

Urticaria Associated With Necrotic Uterine Leiomyomas Infected With Salmonella

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BACKGROUND: We describe a unique case of urticaria associated with a *Salmonella* infection of uterine leiomyomas.

CASE: A 55-year-old woman with a known history of uterine leiomyomas and a chief complaint of recurrent small and coalescing urticarial lesions confined to the abdomen presented with an 18-year history of recurrent fever and flu-like symptoms associated with the urticaria. After confirming the presence of a leiomyoma containing necrotic tissue on the computed tomography scan, a hysterectomy was performed. A large, 11-cm intramural leiomyoma was removed, and a culture of the purulent content grew a previously untyped *Salmonella*. The urticaria resolved on removal of the necrotic tissue. Subsequent follow-up for more than 2 years shows no relapse of symptoms.

CONCLUSION: Our patient harbored *Salmonella* bacteria in a necrotic uterine leiomyoma, where it was difficult to detect until the time of surgery. In patients presenting with localized urticaria of the abdomen, an infection in the pelvic and abdominal tissue should be considered in the differential diagnosis.

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Urticaria can be a primary as well as a secondary disease manifestation. The latter category includes an association with neoplastic, autoimmune, or infectious disease processes. The most commonly described infections leading to a urticarial rash include streptococcal pharyngitis, sinusitis, hepatitis, mononucleosis, and viral and parasitic infections.¹ In one study involving the etiology of different forms of

urticaria in a pediatric population, the most frequently documented infections were those of the urinary tract, followed by serologically defined infections by *Chlamydia pneumoniae* and *Helicobacter pylori*.² *H. pylori* infection has also been implicated in cases of chronic urticaria, but the causal relationship between the infection and the development of urticaria has not been definitively determined.³

Various mechanisms responsible for the development of urticaria continue to be elucidated. Whereas type I hypersensitivity was long thought to be the canonical pathway for chronic urticaria, type II–IV hypersensitivity as well as innate and hapten-mediated immune reactions have also been established as possible etiologic agents. More recently, complement activating IgG antibodies to the alpha subunit of FcεRI have been found to activate basophils in a subset of individuals with chronic urticaria.⁴ Bacterial infections have also been implicated as a potential source of complement-mediated urticaria in case reports involving bacterial sinusitis, otitis media, and dental abscesses. These case reports indicate that resolution of the urticaria occurs in response to treatment of the infection.

We describe here a unique case of urticaria associated with a *Salmonella* infection of uterine leiomyomas. The urticaria resolved after removal of the necrotic tissue. An abscess in a uterine leiomyoma should be considered in the workup of localized abdominal urticaria.

CASE

A 55-year-old Ashkenazi Jewish woman gravida 2 para 2 with a known history of uterine leiomyomas presented with an 18-year history of recurrent fevers, chills, and flu-like symptoms occurring every 2 to 4 months. Episodes would start with headaches, dizziness, and diarrhea lasting a few hours, followed by the appearance of erythematous, punctate wheals confined to her abdomen. The individual lesions would coalesce into larger lesions as shown in Figure 1. She was age 50 when she entered menopause and had no history of hormone replacement therapy. Over the previous few months before presentation to our clinic, the rash also began extending to her chest, back, and neck, sparing her extremities. In this time frame, she also reported a worsening of her symptoms to include fevers to 104°F, fatigue with exertion, weight loss, weakness, and chills with night sweats on a daily basis. She denied arthralgia, arthritis, aphthous ulcers, and gastrointestinal symptoms during that time frame, and her symptoms did not correlate with any menstrual cycles.

The patient recalled a history of pelvic inflammatory disease at age 19 but denied any past surgical procedures. She had two pregnancies resulting in full-term vaginal

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Fig. 1. Abdominal rash. Fine punctate, erythematous lesions beginning to coalesce into a confluent lesion covering the abdominal wall.

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deliveries, and her Pap test results were always normal. She was not taking any medications, denied alcohol or drug use, and conveyed a noncontributory family history. She reported her history of leiomyomas but did not associate any physical symptoms with them. Enlarged uterine leiomyomas were noted at the time of that visit.

On physical examination, her vital signs were normal with no fever. Her hair, skin, and dentition appeared normal with no oral ulcerations. Cardiac and pulmonary examinations were unremarkable. Abdominal examination was remarkable for a soft, nontender 14 cm pelvic mass that was palpable in the suprapubic region. The abdominal wall revealed fine punctate wheals that coalesced into bigger lesions as shown in Figure 1. There were no other physical abnormalities of note.

The differential diagnosis that was initially formulated included a pelvic tumor, malignancy, an abscess, periodic fever syndrome, an infectious disease process such as hepatitis, human immunodeficiency virus, Lyme disease, *H. pylori*, an autoimmune disorder, thyroid disorder, vasculitis, a drug reaction, or a carcinoid syndrome.

Initial laboratory investigations revealed a white blood cell count of 12.9 K/uL (normal 3.28–9.29), erythrocyte sedimentation rates ranging from 20 to 100 mm/h (normal less than 22), and C-reactive protein levels ranging from 6.2 to 18.9 mg/dL (normal less than 0.8). Serum β -tryptase, urinary 5-HIAA, C3, C4, CH50, C1INH, immune complex-C1Q binding assay, and urinalysis were all normal.

Stool studies and further workup for human immunodeficiency virus, Lyme disease, hepatitis serologies, rapid plasma reagin, and known genetic testing for familial Mediterranean fever were all negative. Serum protein electrophoresis and serologic screening for autoimmune markers, including ANA, double-stranded DNA, Scl-70, antinuclear, Sm/RNP, Ro, La, cardiolipin antibodies, thyroid

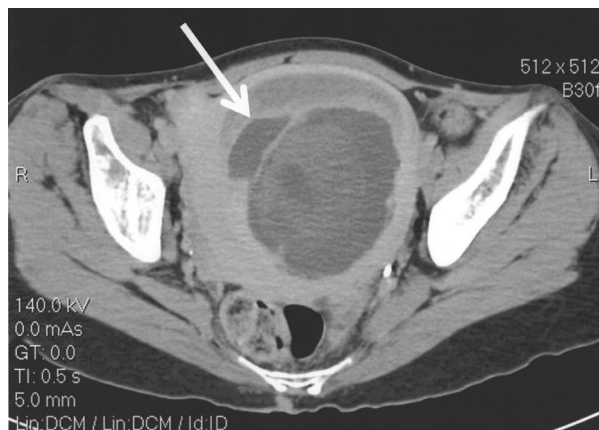


Fig. 2. Computed technology scan of the uterine leiomyoma (arrow). Measurements using the leiomyoma capsule diameter are 11.8 by 11.6 cm.

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microsomal tests, chromatin antibody, and ASO titer, were normal. Rheumatoid factor was elevated at 34 international units/mL (normal less than 20). This laboratory workup ruled out most of the conditions listed on the differential diagnosis except for pelvic disease and malignancy.

An abdominal and pelvic computed tomography scan revealed a low attenuation component within the uterus, suggestive of a necrotic leiomyoma with possible trapped debris in the endometrial cavity (Fig. 2). This finding was confirmed by subsequent ultrasonography revealing necrotic tissue surrounded by fluid and debris in a 7- to 9-cm leiomyoma in the uterine cavity. The patient was referred to gynecology for further workup, and a total abdominal hysterectomy was performed.

During laparotomy, the uterus appeared smooth except for multiple subserosal and exophytic leiomyomas, the largest measuring approximately 3 cm in diameter on the right fundus. A large, 11-cm intramural leiomyoma created the major bulk of the uterine fundus. On opening the endometrial cavity, the lining appeared grossly normal with no intracavity leiomyomas or polyps. The large posterior intramural leiomyoma was entered with a scalpel with expulsion of a copious amount of purulent material. A swab was inserted into the cavity for culture. She received only one dose of cefazoline 1 g intravenously at the time of her hysterectomy, which is routine for this procedure, and she did not receive any other antibiotics.

Pathological examination revealed squamous metaplasia of the cervix and a proliferative endometrium with surface denudation. Eight uterine leiomyomas varying in size from 1.4 to 11 cm also were removed. The largest of these infarcted tumors showed acute and chronic inflammation with granulation tissue and dense plasma cell and histiocytic infiltrates. The myometrium also showed chronic inflammation, but there was no evidence of malignancy. Culture of the pus grew previously untyped *Salmo-*



nella. All of her symptoms, including diarrhea, completely resolved after her surgery.

COMMENT

The key question in this case is whether the growth of an unusual strain of *Salmonella* in a localized body site could explain the localized urticarial reaction. This will expand the vast number of pathophysiological mechanisms that can give rise to urticaria. Several possible explanations exist for making this link. Although mast cells have been identified in the female genital tract, their exact role has not been elucidated.⁵ It has been suggested that the chemokines CCL5 and CCL11 play a role in the recruitment of mast cells to these tumors.⁶ There are various pathways by which pathogens may selectively activate mast cells, including through the activation of complement receptors.

Although complement activation can generate urticaria and plays a role in the defense against *Salmonella*, we did not observe any abnormality in our screening complement assays. Another possible mechanism includes the activation and expression of Toll-like receptor 5, a receptor that recognizes the flagellin component of *Salmonella* species. This and other Toll-like receptors are known to activate the innate components of the immune system, with subsequent activation of the transcription factor NF- κ B. Yet another possible explanation in our patient is the release of circulating endotoxins from the abscess site. A study looking at recurrent urticaria in 330 patients demonstrated that 24% had evidence of circulating endotoxins.⁷

Based on our patient's response to removal of the uterus and the source of infection, our final diagnosis is urticaria secondary to a necrotic intrauterine mass. Intestinal *Salmonella* infection is a well-described cause of urticaria.⁸ What makes our patient unique is that she harbored the *Salmonella* bacteria in a necrotic uterine leiomyoma, where it was difficult to detect until the time of operation. Her symptoms associated

with this infection included fine, punctate urticaria along with fever and flu-like illness. This case reports intrauterine infection associated with urticaria. In the presence of abdominal urticaria, consideration should be given for a diagnostic workup to reveal the presence of infection in pelvic and abdominal tissue.

Postoperatively and in the absence of analgesics, our patient reported complete resolution of her symptoms, highlighted by the disappearance of fever, flu-like symptoms, and urticaria. She has now remained asymptomatic for more than 18 months.

She had an incision check 2 weeks after surgery and said she was "feeling fantastic." At a full postoperative visit 1 month later, she was continuing to feel well and felt that the surgery really helped. During the subsequent 2 years, she has had routine, annual well-woman exams and has not had any febrile or rash episodes.

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