Journal of Infection (2005) **50**, 375–381

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REVIEW

Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature

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Accepted 31 August 2004
Available online 2 October 2004

KEYWORDS
Scabies;
Crusted scabies;
Infection;
Immunological factors;
Mortality;
T-cell subsets;
Indigenous;
Australia;
Leprosy

Abstract *Objectives*. To describe the clinical and immunological features of crusted scabies in a prospectively ascertained cohort of 78 patients.

Methods. All patients requiring inpatient treatment for crusted scabies in the 'top end' of the northern territory of Australia over a 10 year period were prospectively identified. Demographics, risk factors, and immunological parameters were retrospectively compiled from their medical records and pathology databases.

Results. More than half the patients with crusted scabies had identifiable immunosuppressive risk factors. Eosinophilia and elevated IgE levels occurred in 58% and 96% of patients, respectively, with median IgE levels 17 times the upper limit of normal. Seventeen percent had a history of leprosy but 42% had no identifiable risk factors. There was a decrease in mortality after the introduction of a treatment protocol consisting of multiple doses of ivermectin combined with topical scabicides and keratolytic therapy.

Conclusions. Crusted scabies often occurs in patients with identifiable immunosuppressive risk factors. In patients without such risk factors, it is possible that the crusted response to infection results from a tendency to preferentially mount a Th2 response. The treatment regime described was associated with a reduction in mortality. This is the largest reported case series of crusted scabies.

Summary

Crusted or Norwegian scabies is rare and is usually associated with underlying immunodeficiency. It results from hyper-infestation following infection with *Sarcoptes scabiei* and historically had a 5 year

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doi:10.1016/j.jinf.2004.08.033

mortality rate of up to 50%. The clinical and immunological features of a series of 78 prospectively identified patients over a 10 year period are described from northern Australia and compared with the literature. Immunosuppressive risk factors were identified in over half. Eosinophilia and elevated IgE levels occurred in 58% and 96% of patients, respectively, with median IgE levels 17 times the upper limit of normal. Seventeen percent had a history of leprosy but 42% had no identifiable risk factors; a tendency to mount a Th2 response may underlie the apparent pre-disposition to develop crusted scabies. Our treatment protocol consisting of topical scabicides and keratolytic therapy, together with multiple doses of systemic ivermectin has been associated with decreased mortality.

Introduction

Crusted or Norwegian scabies was first described in a group of Norwegian leprosy patients by Boeck and Danielssen in 1848.[1] It is an uncommon variant of scabies,[2,3] and has a mortality rate of up to 50% over 5 years.[4] Although scabies is unusual in urban Australia, it is currently endemic in remote northern and central Australian Aboriginal communities where up to 50% of children may be infested.[5] Rates of crusted scabies in these communities are amongst the highest in the world.[6] Treatment for crusted scabies requires prolonged isolation in hospital with combination topical and oral anti-parasitic therapy.[2] Despite this, re-infection is frequent and relapses have been documented.[6,7]

Crusted scabies results from a failure of the host immune response to control the proliferation of the scabies mite in the skin, with resulting hyper-infestation and a concomitant inflammatory and hyper-keratotic reaction. There are a number of predisposing conditions associated with crusted scabies.[3] These include diseases that alter T-cell function such as HIV,[8-10] HTLV-I,[11] T-cell lymphoma and leukaemia,[12] and moderate immunosuppression used in transplant recipients.[13,14] Systemic lupus erythematosus,[15] rheumatoid arthritis, diabetes, malnutrition, and various neuropathies have also been associated.[16,17] However, crusted scabies has also been recognised in people with no evident immunological deficit.[18,19] We present data on the 78 patients diagnosed with crusted scabies at Royal Darwin Hospital over a 10 year period and compare our findings with previous reports.

Methods

Cases

The tropical 'top end' of the northern territory of Australia has a population of approx. 140 000 in an area of 516 945 km^2. Around 24% of the population are indigenous (Aboriginal) Australians, many of whom live in small remote communities. Royal Darwin Hospital is the 300 bed referral hospital for the region. All patients in the top end of the northern territory requiring in-hospital treatment for crusted scabies over the 10 year period January 1991 through December 2000 were included. The diagnosis of crusted scabies was based on the presence of typical skin lesions (Figs. 1 and 2), confirmation of scabies mites, and response to anti-scabies treatment regimes.

The scabies mites were collected from patients via gentle skin scrapings using a scalpel blade. Scrapings were analysed using a dissecting light microscope ($\times$100–160) and counts were considered high if 10 or more mites were observed.

Identification of cases was prospective. Their names were recorded in a dedicated database as they presented to hospital. Additional data such as the demographics, immunosuppressive risk factors, and immune parameters were compiled retrospectively from patient medical histories. This analysis is part of a larger study investigating crusted scabies, with approval given by the Human Research Ethics Committee of NT Department of Health and Community Services and Menzies School of Health Research, Approval No 99/50.

Analysis

Immunological tests were performed by the pathology service at the Royal Darwin Hospital using internationally accepted testing standards.

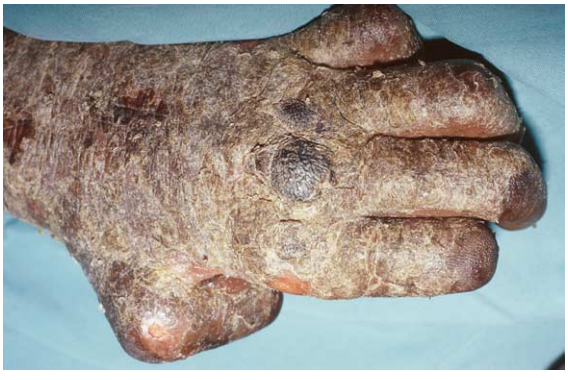

Figure 1 Crusted scabies in a patient with claw hand from past leprosy.

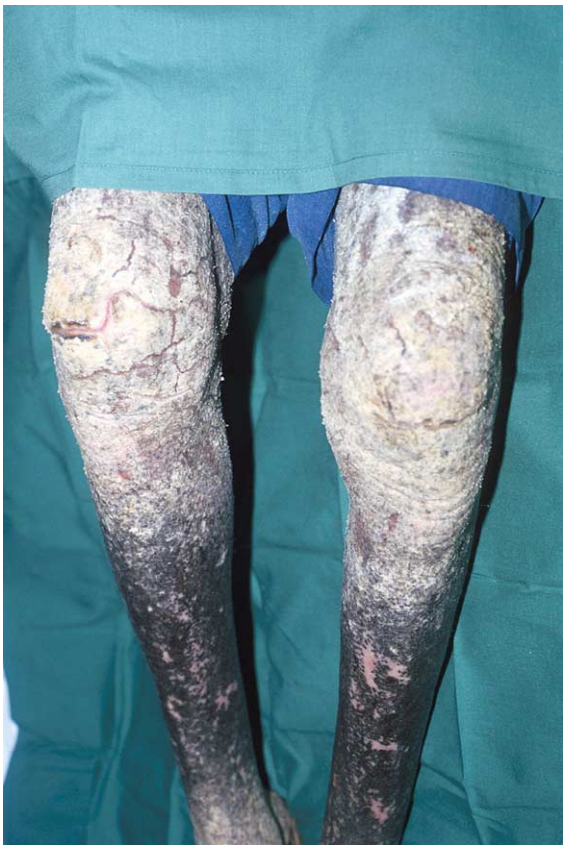

Figure 2 Crusted scabies in a patient with no overt immunosuppressive illness.

Reference ranges reported are based on the 95% normal range.

Results

Seventy-eight patients with crusted scabies from the top end of the northern territory were identified and treated over the 10 years (Table 1). There were only two children, aged 1 month and 15 years. Disease was otherwise spread evenly across the adult years, with the mean age being 43 years and the oldest patient 76 years of age (Fig. 3). All but 2 patients were indigenous Australians from remote Aboriginal communities. High mite counts were demonstrated by light microscopy in 71% of patients.

Immunosuppressive risk factors were divided into definite and possible based on their known association with impaired cell-mediated immunity (Table 2). Possible risk factors were identified in over half the patients and definite risk factors in over one quarter (Table 1). The most common possible risk factors were heavy alcohol use, past leprosy (Fig. 1), and heavy kava use. The more common definite risk factors were diabetes mellitus, and immunosuppression associated with renal transplants. Three patients were seropositive for HTLV-I. Of note, no patient was infected with HIV. Overall 33 patients (42%) had no identifiable risk factor and except for their skin disease these individuals appeared healthy (Fig. 2).

Table 1 Demographics of people with crusted scabies

Demographic features and death rates	
Number of cases	78
Mean age	43
Year of presentation (range)	1991–2000
High mite count confirmed	71%
Definite immunosuppressive risk factor	26%
Possible immunosuppressive risk factor	60%
Indigenous	97%
Annual death rate prior to 1997[a]	4.3%
Annual death rate from 1997	1.6%

[a] Rates of death directly attributable to crusted scabies are shown before and after the routine use of ivermectin during 1996. This difference is significant $p=0.02$, Fisher Exact test.

The annual rate of death in the years prior 1997 was 4.3% (8 patients died out of 31 over 6 years) and fell to 1.1% (3 patients died out of 47 over 4 years) in the years from 1997 onward ($p=0.02$, Fisher exact test) (Table 1). This substantial difference in death rates corresponds to the commencement of the use of multiple dose ivermectin in the treatment of all patients with crusted scabies since mid 1996, together with a protocol for early empirical broad spectrum antibiotic cover for suspected secondary sepsis.

Various measures demonstrated markedly altered immune function in many of the patients with crusted scabies (Table 3). Most patients had

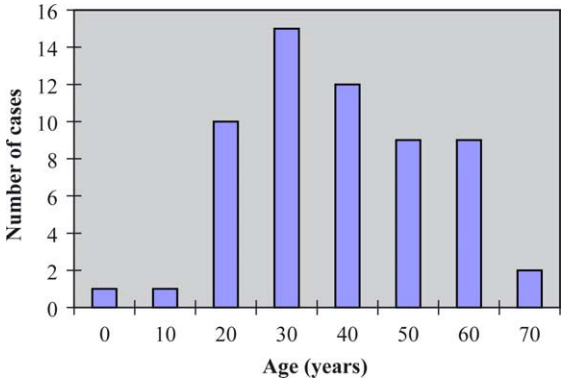

Figure 3 Age distribution of patients with crusted scabies.

Table 2 Potential risk factors leading to an immunosuppressed state in patients with crusted scabies

Immunosuppressive risk factor	Frequency
Heavy ethanol use	17
Past leprosy	13
Heavy kava use	8
Type 2 diabetes mellitus[a]	8
Malnutrition	5
Hepatic cirrhosis	5
Renal transplant immunosuppression[a]	4
Systemic lupus erythematosus[a]	3
Chronic hepatitis B infection	3
Renal dialysis[a]	2
Hypothyroidism	2
Mixed connective tissue disease[a]	2
Syphilis	2
Behcet's disease[a]	1
Scleroderma[a]	1
Chronic Myelogenous Leukemia[a]	1
Chronic petrol inhalation	1
Sturge-Weber Syndrome[a]	1
HTLV-I infection	3
HIV infection	0
No risk factor identified	33 (42%)[b]

Some patients had more than one risk factor.
[a] Definite immunosuppressive risk factor as described in Table 1.
[b] Percentage of patients without an identifiable risk factor.

elevated levels of circulating antibodies of the IgG (96%), IgA (64%), and IgE (96%) subclasses. Most dramatic were the elevated IgE levels, with 38/52 (73%) over 1000 mcg/l (10 times the upper limit of normal), 5/52 (10%) over 10 000 mcg/l and the highest being 217 260 mcg/l in a patient with especially, severe crusted scabies (Fig. 4). Overall 34/59 (58%) had an eosinophilia and in all these cases the eosinophil level was above 1.0×10^9/l, with 7/59 (12%) over 7.0×10^9/l (10 times the upper limit of normal) and the highest being 13.0×10^9/l.

Anti-nuclear antibodies (ANA) were common in these patients with crusted scabies. Twenty eight percent had low titres (40–320), and an additional 13% of patients had titres of 640 or greater. In many patients levels of complement components C3 and/or C4 were also low (Table 3). There was no difference in complement levels between ANA positive and ANA negative groups ($p>0.05$ for C3 and C4, *t*-test). Although $CD4^+$ lymphocytes were reduced in a minority, $CD4^+/CD8^+$ ratios were within normal limits in those tested (data not shown).

Discussion

This is the largest reported case series of crusted scabies. Although these 78 cases over 10 years represent an overall prevalence of less than 0.1%, crusted scabies in northern Australia is almost unique to the Aboriginal population in which the prevalence is higher. Crusted scabies is associated with substantial morbidity and stigma related to the debilitating skin condition. It has also been associated with high mortality, either from secondary sepsis or from the underlying predisposing condition present in many patients. Furthermore, we have

Table 3 Markers of immune function in patients with crusted scabies

Immune parameter	Normal range[a]	Frequency of cases outside[b] normal range (%)	Number tested	Range	Median
IgG	6.3–13.5 g/l	96	56	6–64	33
IgA	0.5–3.12 g/l	64	56	0.8–33	3.9
IgM	0.52–3.34 g/l	11	56	0.37–4	1.3
IgE	0–100 mcg/l	96	52	1.34–217 260	1700
Eosinophils	$0.04–0.7\times10^9$/l	58	59	0.02–13	1.6
C3[c]	0.86–1.84	29	58	0.39–1.55	1.04
C4[c]	0.2–0.59	45	58	0.09–0.48	0.21
C3 and C4 low		22			
CD4[c]	$0.41–2.21\times10^9$/l	13	40	0.30–3.2	0.61
CD8	$0.17–1.33\times10^9$/l	3	40	0.18–3.4	0.56
ANA titre	1:80–1:320	28			
ANA titre	>1:320	13			

[a] 95% normal reference range for the top end population.
[b] The frequency of cases with values above the normal range is shown unless indicated.
[c] The frequency of cases with values below the normal range is shown.

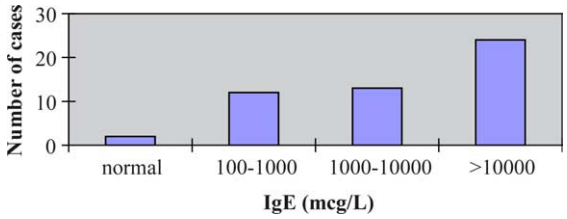

Figure 4 IgE levels in patients with crusted scabies.

identified patients with crusted scabies as 'core transmitters' in the ongoing scabies epidemic cycles in remote Aboriginal communities in northern Australia.[5] This is not surprising, given the enormous mite burden in these individuals. In one of our patients in this series we previously estimated there were 4700 *S. scabiei* mites per gram of crusted skin, making a total skin burden of over a million mites.[20] This is analogous to the increasingly recognised scenario of elderly residents of nursing homes with undiagnosed crusted scabies being responsible for institution wide outbreaks.[21,22]

The strengths of this study lie in unique conditions that the top end offers for studying serious illness in populations. Migration to and from the region is low. Cases of crusted scabies are routinely referred to the only tertiary referral hospital in the region, which is in Darwin. These characteristics minimized inter-observer bias, minimized the number of cases that would be missed, and facilitated careful follow up. While we have prospectively identified all the patients diagnosed with confirmed crusted scabies in the region and have accurate information on their demographics and outcomes, analysis of laboratory parameters reported here was performed retrospectively and information was not available on the entire cohort. However, no selection bias was evident in missing results and overall data are still likely to accurately reflect those of crusted scabies patients in our setting.

There are a variety of risk factors for crusted scabies described in previous studies and corroborated here. Many of these presumably confer their risk by impairing the cell-mediated immune response. In the normal situation, an individual mounts a cell-mediated immune response to salivary antigens secreted by the scabies mite during its feeding. This acquired immunity, although not absolute, limits the spread of the mites preventing overwhelming infestation.[23-25] It is presumably an impairment of the cell-mediated immune response that allows the hyper-infestation of crusted scabies to develop in the conditions described above.[26] Consistent with this, crusted scabies is being increasingly recognised in those infected with HIV.[2,10]

Crusted scabies also occasionally occurs in malnutrition, in Down's syndrome, in the elderly and institutionalized and in those with cognitive deficiency or physical debility who are unable to properly interpret or respond to the itch by scratching.[3,21,22] Interestingly, susceptibility to scabies has been linked to HLA-A11 in two studies[27,28] though has not been previously shown to be associated with a racial group.[25] As previously recognised[19,20] a considerable number of the patients in our study are indigenous Australians who do not have any of the traditional risk factors associated with susceptibility to scabies. We have hypothesized that such patients may have a specific immune deficit predisposing them to hyper-infestation.[29]

Interestingly, a major risk factor in this study was a past history of leprosy, which was found in 17% of patients and is an historically recognised association.[1] Susceptibility to lepromatous leprosy has been shown to relate to a Th2 type of T helper immune response.[30-32] This group of patients may therefore represent natural Th2 type responders rendering them susceptible to both leprosy and crusted scabies. It is further possible that a similar immune mechanism accounts for the 42% of patients without identifiable risk factors in our study.

Crude measures of immune function such as antibody levels, T cell numbers, and complement levels, did not yield any specific immunological diagnoses. The massive antibody response is not surprising given the antigenic load imparted by the scabies infestation. The IgE levels are especially high in the patients reported here (Fig. 4) and are likely to reflect the aberrant immune response. Clearly this IgE response is not effective at clearing *S. scabiei* parasites. The low complement levels are more difficult to explain since a large inflammatory response would usually produce hyper-complementaemia. Importantly, hypo-complementaemia did not correlate with ANA positivity. No patients were HIV positive and three had HTLV-I infection, although this has been recognised as a more common risk factor for crusted scabies in Australian Aboriginal communities further south in central Australia.[11] The association between HTLV-I and scabies has also been seen in Dominica[33] and Brazil.[34] The top end of the northern territory is not endemic for HTLV-I.[35]

Preliminary studies on cytokine production using RNase-protection assays on mRNA obtained from fresh PBMC collected from a subset of the described crusted scabies patients, demonstrated a statistically significant elevation of IL-4 in crusted scabies (data not shown). That elevated IL-4

production is observed in unstimulated PBMC is similar to the highly Th2-polarised immune response seen in atopic dermatitis.[36] Perhaps not only is the Th2 response ineffective at removing the mite infestation, but the IL-4 produced in this response may contribute to the hyper-proliferative skin disease characteristic of crusted scabies. It has been shown that IL-4 can stimulate keratinocyte proliferation,[37] that epidermal cells have IL-4 receptors, and that IL-4R expression is elevated in psoriasis, a disease with some clinical similarities to crusted scabies.[38]

ANA positivity was over-represented in our patients with crusted scabies. ANA positivity and systemic lupus erythematosis has been shown previously to be more common in the indigenous population in this region,[39] however, the rates of low and high ANA titres of 28% and 13%, respectively, are even greater than reported in the general indigenous population. This may represent a group of people at risk of connective tissue diseases with the coexisting altered immune state making them susceptible to crusted scabies. Alternatively, it may simply reflect a non-specific anti-nuclear antibody response due to the massive antibody production during scabies infestation.

There are currently no documented studies on scabietic patients' in vitro T-cell responses to scabies mite antigens. Interestingly limited immunohistology studies on two of the crusted scabies patients suggest the inflammatory skin response comprises predominantly $CD8^+$ T-cells (Currie, B., Bradley, J., Beroukas, D., Roberts-Thomson, P. and Walton, S.F., unpublished observations). The proportion of lymphocytes in the blood of scabietic patients and the T-cell subsets were normal. The ratio of T-cells to B-cells was greater in infiltrates than peripheral blood suggesting a selective movement of T-cells into the dermis and signifying their role in a cell-mediated response to scabies.

The treatment of crusted scabies is difficult, often requiring a prolonged hospital admission. Septicaemia is a common complication and is frequently polymicrobial. It should be anticipated and aggressively treated with broad-spectrum antibiotics. Specific treatment for crusted scabies consists of topical scabicides and systemic ivermectin, together with keratolytic therapy.[2,6] Ivermectin was first used in our patients in 1992,[4] following its successful use in animals with sarcoptic mange, and its use in humans since the mid 1980s for *Onchocerca volvulus*, *Wuchereria bancrofti*, and other parasitic infections.[40] However, with single dose ivermectin treatment failure or early recrudescence is common and multiple doses are usually required to achieve a cure.[6] Molecular genotyping studies of mites showed evidence that in severe crusted scabies treatment with even three doses of ivermectin 14 days apart may be inadequate to prevent relapse.[7] The importance of concomitant keratolytic therapy and topical scabicides to kill mites in the thick crusts has also been emphasised.[2,3,6] Concerns that a 2 weekly dosing interval can be inadequate resulted in modifications of our protocol for crusted scabies. We now use a five dose regimen with doses (200 μg/kg) on days 1, 2, 8, 9, 15, with an additional two doses on days 22 and 29 for the most severe cases. We attribute the significant decrease in mortality in crusted scabies over the period of our study to our more intensive ivermectin use together with a protocol for early use of antibiotics in suspected secondary bacterial sepsis.

In conclusion, crusted scabies remains a debilitating condition with potentially high mortality. While many patients with crusted scabies have a clear underlying immunosuppressive condition, ongoing research on the cohort of indigenous Australians with recurrent crusted scabies who have no apparent immunodeficiency may help elucidate the possible immunological basis for their susceptibility. These studies in combination with recent molecular approaches including the development of *S. scabiei* cDNA libraries provide the potential for novel immunotherapy strategies. Further studies are required to define optimal ivermectin dose, dose numbers and dosing intervals for treating crusted scabies of varying degrees of severity.

Acknowledgements

We are indebted to our medical and nursing colleagues at Royal Darwin Hospital, including Gabriel O'Kane, Alison Bucklar, Daniel O'Brien, Adam Jenney, Julian Elliott, Mark Douglas, Marilyn Hassell, Josh Davis, Anna Ralph, Emma Spencer, Dale Fisher, Nick Anstey and Ric Price for meticulous patient care and assistance with these studies.

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