

# Multiple autoimmune syndrome (Graves' disease, systemic lupus erythematosus, and systemic sclerosis) in a young woman in Jakarta

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Multiple autoimmune syndrome (MAS) is a condition in which patients have at least three distinct autoimmune conditions. The definition of MAS is based on 91 reported cases of such associations in the literature. A review of the literature and cluster analysis of MAS disclosed systemic lupus erythematosus (SLE), Sjögren's syndrome, and autoimmune thyroid disease (AITD) as the "chaperones" of autoimmune diseases. This entity was described by Humbert and Dupond in 1988 as a syndrome consisting of the presence of three or more autoimmune diseases in a single patient. While describing the syndrome, their observations led them to a rough classification of clusters based on the co-occurrence of autoimmune disease, which they identified as types one through three.<sup>1</sup> In MAS-1, the authors grouped myasthenia gravis, thymoma, dermatopolymyositis, and autoimmune myocarditis together. In MAS-2, they grouped Sjögren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, systemic sclerosis (SSc), and AITD. MAS-3 consists of AITD, myasthenia gravis and/or thymoma, Sjögren's syndrome, pernicious anemia, idiopathic thrombocytopenic purpura, Addison's disease, type 1 diabetes, vitiligo, autoimmune hemolytic anemia, and SLE.<sup>1,2,3</sup> The importance of this concept is the probability that having three autoimmune diseases simultaneously in one patient goes beyond epidemiological inferences or statistical chance. Disorders of autoimmune pathogenesis occur with increased frequency in patients with a history of another autoimmune disease. The tendency to develop another disease occurs in about 25% of these patients.<sup>3,4</sup>

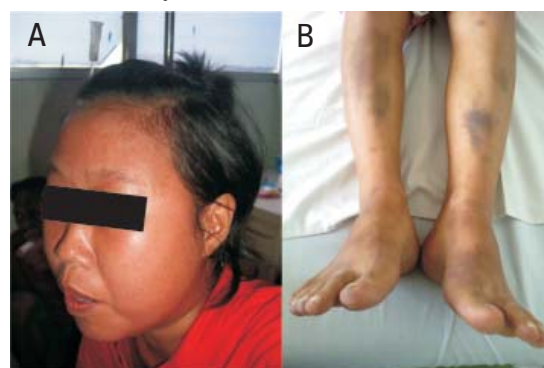
We report a case in which the presence of Graves' disease/AITD, SLE, vasculitis, and SSc with pulmonary hypertension and Raynaud's phenomenon in one patient.

## CASE REPORT

A 30-year-old Indonesian woman, was first diagnosed with Graves' disease when she was 17 years old based on the presence of hyperthyroidism, diffuse goiter, and specific laboratory findings. She was an outpatient of the endocrinology clinic at Cipto Mangunkusumo General Hospital and treated with propylthiouracil 100 mg t.i.d and propranolol 10 mg t.i.d. For the past 3 years, she

had been complaining of photosensitivity, hair loss, recurrent oral ulcer, and bilateral pretibial edema. She also had a history of a focal neurological deficit in the form of involuntary movement. She underwent a renal biopsy on June 2007 and was given the diagnoses of SLE with lupus nephritis and lupus cerebritis. She was treated with steroid and mycophenolate mofetil. For the past 6 months, she had been presenting clinical characteristic of Raynaud's phenomenon and scleroderma. The symptoms became worse and her fingers developed gangrene. She had been hospitalized for two months, underwent many examinations and was given the diagnoses of SSc with pulmonary artery hypertension, Raynaud's phenomenon, and vasculitis.

The results of her physical examination were as follows: she was *compos mentis*, blood pressure was 120/80 mmHg, pulse rate was 88 beats/minute, respiratory rate was 20 breaths/minute, and body temperature was 36.7°C. On head examination, we found lupus hair, mask-like face, moon face with salt-and-pepper appearance, no lid retraction, no proptosis, no trismus, no pale conjunctiva, and no oral ulcers. There was diffuse goiter on her neck. On heart auscultation we found loud pulmonary valve sound without audible murmur or pericardial friction rub. On the extremities, there were vasculitis in both arms and both legs, Raynaud's phenomenon and gangrene of finger II, III, and IV of the left hand, and thickening of the skin from fingers to trunk (shoulder, back, and neck). We also found peripheral neuropathy and moist hand. We did not find any arthritis, tremor, or edema.



**Figure 1** (A) Lupus hair; "salt-and-pepper" appearance of the face. (B) Vasculitis of the legs.



**Figure 2** Raynaud's phenomenon and vasculitis of the left hand.

Laboratory studies disclosed the following values: hemoglobin 12.9 g/dL, hematocrit 38.5%, leukocyte count  $4.31 \times 10^3/\text{mm}^3$ , platelet count  $295 \times 10^3/\text{mm}^3$ , erythrocyte sedimentation rate 15 mm/hr, blood glucose 83 mg/dL, blood urea nitrogen 33 mg/dL, serum creatinine 0.5 mg/dL, Na 137 mEq/L, K 3.38 mEq/L, aspartate aminotransferase 61 IU/L, alanine aminotransferase 34 IU/L, total protein 7.2 U/L, albumin 3.71 U/L, globulin 3.49 U/L, total cholesterol 161 mg/dL, low-density lipoprotein cholesterol 63 mg/dL, high-density lipoprotein cholesterol 71 mg/dL, fibrinogen 268 mg/dL, D-dimer 1800 ng/mL, activated partial thromboplastin time 0.7 times control, prothrombin time 0.7 times control. The urinalysis showed proteinuria (+1), hematuria, and sediment of erythrocyte and leukocyte. The creatinine clearance test was 137.23 mL/min, and the total urine protein was 65 mg/24 hours (with a history of total urine protein of 800 mg/24 hours). Thyroid function test revealed as follows: stimulated thyroid-stimulating hormone (TSHs) 0.010 IU/mL (normal value 0.270-4.200), total T4 13.64 mg/dL (normal value 5.100-14.100), total T3 1.640 ng/mL (normal value 0.800-2.000), free T4 3.07 ng/dL (normal value 0.70-1.48), thyrotropine receptor antibodies (TRAb) 2.5 mg/dL (positive). Antinuclear antibodies (ANA) profile was positive for anti-SS-A (+), anti-SS-B (+), anti-Scl-70 (+++), and anti-Rib-P protein (+++), with nucleolar pattern. Anticardiolipin antibodies (ACA) IgM was 3.5 (negative), ACA IgG was 2.4 (negative), IgG and IgM of  $\beta_2$ -glycoprotein I was negative, and Complement component (C)3 was 56.50 mg/dL (normal value 90-180), C4 was 20.80 mg/dL (normal value 10-40). Anti-double-stranded DNA (anti-dsDNA) was positive by enzyme-linked immunosorbent assay method.

The chest radiograph was normal; there was no infiltration. Echocardiography showed ejection fraction 69%, normal left ventricular systolic and diastolic function, and pulmonary artery hypertension. Skin biopsy confirmed SLE-related vasculitis. Thyroid scanning showed diffuse goiter with high radioiodine uptake. Renal biopsy confirmed nephritis lupus class I. Arteriography showed total occlusion of finger II, III, and IV of the left hand. Cerebral magnetic resonance imaging was normal. Electroencephalography (EEG) showed episode of epileptiform activity on the left frontotemporal area. Ankle-brachial index (ABI) was 0.84/0.91.

The diagnoses were finally established: type 3 MAS consisting of Graves' disease/AITD, SLE and vasculitis, SSc with pulmonary artery hypertension and Raynaud's phenomenon. The patient was treated with warfarin 2 mg

with dose titration to international normalized ratio target of 2.5-3.5 (after intravenous heparin), acetyl salicylic acid 80 mg q.d., nifedipine 10 mg b.i.d., and cilostazol 50 mg b.i.d. for Raynaud's phenomenon; beraprost  $3 \times 20$  mcg t.i.d. for pulmonary hypertension; cefotaxime 1 g t.i.d., and bacitracin cream; methylprednisolone pulse dose 125 mg for 3 hour, tapered down to 16 mg t.i.d., mycophenolate mofetil 500 mg b.i.d. for vasculitis and SLE; thiamazole 40 mg q.d. and propranolol 10 mg t.i.d. for AITD (Graves' disease); calcium hydrogen phosphate 500 mg and cholecalciferol 133 IU 1 tablet t.i.d.; diclofenac sodium 25 mg b.i.d., omeprazole 20 mg b.i.d., cyclophosphamide 500 mg i.v. (Euro-Lupus Nephritis protocol) 3 times per 2 weeks followed by 6 times per 4 weeks.

The clinical response to all treatments were remarkably good; the thickening of the skin and gangrene of the fingers were resolved in the fifth month of therapy.



**Figure 3** Fingers of the left hand after 5 months therapy.

## DISCUSSION

Disorders of autoimmune pathogenesis occur with increased frequency in patients with history of another autoimmune disease. The tendency to develop another disease occurs in about 25% of these patients.<sup>3,4</sup> Multiple autoimmune syndrome can be classified into three groups according to the prevalence of their associations with one another. For these groups, HLA-B8 and/or -DR3 or -DR5 seems to be an important factor.<sup>2,3,4</sup> This classification helps to detect a new condition liable to appear in a patient who has had two previous autoimmune diseases. It provides a basis for analysis of the pathophysiological mechanisms of autoimmunity. In MAS, patients often have at least one dermatological condition, usually vitiligo or alopecia areata. In many cases of MAS reported in the medical literature, vitiligo is the first autoimmune disease to be diagnosed. In these cases, vitiligo is usually bilateral and symmetrical, and in most cases of vitiligo that occurred in MAS, AITD was also present.<sup>5,6,7</sup>

Familial or genetic, infectious, immunologic, and psychological factors have all been implicated in the development of MAS. Cytomegalovirus, for instance, is shown to cause the development of multiple autoantibodies, and certain autoantibodies are found in disorders affecting multiple organs.<sup>2,4,8,9</sup> Multiple autoantibodies can be found in a patient

and some of the specific mono- or polyclonal autoantibodies may be multiple organ-reactive. In conclusion, the presence of one autoimmune disease should alert one to watch for another one. The occurrence of multiple autoimmune phenomena in these cases indicates the need for continued surveillance for the development of new autoimmune disease in predisposed patients.<sup>2,3,4,9</sup>

MAS-3 consisted of AITD, myasthenia gravis and/or thymoma, Sjögren's syndrome, pernicious anemia, idiopathic thrombocytopenic purpura, Addison's disease, type 1 diabetes mellitus, vitiligo, autoimmune hemolytic anemia, and SLE.<sup>3,6,7,10,11</sup> Our case was defined as the type 3 MAS with AITD/Graves' disease, diffuse-type SSc, and SLE.

The diagnosis of AITD/Graves' disease was based on the clinical characteristics (hyperthyroidism, diffuse goiter with high radioiodine uptake on thyroid scanning) and specific laboratory results (positive TRAb (2.5 mg/dL), low level of TSHs (0.010 IU/mL), and high level of free T4 (3.07 mg/dL)).

Graves' disease is an AITD characterized clinically by the presence of hyperthyroidism, diffuse goiter, and in some patients, ophthalmopathy and dermatopathy. Graves' disease is caused by circulating antibodies directed against TRAb that activate the thyrotropin receptor causing thyrotoxicosis. The cause of Graves' ophthalmopathy and dermatopathy is still unknown, but a cross-reaction between thyroidal and orbital and/or connective tissue antigens has been postulated. In this case, it has also been documented for the diagnosis of Graves' disease, and gave a good response to thiamazole. In several case reports, treatment of one autoimmune disease may result in the emergence of yet another disease such as SLE or systemic sclerosis. In our patient, methylprednisolone combined with intravenous cyclophosphamide for the treatment of SLE (cerebral and renal involvement) was associated with the emergence of Raynaud's phenomenon with digital gangrene as well as SSc. The term "kaleidoscope of autoimmunity" has recently been used to describe the shift of one autoimmune disease to another, and that more than one autoimmune disease may coexist in a single patient or in the same family.<sup>4,5,6</sup> We did not find the same case in her family.

Autoimmune thyroid disease occurs in 5–10% of patients with myasthenia gravis. It also seems as if AITD is found in excess in patients with SLE and secondary Sjögren's syndrome, as well in SLE-unaffected relatives with a diagnosis of primary Sjögren's syndrome.<sup>4,9,10,11</sup>

The diagnosis of SLE with vasculitis was based on the ACR criteria for SLE. Our patient fulfilled 7 of 11 criteria, i.e. photosensitivity, oral ulcers, nonerosive arthritis, renal disorder, neuropsychiatric involvement (abnormal EEG), immunologic disorder (positive anti-dsDNA), and positive ANA (positive anti-Scl-70, anti-Rib-P protein, anti-SS-A, and anti-SS-B, with negative anti-mRNP). She also had SLE-related vasculitis (confirmed by skin biopsy) and nephritis lupus class I (confirmed by renal biopsy).

Systemic lupus erythematosus is the most diverse of the autoimmune diseases, characterized by a wide range of clinical features and the production of multiple autoantibodies. The diagnosis is based on the clinical features and the presence of

a wide variety of autoantibodies, most of which are directed to double-stranded DNA, nuclear antigens, ribonucleoproteins, and cell surface antigens. The treatment includes the use of antimalarial agents to corticosteroids and/or immunosuppressive agents. The primary pathological findings are those of inflammation, vasculitis, immune complex deposition and vasculopathy. The course of the disease is characterized by periods of flares and remission. The incidence of SLE varies from 2 to 7.6 cases per 100,000 individuals per year; the highest prevalence is in Afro-Caribbeans, followed by Asians. The sex ratio is 9:1 in favour of females with the disease onset between the ages of 15-55. The laboratory hallmark of the disease is the presence of ANA, appearing in more than 95% of individuals with lupus. The most common pattern is a diffuse or homogeneous nuclear staining. Anti-DNA and anti-Sm antibodies are rarely seen in other conditions and have therefore high specificity for SLE.<sup>4,9,10</sup>

The diagnosis of SSc with pulmonary hypertension and Raynaud's phenomenon-related gangrene on finger II, III, and IV of the left hand was supported by laboratory findings, i.e. positive ANA with positive anti-SS-A, anti-SS-B, and anti-Scl-70 on ANA profile; hypercoagulable state, arterial stenosis of the left hand in angiography, and ABI of 0.84/0.91.

Systemic sclerosis is a chronic disease of unknown etiology, and its classification as a systemic autoimmune rheumatic disease is supported by clinical and experimental observations that include the presence of autoantibodies and autoreactive T cells. Systemic sclerosis is a connective tissue disorder characterized by endothelial dysfunction, fibrosis, and the production of autoantibodies. Although some autoantibodies are specific markers for the disease, there has not been widespread adoption of them as specific classification criteria. Excessive collagen deposition results in skin thickening and changes in internal organs that include the lung, vasculature, gastrointestinal tract, and kidney. Endothelial damage leading to vascular dysfunction manifests as Raynaud's phenomenon, digital ulceration and gangrene, pulmonary arterial hypertension, and renal vascular damage. Systemic sclerosis is usually subclassified as limited or diffuse depending on the extent of skin involvement. The distinction between limited and diffuse SSc varies, but most authors would concur that patients with truncal and acral involvement have diffuse disease, whereas changes of distal to the metacarpophalangeal and metatarsophalangeal joints are consistent with limited disease. There is continuing debate over the degree of acral involvement that constitutes limited versus diffuse disease. Typically, patients with limited SSc have a more insidious disease onset, and they describe Raynaud's phenomenon for some years prior to the onset of sclerodactyly. In contrast, in those with diffuse SSc the onset of Raynaud's phenomenon and the disease course is more acute, with most internal organ involvement occurring within 5 years.<sup>4,8,9</sup> Our patient typically had diffuse SSc, based on the truncal and acral skin involvement, pulmonary arterial hypertension, and Raynaud's phenomenon-related digital gangrene.

## CONCLUSIONS

The diagnosis of MAS depends on the physician's accuracy and the age of onset of the first autoimmune disease. Our patient presented the symptoms of AITD (Graves' disease) and systemic autoimmune disease (SLE and SSc). The diagnosis of one disease could only be achieved when it was suspected because most of the symptoms related to pulmonary artery hypertension, skin involvement, and vasculitis might be hidden by the symptoms of other disease. The confirmation will be made only by appropriate tests (i.e. abnormal immunology

tests, abnormal arteriography, the presence of TRAb, or confirming skin and renal biopsy). Each individual disease included in the MAS group should be considered and treated accordingly.<sup>4,9,10,11</sup>

The presence of one autoimmune disease should alert one to watch for another one. The occurrence of multiple autoimmune phenomena in this case indicates the need for continued surveillance for the development of new autoimmune disease in predisposed patients.

## REFERENCES

1. Humbert P, Dupond JL. The multiple autoimmune syndromes. *Br J Dermatol* 1997;136:468–9.
2. Lipsky PE, Diamond B. Autoimmunity and autoimmune diseases. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jamson JL, editors. *Harrison's principles of internal medicine*. 15th ed. New Delhi: McGraw-Hill; 2001. p. 1839–43.
3. Amital H, Gershwin E, Shoenfeld Y. Reshaping the mosaic of autoimmunity. *Semin Arthritis Rheum* 2006;35:341–3.
4. Rahamim-Cohen D, Shoenfeld Y. The mosaic of autoimmunity. A classical case of inhalation of a polyclonal activating factor in a genetically and hormonally susceptible patient leading to multiple autoimmune diseases. *Isr Med Assoc J* 2001;3:381–2.
5. Gharia MJ, Fairley JA, Lin MS, Liu Z, Giudice GJ, Diaz LA. Autoimmune diseases of the skin. In: Lahita RG, Chiorazzi N, Reeves WH, editors. *Textbook of the autoimmune diseases*. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 409.
6. Dervis E, Acbay O, Barut G, Karaoglu A, Ersoy L. Association of vitiligo, morphea, and Hashimoto's thyroiditis. *Int J Dermatol* 2004;43:236–7.
7. Klisnick A, Schmidt J, Dupond JL, Bouchou K, Rousset H, Thieblot P, et al. Vitiligo in multiple autoimmune syndrome: a retrospective study of 11 cases and a review of the literature. *Rev Med Interne* 1998;19:348–52.
8. Somers EC, Thomas SI, Smeeth L, Hall AJ. Autoimmune diseases co-occurring within individuals and within families: a systematic review. *Epidemiology* 2006;17:202–17.
9. Anaya JM, Corena R, Castiblanco J, Rojas-Villaraga A, Shoenfeld Y. The kaleidoscope of autoimmunity: multiple syndromes and familial autoimmunity. *Expert Rev Clin Immunol* 2007;3:623–35.
10. Sconfield H, Bruner R, Gail R, Harley JB. Autoimmune thyroid disease is associated with a diagnosis of secondary Sjögren's syndrome in familial systemic lupus. *Ann Rheum Dis* 2007;66:410–3.
11. Szyper-Kravitz M, Marai A, Shoenfeld Y. Coexistence of thyroid autoimmunity with other autoimmune diseases: friend or foe? Additional aspects of the mosaic of autoimmunity. *Autoimmunity* 2005;38:247–55.