

Sequelae of World War II: An Outbreak of Chronic Cutaneous Nontuberculous Mycobacterial Infection among Satowanese Islanders

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Background. After World War II, residents of Satowan (population, 650 persons), an outer island in the state of Chuuk, Federated States of Micronesia, noted a high prevalence of a chronic, progressive skin disease known locally as “spam.”

Methods. Island residents who had chronic, progressive verrucous or keloidal plaques for >3 months were considered case patients. Tissue specimens were obtained for culture, histopathological analysis, mycobacterial polymerase chain reaction (PCR), and comparison with the *hsp65* gene of *Mycobacterium marinum*. We performed a case-control study involving all cases and randomly selected control individuals from the community.

Results. A total of 39 case patients were identified, with a median age of 26.0 years (range, 8–82 years); 74.4% were male, and the mean duration of disease was 12.5 years. A total of 98 control individuals were enrolled. Results of all 19 mycobacterial tissue cultures were negative, and histopathological analysis of all 9 lesions showed suppurative granulomatous inflammation with negative results of mycobacterial and fungal stains. In 7 of 9 paraffin-embedded samples, nontuberculous mycobacterial DNA was detected by PCR, and 2 sequenced products had 95% and 87% identity to *M. marinum*. All case patients were taro farmers (odds ratio, undefined; $P < .01$), and among taro farmers, when the analysis was controlled for sex, contact with water-filled World War II-era bomb craters was associated with infection (odds ratio, 8.2; $P < .01$).

Conclusions. “Spam disease” is a chronic, progressive skin disease of high prevalence on Satowan and is associated with taro farming and contact with World War II-era bomb craters. Histopathological and PCR data demonstrate a nontuberculous mycobacterial infection as the cause.

In the summer of 2004, health officials from the Federated States of Micronesia reported an epidemic of a disfiguring skin disease affecting >10% of the inhabitants of Satowan (population, 650 persons). Satowan is an island in the state of Chuuk, Federated States of Micronesia, located on the southwestern tip of the Satowan atoll. According to health officials in Chuuk, residents had chronic, progressive, large, warty plaques,

primarily affecting the upper and lower limbs, and, in some cases, involving >50% of the surface area of the lower limbs. According to local inhabitants and health officials, the first cases of this mysterious skin affliction were noted shortly after World War II. Residents of nearby islands, including Ta, which is located less than one-half a mile away, were not affected. Local health officials referred to this condition as “island psoriasis,” and residents termed the condition “spam,” named after the processed food product that the skin lesions were said to resemble. Historical treatments were primarily surgical and often proved ineffective, resulting in disease recurrence and disfigurement. Although anecdotal reports point to the first cases emerging shortly after World War II, there had never been a formal investigation on the island.

Received 31 October 2008; accepted 22 January 2009; electronically published 30 April 2009.

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Clinical Infectious Diseases 2009;48:1541–6

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1058-4838/2009/4811-0007\$15.00

DOI: 10.1086/598928

In 2006, a 29-year-old man from Satowan presented to an indigent care clinic in Portland, Oregon, with an 18-year history of enlarging verrucous plaques on his left lower extremity that had developed while he was living on Satowan. Tissue culture demonstrated *Mycobacterium marinum*, identified by gas liquid chromatography (Sherlock Microbial Identification System; MIDI) [1], and treatment with doxycycline resulted in dramatic improvement [2]. As in previous reports from Chuuk health officials in 2004, he reported that numerous people on his native island had similar lesions. Through the Aloha Medical Mission, information regarding this case reached the Chuuk Director of Health who, in turn, formally invited our medical team to investigate further. Our objectives were to determine the cause of the skin disease epidemic, to identify the source of the infection, and if possible, to initiate epidemic control measures.

MATERIALS AND METHODS

Study design. Local health officials in Chuuk approved the study, and we obtained exemption from the Oregon Health and Sciences University institutional review board. We traveled to Satowan in June 2007 to evaluate residents with chronic skin disease. Local health officials asked residents of Satowan to come to an island medical care facility if they had the skin condition known locally as “spam.” We based our case definition on the morphology of the lesions in the index case treated in Portland, defining case patients as individuals who had verrucous or keloidal plaques on the upper or lower extremities that were >2 cm in size and had been present for >3 months. Verrucous or keloidal lesions readily identified as verruca vulgaris, keloids, or other common skin conditions were excluded.

During a 2-day period, we examined presenting patients and conducted a case-control study to examine risk factors for disease. We randomly selected population-based controls from the central island road at a school graduation ceremony attended by the entire island population. After the ceremony, consecutive individuals congregating outside the school were asked by local health officials to participate and were included if they reported no history of “spam” disease.

Exposure assessment. We administered a standardized questionnaire to collect basic demographic information, with the aid of trained interpreters and medical personnel. All case and control individuals were interviewed in person, and a full skin examination was performed. Because the tissue culture from the index case grew *M. marinum*, histories focused on aquatic exposures on the island. We asked participants about potential exposures to fresh water on the island, including taro fields, ponds, and streams. Local inhabitants reported that water-filled depressions in the center of the island were the result of bombing during World War II [3]. We used a laminated

satellite map to determine specific taro fields and bomb craters to which island residents were exposed. Oceanic exposure was not included in the questionnaire because it was ubiquitous. In addition, we collected information regarding underlying medical conditions and the presence of disease in family members.

Microbiological assessments. For discussion of microbiological assessments, see the Appendix (online only).

Statistical analyses. Case and control individuals underwent unmatched comparison. We performed univariate analysis to compare differences between cases and controls and calculated Mantel-Haenszel odds ratios (ORs), 95% confidence intervals (CIs), and Fisher’s exact *P* values (with the use of 2-sided tests), using EpiInfo, version 3.4.2 (Centers for Disease Control and Prevention). Variables that were found to have association with disease ($P < .20$) were included in a multivariate model, and backward stepwise logistic regression analysis was performed to evaluate the independent effect of each variable on the outcome of disease.

RESULTS

We evaluated 45 patients and identified 39 cases. Of the case patients, 29 (74%) were male, and the median age was 26.0 years (range, 8–82 years). We enrolled 98 control individuals. Case patients and control individuals were similar with regard to age (median age, 26.0 vs. 23.0 years; $P < .14$), but control individuals were more likely female (53% vs. 26%; $P < .01$).

Twenty-nine cases had only 1 affected region of the body, and the knee was the most frequently affected area (17 [44%] of 39 patients) (figure 1). Other areas of involvement included the ankle (9 [23%]), leg away from knee or ankle (12 [31%]), arm (7 [18%]), foot (9 [23%]), hand (7 [18%]), finger (4 [10%]), buttock (1 [3%]), and toe (2 [5%]). The mean length of time that lesions were present was 12.5 years (range, 3 months to 53 years). Most (95%) of the patients reported a history of a preceding cut or abrasion near the area of involvement. All patients were otherwise healthy; only 2 had underlying medical conditions (history of pulmonary tuberculosis and history of stroke). No case patients reported a history of leprosy or human immunodeficiency virus infection. Seven patients had been treated with short courses of oral antibiotics for their skin disease, and 3 patients had undergone surgery, but most patients had tried only topical treatment (antibiotic creams, oral antibiotics in coconut oil, bleach, lemon juice, or cigarette burns) or no treatment at all.

Risk factors for disease. All 39 case patients were taro farmers, compared with 73 (74%) of 98 control individuals (OR, undefined). Among taro farmers, swimming or bathing in water-filled World War II-era bomb craters (figure 2) was significantly associated with disease in 34 (87%) of case patients, compared with 28 (36%) of 78 control individuals reporting



Figure 1. Representative large verrucous plaque on the lower extremity of a Satowan resident.

contact with them (OR, 12.2; $P < .01$). Of the 25 control individuals who did not farm taro, only 1 (4%) had exposure to the bomb craters. Case patients were no more likely to have affected family members than were control individuals (OR, 1.04; $P < .49$) (table 1). In multivariate analysis controlled for sex and taro farming, swimming in water-filled World War II-era bomb craters remained significantly associated with skin disease (OR, 8.56; 95% CI, 2.7–26.4; $P < .01$).

Histopathological analysis and molecular results. Hematoxylin and eosin-stained tissue biopsy specimens from 9 case patients demonstrated pseudocarcinomatous hyperplasia of follicles with a dense nodular and perifollicular infiltrate of neutrophils and epithelioid histiocytes, dermal fibrosis, and collections of neutrophils within follicles, findings typical of mycobacterial and deep fungal infections [4]. For all biopsies, Fite and periodic acid–Schiff special stains were negative for organisms. The 19 tissue culture specimens obtained from the island investigation failed to grow organisms.

The 10 paraffin-embedded patient specimens were analyzed by polymerase chain reaction (PCR), including those from the culture-positive index case [2]. PCR products representing a specific 97–base pair (bp) region in the *hsp65* gene of *M. mar-*

inum were obtained using the MmarHSP1 and MmarHSP2 primers in 8 of 10 patient samples. These primers were specific to mycobacterial species other than *Mycobacterium tuberculosis* and *Mycobacterium leprae*. An ~97-bp band was visualized for our positive control (*M. marinum*), the index case, and 7 case patients. A band was not visualized for our negative control (sterile water), *M. tuberculosis*, and 2 of the case patients. The PCR products were further analyzed by DNA sequencing of both strands of the product. Of all PCR products, only those of the *M. marinum* positive control, the index case, and 2 case patients (patients 6 and 7) could be sequenced. These sequences were compared with all nonredundant sequences in GenBank by using BLAST searches. The PCR product from the culture-proven index case showed 100% sequence alignment with complete identity to the *M. marinum hsp65* sequence (GenBank accession number DQ985338.1). The sequences obtained for PCR products from case patients 6 and 7 were homologous to the *M. marinum hsp65* sequence, although the degree of identity was reduced. Direct comparisons with the DNA sequence of *M. marinum hsp65* revealed 95% identity for the PCR product from case patient 6 and 87% identity for the PCR product from case patient 7. Comparison with the *hsp65* gene of other species was also performed, including comparison with *Mycobacterium ulcerans hsp65*, which demonstrated 94% and 87% identity for the PCR products from case patients 6 and 7, respectively.

Of the 9 paraffin-embedded patient specimens evaluated by our laboratory, we chose the 3 with the densest neutrophilic infiltrate to be evaluated by the University of Arkansas for Medical Sciences. They confirmed that 2 of these 3 specimens were positive for nontuberculous mycobacteria, with use of primers that excluded *M. tuberculosis* and *M. leprae*. They did not attempt further speciation of the organism.

Response to therapy. We treated all affected Satowanese patients with doxycycline (100 mg twice a day), with a planned 3-month treatment course. Rifampin (100 mg twice a day) and doxycycline (100 mg twice a day) were provided to 6 patients with more-extensive disease. The response to treatment can be evaluated in only a few documented cases (figure 3), the dramatic initial response to therapy in the index case [1], and second-hand accounts from local health care workers, but it appears that patients with limited disease are showing dramatic improvement.

DISCUSSION

We investigated a 50-year epidemic of a disfiguring skin disease on the Micronesian island of Satowan that affected at least 6% of the local population and that is due to nontuberculous mycobacterial infection. The clinical appearance of these lesions closely resembles the morphology and disease course reported in 4 published cases of culture-proven *M. marinum* infection in Pacific Islanders [2, 5], including a recently described patient



Figure 2. World War II-era bomb crater lake

who developed lesions while living on Satowan [2]. Our case-control study demonstrated that exposure to water-filled World War II-era bomb craters and water-filled taro fields are significant risk factors for disease. Freshwater environments such as these are favorable to *M. marinum* and other related environmental mycobacterial growth. Although we were unable to obtain positive results of tissue culture, the histopathological analysis, PCR analysis, and DNA sequencing of PCR products were consistent with infection caused by nontuberculous mycobacteria.

Soon after World War II ended, residents of Satowan noted a high prevalence of a chronic, progressive skin disease known locally as “spam.” This skin disease resulted in a high degree of morbidity, because local islanders were unable to determine its cause and struggled to find adequate therapy. Many islanders resorted to disfiguring surgical procedures or painful, ineffective local therapies. Our investigation demonstrated a prevalence of at least 6% of the island population, and although these cutaneous lesions were not associated with reported systemic sequelae and the scarring did not result in contractures

or other functional impairment, they were locally destructive, disfiguring the skin, and their appearance has caused a high degree of morbidity in the community.

M. marinum infection typically presents as small nodules or plaques on the upper extremities after exposure of traumatized skin to an infectious source. It is generally treated with several months of antibiotic therapy [6, 7] and occasionally has been reported to resolve on its own. *M. marinum* typically causes disease in freshwater and saltwater fish and rarely causes disease in humans, except through aquatic exposure of traumatized skin [8, 9]. Chronic infection with *M. marinum* can form crusted ulcers, abscesses, or verrucous nodules [6, 7]. Although the large lesion size and chronic, progressive disease course described for many of the case patients are not the most common manifestation of *M. marinum* infection, the appearance is similar to that of 4 cases of *M. marinum* infection previously reported in Pacific Islanders [2, 4]. Long-standing, untreated disease might explain the unusual clinical presentation, for which medically underserved Pacific Islanders are at particular risk. It also may be a result of chronic environmental exposure,

Table 1. Reported island water exposures and family history of disease among case patients and control individuals.

Factor	No. (%) of case patients	No. (%) of control individuals	OR (95% CI)	P
Bomb crater exposure	34 (87)	28/78 (36)	12.2 (4.3–35.6)	<.01
Taro farming	39 (100)	73 (74)	Undefined	<.01
Family history of disease	12 (31)	28 (29)	1.09 (0.49–2.5)	<.49

NOTE. CI, confidence interval; OR, odds ratio.



Figure 3. Clinical appearance before treatment (A), after 3 months of treatment with doxycycline (100 mg twice a day) (B), and at 9 months after treatment (C).

an underlying altered immune response to mycobacterial infection, coinfection with another organism that we were unable to identify, and/or a particularly virulent strain of *M. marinum* or other nontuberculous mycobacteria. These cases from Satowan demonstrate an aquatic exposure history typical of *M. marinum* infection. Nearly all of the case patients reported swimming in water-filled bomb craters or working in the taro fields with existing cuts or abrasions near the areas of skin disease. These bomb craters collect stagnant rainwater and are filled with small medaka fish (*Oryzias latipes*), which were introduced by the Japanese during World War II to decrease mosquito populations. This species is known to tolerate chronic infection with *M. marinum* [10]. The taro fields typically have standing water that reaches ankle height. When harvesting taro, islanders either squat down or kneel with their hands, feet, or knees in contact with stagnant water. Among the 5 case patients who did not report a history of exposure to the bomb craters, there was 1 case that involved a finger, and all others had involvement of the lower extremities, body areas in contact with stagnant water during taro field work.

We were unable to definitively identify *M. marinum* in the tissue samples obtained from case patients on Satowan. The negative results of tissue cultures may be explained by the 5-day interval between collection of the tissue and plating the culture or by the fact that the tissue samples may have been inadvertently stored at suboptimal temperatures on our return trip. Histopathological findings were consistent with nontuberculous mycobacterial or deep fungal infection [4]. The inability to identify organisms in acid-fast bacilli–stained sections is not unusual in nontuberculous mycobacterial cutaneous infection, because acid-fast bacilli stain has poor sensitivity for this use [11]. Of note, most deep fungal infections have readily identifiable organisms on sections stained with periodic acid–Schiff stain.

PCR was performed in an attempt to demonstrate nontuberculous mycobacterial DNA and to evaluate DNA sequence homology to known *M. marinum* organisms. PCR analyses

demonstrated positive results for 8 of 10 specimens, including the specimen from the index case, with specificity only for nontuberculous mycobacteria. This was corroborated by an outside laboratory that performed PCR on 3 of the tissue samples. Because of the poor quality of the DNA in the paraffin-embedded specimens from Satowan, only PCR products from patients 6 and 7 could be sequenced. Of note, the paraffin-embedded sections from Satowan were in formalin for >1 week before being embedded, compared with the index case, for which the section was embedded within 1 day. This may explain the negative results of PCR for 2 of the patients and the difficulty in DNA sequencing for PCR-positive cases. Another possibility is that nontuberculous mycobacteria organisms other than *M. marinum* were causing disease in some individuals, because these sequence data are not adequate to differentiate between many related nontuberculous mycobacterial species.

Other nontuberculous mycobacteria considered include *M. ulcerans*, an emerging infectious organism acquired from water sources that is genetically similar to *M. marinum* [12]. Although our microbiological assessment and epidemiological findings are insufficient to rule out *M. ulcerans*, the morphology of the chronic lesions and their response to antibiotic therapy more closely resemble *M. marinum* infection. Chronic *M. marinum* infection causes verrucous-appearing papules and plaques, whereas chronic *M. ulcerans* infection causes progressively expanding noninflammatory ulcers [13]. Furthermore, chronic *M. ulcerans* lesions respond poorly to antibiotic therapy [13], whereas chronic *M. marinum* lesions frequently respond well. Although these chronic verrucous plaques that have shown response to antibiotic therapy more closely resemble *M. marinum* than *M. ulcerans* infection, molecular analyses using fresh tissue, repeated tissue cultures, or environmental samples are needed to address this issue more definitively.

Further clinical follow-up is needed to fully assess the response to treatment and to document other cases on Satowan and other surrounding islands. It is encouraging to see patients

with limited disease demonstrating prolonged clearance while receiving monotherapy, but a more formal evaluation will help determine whether dual therapy is a more effective approach. A more thorough evaluation of the extent of disease is also needed. Local health officials report that word of treatment success has led to the identification of more cases on the island; thus, the prevalence of “spam” on Satowan is likely higher than what we documented. In addition, since our visit, officials in Houk, one of the westernmost outer islands in Chuuk, have reported a high prevalence of a skin condition with similar appearance.

Beyond treatment of affected individuals, we also made recommendations for prevention of additional infections. Most of the infections were on the lower extremities, areas that are prone to trauma and that would come into contact with standing water while harvesting taro. Although we cannot limit their exposure to the taro fields, because taro is a major food source, we have recommended that individuals refrain from standing in areas where there is stagnant water, especially when they have abraded or lacerated skin. We also recommended that island residents do not swim or bathe in the water-filled bomb craters in the center of the island, encouraged islanders to seek medical attention when lesions are small, and trained local health care workers in the detection and treatment of early infection.

In summary, we have identified an epidemic of a chronic, progressive cutaneous infection affecting a large percentage of the Satowanese population that is due to nontuberculous mycobacterial infection. Swimming and bathing in the stagnant water of bomb craters created by Allied bombing during World War II [3] appears to be the strongest risk factor for infection. To our knowledge, this is the only infectious disease outbreak currently in existence that can be considered a sequelae of World War II. Taro farming, an activity in which extremities can be submerged in standing water for hours, may also be another important risk factor. Doxycycline has been shown to be effective for treatment of cases with limited skin involvement, but dual therapy may be needed for those with more-extensive disease [2]. Further microbiological assessment of these lesions is needed to definitively identify the causative nontuberculous mycobacterial organism. With intervention and therapy, we suspect that mitigation of this significant public health problem on Satowan is possible.

Acknowledgments

We thank Dr. Edward Desmond, Dr. Michael Yarkus, and the state of California Department of Health Services mycobacterial laboratory, as well as the Department of Molecular Diagnostics, Pathology, and Laboratory Medicine Service at the John L. McClellan Memorial Veterans Hospital in association with the laboratory of Dr. K. Eisenach at the University of Arkansas for Medical Sciences (Little Rock), for their assistance in the investigation. We also thank the Aloha Medical Mission for their help in providing treatment for affected individuals.

Financial support. K.L.W.’s work was funded by the Agency for Healthcare Research and Quality (grant 1K08HS017552-01).

Potential conflicts of interest. All authors: no conflicts.

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