

Mycobacterium ulcerans infection: factors influencing diagnostic delay

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Bairnsdale or Buruli ulcer (BU) is an ulcerative skin and soft tissue infection caused by *Mycobacterium ulcerans*, and predominantly occurs in sub-Saharan Africa.^{1,2} Although small foci exist in East Gippsland (Victoria) and Queensland, most Australian cases have occurred in coastal Victorian towns.^{3,4} Risk factors for BU have been investigated, but the mode of transmission remains unknown.⁵⁻⁸ Late diagnosis of BU contributes to significant morbidity and treatment costs.^{2,9}

In Victoria, the incidence of BU is increasing, from four cases in 1999, to 61 notified cases in 2006. Half the cases in 2006 were linked to the Bellarine Peninsula, where BU was first described in 1998.^{10,11} Within the Bellarine Peninsula, most cases have been clustered in the towns of St Leonards (since 1998), Point Lonsdale (since 2002) and Barwon Heads/Ocean Grove (since 2005).

This retrospective study was designed to describe the epidemiology, patient symptomatology and health-seeking behaviour, and outcomes of initial medical consultations during the sustained BU outbreak on the Bellarine Peninsula.

METHODS

Participants

Patients diagnosed with BU between January 1998 and August 2006 were identified retrospectively through medical records of physicians in the region (including 40 patients whose diagnosis and management have been described previously¹¹) or the Victorian Department of Human Services (DHS) notifiable diseases database (BU became notifiable in 2004). BU was diagnosed by a positive *M. ulcerans* culture and/or polymerase chain reaction from a clinical specimen.¹² Only patients epidemiologically linked to the Bellarine Peninsula were included. Patients were excluded if they could not be contacted (3), had dementia (1) or had died (1).

The area of permanent residence was divided into six regions: Point Lonsdale, St Leonards, Barwon Heads, other regions on the Bellarine Peninsula, Geelong, and Greater Victoria (all of Victoria excluding Geelong and the Bellarine Peninsula). Patients were classified as living in a non-

ABSTRACT

Objective: To document the epidemiology, clinical characteristics and diagnosis of an outbreak of *Mycobacterium ulcerans* infection (Bairnsdale or Buruli ulcer [BU]) during the period 1998–2006, and compare delays in diagnosis between residents of endemic and non-endemic regions.

Design and setting: Retrospective case study of patients identified through infectious disease physicians on the Bellarine Peninsula and the Victorian Department of Human Services notifiable diseases database.

Main outcome measures: Description of events leading to diagnosis of BU.

Results: Eighty-five BU patients recalled their experience. Fifty-three patients were older than 60 years, and 61 permanently resided on the Bellarine Peninsula. The onset of symptoms occurred most frequently in mid winter. Twenty-eight patients had lesions on the arm and 51 on the leg. The median time between onset of symptoms and first medical contact was shorter for those living in the endemic area (3.0 weeks; interquartile range [IQR], 1.0–5.0 weeks) compared with non-endemic areas (5.3 weeks; IQR, 2.0–9.5 weeks) ($P = 0.05$). Patients who resided in the endemic area had a shorter median time from their first medical appointment to diagnosis (1.0 week; IQR, 0.0–3.9 weeks) than those who resided in non-endemic areas (5.0 weeks; IQR, 1.3–8.0 weeks) ($P = 0.001$).

Conclusion: Delay in presentation and time to diagnosis of BU are longer in non-endemic than endemic areas. Measures should be taken to raise awareness of the disease in non-endemic areas.

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endemic area if they lived in Geelong or Greater Victoria. Geelong is the largest city close to the Bellarine Peninsula, but is not linked to known transmission.

Ethics approval to contact patients was granted by Barwon Health and DHS Human Research Ethics and Advisory Committees.

Data collection

A questionnaire was mailed to patients. Non-responders were encouraged to participate by follow-up contact.

Statistical analysis

Statistical analysis was completed using Minitab, version 14 (Minitab Inc, State College, Pa, USA). Comparison of the time from first onset of symptoms to seeking medical attention, and from first medical appointment to diagnosis was completed using the Kruskal–Wallis or Mann–Whitney test. The Edwards test for seasonal trends¹³ was used to determine the periodicity of monthly totals for incident cases identified as time of onset of BU symptoms. An estimated incidence was calculated using patients who resided permanently on the Bellarine Peninsula and the 2001 Australian census data.

RESULTS

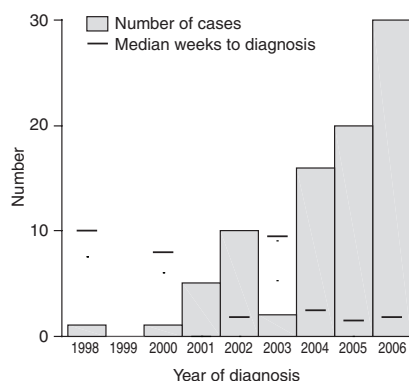
Patient demographics

Of 110 eligible patients, 85 participated (77% participation rate). The median time between diagnosis of BU and completion of the questionnaire was 6 months (interquartile range [IQR], 2.0–14.3 months). There were 45 male and 40 female participants (median age: men, 63 years [IQR, 36–72 years], women, 81 years [IQR, 51–85 years]; $P < 0.01$), and most cases occurred in 2006 ($n = 30$) (Box 1). Sixty-one patients resided in the endemic regions. For patients resident in the endemic area, the estimated annual incidence of BU for the period March 1998 to August 2006 was 3.1 per 10 000 people.

Clinical characteristics

Twenty-eight patients had lesions on the arm, and 51 on the leg (Box 2). Forty-one patients described a papule, 19 a small ulcer, and seven an eschar as the first symptom. Ten patients recalled an injury before BU symptoms, and 17 recalled an insect bite; however, most patients were unable to report how much time had elapsed from this until the onset of BU symptoms.

1 Number of cases and median time to diagnosis of Bairnsdale ulcer for 85 patients



2 Clinical characteristics of presentation and initial diagnosis for Bairnsdale ulcer for 85 patients

	Number
Site of lesion	
Lower legs	39
Upper arms	18
Upper legs	6
Feet	6
Forearms	5
Hands	5
Torso	5
Head	2
Reasons for seeing doctor (more than one answer cited)	
Lesion was not getting better	65
Lesion was getting bigger	44
Area was becoming swollen	40
Saw a media report on Bairnsdale ulcer	19
Lesion was becoming painful	11
At spouse or partner's urging	8
I knew someone with an ulcer	6
I felt sick	1
I had a fever	1
Other	12
Diagnosis by doctor at first appointment	
Bairnsdale ulcer	30
No diagnosis	22
Infection	13
Spider bite	10
Cancer	6
Ulcer (but not Bairnsdale ulcer)	4

The monthly variation in the date of first symptoms was best described by a simple harmonic curve ($P < 0.01$) (Box 3), with the trough in early January and the peak in early July. Based on incubation periods of three patients who reported specific timing of exposure relating to stays on the Bellarine Peninsula limited to a week, we estimate that the latent period was 1–4 months.

Patients' health-seeking behaviour

Nineteen patients cited viewing media reports of BU as a significant factor in seeking medical attention (Box 2). The median time between patients first noticing symptoms and seeking medical attention was 3.5 weeks (IQR, 1.0–8.0 weeks) and by location ranged from 2 to 6 weeks (Box 4). This time was shorter for people living in endemic regions (3.0 weeks; IQR, 1.0–5.0 weeks) than in non-endemic areas (5.3 weeks; IQR, 2.0–9.5 weeks) ($P = 0.05$).

Diagnosis

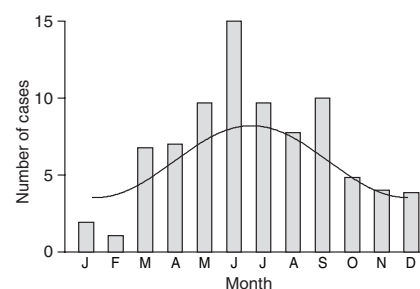
The median time between the first medical consultation and BU diagnosis was 2.0 weeks (IQR, 0.0–6.0 weeks). For residents of Point Lonsdale and St Leonards, the delay from presentation to diagnosis was less than for Barwon Heads and Greater Victoria ($P = 0.01$) (Box 4). Patients who resided in an endemic area had a shorter median time to diagnosis (1.0 week; IQR, 0.0–3.9 weeks) than those who resided in non-endemic areas (5.0 weeks; IQR, 1.3–8.0 weeks) ($P = 0.001$). There was a decrease in time elapsed for cases diagnosed later in the outbreak ($P = 0.23$) (Box 1).

Thirty patients were diagnosed with BU at the first consultation with their general practitioner. Alternative initial diagnoses included non-specific infection and spider bite; for 22 patients, no diagnosis was made at the first visit (Box 2). Thirty-seven patients reported a test was ordered for BU, and 40 patients had medication prescribed. More than three-quarters were prescribed non-antimycobacterial oral antibiotics; topical treatments were prescribed for the others.

DISCUSSION

In our series of patients with BU on the Bellarine Peninsula, 30% lived outside the endemic area. Previous research has highlighted the importance of increased awareness of BU symptoms in affected communities in reducing the delay in presentation to health care providers and reducing illness severity and treatment costs.^{9,14}

3 Time of symptom onset of Bairnsdale ulcer for 85 patients



The sine curve shows the seasonal periodicity. ♦

In this study, a delay of 2–6 weeks occurred from first symptoms to seeking medical treatment. This is similar to the elapsed time in southern Benin, where a national program aimed at improving the detection of BU reduced the time from 9 months to 1 month before patients sought medical attention.² Although BU still has a low profile in Australia, most residents on the Bellarine Peninsula have been made aware of it through DHS alerts between 2002 and 2006 (two residential alerts to Point Lonsdale and one to St Leonards, and six general alerts to GPs), and extensive media coverage in the regions. This is likely to have contributed to the comparative timeliness of presentation.

Although 60 patients first noticed a papule or small ulcer, most of these patients delayed seeking care until the lesion had deteriorated. It is possible that the painless nature, slow progression and misinterpretation of symptoms were the main reasons for not seeking medical attention sooner. Most patients were not diagnosed at the first consultation, and diagnosis took longer in those who resided outside the Bellarine Peninsula. It is likely that this delay resulted from low awareness in patients and doctors, especially outside the endemic regions. Time trends also suggest that BU was recognised more rapidly as the epidemic unfolded on the Bellarine Peninsula. These findings support the need to raise awareness in newly endemic areas, and to concentrate efforts on alerting those outside endemic areas.¹⁵

There has been a steady increase in the annual number of cases over the past 5 years, with new cases linked to Barwon Heads; this could indicate a continuing spread of the bacteria across the Bellarine Peninsula through a change in vector or environmental conditions. The month in which patients first noticed symptoms peaked in mid winter, although symptoms

occurred throughout the year. Thus, emphasis on awareness campaigns during winter may be warranted. Of note, the first seasonal rainfall peak on the Bellarine Peninsula, from April to May, closely precedes the peak incidence of BU.¹⁶ Rainfall events trigger increased mosquito activity, and there is increasing evidence that mosquito exposure may be linked to BU.^{17,18}

Our study was limited by the accuracy of patient recall. However, validation of the time elapsed from first symptoms to the doctor's diagnosis was aided by DHS notification dates and contemporaneous notes made by physicians. There is uncertainty regarding our estimated BU incidence, as the regional population varies greatly during the year, peaking during summer, and we cannot exclude misdiagnoses,¹⁹⁻²¹ or under-reporting of cases to the DHS. We also acknowledge the uncertainty of the incubation period derived based on three patients; incubation periods of 3 and 7 months have been reported elsewhere.²²

Our study confirms concern that BU patients who reside outside endemic areas present later for medical care and experience delayed medical diagnosis. As one-third of cases from the Bellarine Peninsula occurred in visitors, we recommend raising the profile of BU outside endemic regions.

COMPETING INTERESTS

None identified.

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4 Time to presentation and diagnosis for Bairnsdale ulcer

	Number	Median delay to presentation (IQR)*	Median delay to diagnosis (IQR)†
Site of permanent residence			
Point Lonsdale	40	3.0 (1.0–4.0)	1.0 (0.0–3.0)
St Leonards	7	5.0 (1.5–12)	1.0 (0.0–4.0)
Barwon Heads	5	3.5 (2.0–8.0)	5.0 (3.0–8.0)
Bellarine Peninsula (other)	9	2.0 (0.63–7.0)	1.8 (0.3–8.3)
Geelong	7	2.5 (1.5–10.0)	2.0 (0.0–8.0)
Greater Victoria	17	6.0 (2.0–9.0)	6.0 (2.0–8.5)
Sex			
Female	40	2.0 (1.0–4.0)	2.0 (0.0–8.0)
Male	45	4.0 (1.8–8.5)	2.0 (0.0–3.8)
Age			
< 60 years	32	4.3 (3.0–8.8)	3.3 (0.3–6.0)
≥ 60 years	53	2.0 (0.0–6.0)	1.0 (0.0–3.8)

*Weeks from onset of symptoms to first presentation to doctor. †Weeks from first presentation to doctor until diagnosis of Bairnsdale ulcer. ◆

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