

Propylthiouracil-Induced Lupus, Antiphospholipid Syndrome, and Stroke in a Patient With Graves Hyperthyroidism

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Objective: To describe a case of propylthiouracil-induced lupus, complicated with antiphospholipid syndrome and acute ischemic stroke.

Design: Case report.

Setting: Academic medical center.

Patient: A 27-year-old man with a diagnosis of Graves disease developed multiple ischemic strokes 2 weeks after starting treatment with propylthiouracil. Thyrotoxicosis and abnormal hypercoagulable and rheumatological profiles were remarkable, with prolonged partial thromboplastin time, elevated anticardiolipin antibody level, and positive antinuclear antibody, lupus anticoagulant, Sjögren antibody, and anti-double-stranded DNA antibody test results, which were more than 8-fold greater than normal values. No clinical manifestations of systemic lupus erythematosus were present.

Intervention: Discontinuation of propylthiouracil and treatment with radioactive iodine.

Results: Hyperthyroidism resolved and anti-double-stranded DNA antibodies returned to normal levels. Eventually, antiphospholipid syndrome was diagnosed. He was treated with oral anticoagulation and remained asymptomatic for 1 year of follow-up.

Conclusion: In this young man with Graves hyperthyroidism, treatment with propylthiouracil was associated with transient autoimmune reactions suggestive of drug-induced lupus, antiphospholipid syndrome, and acute ischemic stroke.

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HYPERTHYROIDISM HAS BEEN linked to increased risk of stroke due to different mechanisms, including atrial fibrillation, hypercoagulable states, moyamoya-like vasculopathy, and vasculitis.¹⁻³

Propylthiouracil, a thionamide commonly used to control hyperthyroidism, is associated with several toxic adverse reactions, such as agranulocytosis, aplastic anemia, hepatitis, myalgias, abnormal hair pigmentation, and enlargement of lymph nodes or salivary glands,⁴ as well as rheumatologic disorders like propylthiouracil-induced vasculitis and lupus.⁵⁻⁹

REPORT OF A CASE

A 27-year-old, right-handed, Hispanic man presented to the emergency department complaining of double vision and numbness of the right arm and face, lasting for about 24 hours. Hyperthyroidism had been diagnosed recently and treatment with pro-

pylthiouracil (150 mg 3 times a day) and extended-release metoprolol (25 mg daily) had been started 2 weeks before.

His medical history was significant only for hyperthyroidism. He had a prior tonsillectomy and his family history was unremarkable. He worked in construction and denied the use of alcohol, tobacco, and drugs. Review of systems was significant for a 14-kg weight loss in 2 months, insomnia, palpitations, and heat intolerance. He denied any difficulty swallowing, shortness of breath, or tremors.

On physical examination, his vital signs were temperature of 36.9°C, pulse of 109/min and regular, respirations of 20/min, and a blood pressure of 147/71 mm Hg. On general appearance, there was no apparent distress. He had no exophthalmos and examination of the neck revealed a diffusely enlarged thyroid gland without nodules. There were no carotid bruits. Cranial nerve examination revealed a right gaze palsy, right homonymous hemianopsia, and vertical nystagmus. Language function was normal and there was no dysar-

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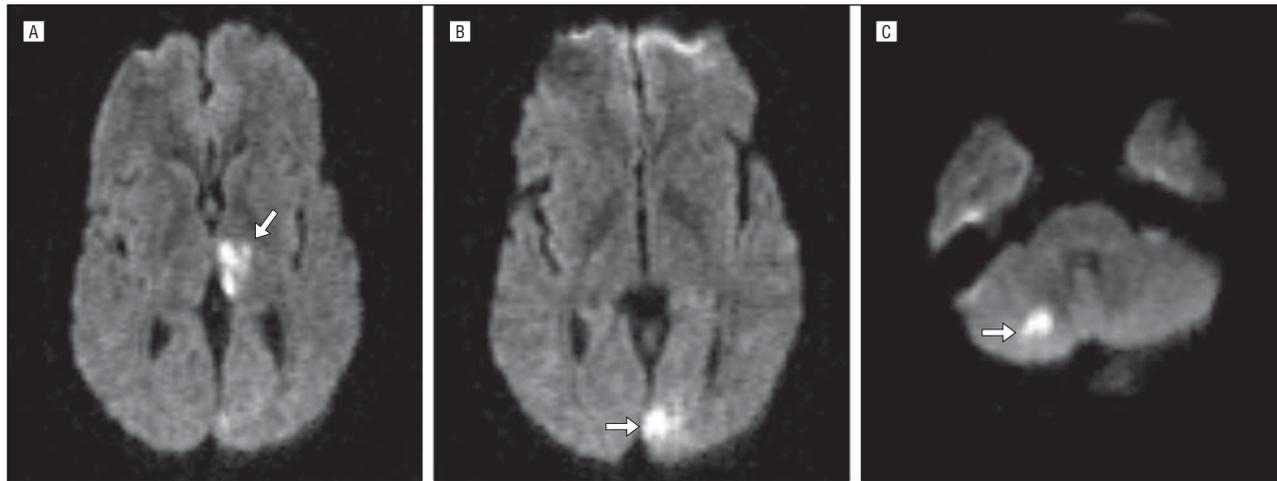


Figure. Diffusion-weighted magnetic resonance imaging of the brain shows hyperintensities suggestive of restricted diffusion due to acute ischemic strokes (arrows in the left thalamus [A], left occipital lobe [B], and right cerebellar hemisphere [C]).

Table 1. Thyroid Function Test Results

Test	Reference Range	Initial Results	3-mo Results
TSH, μ U/mL	0.2-4.0	0.002	1.05
FT ₄ , ng/dL	0.96-0.7	3.86	0.63
T ₃ , ng/dL	80-200	358	57

Abbreviations: FT₄, free thyroxine; TSH, thyrotropin; T₃, total triiodothyronine.

SI conversion factors: To convert FT₄ to picomoles per liter, multiply by 12.871; T₃ to nanomoles per liter, multiply by 0.0154.

thria. Muscle strength was normal in 4 extremities, but there was a mild right pronator drift. Sensory examination was intact to all modalities. Deep tendon reflexes scored 2+ throughout and plantar responses were extensor, bilaterally. His coordination and gait were intact.

Brain magnetic resonance imaging showed acute ischemic strokes in the left thalamus, left occipital lobe, and right cerebellum (**Figure**). Brain magnetic resonance angiography showed lumen irregularities (flow gap) in the right posterior cerebral artery but was otherwise unremarkable.

Pertinent initial laboratory results showed a very suppressed thyrotropin level, high levels of free thyroxine and triiodothyronine, prolonged partial thromboplastin time, positive lupus anticoagulant test results, mild elevation of anticardiolipin IgA level, borderline positive antinuclear antibody (ANA) test results, positive Sjögren antibody test results (Sjögren syndrome antigens A and B), and very high titers of anti-double-stranded DNA (anti-dsDNA) antibodies, more than 8-fold greater than normal values.

Thyroid function and results of hypercoagulable and rheumatological workup are shown in **Tables 1, 2, and 3**. Results of other studies, such as complete blood cell count and a comprehensive metabolic panel, were unremarkable. He was initially treated with intravenous anticoagulation, oral β -blockers, and discontinuation of propylthiouracil.

Transcranial Doppler ultrasonography revealed normal flow velocities in all intracranial vessels and the em-

boli detection study showed 2 high-intensity transient signals in the basilar artery. Results of 24-hour Holter monitoring were negative for arrhythmias. Transthoracic echocardiogram suggested the presence of a patent foramen ovale but otherwise was normal. Transesophageal echocardiogram with bubble study was not confirmatory for patent foramen ovale and did not reveal any other source of emboli from the heart or the aortic arch. Neck magnetic resonance angiography was normal.

Radioactive iodine scan showed diffuse homogeneous uptake of the thyroid gland at 62% (consistent with a diagnosis of Graves disease), and subsequently, radioactive iodine ablation was achieved with 9.25 million becquerel (to convert to curie, multiply by 2.7×10^{-11}) of radioactive iodine.

All neurological deficits improved during his hospital stay and he eventually made a full recovery. At hospital discharge, he was taking β -blockers and warfarin (oral anticoagulation). Three months after radioactive iodine ablation, his clinical hyperthyroidism was resolved, thyroid function test results were normal, and anti-dsDNA antibodies had returned to normal values. During the next 12 months of follow-up, his anticardiolipin IgA level returned to normal, but his anticardiolipin IgG level increased and remained high (Table 2).

The patient was stable for 1 year of follow-up, with no further thromboembolic events or any clinical manifestations of connective tissue disorders.

COMMENT

In this patient, a comprehensive evaluation of the heart and extracranial arteries was unremarkable and no arrhythmias were detected during continuous monitoring in the unit or with a 24-hour Holter monitor. Vertebrobasilar disease was excluded by magnetic resonance imaging and magnetic resonance angiography of the neck and brain. A focal stenosis in the right posterior cerebral artery seen on brain magnetic resonance angiography could not explain the contralateral (thalamic and occipital) or cerebellar strokes. There was no evidence of premature intracranial

Table 2. Hypercoagulable Profile

	Reference Range	Patient Values		
		Initial Results	4-mo Results	12-mo Results
aCL IgG, GPL units/mL	<10	8.1	35.1	53.8
aCL IgA, APL units/mL	<10	10.4	7.3	6.2
aCL IgM, MPL units/mL	<10	5.5	3.2	12.6
Antithrombin III, %	88-124	108		
PT 20210	Normal	Normal		
Protein C, %	8-156	108		
Protein S, %	53-138	71		
Factor V Leiden	None	None		
LAC	None	Present		Present
Homocysteine, μ mol/L	4.4-12.4	6.6		

Abbreviations: aCL, anticardiolipin antibodies; APL, IgA phospholipid; GPL, IgG phospholipid; LAC, lupus anticoagulant; MPL, IgM phospholipid; PT 20210, prothrombin 20210 mutation.

SI conversion factors: To convert antithrombin III to milligrams per liter, multiply by 10; homocysteine to milligrams per liter, divide by 7.397.

Table 3. Rheumatological Profile

	Reference Range	Patient Values			
		Initial Results	1-mo Results	4-mo Results	12-mo Results
ANA, titer	0	Homogeneous pattern, titer: 40			
Anti-dsDNA Ab, IU/mL	<30	254.1	231.2	9.92	5.2
RF, IU/mL	<20	<20			
Smith Ab, IU/mL	-	-			
Smooth muscle Ab, IU/mL	-	-			
Anti-Jo Ab, IU/mL	-	-			
Anti-RNP Ab, IU/mL	-	-			
Anti-SSA	-	+			
Anti-SSB	-	+			
C3, mg/dL	79-152	77.5	90		74.6
C4, mg/dL	16-38	14	15.1		14.1
Anti-Scl-70 Ab, U/mL	-	-			
ESR, mm/h	0-10	5		4	
CRP, mg/L	<10	10		6	
TPO Ab, IU/mL	<35		1034		2073
Thyroglobulin Ab, IU/mL	<40	526			

Abbreviations: Ab, antibody; ANA, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA; anti-RNP, antiribonucleoprotein; anti-Scl-70, antiscleroderma 70; CRP, C-reactive protein; C3 and C4, complement components; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SSA, Sjögren syndrome antigen A; SSB, Sjögren syndrome antigen B; TPO, thyroid peroxidase; -, negative; +, positive.

SI conversion factor: To convert CRP to nanomoles per liter, multiply by 9.524.

atherosclerotic disease, so this lesion was interpreted as most likely a recanalized thromboembolus.

Drug-induced vasculitis was considered unlikely, since the erythrocyte sedimentation rate and C-reactive protein level were not elevated and the clinical presentation was not suggestive of a vasculitic syndrome. We did not perform a cerebral angiography because of concerns of iodine overload. Subsequently, despite the negative workup, cardioembolism in the setting of a hypercoagulable state was deemed to be the most likely mechanism of stroke.

Antiphospholipid antibody syndrome is characterized by recurrent venous and/or arterial thromboses, recurrent miscarriages, and thrombocytopenia. The most common clinical presentation is deep vein thrombosis (32%) followed by thrombocytopenia (22%), livedo reticularis (20%), and stroke (13%).¹⁰

Diagnosis of antiphospholipid antibody syndrome requires the presence of at least 1 clinical criteria ([1] vas-

cular thrombosis and [2] pregnancy morbidity) and 1 of the following laboratory criteria: (1) the presence of lupus anticoagulant in plasma, (2) anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in a medium or high titer (>40 IgG phospholipid [GPL] units or IgM phospholipid units or > the 99th percentile), and (3) anti-b2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma. Either of these should be present on 2 or more occasions, at least 12 weeks apart.¹¹

In this case, only a borderline moderate increase in anticardiolipin IgG level was noted at 4 months (35 GPL units/mL), but eventually levels were much higher at 12 months (58 GPL units/mL). This, in the context of thromboembolism and recurrently positive lupus anticoagulant test results, was considered suitable to reach a diagnosis of antiphospholipid antibody syndrome.

Several positive autoimmune markers were found in this patient, including elevated levels of anticardiolipin, ANA,

lupus anticoagulant, Sjögren syndrome antigen A antibody, Sjögren syndrome antigen B antibody, and, most remarkably, very high levels of anti-dsDNA antibodies.

Drug-induced lupus has been defined by the presence of ANA associated with symptoms such as fever, malaise, arthritis, myalgias, serositis, and/or rash that appear during treatment with certain medications, such as propylthiouracil.¹² It occurs predominantly in white individuals and has less female predilection than systemic lupus erythematosus. The brain and kidneys are rarely affected and usually antibodies to histones are present, but high anti-dsDNA antibody titers are less common. Resolution over several weeks after discontinuation of the inducing drug is usually seen. Patients with systemic lupus erythematosus may synthesize different immunoglobulins against nuclear antigens (ANA), some of which are also found in other connective tissue diseases. Anti-Sjögren syndrome antigen A and anti-Sjögren syndrome antigen B antibodies are directed against 2 extractable nuclear antigens and are typically present in patients with Sjögren syndrome, but they can be present also in patients with systemic lupus erythematosus.¹³ Both anti-dsDNA antibodies and Sjögren antibodies have been reported in other cases of propylthiouracil-induced lupus.¹⁴

Even though there were no “classic” symptoms in our patient, it can be argued that the presence of ANA, Sjögren syndrome antigen A antibodies, and Sjögren syndrome antigen B antibodies and the transient elevation of anti-dsDNA antibody level, resolving after discontinuation of treatment with propylthiouracil, strongly suggest drug-induced lupus. In this case, drug-induced lupus presented with transient elevation of anti-dsDNA antibody level and thromboembolic strokes.

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