



Letter

Intrauterine uterine contraception and chronic urticaria: a case series

Chronic urticaria and angioedema are skin diseases marked by the daily or almost daily occurrence of urticaria and/or angioedema for longer than 6 weeks. Although drug, food, aeroallergen, contact allergen, thyroid autoimmunity, and vitamin D associations and autoantibodies to the high affinity immunoglobulin E (IgE) receptor or free IgE might be discovered, in most cases the etiology remains idiopathic.^{1,2} Women represent most cases of chronic urticaria.

Progesterone-induced urticaria, characterized by cyclic skin eruptions that fluctuate with menses, is considered a subset of a rare disorder, autoimmune progesterone dermatitis (APD).³ The use of intrauterine devices (IUDs) for contraception has been increasing.⁴ In the United States, use of long-term removable contraception (primarily IUDs, but also implants) is increasing, from 2% in 2002 to 12% in 2012.⁴ Current options include the copper IUD (ParaGard, Teva Pharmaceuticals, Jerusalem, Israel) and the levonorgestrel IUD (Mirena and Skyla, Bayer, Whippany, New Jersey; Liletta, Allergan, Parsippany, New Jersey). However, IUDs are not commonly included on medication lists or remembered by patients unless specifically probed. Furthermore, there is often amenorrhea (70%) with these devices⁵; therefore, the usual clinical cyclic cues of APD are absent.

Our sentinel case involves a 29-year-old woman (patient 1) who presented with a 7-month history of full body hives, skin pruritus, and burning, with episodes of angioedema of the lips, eyelids, hands, and feet. A skin biopsy finding was consistent with urticaria. The patient was started on 20 mg of cetirizine twice a day, 150 mg of ranitidine twice a day, and 10 mg of montelukast daily, which did not alleviate symptoms. Cyclosporine at 100 mg daily was added, without success. Further history showed that the levonorgestrel IUD was placed approximately 2 years before the onset of urticaria. The patient was given the option to remove the IUD. Two weeks after removal, she was free of hives and was able to discontinue all urticaria medications.

We present this case series on 6 additional women with unexplained chronic urticaria for which the IUD was a suspected cause. This retrospective medical research record review of patients seen at a single academic center after January 1, 2013 was conducted with approval from the institutional review board. Using codes from the ninth and tenth revisions of the *International Classification of Diseases*, patients with any urticaria, dermatographism, and any angioedema were included. Patients with hereditary angioedema were excluded. Of these 192 patients, patients were excluded if they were men or women without mention of an IUD or progesterone use. Of the 21 patients, 9 had urticaria that was attributed to progesterone but had no IUD. Five patients had an IUD, but IUD removal was not recommended because other etiologies were established in 3 (ie, trimethoprim and sulfamethoxazole, peanut, and thyroid disease); urticaria in 1 patient was easily controlled on antihistamines, and 1 patient was lost to follow-up. The clinical

cases of the 7 subjects (3.7%) with an IUD and idiopathic urticaria are presented in Table 1.

These cases demonstrate a potential role for IUDs, particularly levonorgestrel IUDs, as a cause for urticaria and angioedema but also highlight the variability in response to removal. Of the 6 subjects who opted for IUD removal, 3 had complete resolution of urticaria symptoms. There has been only 1 other case report of a woman having urticaria to a levonorgestrel IUD (Mirena).⁶ In contrast to our patients, that woman had acute urticaria within 2 hours of IUD insertion. Patient 3 had a copper IUD. There have been fewer than 5 case reports of skin reactions to copper IUDs. Of these, the urticaria occurred within the first month after placement.⁷ The other cases were described as contact dermatitis reactions (with and without abdominal pain) in which a positive patch test reaction to copper was demonstrated.^{8,9} Patient 3 had been on bupropion for 1 month and her copper IUD had been in place for 5 months before the onset of symptoms. Because of the severity of her allergic symptoms, there was simultaneous removal of the IUD and cessation of bupropion; therefore, these symptoms cannot be accurately ascribed to the IUD.

Progesterone sensitivity was demonstrated by skin testing in several subjects who were able to discontinue antihistamines for test purposes, which suggested that levonorgestrel could be driving the urticaria. A review by Nguyen and Razzaque Ahmed³ evaluated 89 patients with APD and noted relations with oral contraceptive use and progesterone injections; however, IUD use was not discussed. They suggested prior sensitization by exogenous progesterone use as a possible explanation for the cutaneous manifestations observed in APD.³ APD is a clinical diagnosis but is often confirmed with positive progesterone skin test reactions.³ Data on the sensitivity and specificity of this progesterone skin test are lacking, and the sensitization rates to progesterone (or to levonorgestrel) are not known. However, a review by Snyder and Krishnaswamy¹⁰ offers clinicians a proposed algorithm for the evaluation of patients, in whom skin testing with intramuscular aqueous progesterone is recommended as the initial step. Development of standardized progesterone, and perhaps also levonorgestrel, skin testing might be warranted to aid in the diagnosis. In vitro assays for progesterone or levonorgestrel also could be explored but were not conducted in case subjects.

The present subjects had an IUD in place for a prolonged duration before the symptoms manifested, and the explanation for these observations remains unknown. It has been suggested that there are type I and IV hypersensitivity reactions in APD.³ Moreover, it has been speculated that a threshold for tolerance to progesterone exists, and when levels increase above their physiologic state, patients can develop an inflammatory response.³ We suspect that the extended-release nature of the levonorgestrel in the IUD is playing a role, because it could relate to variable hormone releases over time for up to 5 years. Moreover, we highlight that despite our sentinel case demonstrating a strong association with

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Table 1
Clinical Characteristics and Outcomes of 7 Cases of Unexplained Chronic Urticaria in Which IUD Use Was Suspected

Patient number	Age (y)	Symptoms (duration)	IUD (duration)	Testing	Outcome
1	29	Urticaria, angioedema of lips, eyelids, hands, feet (7 mo)	Levonorgestrel IUD (2 y)	CD203c positivity; skin biopsy result consistent with urticaria	No prior relief with cyclosporine; symptoms resolved 2 wk after IUD removal
2	36	Flushing, pruritus, vaginal itching (6 mo)	Levonorgestrel IUD (3 y)	Positive intradermal progesterone test result	Symptoms resolved with IUD removal
3	30	Urticaria, lip angioedema, anaphylaxis requiring hospitalization (1 d)	Copper IUD (5 mo)	none	Simultaneous removal of copper IUD and discontinuation of bupropion resulted in resolution of symptoms
4	46	Urticaria, angioedema (11 mo)	Levonorgestrel IUD (2 y)	Positive progesterone skin test result; positive progesterone oral challenge result; CD203c positivity	Symptoms resolved with IUD removal for 3 mo; subsequent failed treatment with cyclosporine, azathioprine, hydroxychloroquine, and prednisone; after 2 y, underwent bilateral oophorectomy; urticarial flares decreased to every 6 wk; omalizumab was decreased
5	40	Urticaria, mouth sores, migraines, pruritus, abdominal cramping with diarrhea (2 mo)	Levonorgestrel IUD (7 y)	Equivocal progesterone skin test result; negative gastrointestinal evaluation result	Urticaria and pruritus and lower abdominal pain resolved with IUD removal; abdominal symptoms recurred 4 mo later
6	26	Urticaria, unspecified reactions to multiple foods (1 mo)	Levonorgestrel IUD (4 y)	Negative food allergy test result	Opted for IUD removal but no improvement in symptoms
7	26	Urticaria and angioedema, pressure-induced urticaria (2 y)	NuvaRing ^a (2007) levonorgestrel IUD (4 y)	Negative autologous serum skin test result; CD203 positivity	Symptoms resolved with NuvaRing removal; 2 y later had IUD placed; hives returned; IUD removal was declined

Abbreviation: IUD, intrauterine device.

^aEtonogestrel and ethinyl estradiol vaginal ring (Merck Sharp & Dohme BV, Kenilworth, New Jersey).

IUD and chronic urticaria, there were variable clinical responses to removal of the IUDs in subsequent patients. In summary, trends for using IUDs have sharply increased in the past decade, and this case series suggests that clinicians be aware of this increase and consider a trial of IUD removal in patients with refractory and/or unexplained urticaria and angioedema.

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