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# Reactive nonsexually related acute genital ulcers: Review of cases evaluated at Mayo Clinic

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**Background:** Reactive nonsexually related acute genital ulcers (RNSRAGU) occur in pubertal girls after an acute systemic infection.

**Objective:** We sought to characterize RNSRAGU by reviewing the medical records of patients with this disorder.

**Methods:** We searched our medical index database from 1997 to 2007 for RNSRAGU cases. Questionnaires were mailed to identified patients.

**Results:** The study included 10 patients; 5 responded to the questionnaire. The mean age at onset was 11.5 years. Vulvar ulcers were preceded by viral gastroenteritis (n = 3), viral upper respiratory tract infection (n = 3), streptococcal pharyngitis (n = 1), influenza (n = 1), and other nonspecific febrile illnesses (n = 2). Seven patients had oral involvement also; 6 had at least one recurrence; and 3 were hospitalized for pain control. Analgesics and topical corticosteroids were the most common treatments. Ulcerations resolved within several weeks in all patients.

**Limitations:** Retrospective study design, small study size, and 50% questionnaire response rate are limitations.

**Conclusions:** Although rare, RNSRAGU should be considered when genital ulceration follows an acute systemic illness. (J Am Acad Dermatol 2010;63:44-51.)

**Key words:** genital ulcers; Lipschütz ulcer; ulcus vulvae acutum.

Reactive nonsexually related acute genital ulcers (RNSRAGU) (formerly termed “ulcus vulvae acutum” or “Lipschütz ulcer”) are a variant of complex aphthosis.<sup>1,2</sup> They are characterized by the abrupt appearance of genital ulcers in adolescents, usually girls. The onset may be preceded by an acute systemic illness. Lesions appear as well-demarcated, shallow erosions with a clean fibrinous base, and with ensuing necrosis in some cases. They are very painful and can cause

#### Abbreviations used:

EBV:	Epstein-Barr virus
HSV:	herpes simplex virus
PCR:	polymerase chain reaction
RNSRAGU:	reactive nonsexually related acute genital ulcers

considerable emotional distress. RNSRAGU is under-recognized by health care providers and its pathogenesis is not fully understood.<sup>3</sup> We sought to further evaluate this uncommon condition by reviewing the clinical records of patients with RNSRAGU.

#### METHODS

After receiving approval from our institutional review board, we searched our medical index database from January 1997 to August 2007. We used the following search terms: “ulcus vulvae acutum,” “Lipschütz,” and “genital ulcer”; when using the term “genital ulcer,” we applied the additional criteria

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of female sex and age younger than 18 years to increase search specificity. We asked members of our department who specialize in women's dermatology and pediatric dermatology to identify additional cases.

Patients were excluded from analysis if a cause of genital ulceration other than RNSRAGU was documented or if a reasonable investigation to exclude other causes, such as herpes simplex virus (HSV) infection, was not performed. Only patients evaluated at Mayo Clinic in Rochester, MN, and those whose legal guardians had authorized involvement in research studies were included.

Pertinent demographic, clinical, laboratory, and histopathologic information were extracted from the medical records of patients who fulfilled the inclusion criteria. An institutional review board–approved questionnaire was mailed to each study patient (or legal guardian, if the patient was <18 years of age) (Appendix); this was the only attempt we made to contact the patient. The questionnaire sought to elicit information about RNSRAGU recurrence and its treatment, occurrence and treatment of oral ulcers, and subsequent development of any other medical condition. A question about the family history asked if a relative had developed lupus erythematosus, psoriasis, rheumatoid arthritis, Behçet disease, Sjögren syndrome, recurrent aphthosis, or other disease since the patient was treated for RNSRAGU. A final question asked about ancestral countries of origin.

## RESULTS

Ten patients met the criteria for a diagnosis of RNSRAGU (Fig 1); one was reported previously by our group.<sup>4</sup> Five patients responded to the questionnaire. The data reported are based on both medical record review and questionnaire responses.

The mean age of onset was 11.5 years (range, 9–16 years). One patient developed oral ulcers synchronous with genital ulceration; 6 other patients had a documented history of oral aphthosis but no oral lesions at the time of presentation. One patient had no history of oral aphthosis, and the presence or absence of oral lesions was not recorded in two patients. Nine patients denied a history of sexual activity or sexual abuse; one patient had participated in consensual orogenital sex within 3 months before

ulcer development, but microbiologic evaluation of lesional skin swabs by polymerase chain reaction (PCR) assay demonstrated no evidence of chlamydial, gonorrheal, or HSV infection. No patient had a comorbid condition or known immunosuppression. Of the 5 patients who responded to the questionnaire, two reported a family history of autoimmune

disease (one patient with lupus and rheumatoid arthritis in unknown family members; one patient's paternal grandfather had psoriasis and multiple sclerosis, multiple maternal aunts had rheumatoid arthritis, a sister had Hashimoto thyroiditis, and a cousin had rheumatoid arthritis). All patients were of Northern European descent, which is consistent with the origin of much of the population of the upper Midwestern United States.

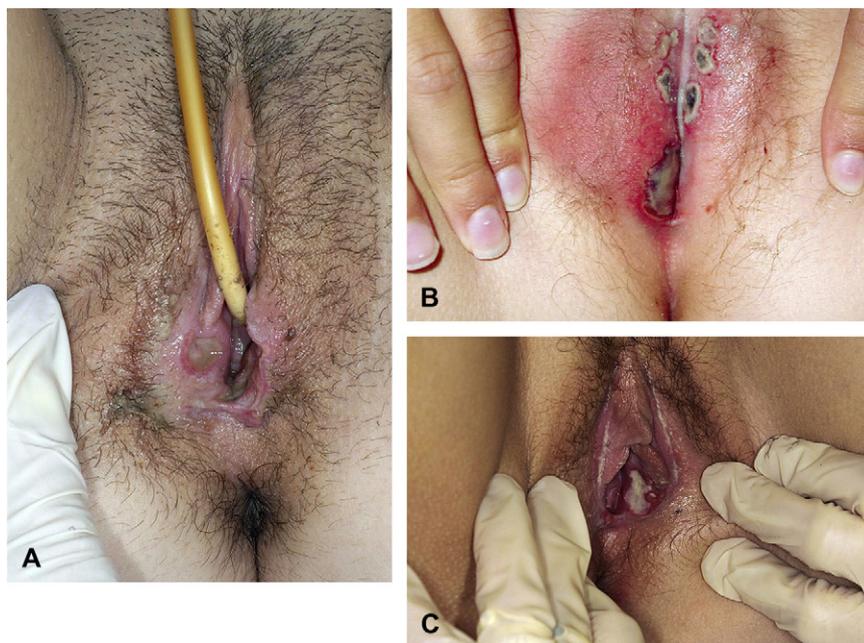
Fever occurred before onset of genital ulceration in 9 patients. Conditions that preceded the development of vulvar ulcers included upper respiratory tract infection (n = 3), a viral diarrheal illness (n = 3), streptococcal pharyngitis (n = 1), influenza A infection (n = 1), fever of uncertain origin (n = 1), and nonspecific symptoms including myalgias and neck stiffness (n = 1). All patients reported dysuria, and 3 were hospitalized for pain control. Several patients were reported to be distressed emotionally by the presence of painful genital ulcerations.

Ulcers were described as "black" or "necrotic" in 3 patients. Otherwise, vulvar lesions were described as "shallow ulcers" or "red erosions." All were negative for lesional HSV by PCR analysis. Serologic studies of acute and convalescent Epstein-Barr virus (EBV) antibodies were performed in 3 patients. Although acute and convalescent EBV antibodies were positive in one patient, suggesting acute and previous infection, there were no classic clinical findings of infectious mononucleosis; thus, the importance of this finding as a potential precipitating factor was unclear. Skin biopsy specimens for histopathologic evaluation were obtained in two patients and showed nonspecific acute and chronic inflammation, with or without erosion and reactive epithelial hyperplasia (Fig 2). Periodic acid–Schiff and Gram stains were negative for micro-organisms in both biopsy specimens.

The mean duration from onset of symptoms to last clinical follow-up or return of the questionnaire was 2.5 years (range, 3.4 months–6.7 years). Four patients

## CAPSULE SUMMARY

- Reactive nonsexually related acute genital ulcers should be considered in adolescent girls who develop genital ulceration after an acute febrile illness.
- Pain is severe in most patients.
- In a series of 10 patients with reactive nonsexually related acute genital ulcers, the ulcerations resolved within several weeks regardless of treatment. Six patients had at least one recurrence.



**Fig 1.** Vulvar ulceration in 3 girls (A, B, and C) with reactive nonsexually related acute genital ulcers. A, Note that patient required urinary catheterization for pain control.

had a single episode of genital ulceration, and 6 patients reported recurrent ulceration (2 patients with 4 episodes, 3 patients with 3 episodes, and 1 patient with 2 episodes). The average time to recurrence was 10 months. No patient was given the diagnosis of inflammatory bowel disease, celiac disease, or Behçet disease during the follow-up period.

All patients experienced resolution of the ulcerations after several weeks regardless of treatment, which included topical or systemic corticosteroids, topical or systemic antibiotics, local debridement, and oral nonsteroidal anti-inflammatory drugs. Only one patient with multiple recurrences, preceded by fever of unknown origin, required long-term treatment (oral colchicine, 0.6 mg daily). Several patients reportedly experienced symptomatic relief from medications, including topical lidocaine gel, topical antacid (aluminium hydroxide and magnesium hydroxide: Maalox [Novartis, Parsippany, NJ] formulated in Plastibase [E.R. Squibb & Sons, LLC, Princeton, NJ]), oral nonsteroidal anti-inflammatory drugs, and oral opioid analgesics. Urination in a bath of warm water improved dysuria in several patients. Four girls were treated empirically with an oral antiviral medication on at least one occasion.

To our knowledge, no patient developed scarring or persistent pain, but these potential sequelae were addressed specifically in the documentation of only two patients.

The assigned diagnosis was nonspecific in 7 patients (eg, vulvar ulcerations, acute genital ulcers, major aphthous ulcer). The specific term “ulcus

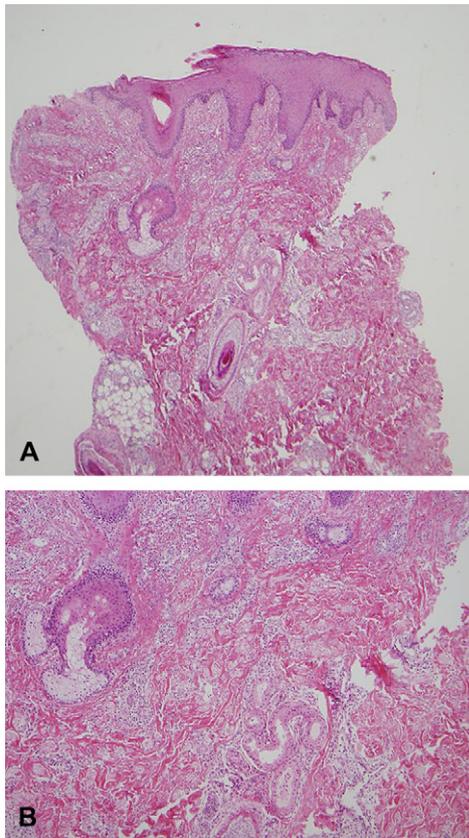
vulvae acutum” was used in 3 patients, each time by the same practitioner.

## DISCUSSION

The phenomenon of acute self-limited genital ulcers in adolescent girls, in whom other causes of genital ulceration have been excluded, has been previously termed “ulcus vulvae acutum” and “Lipschütz ulcer.”<sup>5-11</sup> Nonsexually related acute genital ulcers may arise in adolescents with other conditions such as Crohn disease or Behçet disease. We advocate the term “reactive nonsexually related acute genital ulcers” to refer to genital ulceration that appears to occur in response to an acute illness rather than as a manifestation of an underlying chronic systemic disease. Despite its historical longevity, this condition is not well recognized and its cause is poorly understood. It may fail to be recognized because of its rarity, misdiagnosis, or a lack of awareness among clinicians. Much of the English-language literature on this entity was published more than 50 years ago, when infectious disease epidemiology differed substantially from that of today. It is possible that previous associations with typhoid and conditions now rare in the developed world may have steered contemporary clinicians away from this diagnosis.

## Demographic information

A search of our institution’s medical index database identified 10 patients with clinical features of RNSRAGU in the past 10 years. RNSRAGU



**Fig 2.** Nonspecific histopathologic findings included reactive epithelial hyperplasia, epidermal ulceration, abscess formation, and granulation tissue response. (A and B, Hematoxylin-eosin stain; original magnifications: A,  $\times 40$ ; B,  $\times 100$ .) Gomori methenamine silver, periodic acid-Schiff, and acid-fast bacilli stains showed absence of micro-organisms.

preferentially affects adolescent girls.<sup>12-14</sup> Most affected patients were believed to be virginal, a characteristic that has been reported previously.<sup>3,4,8,11,12,14-17</sup> We found an average age of onset of 11.5 years, similar to the findings of a previous study<sup>15</sup> and considerably younger than those of another.<sup>11</sup> Seven patients (70%) either had a history of oral aphthosis or had active oral lesions at the time of presentation. Another group reported a history of transient oral erosions in 9 of 13 patients (69%).<sup>11</sup> This is higher than the 20% to 50% prevalence of oral aphthae expected for otherwise healthy individuals in this age group.<sup>1,2</sup>

### Preceding illnesses

In our series, patients universally experienced fever before development of genital ulcers. Associated infections were diverse and included influenza A, viral gastroenteritis, viral upper respiratory tract illness, and streptococcal pharyngitis. The

precise etiology of the acute fever was not determined in several cases, but no patient had convincing serologic evidence of acute EBV infection. A previous report of RNSRAGU found that 10 of 13 (77%) patients experienced preceding fever and 4 of 13 (31%) had primary EBV infection. It is possible that fever may be part of the genital aphthosis phenomenon rather than necessarily indicative of a preceding infection.

Several associated illnesses have been reported previously. In the first half of the 20th century, at least 9 cases were reported in association with typhoid infection.<sup>6</sup> More recently, numerous reports have linked cases of vulvar ulceration with acute EBV infection (infectious mononucleosis).<sup>3,8,10-12,16-20</sup> Other case reports demonstrated an association between RNSRAGU and paratyphoid fever,<sup>7</sup> *Mycoplasma pneumoniae*,<sup>21</sup> and cytomegalovirus-associated acute mononucleosis.<sup>9</sup> Our group recently reported RNSRAGU arising in a patient with influenza virus infection.<sup>4</sup> Although much emphasis has been placed on the link between genital ulceration and EBV infection,<sup>11</sup> our findings indicate that a diagnosis of RNSRAGU should be suspected after any acute febrile illness in the appropriate clinical setting. Of the patients who responded to our questionnaire, no patient reported new medical problems.

### Physical findings

RNSRAGU is characterized by the development of painful ulcers on the external genitalia, most often the labia minora of adolescent girls.<sup>9,10,12,13</sup> We found that most lesions were shallow ulcers or erosions with a clean or fibrinous base (ie, aphthae), although 3 patients developed necrotic ulcers, a complication described previously.<sup>6,8</sup> Taylor et al<sup>10</sup> noted a purple-red margin around the ulcers of several patients with RNSRAGU; this finding was not documented in the medical records or identified in the photographs of patients in our study. The typical morphology of HSV (multiple clustered, punched-out erosions) was not present. All patients in our study experienced dysuria, which is characteristic.<sup>15</sup>

### Diagnosis

RNSRAGU is a clinical diagnosis that can be made on the basis of consistent clinical findings and the exclusion of other causes of genital ulceration with adjunctive laboratory tests, as needed (Table I). This condition should be considered when vulvar lesions are recognized as aphthae in an otherwise healthy adolescent without a sexual history and with a preceding fever or other acute systemic illness.

**Table I.** Evaluation of patients with vulvar ulcers

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Thorough history and physical examination (including ocular, oral, and genital mucosa)
Screening laboratory tests
Complete blood cell count with differential
Microbiologic studies
HSV PCR assay from lesional swab specimen (or IgG and IgM antiviral capsid antigen test for HSV)
Potassium hydroxide preparation or fungal culture
Bacterial culture from lesional swab specimen
Smear for acid-fast bacilli from lesional swab specimen
Rapid streptococcal throat swab or culture or antistreptolysin O titer
IgG and IgM antiviral capsid antigen for Epstein-Barr virus
IgG and IgM antiviral capsid antigen for cytomegalovirus
<i>Mycoplasma pneumoniae</i> serologies
HIV and syphilis serologies

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HSV, Herpes simplex virus; PCR, polymerase chain reaction. These evaluations are done on the basis of clinical findings.

**Table II.** Recommended approach to treatment of reactive nonsexually related acute genital ulcers, based on clinical severity

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Mild: Local analgesics; observation; reassurance
Moderate: Local analgesics; NSAIDs; topical corticosteroids; close follow-up
Severe: Local analgesics, NSAIDs, opioid analgesics as needed; systemic antibiotics (when ulcers are necrotic); systemic corticosteroids; if persistent/refractory, consider brief hospitalization

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NSAIDs, Nonsteroidal anti-inflammatory drugs.

The most common cause of genital ulceration is HSV infection, and it is reasonable to test for HSV. Viral PCR assay from a lesional swab is preferred, although serum HSV capsid antibody testing may be done if HSV PCR assay is unavailable. To evaluate for recent infectious mononucleosis, IgG and IgM antiviral EBV and cytomegalovirus capsid antibody tests are recommended. Potassium hydroxide examination and culture of an exudate swab specimen to exclude occult local fungal or bacterial infection may be indicated. Other investigations (eg, throat culture or antistreptolysin O antibody titer) should be performed as dictated by the clinical findings. If appropriate, assessment for the presence of HIV could be done. Because syphilis and chlamydial and gonorrheal infections do not classically cause painful acute genital ulcerations, testing for these conditions is indicated only if clinical suspicion exists. Immune-mediated diseases such as Crohn disease, Behçet disease, erythema multiforme, immunobullous

disorders, and pyoderma gangrenosum should be considered in patients with ulcerations that do not spontaneously remit in several weeks or in patients who have a coexisting systemic disease. A careful and sensitively obtained history and meticulous physical examination should exclude local trauma, sexual injury or abuse, and local application of caustic substances.

Histopathologic findings from lesional biopsy specimens were nonspecific in the 3 patients tested in our study and in those tested by other investigators.<sup>11</sup> We believe that skin biopsy is of low use in the absence of a strongly suspected alternative diagnosis. Accurate recognition of RNSRAGU by an astute clinician may prevent the unnecessary trauma involved with a lesional biopsy.

### Treatment

Because RNSRAGU spontaneously resolves and the number of patients in the series was small, we could not ascertain whether any particular intervention accelerated healing. Supportive measures and good wound care alone may be sufficient in mild cases, characterized by mildly symptomatic, superficial genital erosions (Table II). Patients with moderately severe RNSRAGU (ie, pain tolerable but uncomfortable, ulceration without necrosis) may benefit from application of a class 1 or 2 topical corticosteroid (eg, clobetasol propionate or fluocinonide ointments, respectively), oral nonsteroidal anti-inflammatory drugs, and local anesthetics (eg, lidocaine jelly) to hasten resolution of associated inflammation and pain.<sup>12,13</sup> Despite the theoretical risk of exacerbating a recent or current infection, systemic corticosteroids may be required in patients with severely painful, multiple, or necrotic ulcers. In cases associated with ulcer necrosis, systemic antibiotics may be indicated on the basis of culture of the exudate and antimicrobial sensitivity data.<sup>16</sup> Three of our patients required hospitalization for pain control with intravenous opioid medications and placement of a urinary catheter. This highlights the considerable morbidity associated with this condition.

### Prognosis

We found that 60% of patients had at least one recurrence. Berlin<sup>6</sup> organized the prognosis of RNSRAGU into two categories: (1) acute, self-limited gangrenous ulceration associated with a systemic illness; and (2) subacute, frequently relapsing ulcers. The latter could be regarded as recurrent RNSRAGU, although patients with this phenomenon could also be considered to have complex aphthosis. In our 6 patients with at least one recurrence of genital ulceration after the initial episode, the average time to

recurrence was 10 months. Previous authors estimated that the ulcers of RNSRAGU heal spontaneously after 2 to 6 weeks regardless of treatment,<sup>10-12,16,17</sup> which is consistent with our observations.

### Pathogenesis

We believe that RNSRAGU is a subset of complex aphthosis, a hypothesis strengthened by the observation that 70% of our patients also had a documented history of oral aphthosis. There are multiple theories regarding the pathogenesis of RNSRAGU. Several groups have hypothesized that genital ulceration results directly from infection of the genital mucosa. In 1912, Lipschütz<sup>5</sup> proposed that *Bacillus crassus* was the cause of RNSRAGU because this organism was isolated from vulvar ulcer cultures. Since then, however, *B crassus* has been classified as normal vaginal flora. McKenna et al<sup>20</sup> purported that pathogenic micro-organisms are transmitted from oral secretions to the genitalia by the patient or sexual partner. Hematogenous transport of infectious organisms to the genitalia by circulating infected T lymphocytes also has been proposed,<sup>8</sup> although in studies of patients with EBV-associated RNSRAGU, the virus is usually not detectable in lesional tissue.<sup>18</sup> When RNSRAGU is associated with paratyphoid fever, production of endotoxin by *Salmonella enterica* subspecies *enterica* serovar Paratyphi A (*S paratyphi*) may induce ulceration, as occurs in the gastrointestinal tract.<sup>7</sup>

Perhaps the most likely etiologic theory is that the vulvar lesions of RNSRAGU result from an exuberant systemic immune response to acute infection.<sup>6</sup> Pelletier et al<sup>7</sup> proposed that cytotoxic T lymphocytes are recruited in response to systemic viral illness and mediate the inflammation that results in genital ulceration. This type of reactive dermatosis is analogous to the mucocutaneous lesions of erythema multiforme, pathergic lesions in Behçet disease and pyoderma gangrenosum, and erythema nodosum. Such a rationale may explain why the acute infectious illnesses associated with RNSRAGU have varied, paralleling changes in infectious disease epidemiology over the past century.

### Limitations

Given the social stigma associated with genital ulceration and the self-limited nature of RNSRAGU, it is possible that patients did not present for medical attention and were not captured in our study. Database searching was limited to female patients younger than 18 years old. Candidate cases were excluded if an HSV assay was not performed. Other cases may have been misdiagnosed. These search limits could have led to an underestimation of

the number of patients with RNSRAGU at our institution. We did not attempt to further correspond with patients who did not reply to the written questionnaire.

### CONCLUSIONS

Recognition of RNSRAGU is important so that patients receive appropriate and timely treatment and prognostic counseling, involving their parents as needed. It is essential that patients with RNSRAGU are not given a misdiagnosis of, or treated empirically for, sexually transmitted HSV infection. An accurate diagnosis of RNSRAGU will prevent invasive investigations and subspecialty consultation and provide reassurance to the patients and their families.

The authors thank Pauline J. Funk, Mayo Clinic, for her assistance with patient database searches.

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**APPENDIX**

Mayo Clinic  
200 First St SW  
Rochester, MN 55905

DATE

Dear \_\_\_\_\_ (or legal guardian of \_\_\_\_\_):

We are part of a group investigating a particular condition associated with the appearance of ulcers in the vulva (female private parts). Our medical records indicate that this is a condition that you (or your legal dependent) may have experienced in the past.

In order to better define this condition, we have developed a questionnaire to find out more about whether these symptoms have returned or whether you (or your legal dependent) have/has developed related symptoms or other medical conditions.

If you agree to participate in this study, please complete the attached questionnaire and consent form and return them to us in the provided self-addressed stamped envelope within 2 to 4 weeks of receiving this letter. This should take no longer than 5 to 10 minutes. Participation in this study is entirely optional. Your decision to participate or to not participate will in no way affect your medical care at Mayo Clinic. You will not receive compensation for participating in this study, although your responses may help us better understand this condition.

Thank you for your consideration. Please do not hesitate to contact us at XXX should you have any questions or concerns.

Sincerely,

Julia S. Lehman, MD  
Alison J. Bruce, MD  
Principal Investigators

**Questionnaire:**

1. Since you were seen at Mayo Clinic last for sores of the genitalia (private parts), have you had new sores of the genitalia at any time?

YES / NO / UNSURE (circle one)

If no or unsure, skip to question #2.

If yes, how many times (approximately) and when?

\_\_\_\_\_

What treatments did you use for this and what response did you have? (write "none" if no treatment was used)

\_\_\_\_\_

2. Have you had sores in the mouth?

YES / NO / UNSURE (circle one)

If no or unsure, skip to question #3. If yes, how many times (approximately) and when?

\_\_\_\_\_

What treatments did you use for this and what response did you have? (write "none" if no treatment was used)

\_\_\_\_\_

3. Have you developed other medical conditions since your last visit at Mayo Clinic?

YES / NO / UNSURE (circle one)

If no or unsure, skip to question #4. If yes, what conditions have you developed?

\_\_\_\_\_

4. Has anyone to whom you are related by blood developed any of the following conditions, to your knowledge?

If no, skip to question #5.

If yes, please circle all that apply and list which relative(s) has this condition:

LUPUS / PSORIASIS / RHEUMATOID ARTHRITIS /  
BEHCET'S DISEASE / SJOGREN'S SYNDROME /  
RECURRENT APHTHOSIS / OTHER \_\_\_\_\_

5. Which countries are your ancestors from (leave blank if unknown)?

\_\_\_\_\_  
\_\_\_\_\_

=====

If we need to call to clarify an answer, is it ok if we call you?

Yes \_\_\_ If so, what is the best telephone number to use? \_\_\_\_\_

No thanks \_\_\_

=====

Thank you for your participation. Please send this questionnaire with the signed consent form in the self-addressed envelope back to Mayo Clinic. Call XXX with any questions.