

# Minocycline-Induced Drug Hypersensitivity Syndrome Followed by Multiple Autoimmune Sequelae

Rebecca J. Brown, MD; Kristina I. Rother, MD; Henry Artman, MD; Mary Gail Mercurio, MD; Roger Wang, MD; R. John Looney, MD; Edward W. Cowen, MD, MHS

**Background:** Drug hypersensitivity syndrome (DHS) is a severe, multisystem adverse drug reaction that may occur following the use of numerous medications, including anticonvulsants, sulfonamides, and minocycline hydrochloride. Long-term autoimmune sequelae of DHS have been reported, including hypothyroidism.

**Observations:** A 15-year-old female adolescent developed DHS 4 weeks after starting minocycline therapy for acne vulgaris. Seven weeks later she developed autoimmune hyperthyroidism (Graves disease), and 7 months after discontinuing minocycline therapy she developed autoimmune type 1 diabetes mellitus. In addition, she

developed elevated titers of several markers of systemic autoimmune disease, including antinuclear, anti-Sjögren syndrome A, and anti-Smith antibodies.

**Conclusions:** Minocycline-associated DHS may be associated with multiple autoimmune sequelae, including thyroid disease, type 1 diabetes mellitus, and elevated markers of systemic autoimmunity. Long-term follow-up is needed in patients with DHS to determine the natural history of DHS-associated sequelae.

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## Author Affiliations:

Developmental Endocrinology Branch, National Institute of Child Health and Human Development, Rockville, Maryland (Dr Brown); Clinical Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland (Dr Rother); Division of Endocrinology, Departments of Pediatrics (Dr Artman) and Dermatology (Dr Mercurio), and Section of Allergy/Immunology and Rheumatology, Department of Medicine (Drs Wang and Looney), University of Rochester School of Medicine and Dentistry, Rochester, New York; and Dermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda (Dr Cowen).

**D**RUG HYPERSENSITIVITY SYNDROME (DHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is a severe, multiorgan system adverse drug reaction characterized by cutaneous eruption, fever, lymphadenopathy, eosinophilia, hepatitis, and less frequent involvement of the kidneys, lungs, and heart. Autoimmune thyroiditis is a known long-term sequela of DHS; however, other autoimmune manifestations are uncommon. We report a case of minocycline hydrochloride-associated DHS with subsequent development of autoimmune hyperthyroidism, type I diabetes mellitus, and additional serologic findings suggestive of evolving systemic autoimmunity.

## REPORT OF A CASE

A 15-year-old female adolescent with no significant medical history developed fever and a diffuse erythematous skin eruption 4 weeks after initiating treatment with minocycline hydrochloride, 100 mg daily, for acne vulgaris. Minocycline therapy was discontinued, and the patient was treated with oral antihistamines for 1 week, followed by 4 days of prednisone therapy at

escalating doses from 10 mg once daily to 40 mg twice daily. Despite corticosteroid treatment, she developed progressive erythroderma associated with facial swelling, pruritus, pharyngitis, and diffuse lymphadenopathy, leading to hospital admission (**Figure**). At the time of admission, she had an elevated white blood cell count (22 000  $\mu$ L; reference range, 4800-10 800  $\mu$ L [to convert to  $\times 10^9/L$ , multiply by 0.001]) with eosinophilia (14%; reference range, 0%-6%) and reactive lymphocytosis (14%; reference range, 0%-6%). During her hospitalization, she developed elevated transaminase levels (maximum alanine aminotransferase level, 340 U/L [reference range, 10-44 U/L], and maximum aspartate aminotransferase level, 256 U/L [reference range, 0-34 U/L] [to convert both types of transaminase values to microkatal per liter, multiply by 0.0167]), hypoxia, and pyuria, consistent with DHS. A chest radiograph showed no abnormalities. Findings from viral studies were negative for cytomegalovirus, Epstein-Barr virus, toxoplasma, and herpes simplex viruses 1 and 2. The patient did not have any family history of autoimmune disease or drug hypersensitivity.

The patient remained hospitalized for 9 days and was treated with corticoste-



**Figure.** Facial erythema and edema associated with pharyngitis and diffuse lymphadenopathy consistent with drug hypersensitivity syndrome.

roids, with gradual improvement in her cutaneous symptoms, hepatitis, eosinophilia, and leukocytosis. She experienced 2 recurrences of cutaneous symptoms during attempts at corticosteroid tapering and eventually discontinued prednisone therapy 4 months after developing her first DHS symptoms. Although laboratory evaluations performed at the time of hospitalization for DHS revealed no evidence of thyroid or other autoimmune disease, over the months that followed, multiple autoimmune complications were detected.

During the hospitalization, thyroid function test results were normal and antithyroid antibodies were negative. Repeated testing 6 weeks after discharge identified low thyrotropin (TSH) and high free thyroxine (FT<sub>4</sub>) levels and markedly elevated antithyroglobulin and antithyroid peroxidase antibody titers. The patient manifested no symptoms of hyperthyroidism at that time. Markers of Graves disease (thyroid-stimulating immunoglobulin [TSI] and TSH receptor antibody) were negative, and a diagnosis of autoimmune thyroiditis in the thyrotoxic phase was made. With the exception of a 2-week period of euthyroidism, the patient remained hyperthyroid for the next several months (total triiodothyronine [T<sub>3</sub>] level, 210-320 ng/dL; reference range, 60-181 ng/dL [to convert to nanomoles per liter, multiply by 0.0154]). Five months after discontinuing minocycline therapy, she developed palpitations, irritability, and difficulty sleeping. Studies at that time identified a further increase in T<sub>3</sub> (452 ng/dL) and FT<sub>4</sub> (4.9 ng/dL; reference range, 1.1-1.8 ng/dL levels [to convert to picomoles per liter, multiply by 12.871]). Her TSI level also increased to 175% (reference range, <129%) and TSH receptor antibody titer increased to 65% (reference range, <10%). A revised thyroid diagnosis of Graves disease was confirmed by an increased 24-hour uptake of radioactive iodine (75%; reference range, <32%), and she was treated with radioactive iodine thyroid ablation.

Seven months after discontinuing minocycline therapy, the patient developed polydipsia and polyuria. Her fasting blood glucose level was 286 mg/dL (to convert to millimoles per liter, multiply by 0.0555), and glycosuria and

ketonuria were present. Her hemoglobin A<sub>1c</sub> level was elevated at 8.1% (reference range, <5.9%), and elevated glutamic acid decarboxylase (GAD) level and IA<sub>2</sub> antibody titer were detected. New-onset type 1 diabetes mellitus was diagnosed, and she began multiple daily injections of insulin. HLA antigen typing identified the following DRB1-DQA1-DQB1 haplotypes: (1) 0401-0303-03 and (2) 1302-0102-0604.

Serum markers of systemic autoimmune disease (anti-Ro, anti-La, anti-double-stranded DNA [dsDNA], anti-Smith, anti-Sm/RNP, antimitochondrial, anti-F-actin, and antihistone antibodies; cardiolipin IgG/M; antinuclear antibody [ANA]; antineutrophil cytoplasmic antibody; C1q binding; and complement factors C3 and C4) were initially negative during the patient's hospitalization, 10 days after the discontinuation of minocycline therapy. However, repeated serologic testing performed 7 months after minocycline therapy's discontinuation identified elevated ANA, anti-Smith and anti-Sjögren syndrome-A (SS-A/Ro) antibody titers. Screening for other organ-specific autoantibodies, including those associated with pernicious anemia, celiac disease, and Addison disease, was negative. Twelve months after drug exposure, the patient had not developed signs or symptoms of systemic autoimmune disease, and the anti-Smith antibody was no longer detectable.

#### COMMENT

Drug hypersensitivity syndrome is a rare and potentially fatal drug reaction. Although most commonly associated with anticonvulsant medications, DHS has been reported with a variety of drugs, including sulfonamides, allopurinol, antiretroviral agents (eg, nevirapine, abacavir), and minocycline.<sup>1</sup> The etiology of DHS is unclear but has been linked to reactivation of human herpes virus 6 in several reports.<sup>2-5</sup> In certain populations, susceptibility to drug hypersensitivity has also been linked to specific HLA haplotypes, including HLA-B\*1502 and HLA-B\*5801.<sup>6-8</sup>

Although minocycline is thought to have anti-inflammatory properties, the drug has been linked to numerous autoimmune phenomena, including drug-induced lupus erythematosus, autoimmune hepatitis, serum sickness-like reactions, and vasculitis.<sup>9,10</sup> The mechanisms underlying these reactions are not well understood; proposed hypotheses include decreased production of free radicals,<sup>11</sup> inhibition of phospholipase A<sub>2</sub>,<sup>12</sup> and altered expression of tumor necrosis factor and interferon- $\gamma$ .<sup>13</sup>

Our patient developed Graves disease, type 1 diabetes mellitus, and positive antinuclear and anti-Smith antibodies over a period of several months following minocycline exposure, suggesting a long-term immune system alteration following DHS rather than a short-term acute effect of minocycline. The delayed onset of autoimmune symptoms is unusual for minocycline-associated lupuslike reactions, which are typically observed with an elevated ANA level and arthralgia symptoms that resolve following a drug's discontinuation.<sup>9</sup> In contrast, our patient did not exhibit arthralgia symp-

**Table. Reported Cases of Thyroid Disease and Diabetes Following Drug Hypersensitivity Syndrome (DHS)**

Case	Endocrinopathy	Time From DHS <sup>a</sup>	Drug Therapy <sup>b</sup>	Antibodies	Comments
1 <sup>14</sup>	Fulminant diabetes	2 wk	Carbamazepine	Islet cell/GAD negative	
2 <sup>15</sup>	Fulminant diabetes	0 d	Mexiletine	GAD negative	Preexisting type 2 diabetes mellitus, concurrent pancreatitis
3 <sup>16</sup>	Fulminant diabetes	7 d	Allopurinol	Not reported	Concurrent pancreatitis
4 <sup>17</sup>	Fulminant diabetes	2.5 mo	Penicillin, diclofenac, ibuprofen	Islet cell/GAD negative	
5 <sup>18</sup>	Type 1 diabetes mellitus	4 mo	Methimazole	GAD positive	
6	Type 1 diabetes mellitus	7 mo	Minocycline	GAD positive, IA <sub>2</sub> positive	Our patient
7 <sup>19</sup>	Hyperthyroidism	0 d	Minocycline	TPO, TG, TSI negative	Lupuslike syndrome, not DRESS
8 <sup>20</sup>	Hypothyroidism	4 wk	Phenytoin	TPO positive	
9 <sup>20</sup>	Hypothyroidism	4 wk	Salazopyrin	TPO positive	
10 <sup>20</sup>	Hypothyroidism	8 wk	Phenobarbital	TPO positive	
11 <sup>20</sup>	Hypothyroidism	8 wk	Phenobarbital, carbamazepine	unknown	
12 <sup>20</sup>	Hypothyroidism	Unknown	Phenytoin, phenobarbital, carbamazepine	TPO negative	
13	Hyperthyroidism	7 wk	Minocycline	TPO, TG, TSI, TSHR positive	Our patient

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; GAD, glutamic acid decarboxylase; TG, thyroglobulin; TPO, thyroid peroxidase; TSHR, thyrotropin-receptor; TSI, thyroid-stimulating immunoglobulin.

<sup>a</sup>Time between presentation of DHS and presentation of endocrinopathy.

<sup>b</sup>Minocycline administered as minocycline hydrochloride.

toms at the time of her initial hospitalization and her ANA profile at that time was negative.

Hypothyroidism is a well-recognized but uncommon sequela of DHS (**Table**). In a series of 202 patients who developed hypersensitivity to anticonvulsants or sulfonamides, 5 developed hypothyroidism 4 to 8 weeks following the drug hypersensitivity reaction.<sup>20</sup> On the basis of *in vitro* thyroid cell toxicity studies, the authors postulated that thyroid peroxidase metabolized the drug into reactive intermediates that damage the thyroid, followed by a secondary autoimmune process.<sup>20</sup> Only 1 case of hyperthyroidism has been reported with minocycline use in a patient who developed minocycline-induced lupus, rather than DHS.<sup>19</sup> Our patient developed hyperthyroidism with elevated anti-thyroid peroxidase and anti-thyroglobulin antibodies 7 weeks after the development of DHS, with the subsequent appearance of elevated levels of TSI and TSH receptor antibodies 8 months after the development of DHS. To our knowledge, this pattern of thyroid disease has not been previously reported with DHS and is atypical for autoimmune thyroid disease in the general population.

Rapid loss of insulin secretion (fulminant diabetes) has been described following DHS (Table).<sup>14-18</sup> In 3 reported cases findings for anti-islet cell or glutamic acid decarboxylase (GAD) antibodies were negative, indicating that the  $\beta$ -cell failure was not of autoimmune origin. In one report, the presence of antibodies was not described, but the onset of diabetes was associated with severe pancreatitis, which is also suggestive of a nonautoimmune cause.<sup>16</sup> One case has been reported of GAD-positive type 1 diabetes mellitus associated with DHS, following exposure to methimazole.<sup>18</sup>

To our knowledge, this is the first reported case of type 1 diabetes mellitus following minocycline-induced DHS. Since GAD and IA<sub>2</sub> antibodies were not obtained in this

patient early in the course of her DHS, we cannot establish the exact chronology of the elevated antibody titers against pancreatic islet antigens. Because our patient's HLA type does not confer a markedly increased genetic risk for type 1 diabetes mellitus,<sup>21,22</sup> and given the development of multiple other markers of autoimmunity after exposure to minocycline, we believe that her pancreatic disease is most likely an unusual autoimmune sequela of minocycline-induced DHS.

Although the patient did not fulfill American College of Rheumatology criteria for systemic lupus erythematosus, high titers of ANA and anti-Smith antibodies in the presence of autoimmune thyroid and pancreatic disease raised concern for the future development of additional autoimmune diseases. In a recent report of patients with autoimmune thyroid disease, 74.5% had an elevated anti-dsDNA titer, and 90.1% had an elevated anti-single-stranded DNA titer.<sup>23</sup> The prevalence of systemic autoimmune disease (including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, mixed connective tissue disease, Sjögren syndrome, and polymyositis/dermatomyositis) has been reported to be as high as 51% in patients with Hashimoto thyroiditis and 16% of those with Graves disease.<sup>24</sup> An increased prevalence of positive ANA status has also been reported in patients with acne, and higher ANA titers have been associated with minocycline exposure.<sup>25</sup> To our knowledge, the presence of anti-Smith antibodies, which are highly specific for systemic lupus erythematosus, have not been reported in the setting of minocycline-induced lupus.<sup>26</sup> The significance of the transient elevation of anti-Smith antibody in our patient is not clear but may indicate components of autoimmunity that may finally be diminishing.

In conclusion, long-term autoimmune sequelae may develop following DHS, including hypothyroidism and

hyperthyroidism and diabetes. Long-term monitoring of autoimmune markers in patients with minocycline-associated DHS will help establish the natural history of this disorder.

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**Correspondence:** Edward W. Cowen, MD, MHS, Dermatology Branch, National Cancer Institute, National Institutes of Health, 10 Center Dr MSC 1908, Bldg 10, Room 12N238, Bethesda, MD 20892 (cowene@mail.nih.gov).

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