are rare in the latter.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease of connective tissues having multifactorial etiologies yet to be fully understood. It is associated with a variety of clinical manifestations with significant morbidity and mortality. The prevalence is greater in the female population than male in a ratio of 9:1 affecting mostly women of an African lineage between 25 and 45 years of age [1-6]. Many drugs have potential toxic effects of mimicking autoimmune syndromes [7,8]. This review focuses on drugs-induced lupus erythematosus (DILE). DILE is a lupus-like syndrome that occurs due to continuous long exposure to the drugs. The symptoms manifest after initiation of therapy with a drug and must resolve upon cessation of that drug [9,10]. As of now there is no established criteria for the diagnostic of DILE [11]. The symptoms usually associated with DILE are arthritis, serositis, anti-nuclear and antihistone antibodies and skin manifestations. Similarly to idiopathic SLE, DILE can be classified into systemic (SLE), sub-acute cutaneous (SCLE) and chronic cutaneous lupus (CCLE) but contrarily affects older patients and is less common in women and African.

Several prescribed drugs across different therapeutic classes have been shown to cause lupus [11,12]. There are enough evidences showing that 20% of patients on procainamide and 5-8% of patients on hydralazine develop clinical manifestations of lupus within 1 year of therapy [8].

Drugs associated with lupus

There are more than 80 drugs that have a connection with lupus and this keeps increasing overtime. Low exposure to some drugs such as NSAIDs, antibiotics, estrogens and

anticonvulsant may increase the damages in an underlying SLE [9,10,13]. There are evidences that continuous exposure of about 1 year to certain drugs namely hydralazine, procainamide, isoniazid, methyldopa, quinidine, minocycline and chlorpromazine can induce lupus. Hydralazine and procainamide are classified as high risk, quinidine as moderate risk and with the rest as low risk.

The mechanism of how drugs cause lupus is unclear but it can be inferred from data that several mechanisms are responsible to induce autoimmunity from those drugs. There are risk factors associated with certain gene traits like slow acetylator, HLA-DR2, HLA-DR3, HLA-DR4, and null allele of complement C4 [9].

Systemic DILE

Systemic DILE is rare and is similar to a tempered down version of idiopathic SLE, however it occurs equally in both female and male of older age [14]. It presents with symptoms like joint and muscle pain, fever, and inflammation to the pleura and pericardium. In DILE contrarily to idiopathic SLE, malar or discoid rash, oral ulcers, renal and neurological involvement are rarely seen [6]. There is some skin involvement that is less frequent and milder to SLE with symptoms like photosensitivity, purpura and erythema nodosum. Urticarial vasculitis, livedo reticularis and skin ulcers are non-specific lesions that may present clinically in systemic DILE [15].

A study carried out by Zirwas et al. showed that anti-histone antibodies in DILE have a sensitivity of 67% and a specificity of 95% [16]. There are already more than 80 drugs contributing to DILE and this number keeps piling up with more drugs constantly being discovered [14]. Common drugs that can induce systemic DILE are hydralazine, procainamide, isoniazid, methyldopa, quinidine, chlorpromazine and minocycline. The presence of anti-DNA antibodies are very rare in DILE while anti-ds DNA antibodies are generally not found

in DILE caused by procainamide, hydralazine and isoniazid but are seen in SLE [17].

Evidences from two studies showed the association of the tetracyclic antibiotic minocycline and SLE in treating acne vulgaris [18,19]. It is to be noted that also in addition to DILE features, patients present with skin involvement like Raynaud's phenomenon, polyarteritis nodosa and erythema nodosum and also involving the liver. P-ANCA can be seen in 80% of cases and the association of positive anti-histone antibodies is rare [20].

It has also been reported there is an association between Interferon-α and DILE [21]. It differs from other DILE due to frequently involving the kidney and mucocutanous. In addition, in half of cases there is the development of anti-dsDNA antibodies [22]. It has also been found that there is an association between systemic DILE and interferon-ß1 [23]. There is a report by Yokoyama et al. of two cases of systemic DILE caused by the widely used drug ticlopidine in patients with ischemic vascular disease [24]

Some common drugs causing systemic DILE

Procainamide

Procainamide has been widely used to manage cardiac arrhythmias [25,26] and also in the therapy of myotonic dystrophy [27,28]. But, it is well known that using procainamide for treatment may induce a systemic lupus erythematous like syndrome [29-31]. Drugs such as procainamide, isoniazid and hydralazine require liver enzyme acetyltransferase to be metabolized through the process of acetylation and if the gene expressing it is homozygous recessive, making the patient to be a slow acetylator [32], might possibly explain how procainamide induce lupus.

More than 50% of patients being treated with procainamide have positive circulating anti-nuclear antibodies (ANA) [33,34] and around 10% of which may exhibit a systemic

lupus like syndrome [33]. Similarly to idiopathic systemic lupus, patients present with arthralgia and around a third of them show pulmonary infiltrates but as oppose to idiopathic SLE, renal and neurological involvement are rare [35]. However in patients with myotonia, it is difficult to establish a link between procainamide and pulmonary infiltrates as those patients are highly at risk to get pulmonary infections [36]. It is advisable to obtain a base line anti nuclear factor (ANF) when starting long-term therapy with procainamide in patients. This is because there is a high incidence of positive ANF in patients on procainamide for a period of more than 2-3 months [33,34] and also may help in the differential diagnosis.

Hydralazine

It is known that hydralazine is a drug that can induce DILE. Hydralazine causing DILE occurs in 5-10% of cases. Patients commonly present with fever, serositis and pain to the muscles and joints [37]. A rare feature that appears in less than 5% of cases reported in medical archives is pericardial effusion [38]. From a trial carried out by Taylor et al, it was reported that the usage of hydralazine in patients with heart failure was increasing [38,39]. Thus, DILE should be mentioned as a differential diagnosis in heart failure patients being treated with both hydralazine and isosorbide dinitrate in cases where there is suspicion of pericardial effusion. It is indicated in case reports that patients on low dosage of hydralazine (<100mg) have the risk of developing DILE contrarily to the pass belief that it was dependent on dosage [40,41].

The enzyme N-acetyltransferase is required for metabolizing hydralazine in the liver through acetylation and it's rate to be a slow or fast acetylator is decided genetically via the recessive gene causing a decreased activity of hepatic acetyltransferase [42]. As acetylation is responsible to metabolize hydralazine, patients low on acetyl transferase will accumulate the drug and are prone to suffer from toxic or

immunological effects like DILE [43]. Hydralazine can inhibit T-cell DNA methylation preventing deletion of unwanted cell function genes inducing reactivity to self, which result in autoimmunity [44].

Isoniazid (INH)

INH is one of the first line drugs for the treatment of tuberculosis. It is eliminated through urination after being metabolized in the liver by acetylation. ANA can be found in 25% of patients treated with INH. Only 1% of patients being treated with 300 to 900mg/d of INH for duration of 4 weeks to 14 months can suffer from systemic DILE [32]. The real mechanism for INH induced systemic DILE is unclear but theories have been put forward, one being predisposed genetically as a slow acetylator [32]. Another theory is due to reactive intermediate formed when INH act as substrates for myeloperoxidase in activated neutrophils causing the formation of autoantibody which lead to the development of DILE [44]. It varies from 1 month to more than ten years for symptoms to appear after being exposed to INH. The INH induced lupus depends on the dosage of INH and not as a result of immune mediated response targeting the drug [6,45]. In 50% of INH induced lupus, patients appear with symptoms of fever and pleuritis and in 30% of cases with pericarditis [46].

Systemic DILE due to TNF-α

There is an increase usage of drugs targeting TNF-α in the rheumatic and autoimmune diseases, which keep on increasing rapidly, as well as in inflammatory bowel diseases [11,47].

It is taken into account that treatment with anti-TNF can potentially induce SLE [48,49], with anti-TNFα drugs being the latest medications associated with lupus-like syndrome [50]. Most cases of DILE due to anti-TNFα reported were in patients being treated with etanercept or infliximab and only

few cases with adalimumab which may be due to it being recently used as opposed to the former two [7,51-55].

The mechanisms to how treatment with anti-TNFα induces lupus are not clear but most likely are different from classic DILE, though three hypothesis have been forwarded [49]. First hypothesis is TNF blockers suppress the T-helper type 1 response that enhances a T-helper type 2 response leading to SLE [56]. Second hypothesis is the interference of TNF inhibitors with normal cell apoptosis that lead to decreased clearance of auto-reactive T and B cells and cellular debris, including nuclear material, thus increasing the formation of autoantibodies to DNA and other nuclear antigens. Third hypothesis is the inhibition of cytotoxic T cells by anti-TNFα therapy, which decrease the elimination of autoantibodies that are released by B-cells [48,49,56].

Anti-TNFα DILE can be differentiated from classical DILE in that it targets women more than men with an average age ranging from 46.2 to 50.9 years [57,58].

After long-term use of anti-TNFα for an average of 40.6 weeks, generalized symptoms similar to classic DILE appear [14]. The characteristic symptoms are myalgia, arthralgia, lupus-like skin lesions and the presence of autoantibodies in serum. Cutaneous features including malar rash, photosensitivity and sub-acute or chronic cutaneous lupus erythematosus are more common in anti-TNFα DILE than in classic DILE. Cutaneous features are more often seen in patients treated with etanercept while serositis are mostly seen in those treated with infliximab [59]. Organ involvement is common with kidney diseases seen in many cases [60,61]. Cytopenia is the most common blood pathology seen in 2-61 % of patients [50,51].

ANA is usually high in anti-TNFα DILE similarly to classic DILE. Anti-histone antibodies are mostly observed in classic DILE while anti-dsDNA antibodies positivity is mostly

described in anti- TNFα DILE. Also low blood complement level and positive ENAs are seen mostly in anti-TNFα DILE [14].

Management

Before putting patients on drugs that can induce lupus, pre-existing characteristics pointing toward an underlying autoimmune disease should be assessed carefully and not taken lightly. Once treatment with potentially inducing lupus drugs is started, patients should be carefully evaluated both through clinical and laboratory examinations. Abnormal laboratory findings do not mean it is pathogenic and the drugs are stopped only when patients develop lupus-like symptoms. Like with other drugs inducing systemic DILE, the main treatment of anti-TNFα DILE is to stop the drug [42,48]. The symptoms dampen over a couple of weeks but at least a year is required for recovery. NSAIDs are given to control symptoms. Glucocorticoids are used as treatment in cases of pericarditis and pleurisy and hydroxychloroquine can be given to patients if there is persistence of symptoms like fever, skin lesions, muscle and joint pain [17]. Patients should not be re-challenged with drugs known to induce lupus in them, as the disease will recur.

CONCLUSION

DILE is a lupus-like syndrome caused by a number of drugs that keep increasing. It can be divided into systemic, sub-acute cutaneous or chronic cutaneous. Systemic DILE is quite rare and general symptoms are similar to idiopathic lupus but milder. DILE due to TNF-α presents with symptoms similar to classic DILE but also involve skin lesions more. The main marker for classic systemic DILE is anti-histone antibodies while the markers for anti-TNFα DILE are anti-dsDNA and ENAs. However the mainstay primary treatment whether it is classic systemic DILE or TNF- α, is cessation of the inducers drugs.

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