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Short Communications

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

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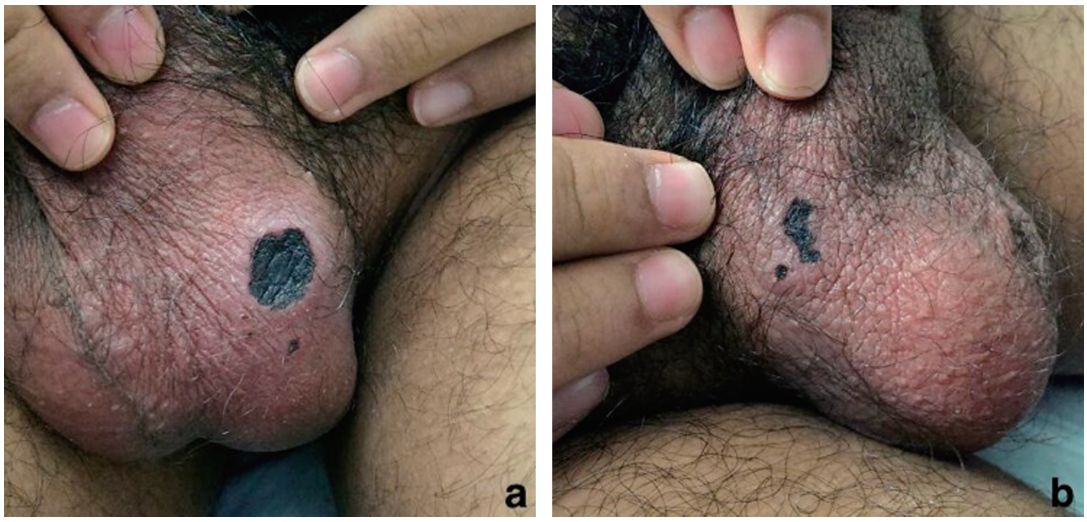

Fig. 1. a Left scrotum showing well-circumscribed, punched-out, necrotic, round ulcer with overlying eschar, b Right scrotum showing two similar but smaller ulcers

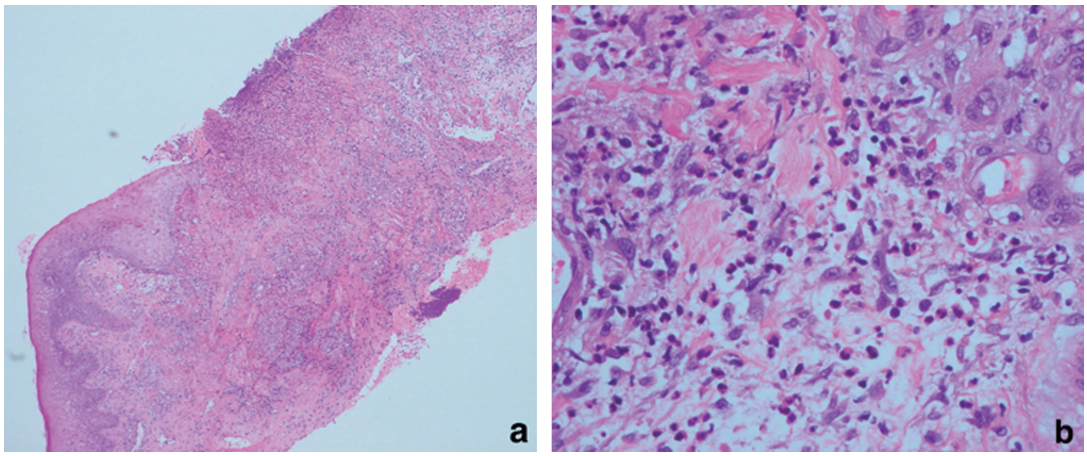

Fig. 2. a Ulcer edge on low power view, b Higher power view showing acute dermal inflammation deep to the ulcer; no granulomas or infective organisms were identified with further staining

were observed. The cardiorespiratory and gastrointestinal examinations were unremarkable. Initial white cell count was 8.5 × 10^9/L (reference range (4–11) × 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-Starry 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 diagno-

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

Differential diagnosis	Investigation/s performed	Result
Syphillis	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. rickettsei 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
Atkinsons & Swartz [21]	2011	1	Typhoid	Labia majora	Single 2 cm ulcer, white-topped
Mustapha et al. [20]	2009	2	Typhoid	Labia minora	Single 3–5 cm ulcer, red border, purulent, central necrosis
Pelletier et al. [22]	2003	1	Paratyphoid	Labia minora	Single ulcer, punched-out, dark purple border
Schmidt et al. [23]	1987	1	Typhoid	Labia minora	Single 2 cm ulcer, punched-out, purulent
van Joost [24]	1971	1	Paratyphoid	Labia minora	Single ulcer, punched out, yellow-grey floor, purulent
Barone et al. [25]	1963	1	Typhoid	Labia majora	2 oval ulcers each side, 5 × 1.5 cm each, sharp edges, bleeding
Roberts & Barron [26]	1958	1	Typhoid	Labia minora	Multiple small oval ulcers, yellow membranous floor
Buchman [27]	1955	1	Typhoid	Labia minora	Single 2 cm ulcer with multiple 2–3 mm satellite lesions, raised edges, grey necrotic floor
Visani [28]	1952	3	Typhoid	Labia minora	Multiple ulcers max 2 cm, oval, purulent
Sedallian [29]	1950	4	Typhoid	Labia minora	2 ulcers, approx. 1.5 cm, red floor, purulent
Braun [30]	1950	1	Typhoid	Labia minora	Single ulcer, bleeding, purulent
Decrop [31]	1948	1	Typhoid	Labia minora	Single approx. 2 cm ulcer, necrotic, purulent
Middelhoven [32]	1946	1	Typhoid	Labia minora	Single ulcer, large, flat, white purulent
Berlin [33]	1939	1	Typhoid	Labia minora	Multiple ulcers, purulent, necrotic floor
Lartigau [34]	1899	1	Typhoid	Labia minora and majora	Multiple ulcers, punched-out, purulent

ses of exclusion and are difficult to determine in the presence of bacteraemia. Differentiating features include avid 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.

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