Acute Scrotal Ulcers in Typhoid Fever: Case Report and Literature Review

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Abstract: Background. In developed countries, typhoid fever is a travel-associated disease that is often overlooked. However, as standard blood and stool culture methods have relatively low sensitivity, diagnosis depends heavily on clinical signs and symptoms and on a high level of suspicion.

Methods. Reported here is the case of an 18-year-old male who presented with fever and acute scrotal ulcers and whose blood cultures were positive for Salmonella enterica serotype Typhi. A review of genital ulcers associated with typhoid fever in the literature is discussed.

Conclusion. This report suggests that typhoid fever is a differential diagnosis of acute genital ulcers.

Key words: Typhoid fever, paratyphoid fever, Salmonella enterica, acute genital ulcer, scrotal ulcer, vulvar ulcer

BACKGROUND

Typhoid fever is a serious and often overlooked systemic bacterial infection caused by Salmonella enterica serotype Typhi. It has been estimated to cause over 20 million infections and 216,000 deaths annually [1, 2]. Most infections occur in under-developed countries where people are exposed to overcrowding, poor sanitation and untreated water—factors conducive to faecal-oral transmission. In developed countries it is a travel-associated disease, with the highest risk being travel to Thailand, India, Indonesia and Egypt [3].

Typhoid fever classically presents as a systemic illness. After ingestion, the bacterium triggers endocytosis into the gut epithelium where it invades macrophages. From the intestine, it is disseminated throughout the body including to the liver and spleen [4]. Presenting symptoms are generally non-specific, including fever (99%), anorexia (85%), diarrhoea or constipation (85%), nausea or vomiting (85%) and cough (35%). The only examination finding with a high specificity is blanching maculo-papular lesions or “rose spots” on the upper body, a condition noted in 7–30% of cases [5, 6]. Since standard blood and stool culture methods have a relatively low sensitivity (40–60%) [7], diagnosis depends heavily on clinical signs and symptoms and a high level of suspicion.

CASE REPORT

A previously healthy 18-year-old male presented with a 3-day history of fever, rigors, nausea and vomiting, and painful scrotal lesions. The lesions were first noticed at onset of fever. Four days prior to the onset of symptoms, the patient had returned to Australia from an urban area in Punjab, India where he had spent six weeks visiting relatives. He reportedly consumed street food and tap water. He said he had not applied any topical substances on the scrotum or suffered trauma or insect bites. He did not receive pre-travel vaccines or anti-malarial chemoprophylaxis. He did not report any history of sexual contact or drug use in response to repeated and confidential questioning. There was no family history of genital or oral ulceration. No further positive symptoms were elucidated on systems review and, importantly, there was no visual disturbance or acute loss of visual acuity. The patient provided informed written consent for the use of his information and photographs in this case report.

On examination, he was febrile (39.3°C) and tachycardic (110 bpm). A well-circumscribed, punched-out, necrotic, round ulcer with overlying eschar 1 cm in diameter was noted on the left side of the scrotum (Fig. 1a), and two similar but smaller ulcers on the right side (Fig. 1b). The scrotal examination was otherwise unremarkable. No generalised rashes, lymphadenopathy, oral lesions, or red eyes
were observed. The cardiorespiratory and gastrointestinal examinations were unremarkable. Initial white cell count was \(8.5 \times 10^9/L\) (reference range \((4–11) \times 10^9/L\)), C-reactive protein was 62.2 mg/L (reference range < 3 mg/L) and activated partial prothrombin time was 41.1 s (reference range 25–35 s). The results of other routine blood tests and the chest radiograph were within normal limits.

The blood culture was positive for *Salmonella enterica* serotype Typhi, sensitive to ciprofloxacin but resistant to nalidixic acid. A punch biopsy of the ulcer edge revealed non-specific acute inflammation with abundant neutrophils (Fig. 2a and 2b). No granulomas, infective organisms or features of vasculitis were identified using Gram, PAS, Grocott, Ziehl-Neelson, Giemsa and Warthin-Sarry stains. Extended broth culture of the tissue biopsy was negative. Further investigations for alternate causes of genital ulcers returned negative (Table 1). Treatment consisted of intravenous ceftriaxone 1 g 24 hourly for 5 days and then oral azithromycin 500 mg daily for a further 9 days. The patient’s condition and ulcers improved within a week of starting treatment, and the ulcers healed over 5 weeks with no scarring.

**DISCUSSION**

Infectious causes of acute genital ulcers with systemic illness include herpes simplex viruses, syphilis, human immunodeficiency virus, chlamydia trachomatis, lymphogra-
nuloma venereum, donovanosis and chancroid. Rare aetiologies have also been described in the literature such as Epstein-Barr virus [8], cytomegalovirus [9], Mycoplasma pneumoniae [10], rickettsial diseases [11], tuberculosis [12], influenza [13], and cutaneous leishmaniasis [14].

Non-infectious causes include Behçet’s disease, juvenile gangrenous vasculitis of the scrotum, and genital pyoderma gangrenosum. Behçet’s disease is a clinically diagnosed entity that primarily presents with recurrent oral ulcers in association with genital ulcers, uveitis, or other skin lesions [15, 16]. Juvenile gangrenous vasculitis of the scrotum is a form of scrotal gangrene that is typically diagnosed in conjunction with features of vasculitis on biopsy [17]. Genital pyoderma gangrenosum is a neutrophilic dermatosis characterised by the protracted course of single or multiple expanding ulcerations with a serpiginous and blue or violet coloured border [18]. These are primarily diagnosed.

### Table 1. Results of further investigations did not reveal an alternate cause for the scrotal ulcers

| Differential diagnosis | Investigation/s performed | Result |
|------------------------|---------------------------|--------|
| Syphilis               | IgG serology, and blood, ulcer and biopsy PCR | –ve    |
| Herpes simplex virus type 1 and 2 | Scrotal swab PCR | –ve    |
| Varicella zoster virus | Scrotal swab PCR | –ve    |
| Epstein-Barr virus     | IgM and VCA IgG serology | –ve    |
| Cytomegalovirus        | IgM and IgG serology | –ve    |
| Influenza A and B virus| Respiratory tract swab PCR | –ve    |
| Human immunodeficiency virus | p24 antigen, type 1 (including group O) and type 2 antibody serology | –ve    |
| Chlamydia trachomatis  | Urine and biopsy NAAT   | –ve    |
| Chancroid              | Biopsy culture          | –ve    |
| Donovanosis            | Biopsy culture          | –ve    |
| Mycoplasma pneumoniae  | IgM and IgG serology, respiratory swab PCR | –ve    |
| Rickettsial diseases   | IgM and IgG serology*   | –ve    |
| Tuberculosis           | Biopsy PCR, interferon gamma assay | –ve    |

Ig = immunoglobulin; PCR = Polymerase Chain Reaction; VCA = Viral capsid antigen; NAAT = Nucleic Acid Amplification Technique

*Immunofluoresence assay detecting IgG and IgM antibody to spotted fever group rickettsia (Rickettsia australis, R. honei, R. conorii, R. africae, R. rickettsii and R. felis), typhus group rickettsia (R. prowazokii and R. typhi) and scrub typhus group rickettsia (Orientia tsutsugamushi serotype Gilliam, Karp, Kato and Cowley Beach, and O. chuto)

### Table 2. Review of case reports describing acute genital ulcers in typhoid and paratyphoid fever

| Authors            | Year | Cases | Diagnosis  | Location          | Description                                                                 |
|--------------------|------|-------|------------|-------------------|-----------------------------------------------------------------------------|
| Atkinson & Swartz  | 2011 | 1     | Typhoid    | Labia majora      | Single 2 cm ulcer, white-topped                                            |
| Mustapha et al.    | 2009 | 2     | Typhoid    | Labia minora      | Single 3–5 cm ulcer, red border, purulent, central necrosis                  |
| Pelliot et al.     | 2003 | 1     | Paratyphoid| Labia minora      | Single ulcer, punched-out, dark purple border                              |
| Schmidt et al.     | 1987 | 1     | Typhoid    | Labia minora      | Single 2 cm ulcer, punched-out, purulent                                    |
| van Joost et al.   | 1971 | 1     | Paratyphoid| Labia minora      | Single ulcer, punched out, yellow-grey floor, purulent                       |
| Barone et al.      | 1963 | 1     | Typhoid    | Labia majora      | 2 oval ulcers each side, 5 × 1.5 cm each, sharp edges, bleeding             |
| Roberts & Barron   | 1958 | 1     | Typhoid    | Labia minora      | Multiple small oval ulcers, yellow membranous floor                         |
| Buchman et al.     | 1955 | 1     | Typhoid    | Labia minora      | Single 2 cm ulcer with multiple 2–3 mm satellite lesions, raised edges, grey necrotic floor |
| Visani et al.      | 1952 | 3     | Typhoid    | Labia minora      | Multiple ulcers max 2 cm, oval, purulent                                   |
| Sedallian et al.   | 1950 | 4     | Typhoid    | Labia minora      | 2 ulcers, approx. 1.5 cm, red floor, purulent                              |
| Braun et al.       | 1950 | 1     | Typhoid    | Labia minora      | Single ulcer, bleeding, purulent                                            |
| Decrop et al.      | 1948 | 1     | Typhoid    | Labia minora      | Single approx. 2 cm ulcer, necrotic, purulent                              |
| Middelbeven et al. | 1946 | 1     | Typhoid    | Labia minora      | Single ulcer, large, flat, white purulent                                  |
| Berlin et al.      | 1939 | 1     | Typhoid    | Labia minora      | Multiple ulcers, purulent, necrotic floor                                   |
| Lartigau et al.    | 1899 | 1     | Typhoid    | Labia minora and majora | Multiple ulcers, punched-out, purulent                                   |
Phase of exclusion and are difficult to determine in the presence of bacteremia. Differentiating features include avian response to glucocorticoid or immunosuppressive therapy, and atrophic scarring upon healing.

Typhoid is seldom cited as a differential diagnosis of acute genital ulcers, even though an association has been made for over 100 years. A literature search of MEDLINE, PubMed, EMBASE and article citations for case reports of genital ulcers in typhoid yielded 21 documented cases of vulval ulcers in typhoid (Table 2). There is evidence of only one previous case report of scrotal ulcers in typhoid fever observed in 1898 [19]. The most common manifestation was 1–2 purulent, punched-out ulcers of the labia minora, 1–2 cm in diameter with necrotic base or eschar. This is consistent with the ulcers described in the present case report.

The pathogenesis of acute genital ulcers in typhoid fever is unknown. Haematogenous spread is a possibility given the fact that Salmonella enterica has a demonstrated ability to embolise to the skin in the form of “rose spots” [7]. However, tissue specimen cultures were negative in our case. Microscopy of the ulcer demonstrated fibrinopurulent slough in the ulcer base with deeper florid neutrophilic inflammation consistent with that found by Mustapha et al. [20]. In both reports, no causative agents were identified on biopsies with further stains.

CONCLUSION

This report describes acute scrotal ulcers developing simultaneously with other symptoms in a patient with typhoid fever. There were no clinical features or investigation results suggesting an alternate cause of the ulcers. This is only the second case report of scrotal ulcers associated with typhoid fever, though a number of cases of vulval ulcer have been reported. Our literature review suggests that typhoid fever is a rare differential diagnosis of genital ulcers. Further studies to characterise the related mechanism are required.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

REFERENCES

1. Crump J, Luby S, Mintz E. The global burden of typhoid fever. Bull World Health Organ 2004; 82: 346–353.
2. Maurice J. A first step in bringing typhoid fever out of the closet. Lancet 2012; 379(9817): 699–700.
3. Leder K, Torresi J, Libman M, et al. GeoSentinel Surveillance of Illness in Returned Travelers, 2007–2011. Ann Intern Med 2013; 158(6): 456–468.
4. House D, Bishop A, Parry C, et al. Typhoid fever: pathogenesis and disease. Curr Opin Infect Dis 2001; 14: 573–578.
5. Crum N. Current Trends in Typhoid Fever. Curr Gastroenterol Rep 2003; 5(4): 279–286.
6. Clark T, Daneshvar C, Pareek M, et al. Enteric fever in a UK regional infectious diseases unit: A 10 year retrospective review. J Infect 2010; 60(2): 91–98.
7. Gilman R, Termine M, Levine M, et al. Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of Salmonella typhi in typhoid fever. Lancet 1975; 1(7918): 1211–1213.
8. Cheng S, Chapman M, Margesson L, et al. Genital ulcers caused by Epstein-Barr virus. J Am Acad Dermatol 2004; 51(5): 824–826.
9. Martin JM, Godoy R, Calduch L, et al. Lipschütz Acute Vulval Ulcers Associated with Primary Cytomegalovirus Infection. Pediatr Dermatol 2008; 25(1): 113–115.
10. Vieira-Baptista P, Machado L, Costa A, et al. Mycoplasma pneumoniae: A Rare Cause of Vulvar Ulcers or an Undiagnosed One? J Low Genit Tract Dis 2013; 17(3): 330–334.
11. Abgueguen P, Chenebault J, Pichard E. A Traveler Returning from South Africa with Rash and Genital Uproar. Clin Infect Dis 2004; 38: 908–909.
12. Toledo-Pastrana T, Ferrandiz L, Pichardo A, et al. Tuberculosis: An Unusual Cause of Genital Ulcer. Sex Transm Dis 2012; 39(8): 643–644.
13. Wetter D, Bruce A, Maclaughlin K, et al. Ulcus Vulvae Acutum in a 13-Year-Old Girl After Influenza A Infection. Skinmed 2008; 7(2): 95–98.
14. Cabello I, Caraballo A, Millan Y. Leishmaniase in the genital area. Rev Inst Med Trop Sao Paulo 2002; 44(2): 105–107.
15. International Team for the Revision of the International Criteria for Behçet’s Disease (ITR-ICBD). The International Criteria for Behçet’s Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol 2014; 28(3): 338–3347.
16. International Study Group for Behçet’s Disease. Criteria for diagnosis of Behçet’s disease. Lancet 1990; 335(8697): 1078–1080.
17. Pulido-Perez A, Parra-Blanco V, Aviles-Izquierdo J. Sudden-Onset Scrotal Ulcer. Actas Dermosifiliogr 2012; 103(3): 239–240.
18. Ruocco E, Sangiuliano S, Gravina A, et al. Pyoderma gangrenosum: an updated review. J Eur Acad Dermatol Venereol 2009; 23(9): 1008–1017.
19. Keen W. Surgical Complications and Sequels of Typhoid Fever. Philadelphia: W. B. Saunders; 1898.
20. Mustapha O, Kanj S, Araj G, et al. Genital ulceration associated with typhoid fever. Am J Obstet Gynecol 2009; 200(5): e6–e7.
21. Atkinson V, Swartz E. Case 1: Fever and a genital ulcer in a recent immigrant. Paediatr Child Health 2011; 16(2):
75–76.

22. Pelletier F, Aubin F, Puzenat E, et al. Lipschutz genital ulceration: A rare manifestation of paratyphoid fever. Eur J Dermatol 2003; 13(3): 297–298.

23. Schmidt R, Kuhn W, Leucht W. Ulcerating vulvitis—A rare complication in typhus abdominalis. Geburtshilfe Frauenheilkd 1987; 47(11): 821–822.

24. van Joost T. An unusual case of vulvar ulcer of acute onset. Ned Tijdschr Geneeskd 1971; 115(25): 1080–1082.

25. Barone A, Persico M, Pellicano A. Acute Ulcerations on the Vulva During ileal typhoid. Arch Ostet Ginecol 1963; 68(4): 385–394.

26. Roberts DWT, Barron SL. Typhoid fever with vulvovaginitis. Lancet 1958; 1(7055): 1043–1044.

27. Buchman M. A typhoid ulcer of the external genitals. Am J Obstet Gynecol 1955; 70(2): 435–437.

28. Visani A. Vulvar ulcerations during typhoid. Acta Med Ital Mal Infett Parassit 1952; 7(1): 10–12.

29. Sedallian P, Monnet P, Moinecourt J. Ulcerations of the vulva in the course of typhoid fever. Presse Med 1950; 58(82): 1445.

30. Braun H. Typhoid ulcer of the vulva. Z Haut Geschlechtskr 1950; 9(6): 251–258.

31. Decrop G. A case of Lipschutz disease. Maroc Med 1948; 27(281): 427–428.

32. Middelhoven A. Difficulties in the diagnosis of typhoid fever. Maandschr Kindergeneeskd 1946; 14(4): 124–128.

33. Berlin C. Ulcus Vulvae Acutum (Lipschutz), Associated with Typhoid Fever. AMA Arch Derm Syphilol 1939; 39(1): 89–91.

34. Lartigau A. Multiple Ulcers of the Vulva and Vagina in Typhoid Fever. Lancet 1899; 154(3971): 968–969.