

Lupus with Graves' disease: Overlap Disease vs Drug Induced Lupus; a Review of Literature

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Keywords Graves' disease; Systemic lupus erythematosus; Overlap syndrome; Immune dysregulation; Drug-induced lupus

Abbreviations DILE: Drug Induced Lupus; DISLE: Drug Induced Systemic Lupus; DISCLE: Drug-Induced Sub-Acute Cutaneous Lupus; DICCLE: Drug-Induced Chronic Cutaneous Lupus

Abstract

Introduction: Graves' disease (GD) is one of the organ-specific autoimmune thyroid diseases, while SLE is an autoantibody mediated systemic autoimmune disease. A literature review lends itself to the known association of hypothyroidism, autoimmune thyroiditis, thyroid cancer but rarely hyperthyroidism to systemic lupus erythematosus in age and sex matched controls. About one third of the patients with autoimmune thyroid diseases are Anti-Nuclear Antibody (ANA) positive. About one tenth of patients with autoimmune thyroid diseases, who are ANA positive, may also be positive for other lupus antibodies such as Anti-Double Stranded DNA (Anti-dsDNA), Anti-Ro, and Anticardiolipin (aCL). The association of Anti Smith Antibody positive SLE and Graves' disease is extremely rare in adults and none reported in the pediatric population.

Case presentation: An 11-year-old Caucasian female from mid-Missouri was diagnosed with Graves' disease and was started on Methimazole. On day 30th of therapy, she presented with small joint arthritis and eventually was diagnosed as systemic lupus erythematosus by the Rheumatologist. This is the first case report of overlap syndrome of juvenile Graves' disease and anti-Smith antibody positive juvenile SLE in the pediatric population.

Discussion and Conclusions: The coexistence of GD with the SLE could be explained as a part of the lupus syndrome, an overlap disease, or drug induced lupus due to methimazole therapy in a Graves' disease patient. It is utmost importance to identify the correct diagnosis to estimate the current treatment and long-term outcome of the patient. It appears from the published literature that the coexistence of thyroid abnormalities and lupus does not affect mutual disease activity, though the type of association affects the patient outcome (REF).

Introduction

Graves' disease (GD) is one of the organ-specific autoimmune thyroid diseases, while SLE an autoantibody mediated systemic autoimmune disease [1]. Both diseases are the result of immune dysregulation. About one third of the patients with autoimmune thyroid diseases are Anti-Nuclear Antibody (ANA) positive. About one tenth of patients with autoimmune thyroid diseases who are ANA positive may also be positive for other lupus antibodies such as Anti-Double Stranded DNA (Anti-dsDNA), Anti-Ro, and Anticardiolipin (aCL) PMID: 15308528. But the association of positive Anti-Smith antibody is not reported. The association of hypothyroidism, Autoimmune Thyroiditis (AT) thyroid cancer and rarely silent hyperthyroidism to systemic lupus erythematosus is known in age and sex matched controls [2-7]. The association of Anti Smith antibody positive SLE and Graves' disease is not as well recognized; Especially it is not reported so far in pediatric populations. Only a case report on a drug induced Vasculitis-lupus like syndrome in a 13-year-old HLA-DR-9 positive girl with GD who was treated with propylthiouracil has been published. The syndrome resolved after discontinuation of treatment with propylthiouracil [8]. To our knowledge, the coexistence of Drug-Induced Lupus Erythematosus (DILE) or overlap syndrome of Graves' disease and anti-Smith antibody positive SLE has not been reported in the pediatric population so far. This is the first case report of the pediatric overlap syndrome of Graves' disease and juvenile onset anti-Smith antibody positive SLE. The differential diagnosis still continues to be DILE, idiopathic SLE and GD overlap syndrome. It appears from the published literature that the coexistence of thyroid abnormalities and lupus does not affect mutual disease activity, though the type of association affects the patient outcome (REF).

Case presentation

An 11-year-old Caucasian female from mid-Missouri presented to her primary care provider for tachycardia and weight loss. Her past history included multiple cases of pneumonias URIs, and seasonal allergies apart from abdominal pain which the family attributed to gluten sensitivity and she was on gluten exclusion diet on presentation. She was not on any medications at the time of presentation. Her family history was positive for bipolar disorder, schizophrenia, hypertension and type 1 diabetes mellitus. The patient was up to date on her immunizations.

She was subsequently found to have an elevated T4 of 19.8 mcg/dL, (free T4 of 7.68 mcg/dL), and a suppressed TSH of 0.005 mcunit/mL. With the suspicion of hyperthyroidism, she was started on 10 mg propranolol every eight hours to avoid thyrotoxicosis and referred to an endocrinologist. Her detailed laboratory evaluation at endocrinology clinic revealed positive tests for thyroid receptor antibodies, thyroid stimulating immunoglobulin (at 22 IU/L and 5.2 TSI index), and a negative celiac panel (patient was on gluten free diet for several weeks). A radioiodine uptake and scan were consistent with hyperthyroidism due to Graves' disease. Subsequently with the diagnosis of Graves' disease treatment options were reviewed and the parents who decided to opt for medical treatment as opposed to radio ablation or surgery. Thus, the patient was started on Methimazole 10 mg three times daily while continuing propranolol.

Approximately three weeks later, the patient again presented to the endocrinology clinic with mottling on legs and worsening joint pain with new multiple joint swellings. With concerns about adverse side effects, Methimazole was discontinued and propranolol was modifying to 10 mg every six hours.

A referral to rheumatology was made for the worsening of joint pain and new onset joint swellings involving both the hands, bilateral ankles and knees. She complained of morning stiffness lasting for several hours, swelling in the joints and severe pain (8/10 most of the times) restricting her routine activities for two weeks. Her constellation of other new symptoms included fatigue, erythematous diffuse rashes on face, neck and arms, hair loss, multiple small painful oral ulcers, nasal ulcers, dry mouth with gritty feeling in eyes, photosensitivity (rash), vision changes, generalized muscle pain, behavior changes (irritability, headaches and anger issues), abdominal pain, palpitations, and non-bloody diarrhea. Methimazole is known to cause arthralgias, but the patient had true arthritis on physical exam in a rheumatology clinic. Other significant findings of rheumatology evaluation revealed patchy alopecia, lymphadenopathy, malar rash, nonspecific photosensitive rash, and fever. The laboratory results showed elevated ESR and CRP, RNP (30.6 RLU-normal range < 20.0), low white cell count (WBC), anti-Smith in high titers (692.9 RLU - normal range < 20.0), positive ANA (1: 1280 speckled), negative SSA/Ro/ SSB/La antibodies and SL70 Antibody. Her Coombs test, lupus anticoagulant and anti-cardiolipin antibodies were negative. Her complement C4 was normal while complement C3 was elevated. Based on her positive findings, the patient was diagnosed with systemic lupus erythematosus and she was initiated on a three week tapering course of oral prednisolone (1mg/kg), hydroxychloroquine (6 mg/kg/day) and once a week methotrexate (15 mg/week).

Once the patient's arthritis and joint pain improved the patient underwent radioablation. She eventually did not respond to the ablation and on patient's choice, she was restarted on Methimazole five months after ablation therapy. Her lupus symptoms, signs or lab results did not show flare after she was re-started on Methimazole. She is under control with Methimazole, propranolol as well as methotrexate and hydroxychloroquine.

Based on the results thus far, it seems more likely that the Graves' disease and SLE were concurrent rather than subsequent in onset. Since the ESR and other markers did not trend downwards with cessation on Methimazole, we cannot infer drug-induced lupus. The Lupus symptoms and ESR began to trend down with the initiation of

steroids, Hydroxychloroquine and methotrexate, also did not worsen with restarting the Methimazole suggests it to be idiopathic SLE rather drug induced.

Discussion and Conclusions

Subclinical autoimmune thyroid disorders are reported to be more common in SLE patients than the overt disease [3,9,10]. The frequency of thyroid antibodies related to overt thyroid diseases (Hashimoto's Thyroiditis) was higher in SLE patients than of patients with non-antibody related thyroid disorders [11,12].

In a prospective case-control study (2016) on 40 Juvenile SLE (JSLE) and 30 age and sex matched normal controls, Abd-Elnabi et al. showed different results as compared to adults [13]. A significant positive correlation was noted by Elnabi et al. between SLEDAI and anti-TG disorders (Hashimoto's Thyroiditis) in children. He concluded that thyroid dysfunction is higher in children with SLE and correlated with severity of the disease.

Watad et al reported in a case-control study involving 5018 adult SLE patients with and 25,090 age and sex matched controls, that the prevalence of thyroid dysfunction was higher in SLE patients than in matched controls ($p < 0.001$, 2.59% in SLE vs. 0.91% in controls) [14]. Boey et al. reported that 8.9% of adult SLE patients had hyperthyroidism in his retrospective review of 129 adult SLE patients in Singapore, although his finding was not compared/ corrected against age-sex matched controlled population [15].

In their research of 319 adult Chinese SLE patients (292 females) Goh et al. Reported nine patients with comorbidity of thyrotoxicosis (in control unmatched data from 1974 to 1984). All but one of the patients in this cohort (9/319) developed thyrotoxicosis several years before they developed SLE [16]. Viggiano et al. reported no difference in incidence and prevalence of hyperthyroidism in SLE patients in a controlled matched cohort [17]. Pyne et al. reported in their retrospective review (between 1978 and 2000) of 300 adult SLE patients in the UK, no significant difference in the prevalence of hyperthyroidism in adult SLE patients and that the age-sex matched in the normal population. Although they confirmed the findings of eleven overt thyroid diseases that were prevalent in their SLE cohort they were thyroid auto antibodies related diseases and not non-antibody related diseases of thyroid [18]. Digne et al. reported from sub-Saharan Africa a case of a 52-year-old female with the diagnosis of SLE (without renal and skin involvement [19]). One year after treatment with hydroxychloroquine and steroids she developed autoantibody-positive thyrotoxicosis syndrome with goiter, but without exophthalmos.

One of the larger reported series of adult patients with Graves' disease and SLE is by Rodrigue et al. in 1988 [20]. In the retrospective review of their 93 adult patients with SLE (1973-1988, all women, between 23 to 41 years of age) he identified six patients who had co-existent Graves' disease. In his series 3/6 were diagnosed with Graves' disease (6months, three years, and five years respectively) before they got diagnosed with SLE. In 2/6 adult patients where both of the diseases began simultaneously, the diagnosis was delayed because of overlapping clinical characteristics of the two diseases. Only one of the six patients in this series was diagnosed with SLE nine years before she was diagnosed with GD. In his series, 6/6 had arthritis, 5/6 had renal disease, 4/6 had serositis, 1/6 had CNS disease,

2/6 had photosensitivity, 1/6 central nervous system involvement, 2/6 oral ulcers, 3/6 had Cytopenia, 6/6 had ANA and 4/6 had Anti dsDNA positive, 4/6 had LE cell positive, and 2/6 tested positive for Venereal Disease Research Laboratory test (VDRL). In this series, 1/6 met four criteria of the American Rheumatism Association, 1/6 met five criteria, 2/6 met six criteria, and 2/6 met seven criteria. Two patients in this series died of renal complications and one of those patients also had CNS lupus involvement. Out of six patients, one had a thyroidectomy while the other five with their remaining thyroids displayed a goiter with abnormal iodine uptake. In the series 4/6 were controlled with methylmercaptoimidazole. This group also reported a higher prevalence of GD in SLE patients than the general population [20].

Another adult series is reported by Goh and Wang [16]. They retrospectively (1974-1984) looked at their 319 (7/9 Chinese, 2/9 Malaysian) SLE patients and identified nine who had the coexisting diagnosis of GD. These nine adult patients included two males and seven females ranging in age from 22 years to 42 years. In 8/9 patients with coexisting SLE and Graves' disease, the GD preceded the development of SLE by one to 11 years. The diagnosis of SLE was recognized to be delayed due coexisting GD and similarities in the symptoms. One of nine patients SLE was diagnosed with GD five years after the diagnosis of SLE. The GD in all the nine patients was treated with Imidazole antithyroid agent; 2/9 patients eventually required thyroidectomy. The SLE manifestations in these nine patients were different to that of remaining 310 SLE patients. The patients with GD and SLE overlap syndrome had the higher incidence of arthritis, mucocutaneous involvement (rash, oral, nasal ulcers), enlarged lymph nodes, and renal disease. The prevalence of neuropsychiatric and hematological involvement was low in the nine with overlapping GD. Theoretically; there is a masking effect of Imidazole antithyroid agents on the development and the diagnosis of SLE [21].

Drug induced Lupus (DILE) is defined as the occurrence of lupus/SLE (with or without anti-histone antibodies) in a patient who has continuous relevant drug exposure and whose lupus syndrome resolve after the offending drug is discontinued. DILE reappears if the patient is re-challenged with the offending drug, but it usually takes 1-2 days before the reappearance of DILE [22,23]. The DILE patients usually meet the required ACR criteria for lupus [23]. Most patients fulfill four criteria including arthritis, serositis, antinuclear and anti-histone antibodies. The symptoms in DILE should have started after initiation (at least one month in the therapy) of the offending drug and should resolve after discontinuation of that drug. The effect of total cumulative dose and duration of exposure is different for different drugs, but in most part, it is directly proportional to the chances of developing DILE. It has also been recognized that some of the drugs known to induce lupus like syndrome can also exacerbate latent lupus or worsen the SLE. The individuals, who are slow acetylators and are positive for HLA-DR4, complement factor C4 null allele, HLA-DR2, and HLA-DR3 run a higher risk for developing DILE when exposed to offending drugs [23,24]. The patients with DILE due to treatment with thioamide derivatives are reported to present with mucocutaneous lesions, arthritis which can be migratory, lymphadenopathy, leukopenia, fevers, myalgia, positive anti-neutrophilic cytoplasmic antibodies (ANCA), vasculitis syndromes, positive ANA, and anti-ds DNA antibodies. These patients are not recognized to have positive anti-Smith antibodies

[8,25,26]. Lupus like syndrome can develop within days to a few years with thioamide derivatives and also resolves at a variable period after stopping the drug. In one reported case, lupus like syndrome took two years to regress [8] while it took only a few days in some other cases. In one patient who had DILE due to a thioamide derivative, the symptoms of lupus syndrome resolved within weeks of stopping the drug, but she indefinitely continued to be positive for anti-dsDNA antibody [27]. This last example suggests that thioamide derivatives may have precipitated lupus in a patient with the latent disease. The difference in presentations, system involvement, and drug exposure time suggest there is no single mechanism responsible for induction of DILE by all the lupus-inducing drugs.

Garden variety DILE is a milder disease with 90% of patients having arthralgia and 50% having myalgia. The ANA is positive with a homogeneous pattern, but it is not complement-fixing in DILE. Anti-histone antibodies are positive in 95% of patients. The severe visceral involvement (especially kidney and central nervous system involvement), low complements, Anti-Double Stranded DNA (anti-dsDNA) and anti-extractable nuclear antigens antibodies (ENA antibodies) are rarely positive, except for anti-Ro/SSA and/or anti-La/SSB antibodies which are common in drug induced lupus [24]. In a classic DILE Erythema Nodosum (EN), photosensitivity, purpura/vasculitis rash is more common while hair loss, malar rash, mouth sores, and skin lesions such as discoid rash are rare. The most common rash in DILE is a photosensitive symmetric, non-scarring annular, polycyclic, and occasionally papulosquamous skin rash. Cytopenia is not as severe in DILE as it can be in the idiopathic cases of SLE. Anti-histone antibodies are more common in DILE but are not specific to DILE and can be found in other rheumatic diseases such as scleroderma, SLE, RA and undifferentiated autoimmune diseases.

Drug induced lupus can present as drug induced systemic Lupus (DISLE), drug-induced sub-acute cutaneous lupus (DISCLE), or the drug-induced chronic cutaneous lupus (DICCLE). The drug-induced sub-acute cutaneous lupus (DISCLE) is more common than DISLE and the most commonly recognized offending drugs include interferons, calcium channel blockers, thiazide diuretics, ACE inhibitors and terbinafine [24]. Drug-induced chronic cutaneous lupus (DICCLE) is not reported widely in the literature. Lately, the cases of DISLE and DISCLE both have been reported with the use of TNF-Alpha inhibitor drugs called anti-TNF induced lupus (ATIL) [28-33]. TNF-inhibitor induced lupus is different from classic DILE in several ways: the incidence of visceral involvement (including renal involvement), skin involvement, and arthritis is higher in patients with TNF inhibitor induced lupus than in patients with classic DILE [24]. Specially, if arthritis is part of ATIL it becomes difficult to separate drug induced arthritis from arthritis as a part of the disease. The incidence of anti-histone antibodies positivity is higher in classic DILE than in anti-TNF inhibitor induced lupus. The DILE associated with interferon- α therapy is further distinct from the other types of DILE because these patients have a higher incidence of mucocutaneous involvement, renal disease, arthralgia, and anti-dsDNA antibodies.

Some researchers believe that part of the SLE patients may; in fact, be wrongly diagnosed DILE patients and the incidence of DILE is higher than SLE [23]. In a retrospective review of matched nested case-control studies using the UK General Practice Research Database

(1987 to 2001), researchers have concluded that drug induced lupus is known, but not common. They identified eleven drugs that had the potential for inducing autoimmunity and lupus like syndromes but named only three drugs in their large database showing the significant causal relationship with drug induced lupus. These three drugs were hydralazine (OR = 6.62, 95% CI 1.03, and 42.74), minocycline (OR = 4.23, 95% CI 2.65, and 6.75) and carbamazepine (OR = 1.88, 95% CI 1.09, and 3.22) [24,34]. Propylthiouracil, an anti-thyroid drug is known to produce DILE, but none of the patients in above reports have been on propylthiouracil. In most cases, GD preceded SLE by several years.

The coexistence of GD with SLE can be speculated to be coexistence as an overlap disease, or lupus occurring in a Graves' disease patient due to drugs used to treat Graves' disease such as methimazole or propylthiouracil [8,27,35-38]. Methimazole and propylthiouracil both are thioamide derivatives.

In our patient at the time of writing this manuscript, it is an overlap syndrome of SLE and GD explained by several features in her presentation, progress and disease course as mentioned above.

The evidence in support of the diagnosis of idiopathic SLE and GD overlap syndrome is also that she was anti-Smith autoantibody positive which the most specific autoantibody is for SLE amongst all the auto antibodies present in lupus. Anti-Smith autoantibody positive DILE has never been reported in the past in adult or in a pediatric population. She did not flare after restarting the Methimazole therapy again.

Interestingly, in the published literature GD is not necessarily higher in SLE female patients as compared to age and sex matched normal controls. It is also recognized that the risk of the thyroid cancer is only higher in the age groups of 20 to 59-year-olds and especially in the females [5]. Some researchers believe that autoimmune thyroid disorders in SLE patients may, in fact, be part of their Lupus syndrome [39,40] although no correlation in the disease duration and severity of autoimmune thyroid disorders and SLE Disease Activity Index (SLEDAI score) has been reported in the adult population [7,41]. There are several auto antibodies produced in SLE patients, but there is no evidence that SLE related auto antibodies can cause organ specific injury to the thyroid gland [16,40,42,43]. Interestingly, in several autoimmune diseases such as Rheumatoid arthritis, osteoarthritis, gout, etc. anti-microsomal and antithyroglobulin antibodies had been detected in the synovial fluid at a higher concentration than the blood suggesting their origin in the joint space [43]. Around 30% of Juvenile Hashimoto's Thyroiditis patients are positive for antinuclear antibodies (ANA) 44 while only 8% of adult Hashimoto's patients are ANA positive.

The coexistence of GD and SLE can be explained through several mutual relationships between the two diseases. Such as an overlap syndrome, or GD as a part of the wider SLE syndrome, delayed diagnosis of coexisting SLE due to similar symptoms, Methimazole inducing overt disease in a latent SLE patient or a DILE syndrome. Only time will tell how GD, SLE, and their respective treatment affect each other's disease course and eventual individual disease outcomes. No previous reported cases in pediatrics make a prediction in our case still difficult. Whichever way the course of this coexistence of SLE and GD goes, it certainly adds information to the existing body of knowledge.

We suggest in conclusion that the incidence of autoimmune thyroid diseases is higher in patients with SLE than in the general population. In most adult cases of coexistence, the GD developed first and SLE developed several years after the development of GD. Though in our patient, they both presented within a week's interval. As a comorbidity with GD, SLE may have a different presentation and disease course than SLE alone with variable masking effects. The knowledge and suspicion of co-existence or possibility of gradual evolution of one of these diseases in the presence of the other are the keys for early detection. Without suspicion, the diagnosis of either disease may be delayed due to overlapping similar symptoms. Routine thyroid function tests should be conducted in SLE patients not only for early diagnosis but to pick up subclinical disease as well. The autoimmune thyroid diseases patients should be evaluated on the slightest suspicion of systemic autoimmune involvement, and appropriate referrals should be made early in the disease course and on an ongoing basis. The consideration for the drug used in the treatment of thyroid diseases or SLE should be taken when evaluating and monitoring the patients with either thyroid illness or SLE because drugs can mask, alter or even induce the symptoms of either disease and affect the outcome of the patient.

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