

New insights into disease pathogenesis in crusted (Norwegian) scabies: the skin immune response in crusted scabies

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Summary

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Conflicts of interest

None declared.

Authors' contributions

S.F.W. participated in the design and coordination of the study, analysis of results and drafted the manuscript. D.B. carried out the immunohistochemical assays, undertook the microscopy and participated in drafting the manuscript. P.R.-T. participated in the design of the study and analysis of results. B.J.C. conceived the study, collection of the samples and coordination. All authors read and approved the final manuscript.

Background Crusted scabies is a rare and severely debilitating disease characterized by infestation of the skin with up to millions of *Sarcoptes scabiei* mites, high total IgG levels, extremely high total IgE levels, and the development of hyperkeratotic skin crusts that may be loose, scaly and flaky or thick and adherent.

Objectives To describe crusted scabies skin pathogenesis and identify markers associated with an inappropriate immune response leading to disease progression.

Patients/methods Serial sections from skin biopsies obtained from two patients with severe crusted scabies were examined by immunohistochemistry for cell surface markers and inflammatory and regulatory cytokines. Concurrent levels of total B- and T-cell subsets and IgE, IgA, IgM, IgG and IgG subclasses were analysed in the blood. In addition antibody levels were recorded in a further 33 patients with crusted scabies and 14 patients with ordinary scabies.

Results A predomination of infiltrating CD8+ T lymphocytes in the dermis was observed compared with minimal helper T lymphocytes (CD4+) and the absence of any B cells. The proportion of T and B lymphocytes and T-cell subsets in the blood of these patients were within normal ranges, indicating a selective movement of CD8+ T cells into the dermis. Furthermore, strong staining for the inflammatory cytokine interleukin-1 β and anti-inflammatory cytokine transforming growth factor- β 1 was observed. Elevated levels of IgE, IgG, IgG1, IgG3 and IgG4 were recorded.

Conclusions Skin-homing cytotoxic T cells contribute to an imbalanced inflammatory response in the dermis of crusted scabies lesional skin. This, in combination with the lack of B cells, is contributing to the failure of the skin immune system to mount an effective response resulting in uncontrolled growth of the parasite.

Scabies is an inflammatory disease of the skin caused by the burrowing 'itch' mite *Sarcoptes scabiei*. A spectrum of disease is described ranging from the most commonly recognized ordinary scabies with an average infestation of 10–15 mites per person to a rare and severely debilitating form of the disease termed crusted (Norwegian) scabies, characterized by infestation of up to millions of mites and the development of hyperkeratotic skin crusts.¹ Crusted scabies is caused by the same variety of mite that causes typical scabies, but with more extensive distribution of mites over the body including neck, scalp, face and under the nails. We have previously reported up to 4700 mites g⁻¹ of skin.² Fissuring and secondary bacte-

rial skin lesions are common and regional lymphadenopathy is frequently present. Secondary bacterial sepsis historically resulted in a high case fatality rate.³ Due to the extreme burden of mites crusted scabies is much more infectious than uncomplicated scabies, with infectivity that persists for longer because of the difficulty in eradicating mites from heavily crusted skin. Local outbreaks of uncomplicated scabies can originate from single, often unrecognized, cases of crusted scabies, as is increasingly documented in nursing homes.⁴

To understand more clearly the pathogenesis of crusted scabies and facilitate improved treatment options an understanding of the immune response mechanisms to scabies mites is

essential. Progression from ordinary scabies to crusted scabies is uncommon. Susceptibility to crusted scabies has been linked with immunosuppression, infection with human immunodeficiency virus (HIV) and human T-lymphotrophic virus type I (HTLV-1).^{5,6} However, it has also been associated with previously treated leprosy, substance abuse, systemic lupus erythematosus, pulmonary tuberculosis, diabetes mellitus and hepatitis B.⁷ Importantly, crusted scabies has also been recognized in people with no known immunological deficit^{2,8} and clustering in families suggests there may be important genetic components to the disease.

To date cell-mediated host immune responses in scabies have been identified primarily by histopathological examination of skin biopsies from scabietic lesions in ordinary scabies and the pathogenesis of crusted scabies has not been fully elucidated. In ordinary scabies, mite burrows are surrounded by inflammatory cell infiltrates comprising eosinophils, lymphocytes and histiocytes. The primary pathophysiological features described for crusted scabies are hyperproliferation of the epidermis, proliferation and hyperpermeability of the dermal vasculature, and an inflammatory cell infiltrate consisting of inflammatory T lymphocytes and eosinophils. The major goal of this study was to further clarify, by immunohistochemical analysis, the predominant lymphoid cells and inflammatory cytokines involved in inflammatory skin of crusted scabietic lesions. A secondary goal was to analyse levels of concordant T and B lymphocytes in the blood and levels of systemic antibody classes and subclasses in these patients.

Methods

Ethical approval

Ethical approval to undertake these studies was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Community Services and the Menzies School of Health Research (Approvals 97/21 and 99/50).

Subjects

Two Australian Aboriginal patients (both male; 27 and 44 years of age) presented to the Royal Darwin Hospital with severe crusted scabies involving hands and feet, thighs, trunk and buttocks (Fig. 1). Both study participants had a history of recurrent severe crusted scabies with no overt immunosuppressive illness. Both were negative for HIV and HTLV-1 serology. Informed consent was obtained and two, 3-mm elliptical, scalpel skin biopsies were obtained from each patient; one piece was immersed in Michel's transport medium for frozen sections and the other piece in 10% neutral buffered formalin for paraffin sections. B and T lymphocytes and T-cell subsets in the blood were determined as well as total serum immunoglobulin levels for IgM, IgE, IgG and IgA. Each patient was treated with topical acaricides and keratolytic therapy, together with multiple doses of oral ivermectin



Fig 1. Crusted scabies.

according to the crusted scabies protocol developed at Royal Darwin Hospital.⁸ On discharge both had no clinical or microscopic evidence of scabies.

A further 33 indigenous Australians with crusted scabies admitted to Royal Darwin Hospital for treatment gave informed consent for blood collection and were tested for total IgE levels. Seven of these patients, including the two patients consenting for skin biopsy analysis, were tested for IgG subclasses. Finally, informed consent was obtained and blood collected for total IgE levels from 14 indigenous and nonindigenous patients with ordinary scabies recruited from the Darwin region.

Immunohistochemical localization on formalin–paraffin-embedded tissue

Indirect immunoperoxidase methods were used to detect the type of lymphocytic and cytokine expression in the formalin–paraffin-embedded tissue samples. Serial 4-µm thick sections were cut and dried onto 2% Histogrip (Zymed Laboratories Inc., South San Francisco, CA, U.S.A.) coated slides overnight on a 37 °C hotplate. Sections were deparaffinized in xylene, rehydrated through descending grades of ethyl alcohol to water and/or Tris-buffered saline (TBS) pH 7.4. Depending on the primary antibodies being used, microwave antigen

retrieval techniques in a citrate buffer pH 6.0 was used to unmask epitopes for antihuman CD45 (T&B cell and polymorphs; Zymed Laboratories, 1 : 10), CD45RO (cellular activation; Dako Australia Pty Ltd, Botony, NSW, Australia, 1 : 10), CD3 (T-lymphocytes; Cell Marque, Austin, TX, U.S.A., 1 : 300), CD4 (inflammatory, helper T-cell subsets; Novacastra Laboratories Ltd, Newcastle upon Tyne, U.K., 1 : 20), CD8 (cytotoxic T-cell subsets; Novacastra Laboratories Ltd, 1 : 20), CD20 (B-cell subsets; Cell Marque, 1 : 200) and mac387 (macrophage marker; Dako Australia Pty Ltd, 1 : 100). For antihuman inflammatory cytokines Proteinase K (Boehringer Mannheim, Mannheim, Germany) was used at 20 µg mL⁻¹ in 10 mmol L⁻¹ Tris-HCl for 15 min at room temperature (RT) for tumour necrosis factor (TNF)-α (Monosan, Uden, the Netherlands; IgG1, 1 : 75), interleukin (IL)-1β (Immuno-Kontakt, Lugano, Switzerland; clone 12E9, IgM, 1 : 4000), and the regulatory cytokines, IL-1-receptor antagonist protein (IRAP) (Upjohn, Kalamazoo, MI, U.S.A.; clone 1.4, IgG1, 1 : 30), transforming growth factor (TGF)-β (R&D Systems Inc., Minneapolis, MN, U.S.A., 1 : 80), IL-10 (Genzyme Diagnostics, West Malling, Kent, U.K., 1 : 8) and an isotype-specific negative control antibody X63 (FMC cell line, neat) were all diluted in 1% Protein Block Serum-Free (PBSF; Dako Australia Pty Ltd), 0.1% Tween 20, 0.02% sodium azide, TBS pH 7.4. Tissues sections were blocked with neat PBSF solution for 20 min at RT and primary antibodies were applied to tissue sections overnight at RT in a moist incubation chamber. Slides were immersed for 20 min into a 3% hydrogen peroxidase-absolute alcohol (3% H₂O₂-AbROH) solution for quenching of any endogenous peroxidases and washed in TBS pH 7.4 and subsequently incubated with biotinylated goat antimouse IgG (Dako Australia Pty Ltd, 1 : 200 in 1% PBSF, 0.1% Tween 20, 0.02% sodium azide, TBS pH 7.4) for 30 min, washed and further incubated for 30 min in horse radish peroxidase conjugated to streptavidin (Dako Australia Pty Ltd, 1 : 500 in TBS pH 7.4) at RT. Finally, for brown colour development, 3,3'-diaminobenzidine solution made in imidazole-HCl buffer pH 7.5 containing hydrogen peroxidase as per specifications for Dako Liquid DAB solution (K3465; Dako Australia Pty Ltd) was applied for 5 min, washed and lightly counterstained with Mayer's haematoxylin to define nuclear morphology.

Sections were viewed using a Leica DMLB-microscope and images were captured using a Leica DC200 digital camera (Leica, Sydney, Australia). Digital images were processed to match contrast and brightness and assembled into a panel with Adobe Photoshop v. 5.5 (Adobe Systems, Mountain View, CA, U.S.A.).

The number of positive cell stainings was determined in the skin biopsy using light microscopy and designated as follows: 0, none; +, moderate; ++, abundant; and two independent individuals accessed the results.

Controls

The specificity of the primary antibody staining was determined by (i) the omission of the primary antibody from the

incubations; (ii) positive staining defined by the company data sheets using normal human tonsil tissue, and (iii) isotype-specific negative control antibody X63.

Immunohistochemical localization on frozen tissue

Direct immunofluorescence was used to detect the expression of human IgG, IgA, IgM, C3, C1q, and fibrinogen in the skin biopsies. Sections (4-µm thick) were cut and placed onto Histo-grip-coated slides (Zymed Laboratories) and allowed to air dry for 2 h at RT. After drying, sections were washed, blocked with neat PBSF solution for 20 min and incubated for 1 h in a moist incubation chamber with rabbit-antihuman IgG, IgA, IgM, C3, C1q and fibrinogen directly conjugated to fluorescein isothiocyanate (FITC), using two dilutions 1 : 10 and 1 : 100 (Dako Australia Pty Ltd) at RT. Unbound antibodies were removed by washing in TBS pH 7.4 and slides were mounted by using 2.5% 1,4-diazabicyclo (2.2.2) octane in phosphate-buffered glycerol (Sigma, Castle Hill, NSW, Australia). Slides were viewed using a Leica DMLB-microscope and images were captured using a Leica DC200 digital camera (Leica) as described earlier.

Results

Clinical investigations

The proportion of T and B lymphocytes and T-cell subsets in the blood were within normal ranges for both patients who consented to skin biopsies. However, eosinophilia, elevated IgG (> 30 g L⁻¹) and extremely elevated levels of total IgE (> 100 000 µg L⁻¹) were documented. Extended IgG subclass serology on both patients revealed elevated IgG1 (3 × upper limit of normal), IgG3 and IgG4. Both were RAST-positive for house dust mite and animal dander.

Immunoglobulin investigations for the additional patients with scabies revealed elevated levels of IgE in both crusted and ordinary scabies comparable with or higher than IgE levels recorded in allergy⁹ (Fig. 2) and elevated levels of IgG1, IgG3 and IgG4 in crusted scabies (Fig. 3).

Immunohistochemical localization on formalin-paraffin-embedded tissue

Skin biopsy sections from crusted scabies lesions showed large numbers of infiltrating lymphocytes and eosinophils in the dermis (Fig. 4). Importantly microscopy showed the strong presence of T cells (CD45+, CD3+) but no evidence of any B cells (CD20+), and only the occasional macrophage was evident among the lymphocytes (Fig. 5). There were significantly greater numbers of cytotoxic T lymphocytes (CD8+) compared with minimal or no helper T lymphocytes (CD4+) in the skin lesion infiltrate (Fig. 6). These results are summarized in Table 1. In addition strong staining of the inflammatory cytokine IL-1β and anti-inflammatory cytokine TGF-β1 was observed, whereas no staining was observed for IRAP, IL-10 or TNF-α (Fig. 7).

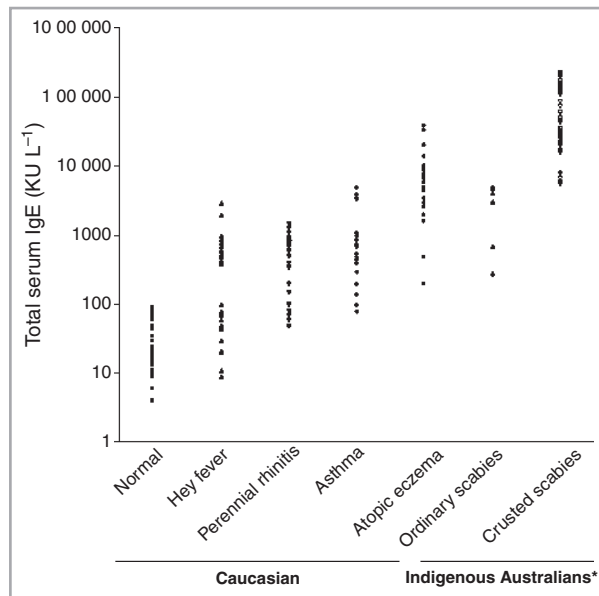


Fig 2. Serum IgE levels in allergy⁹ and indigenous Australians with ordinary and crusted scabies. *Data collected from study participants.

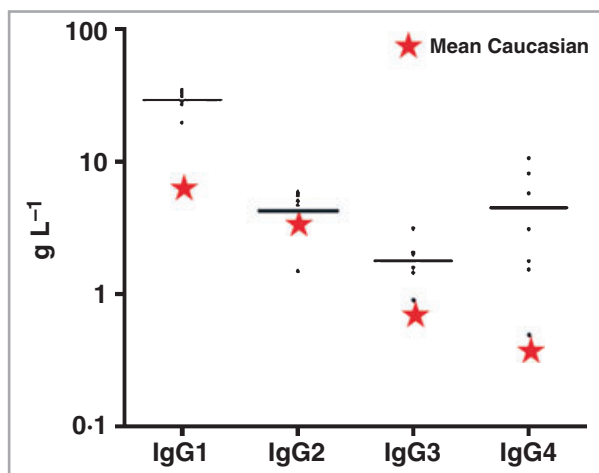


Fig 3. Serum IgG1, IgG2, IgG3 and IgG4 levels in indigenous Australians with crusted scabies. Horizontal lines represent the mean value and stars represent the mean normal caucasian level as per the Department of Immunology, Allergy and Arthritis, Flinders Medical Centre, Australia.

Immunohistochemical localization on frozen tissue

Immunofluorescence studies demonstrated IgM and IgA deposited at the dermal–epidermal junction, C3 deposited in dermal vessel walls, and evidence of fibrinogen in dermal tissue (data not shown).

Discussion

Many skin diseases have an immune component, and understanding the skin immune system is important to prevent or

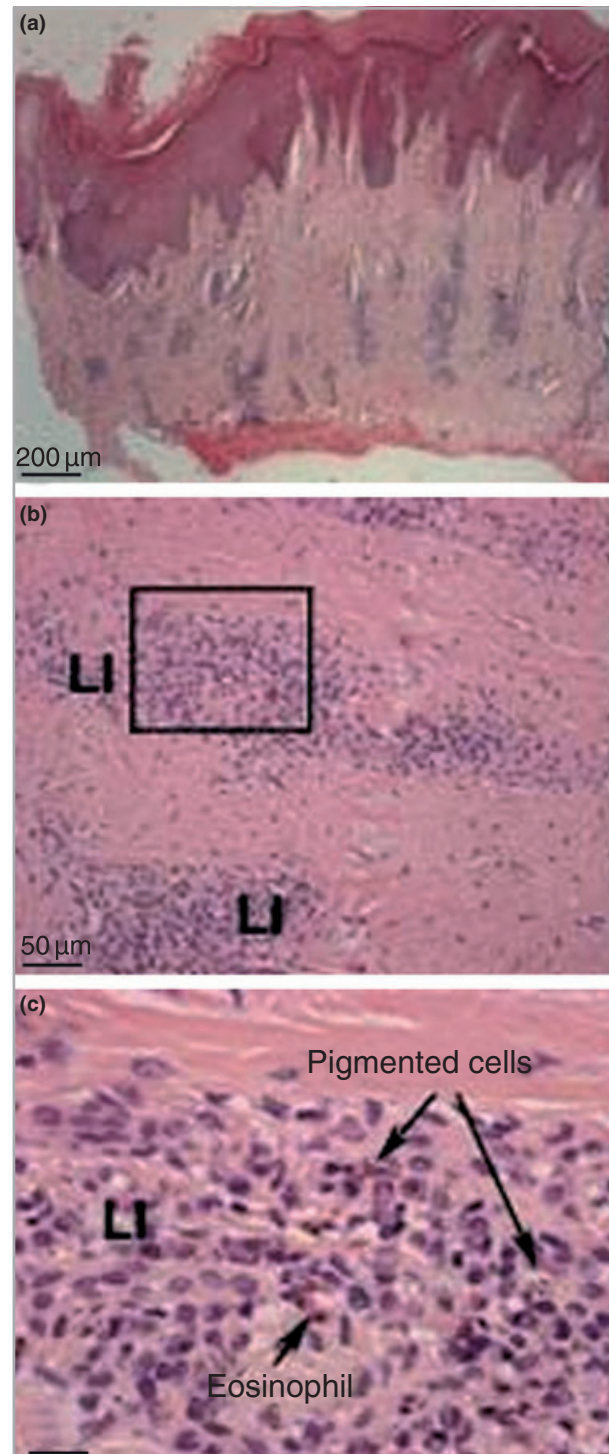


Fig 4. Haematoxylin and eosin staining of scabies mite infested skin biopsy. (a) Low power view of the conified, epidermis and dermis (× 5). (b) Typical lymphocytic infiltration (LI) in the dermis (× 20). (c) Presence of lymphocytes, eosinophils and several pigmented cells (× 63).

treat these diseases effectively. Under normal conditions, the elements of the skin immune system work together in physiological processes such as immunosurveillance and elimination of pathogenic micro-organisms and potentially sensitizing

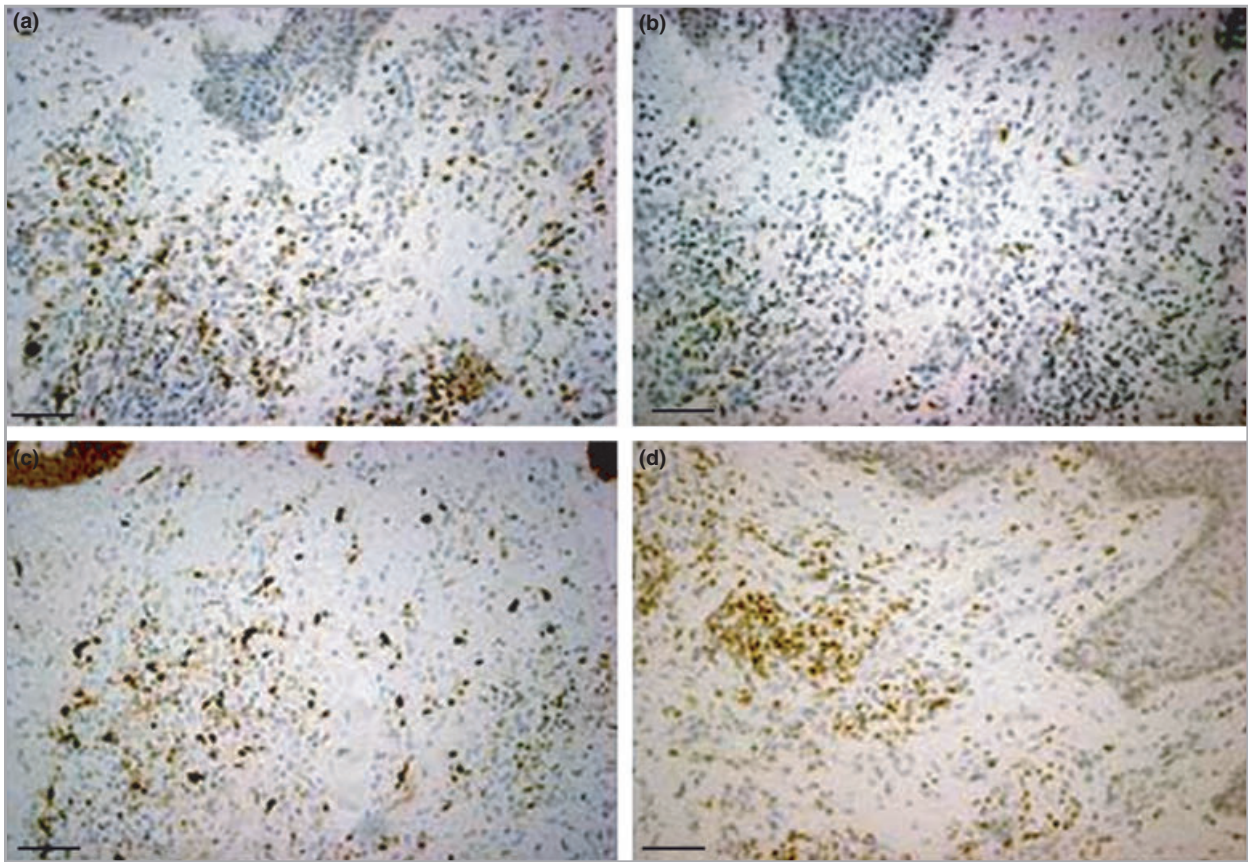


Fig 5. Immunoperoxidase staining of cellular infiltrate in scabies mite infested skin. (a) CD45+ brown reaction product of pan lymphocyte marker. (b) B cells CD20+. (c) Macrophages mac387+. (d) Pan T cells CD3+ ($\times 20$).

materials. Human skin harbours a variety of immune response-associated components that together form the skin immune system, which consists of lymphocytes, Langerhans cells, dermal dendritic cells, keratinocytes and skin-draining regional lymph nodes. Regulation of the skin defence mechanisms is important as abnormal or inappropriate immune reactions lead to skin pathology.

We have previously hypothesized that ordinary scabies is associated with a T-helper (Th) type 1 (Th1) response (cellular) and crusted scabies is associated with a Th2 response (humoral).¹ In a cohort of 78 patients in northern Australia with crusted scabies, the prevalence of extremely high serum levels of total IgE (96%), IgG (96%) and IgA (64%) were noted; in 73% of patients IgE levels were elevated 10 times above normal range.⁸ Overall 58% had eosinophilia, with eosinophils in 12% of patients above $7.0 \times 10^9 \text{ L}^{-1}$ (10 times the upper limit of normal), with the highest being $13.0 \times 10^9 \text{ L}^{-1}$. Limited investigations to date of humoral immunity in patients with ordinary scabies give contradictory results^{10,11} as have tested responses to scabietic extracts from other hosts such as the dog.¹²

It is well established that Th1-biased immune responses, which can redirect Th2 responses, are dominated by CD4+ T-cell populations secreting interferon (IFN)- γ and IL-2.

Th2-biased T cells (i.e. CD4+ T-cell populations able to secrete net IL-4, IL-5, IL-6 and IL-13) are dominant effector cells in the pathogenesis of IgE-mediated hypersensitivity, and are capable of attracting, activating and prolonging the survival of nonspecific effector cells. The Th1/Th2 concept has also been extended to CD8+ cells.¹³ T-regulatory populations expressing IL-10 and TGF- β have also been described. Eosinophils are major effector cells in the pathogenesis of inflammatory diseases such as atopic dermatitis and bronchial asthma and keratinocytes also play an important role in the skin immune system. The production by keratinocytes of pro-inflammatory cytokines IL-1, IL-6, IL-8 and TNF- α is well recognized and furthermore immunomodulatory IL-10 and IL-12 originating from keratinocytes are considered to be responsible for systemic effects.

A significant finding in the crusted scabies skin biopsies analysed in this study was the predomination of infiltrating CD8+ T lymphocytes in the dermis and the absence of B cells. The proportion of T and B lymphocytes and T-cell subsets in the blood of these crusted scabies patients was reported to be within normal ranges, as previously documented for other crusted scabies patients.⁸ However, the ratio CD8+ to CD4+ T cells was greater in the skin infiltrates in crusted scabies lesions indicating a selective movement of these cells into the dermis.

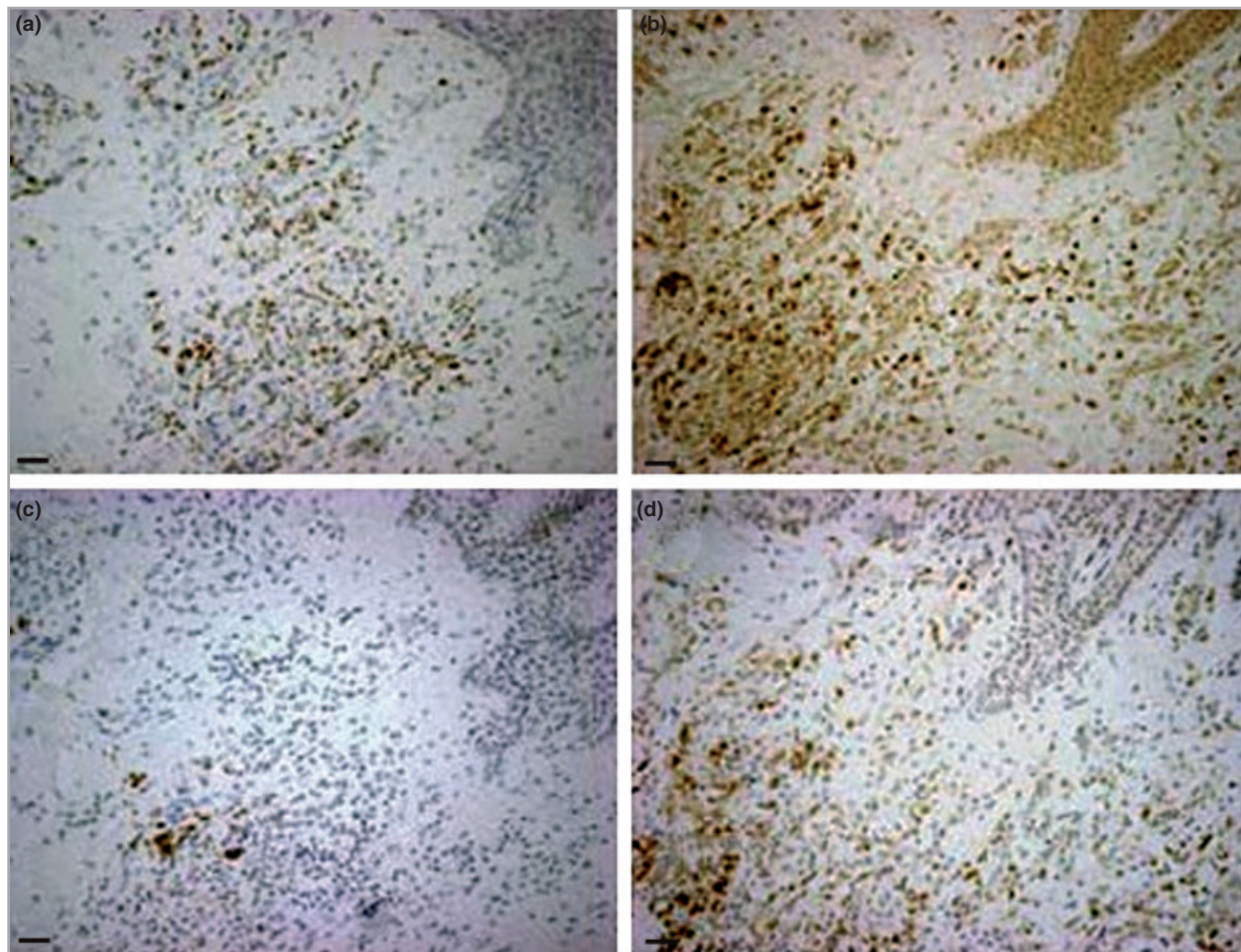


Fig 6. Immunoperoxidase staining of T-cell subsets in scabies mite infested skin. CD8+ staining cells more prominent in the same region cells compared with CD4+ T cells. (a) Brown staining for pan T cells CD3+. (b) Cytotoxic T lymphocytes CD8+. (c) Negative control. (d) Helper T lymphocytes CD4+ ($\times 20$).

Table 1 Lymphocyte and cytokine profile of scabies mite infested skin using immunoperoxidase staining

Case	LCA	B cell	T cell	CD4	CD8	Mac387	TNF- α	TGF- β 1	IL-10	IL-1 β	IRAP
1	++	0	++	0	++	few	0	++	0	++ ^a	0
2	++	0	++	+	++	few	0	++	0	+ ^a	0

LCA, leucocyte common antibody; TNF, tumour necrosis factor; TGF, transforming growth factor; IL, interleukin; IRAP, interleukin 1 receptor antagonist protein.
^aPlasma cell, fibroblast, macrophage staining.

The presence of T lymphocytes has been a consistent feature of the dermal inflammatory response to *S. scabiei* in previous studies of ordinary scabies¹⁴ and generally reflects the development of a delayed-type hypersensitivity (DTH) reaction. DTH reactions or type IV hypersensitivity reactions can be elicited by either CD4+ or CD8+ T cells, depending on the pathway by which the antigen is processed. These cells release mediators that activate local endothelial cells, recruiting an inflammatory cell infiltrate usually dominated by macro-

phages and causing the accumulation of fluid, protein and lesion development.

In other similar studies on ordinary scabies, predominantly CD4+ T cells were observed to dominate the lymphocytic infiltrate of inflammatory skin lesions, with a reported CD4/CD8 ratio of 4 : 1.¹⁴ Likewise studies of inflammatory cells in the biopsies of skin lesions from patients with atopic dermatitis also identified a significantly greater number of infiltrating CD4+ lymphocytes compared with CD8+ subtypes¹⁵

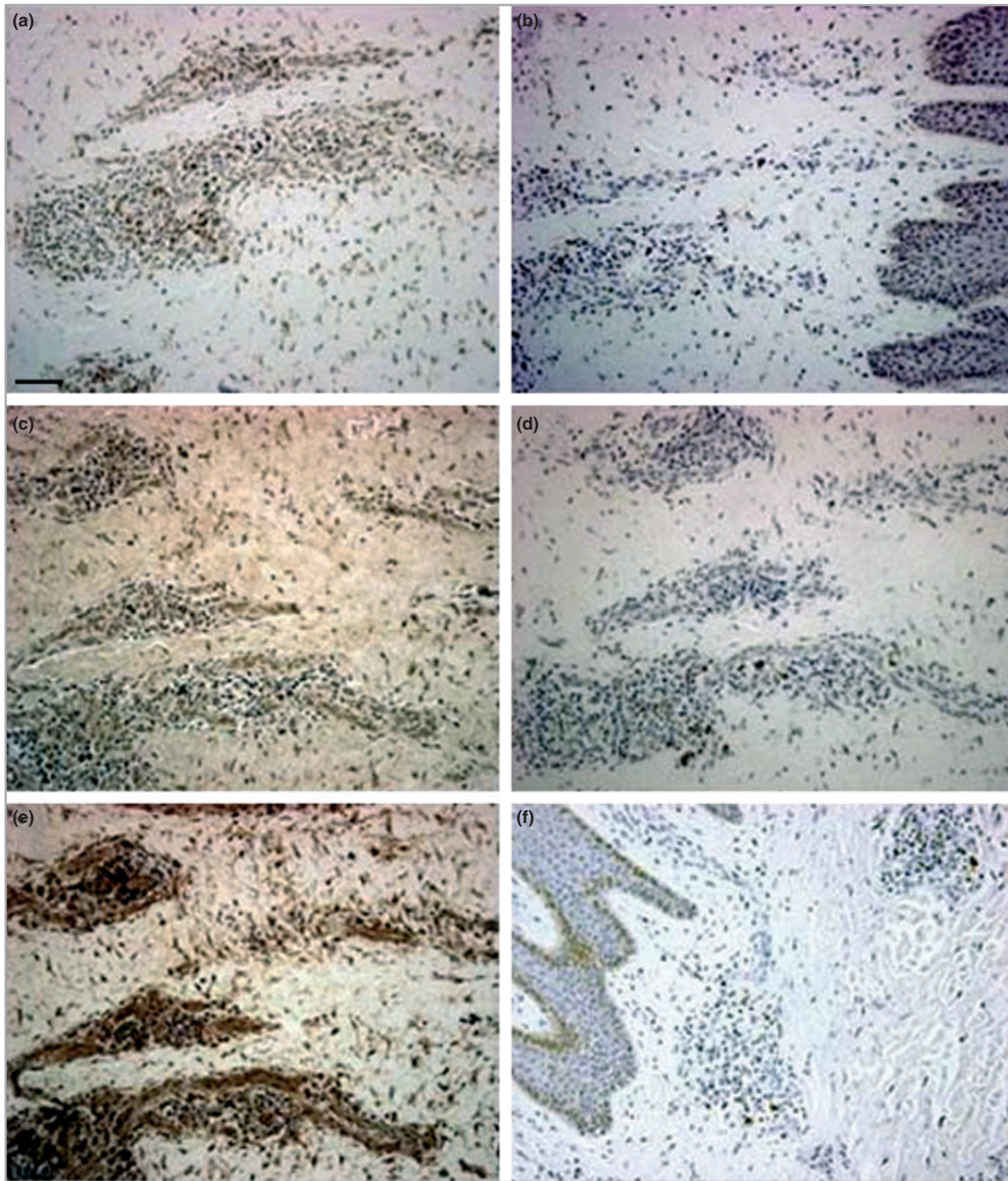


Fig 7. Immunoperoxidase staining for a cytokine profile in scabies mite infested skin biopsy. (a) Interleukin (IL)-1 β ; (b) interleukin 1 receptor antagonist protein (IRAP); (c) IL-10; (d) tumour necrosis factor- α ; (e) transforming growth factor- β ; (f) negative control, note pigmented cell present in the lymphocytic infiltration ($\times 20$).

with CD4/CD8 ratios similar to peripheral blood levels.¹⁶ In contrast, in psoriasis, a disease characterized by erythematous scaly papules and plaque formation as a result of abnormal keratinocyte hyperproliferation, a pronounced CD8⁺ epidermotropism into the epidermis and dermis has been observed.¹⁷ The role of cytotoxic T cells in crusted scabies is

unclear but these data suggest these skin-homing CD8⁺ T cells may play a function in the inflammatory response observed in crusted scabies. The mechanisms of tissue damage may include direct cytotoxicity against keratinocytes and release of cytokines, which could amplify the inflammatory response by targeting resident skin cells. Relative cytokine expression in

peripheral blood CD4+ and CD8+ T cells stimulated with *S. scabiei* antigens will further elucidate their role in crusted scabies pathogenesis.

In this study the most prominent cytokines observed were IL-1 β and TGF- β . IL-1 β is known to be produced by macrophages and epithelial cells and induces fever, T-cell activation and macrophage activation. IL-1 β levels are often high in individuals with systemic inflammatory disease, and synergism with TNF- α has been reported frequently, although TNF- α was not detected in the crusted scabies skin lesions in this study. Triggering of the inflammatory cascade by IL-1 β and TNF- α can lead to inflammation, tissue destruction and loss of function, and IL-1 β appears to be a key effector molecule in the pathogenesis of crusted scabies. In support of this IL-1 α and IL-1 β secretions were observed in the cell culture supernatant of human skin equivalents stimulated with *S. scabiei* var. *canis* mites.¹⁸

The inhibitor protein IRAP is reported to be distributed throughout the living layers of the epidermis in normal skin and also present in areas where the pro-inflammatory cytokine IL-1 α is distributed, suggesting a cytokine regulatory system in normal skin.¹⁹ In this study IRAP was not detected in crusted scabies lesional skin, similar to the situation reported for psoriasis patients. Decreased IRAP expression in lesions of crusted scabies indicates that alterations in the level of this inhibitor protein may be important in the pathogenesis of inflammatory skin conditions.

In contrast, expression of the anti-inflammatory cytokine TGF- β was observed. This is a known immunosuppressive cytokine produced by monocytes and T cells and inhibits cell growth and induces IgA secretion. TGF- β , in particular, suppresses the function of inflammatory Th1 lymphocytes. In addition, macrophage activation is markedly inhibited by cytokines such as TGF- β , IL-4, IL-10 and IL-13. IL-4 is known to stimulate keratinocyte proliferation, epidermal cells have IL-4 receptors, and IL-4R expression is documented as elevated in psoriasis, a disease with some clinical similarities to crusted scabies. Future studies investigating the role of IL-4 in the apparent Th2 immune response observed in crusted scabies disease pathogenesis is essential, as IL-4 could contribute to the excessive IgE synthesis observed and possibly the hyperproliferative skin disease characteristic of crusted scabies.

The clinical syndrome of crusted scabies results from a failure to mount an effective immune response capable of controlling the infestation and preventing subsequent relapses. A range of immune responses within this syndrome is evident, ranging from extensive distribution of mites over the body, to cases in which crusted scabies patients are able to control the spread of the parasite from localized areas but may not have sufficient immunity to clear the infestation.²⁰ Estimation of total serum immunoglobulins in crusted scabies patients shows a significant increase in IgE, IgG, IgG1 and IgG4 in comparison with the normal population (Figs 2, 3). This is supported by other studies displaying elevated levels of *S. scabiei* antigen-specific IgE and IgG4 in crusted scabies.^{21,22}

Even though *S. scabiei* induces a strong humoral response in severe crusted scabies, these antibodies appear to play no role in protection. However, allergen-specific IgE plays a key role in the pathophysiology of allergic disorders. This IgE response is usually accompanied by production of IgG4. The regulation of IgG4 responses and the function of these responses in the pathogenesis of allergy have not been fully characterized. Human Th2 cytokines (IL-4 and IL-13) induce co-expression of IgE and IgG4 through sequential switching and recently IL-4 has been recognized as a dominant cytokine in crusted scabies unstimulated peripheral blood mononuclear cells.^{1,8}

Interestingly, despite elevated blood antibody levels of IgE, IgG and IgG subclasses recorded for these patients, no B lymphocytes (CD20+) were observed in the skin lesions, although evidence of B-cell infiltration and activation has been previously documented in patients with ordinary scabies.¹⁴ Studies in animals with severe parakeratotic sarcoptic mange have also reported the absence of plasma cells and B lymphocytes in the dermis compared with low numbers observed in experimentally infected animals.²³ In this study IgM and IgA were observed deposited at the dermal-epidermal junction, C3 deposited in dermal blood vessels, and fibrinogen observed in dermal tissue, as seen in ordinary scabies.²⁴ These features suggest *S. scabiei*-specific antigen-antibody complexes may be forming in situ, activating the complement system, and generating potent inflammation. The expression of CD40 and its ligand CD40L are required for the induction of IgE synthesis in B cells. Dermal and epidermal infiltrates in skin biopsies obtained from patients with ordinary scabies and atopic dermatitis have been documented with cells expressing IgE, Fc ϵ RI, Fc ϵ RII and CD40/CD40L.²⁵ It is possible that the lack of B cells in the dermis of crusted scabies lesional skin may in part contribute to the failure of the skin immune system to mount an effective response capable of controlling the infestation and that cutaneous tissue may not be contributing to the high levels of circulating immunoglobulins.

This study provides considerable evidence indicating a critical role for T lymphocytes in disease pathogenesis of crusted scabies. Analogous to psoriasis, activated CD8+ T cells in crusted scabies lesions may induce dysregulated keratinocyte apoptosis contributing to the elicitation and progress of epidermal hyperproliferation. The role and importance for the accumulation of eosinophils and enhanced production of IgE remains to be elucidated. Evidence indicates crusted scabies develops largely as a result of a Th1/Th2 imbalance, with a cytotoxic T-cell type 2 response in the skin, high levels of antibody in the blood, and uncontrolled growth of the parasite.

Acknowledgments

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