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Non-HIV AIDS: nature and strategies for its management

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Despite initial claims to the contrary, a cluster of reports of severe opportunistic infections occurring in patients without evidence of HIV infection do not appear to represent a new disease entity or present evidence of epidemiologically associated cases suggesting an infectious agent. Reported cases are reviewed and appear to represent a heterogeneous group, many of which may represent sporadic cases of late onset acquired immunodeficiency. In addition, a small group of asymptomatic subjects have been identified with constitutively low CD4 T cell populations which appear to have little or no clinical significance since these patients have no evidence of clinical immunodeficiency.

Newly identified cases should be fully investigated immunologically and virologically after recovery from their presenting infection and continuous or prophylactic therapy instituted only in cases of substantiated long-term severe immunodeficiency.

Introduction

The possibility that human immunodeficiency virus (HIV) infection is not responsible for the immunodeficiency that characterises acquired immunodeficiency syndrome (AIDS) has held a fascination at various states of evolution of the epidemic, by those involved, members of the scientific community and consistently by the media.

Earlier in the epidemic such questioning was undoubtedly useful and stimulated the search for convincing evidence of causal association. Latterly, such discussion has been not merely scientifically heterodox, but has ignored entirely the epidemiological evidence for HIV as a cause of AIDS which is stronger in this disease than in many other infections. Moreover, certain commentators have raised the significance of the anecdotal case report to a new level of absurdity in an attempt to make the exception (for example, of Kaposi's sarcoma in a homosexual male who was HIV-negative; Friedman-Kien *et al.*, 1990) prove the point that HIV cannot be responsible for AIDS. This may reflect the desire of some to believe that AIDS results from lifestyle rather than a transmissible agent (Dean, 1992) and can thus be ignored by many. The posturing of individual scientists in the face of overwhelming counter-evidence is, however, more difficult to understand (Duesberg, 1991).

The unexpected announcement of the Eighth International AIDS Conference, Amsterdam, that the US Centers for Disease Control (CDC) in Atlanta were investigating a series of reported cases of AIDS in which HIV did not seem to be implicated rekindled many of these issues.

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At this conference the possibility was discussed that many AIDS cases might not be caused by HIV, raising fears that another transmissible agent for AIDS might exist and that this could render national blood supplies unsafe due to another virus for which there was no satisfactory screening test. Later, the CDC in Atlanta convened a meeting on the subject and issued a provisional case definition for the condition 'idiopathic CD4+ T lymphocytopenia' which identified a group of patients with the presentation described above.

Range of problem

Sporadic cases of apparent late-onset cellular immunodeficiency, associated with opportunistic infections, have appeared as case reports over a number of years. Since the emergence of HIV-associated AIDS coincided with the introduction of T cell-specific monoclonal antibodies permitting the identification and quantitation of human CD4-positive T lymphocytes, no T lymphocyte surface marker results are available on many of the earlier sporadic cases. One of the earliest cases to be documented and re-examined many years later was that of a Manchester seaman who died of *Pneumocystis carinii* pneumonia (PCP) in 1959; Williams, Stretton & Leonard, 1960. Re-analysis of histological samples taken at autopsy by polymerase chain reaction initially suggested the presence of HIV infection (Corbitt, Bailey & Williams, 1990), but later examination casts serious doubt on this (Zhu & Ho, 1995) and the case should probably be reclassified as non-HIV AIDS.

The number of similar cases increased in the late 1980s and early 1990s, almost certainly as a result of the increased diligence with which cases of immunodeficiency without apparent secondary cause in adults were being investigated and documented.

Idiopathic CD4+ T lymphocytopenia

The syndrome of idiopathic CD4+ T lymphocytopenia is defined by the Centers for Disease Control (1992) as cases which demonstrate depressed numbers ($<300/mm^3$) and proportions ($<20\%$ of total T cells) on at least two consecutive occasions, with no laboratory evidence of HIV-1 or HIV-2 infection, and the absence of any defined primary or secondary immunodeficiency disease or therapy associated with depressed levels of CD4+ T lymphocytes.

Although a number of patients fulfilling the above criteria have come to light as the result of investigation of possible cellular deficiency suspected on clinical grounds, other cases have been detected as a result of the investigation or screening of healthy populations including blood donors, homosexual men and other groups.

This article deals with three independent issues which are closely overlapping, but have different implications for investigation, classification and future management. Each will be reviewed in detail, their relationship to HIV infection and immunodeficiency discussed, and an approach to management proposed. The three categories are: (i) Non-HIV associated immunodeficiency; (ii) Idiopathic CD4+ lymphopenia without immunodeficiency; (iii) Transient CD4+ lymphopenia secondary to infection, acute inflammation or CD4 sequestration.

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Non-HIV associated immunodeficiency

The majority of cases classified as non-HIV AIDS or CD4+ lymphopenia have been detected following investigation of clinical signs which suggest cellular immunodeficiency. The patients have presented with a history of severe or recurrent infections with intracellular pathogens or virus-associated malignancies which, even before the description of AIDS, were recognised as being highly suggestive of underlying deficiency of cell-mediated immunity. Indeed, it was this constellation of clinical features occurring in circumscribed populations of homosexual/bisexual males, haemophiliacs and later intravenous drug users and heterosexual populations, that clearly identified the new clinical entity of AIDS. The clinical presentation suggested a specific immunodeficiency disease, while the epidemiology strongly suggested involvement of a transmissible agent.

Before the AIDS epidemic, more than 99% of patients with *P. carinii* pneumonia had a predisposing factor associated with secondary immunodeficiency such as lymphoma, leukaemia or a condition treated with immunosuppressive or cytotoxic drugs (Walzer *et al.*, 1974; Brunvand *et al.*, 1991). Indeed, *P. carinii* was first identified as a pathogen amongst severely malnourished (and thus immunodeficient) populations in continental Europe immediately following the Second World War (Hughes, Price & Sisko, 1974). Most remaining case reports were in patients with identifiable primary immunodeficiency diseases (Asherson & Webster, 1980), and reports in apparently non-immunocompromised adults remain extremely uncommon (Anderson & Barrie, 1960; Lyons, Vinijchaikul & Hennigar, 1961; Robinson, 1961). Since most cases were unsuspected during life, diagnosis was only made at autopsy and there was no opportunity for the immunological investigation of such cases. Most sporadic cases were probably examples of rate primary immunodeficiency syndromes or were secondary to some unidentified immunosuppressing disease.

Similar isolated examples were described for other opportunistic pathogens and tumours and tests for cell-mediated immunity were performed on some. However, individual T cell populations could not be quantified before 1978, possible association with low CD4 counts could not be determined. More recently, there has accumulated a small but important group of patients who display some of the clinical infections associated with HIV-induced immunodeficiency and in whom low CD4 counts are reported. Recent published cases have rigorously excluded HIV infection or other diseases responsible for secondary immunodeficiency. A review of published cases is given in Table I and encompasses virtually all the major opportunistic pathogens associated with late HIV infection. These occasionally occur multiply but usually singly.

There are, however, some striking differences between these cases and cases of HIV-associated immunodeficiency. Firstly, whereas some cases have had a fulminant and fatal outcome, others have been associated with longer term survival associated with stabilisation or reversal of the immunodeficiency: a situation unknown in late-stage HIV infection (Seligmann *et al.*, 1991; Duncan *et al.*, 1993; McNulty *et al.*, 1994). The majority of cases show other immunological changes which, whilst they can occasionally be seen in individual HIV infection cases, prove the exception rather than the rule in HIV disease. In particular, most non-HIV immunodeficiency cases have normal or low immunoglobulin levels and also have low CD8 counts (Duncan *et al.*, 1993; Ho *et al.*, 1993). Finally, despite initial unconfirmed reports (Gupta *et al.*, 1992; Laurence *et al.*,

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Table 1. Severe immunodeficiency case reports with low CD4 counts and no obvious secondary cause

Source	Age	Sex	HIV risk	Presentation	Lowest[a] CD4 count/mm^3
Daus, Schwarze & Radtke (1989)	71	M	no	thrombocytopenia, candidosis, zoster	114
Gatenby (1989)	15	F	no	mucocutaneous candidosis	80
Pankhurst *et al.* (1989)	27	F	no	candidosis	216
Hansen *et al.* (1990)	30	M	no	diffuse flat warts	NA
Gautier *et al.* (1991)	60	F	NA	PCP	284
	74	M	NA	PCP	107
Jowitt *et al.* (1991)	51	M	no	dermal cryptococcosis	30
Seligmann *et al.* (1991)	56	F	no	disseminated cryptococcosis	63
Castro *et al.* (1992)	42	M	no	cutaneous KS	120
CDC (1992)	70	M	BT	PCP	50
	38	M	HCW	cryptococcal meningitis	84
	58	F	BT	atypical pneumonia	86
	45	M	no	widespread molluscum contagiosum	68
	70	F	no	disseminated zoster, histoplasmosis and MAI	199
Laurence *et al.* (1992)	38	M	HS	chest rash, candidosis and malaise	280
	73	F	BT	PCP	NA
	37	M	HCW	intractable cutaneous warts, zoster	120
	35	M	HS	pulmonary MTB	270
Duncan *et al.* (1993)	65	M	no	PCP	12
	40	M	no	cryptococcal meningitis	150
	68	F	no	cryptococcal meningitis	20
Ho *et al.* (1993)	69	F	no	oral HSV, PCP	3
	54	M	no	thrombocytopenia	154
Ho *et al.* (1993)	36	M		cerebral toxoplasmosis	207
	61	M	no	paraspinal MTB	205
	45	M	HS	fatigue, night sweats	57
	41	F	BT	genital HSV	127
	40	M	IVDU	pulmonary cryptococcosis	37
	31	M	no	pulmonary histoplasmosis	150

Tijhuis *et al.* (1993)	61	M	no	oesophageal candidosis	50
Burg, Weber & Kucherer (1994)	43	F	no	systemic cryptococcosis salmonella sepsis	48
Dev *et al.* (1994)	48	F	no	cryptococcal and mycobacterial infections	101
Grossman *et al.* (1994)	39	M	no	mycosis fungoides	40
Lin & Tripathi (1994)	33	F	no	pulmonary cryptococcosis red cell aplasia	40
McLane, Weems & Antworth (1994)	35	M	no	retinal CMV	157
McNulty *et al.* (1994)	56	M		oesophageal candidosis	11
	70	M		MAC/cryptococcosis	130
	55	F		disseminated VZV and cryptococcosis	550 (16%)
	35	M		cryptococcal pneumonia	24
	33	M		cerebral cryptococcosis	273
	29	F		oral candidosis	285
Okashi *et al.* (1994)	32	M	no	warts, basal cell carcinoma	48
Wakeel *et al.* (1994)	65	M	no	extensive warts tinea pedis	10

*Lowest reported CD4 count.

MTB, *Mycobacterium tuberculosis*; PCP, *Pneumocystis carinii* pneumonia; HSV, herpes simplex virus; MAI, *Mycobacterium avium-intracellulare*; IVDU, intravenous drug user; HCW, healthcare worker; VSV, varicella zoster virus; BT, blood transfusion; HS, homosexual male; NA, information not available.

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1992), most cases have shown no evidence of any other viral, particularly retroviral, infection (Moore & Ho, 1992; Duncan *et al.*, 1993; Ho *et al.*, 1993; Smith *et al.*, 1993; Spira *et al.*, 1993; Heredia *et al.*, 1994) and there is no evidence of epidemiological clustering or case-to-case transmission of immunodeficiency (Smith *et al.*, 1993; Spira *et al.*, 1993).

Although groups at risk of HIV infection appear to be over-represented amongst the early case reports, these almost certainly represent an ascertainment bias towards early presentation, CD4 investigation and documentation of cases. Many of these cases, had they occurred in the general population, might otherwise have escaped detection (Fauci, 1993). Certainly, since the wave of reports that followed the initial description of this disease group, there is no evidence of increasing case numbers and the condition remains exceptionally rare when contrasted to the early exponential rise in AIDS cases. More importantly, a critical review of the case literature reveals occasional cases or even clusters of opportunistic infections in patients who have no evidence of CD4 depletion (Jacobs *et al.*, 1991; Holland *et al.*, 1994; Lentino & Brooks, 1994). Many of these presumably represent cases where functional immune deficiency in which patients with normal CD4 counts nevertheless are unable to mount specific cell-mediated immune responses to counter the opportunistic pathogens. In these cases it is likely that the spectrum of infectious agents to which each individual is susceptible will be narrower than that encountered in primary immune deficiency states or in HIV immunodeficiency. It is probable that the only difference between these cases and the ones classified as non-HIV AIDS is whether the individuals have low CD4 counts associated with their predisposing immunological lesion.

Low CD4 counts are an uncommon but recognised accompaniment to common variable immunodeficiency which is the most common form of antibody deficiency in adults (Cunningham-Rundles, 1989; Lebranchi *et al.*, 1990; Kazmarski *et al.*, 1992). These patients may also develop severe opportunistic infections, including pulmonary or extra-pulmonary *P. carinii* infection (Rao & Gelfand, 1983; Esolen *et al.*, 1992). Patients with overt hypogammaglobulinaemia were not included in the original series of idiopathic CD4 lymphopenia or non-HIV AIDS cases, but in some individuals the hypogammaglobulinaemia may be marginal or even absent in cases with functional antibody deficiency. Since common variable immunodeficiency is a sporadic cause of immunodeficiency with a wide heterogeneity of presentation at any age, it is probably that at least a proportion of reported cases represents examples of this disease in which cellular immunodeficiency is pre-eminent or where full immunological investigation has not been completed.

Primary immunodeficiency diseases, particularly those in which the T cell compartment is severely affected, are generally considered to occur only in early childhood. However, a recent report (Shovlin *et al.*, 1993) described two sisters age 34 and 35 years who presented with later onset fungal and viral infections and very low CD4 cell counts in the absence of HIV infection. The CD4 counts reported were low enough to have qualified these cases for inclusion as idiopathic CD4+ T lymphocytopenia. Extensive immunological investigations revealed very low levels of adenosine deaminase activity and it is proposed that these cases represent late presentation of a condition which usually presents in early infancy as severe combined immunodeficiency.

The similarity of many of the described case reports of primary immunodeficiency states with those collected under the designation of non-HIV AIDS suggests that the

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majority of the latter group represent sporadic examples of rare and often uncharacterised immunodeficiency syndromes. The lack of any epidemiological support for a transmissible agent, combined with a failure to detect retroviral or other viral infection, emphasises that the majority of recent cases probably reflect heightened awareness and improved diagnosis, at least with regard to CD4 counts, rather than a new or increasing problem.

This conclusion stresses the need for full immunological and virological investigation and classification of such cases before planning their long-term management. If the clinical history is suggestive of a long-term predisposition to infection, then the full immunological investigation should be undertaken irrespective of the CD4 count and should include functional assessment of T lymphocyte and monocyte populations including, where possible, the use of assays that permit the assessment of responses to the particular pathogens to which individual patients are susceptible. The other issue that needs to be considered is whether the low CD4 counts reported in individual patients could be secondary to their particular infections rather than responsible for them.

Transient low CD4 counts have been reported to occur after a number of infections (Williams, Koster & Kilpatrick, 1983; Beck *et al.*, 1985; Laurence 1993), usually associated with elevated CD8 counts. In some cases, CD4 counts that were low initially have returned towards normal levels after treatment of the infection (Ho *et al.*, 1993; McNulty *et al.*, 1994). Depressed cellular immunity can also occur as a consequence of chronic fungal infection (Lehmann *et al.*, 1983; Payan *et al.*, 1984; Murphy, 1988). The transient nature of CD4 depletion and depressed cellular immunity that occurs in some patients as a result of infection indicates that it is essential that investigations of the immunodeficiency are undertaken after clearance of the presenting infection. Since CD4 depletion in the blood can persist for long periods, the current CDC definition is unsatisfactory. I propose that a period of at least 6 months is added to the requirement for consecutive low CD4 counts to rule out short-term secondary effects of infection.

The optimal treatment of patients with non-HIV associated immunodeficiency remains to be determined. If immunological assessment indicates that the CD4 depletion is chronic rather than transient and it is associated with other clinical and laboratory evidence of cell mediated immunodeficiency, then prophylaxis against *P. carinii* should be considered and a close watch for other opportunistic infections maintained. Immunoglobulin levels and quantification of specific antibodies against polysaccharide antigens should be performed. If the latter are low, then pneumococcal and meningococcal polysaccharide immunisation should be undertaken and post-immunisation antibody levels checked. Failure to mount a specific response should raise the possibility of requiring intravenous immunoglobulin replacement therapy, particularly if there is a history of susceptibility to infections with encapsulated bacteria. The occurrence of multiple opportunistic infections and relapses in some of the patients described suggests that an aggressive approach to therapy and prophylaxis may sometimes be required (Duncan *et al.*, 1993).

Idiopathic CD4-lymphocytopenia without immunodeficiency

The CDC definition of idiopathic CD4 lymphocytopenia does not include any clinical parameters. When case reports are scrutinised, it is apparent that there are two different groups of patients contained within this classification. The first group are those

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described above that have opportunistic infections. Among this group population groups at risk from HIV are marginally over-represented, and in whom consistently low CD4 counts have been documented. The second group comprises a series of individuals whose CD4 counts have been measured either as a result of their participation within cohort studies or blood donor panels, and who have CD4 counts which are low but in whom there is no clinical evidence suggestive of immunodeficiency. In Table II, I have reclassified these cases and separated them from non-HIV immunodeficiency because I believe they represent a different entity and require a different management approach.

It is probable that the majority of these cases fall into one or other of two populations. The first is a small number of individuals whose CD4 counts are below the lower end of the normal range and who have constitutionally low CD4 blood levels consistently over a period of time without ill effect. It is not surprising that such individuals have been identified given the large numbers of blood donors and cohort populations under study. These individuals may show consistently low counts but on further investigation they usually have no evidence of functional cellular deficiency. Since these individuals are probably not functionally immunocompromised and show no clinical signs, their low CD4 counts may have no prognostic significance. Most of these individuals will require no active management or prophylaxis. However, follow-up and sequential investigation is advised if laboratory abnormalities persist or progress.

Table II. Idiopathic CD4 lymphocytopenia without immunodeficiency

Source	Sex (age/years)	HIV risk	Lowest[a] CD4 count/mm^3 and comments
Weiss *et al.* (1992)	1/180	IVDU	Three cases with serial CD4 < 500 One case fulfilled CDC definition
Aledort *et al.* (1993)	12 cases out of 2191 blood donors	none	?
Ho *et al.* (1993)		M (55) no M (32) HS M (32) HS M (34) HS	90 252 200 150
Vermund *et al.* (1993)	24 cases out of 2713 cohort males	HS	In all but one a transient phenomenon. This case had gastrointestinal malignancy and was receiving cytotoxic therapy
Tindall *et al.* (1993)	9/653	HS	1 B cell lymphoma on chemotherapy 5 lost to follow-up 3 normal CD4 counts subsequently and remained HIV negative
Busch *et al.* (1994)	5/2030 blood donors	none	On recall, all 5 donors who had initial CD4 < 300 or <20% had levels within normal range
Ferrer *et al.* (1995)		M (55) hetero	27. Polyneuropathy and auto-immune haemolytic anaemia
Sheppard *et al.* (1995)	4/732 males	HS/hetero	Nine met CDC criteria. Only four met criteria on two consecutive bi-annual examinations

[a]Lowest reported CD4 count.
HS, homosexual male; Hetero, heterosexual; IVDU, intravenous drug user; M, male.

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Table III. Comparison of different CD4 depletion states

	CD4 count*	CD8 count*	Immunoglobulins*	Infection susceptibility
HIV infection	↓↓	↑	↑↑	Wide ranging, multiple and progressive
Non-HIV immunodeficiency	↓ or normal	↓, N or ↑	normal or ↓	Narrow, non-progressive
Idiopathic CD4 lymphopenia without immunodeficiency	↓	N or ↓	normal	nil
Common variable immunodeficiency	↓ or normal	↓ N or ↑	↓↓	Bacterial infections, minor opportunistic organisms
CD4 sequestration	↓	↓ or N	normal	nil

*↓, Low; ↓↓, very low; ↑, elevated; ↑↑, markedly elevated; N, normal.

The second group comprises individuals with transient depression of CD4 counts as a result of intercurrent infection or inflammatory disorder. Low counts that were recorded initially are not sustained on recall or follow-up and these cases require no further investigation, follow-up or specific therapy (Vermund, Hoover & Chen, 1993; Tindall *et al.*, 1993; Busch *et al.*, 1994).

Transient or persistent CD4+ lymphopenia secondary to infection, acute inflammation therapy or sequestration

Low CD4 counts have been reported as a transient or more long-lasting feature of a number of common acute and chronic infectious diseases (Table III and IV). However, in most cases the effect is to lower the %CD4 as a result of an absolute increase in CD8+ T cells, rather than as a consequence of absolute reduction of CD4 cells in the blood. Only tuberculosis (Beck *et al.*, 1985) and primary cytomegalovirus infection (Laurence 1993) regularly reduce absolute blood CD4 counts and then rarely to the levels required to allow classification as idiopathic CD4+ T lymphocytopenia. It remains possible however that some of the cases in Table I represent rare examples of this secondary reduction.

Acute steroid therapy leads to reduction of both CD4+ and CD8+ T cell populations with tissue sequestration but the effect is transient and levels return towards normal within 48 h (Bast *et al.*, 1983). Cytotoxic immunosuppressive drugs, particularly cyclophosphamide, can induce more long-lasting reductions in T cell subpopulations.

Finally, a series of recent case reports indicates that CD4 cell reductions of a degree severe enough to qualify for inclusion as idiopathic CD4+ lymphocytopenia can be associated with dermatoses involving CD4 infiltration (Table V). None of these reported cases has any other problems with immunodeficiency-related infections, apart from the case with documented hypogammaglobulinaemia. The most likely explanation for the CD4 lymphopenia noted in these cases is that they result in sequestration in the skin of CD4+ T cells from blood during the inflammatory phase of the illness. Functional T cell studies have not been performed on these patients, but it is likely that in many

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Table IV. Factors influencing level of absolute CD4 count

	Influence on CD4 count*
Temperature of specimen in transit	↓
Diurnal variation	↓ max. at 12.30 h ↑ max. at 20.30 h
Splenectomy	↑ CD4% but not absolute count
Acute steroid therapy	↓

*↓, low; ↓↓, very low; ↑, elevated; ↑↑, markedly elevated.

cases the residual blood T cells will function normally, as in some of the asymptomatic cases of idiopathic CD4+ lymphocytopenia.

The implications for long-term management in such cases is likewise less clear and there are probably no immediate indications for prophylaxis, unless there is clinical or laboratory evidence of functional immunodeficiency superimposed upon the presenting dermatological condition. Prospective follow-up of these patients is required before the full natural history of these sporadic cases can be elucidated. It is probable, however, that the CD4 blood depletion will prove temporary in some of these cases.

Conclusions

Non-HIV associated immunodeficiency and idiopathic CD4+ T lymphocytopenia include patient populations with a range of immunodeficiency syndromes, infections and inflammatory disorders. There is no evidence that these conditions are new or increasing in frequency and their recent recognition probably represents increasing awareness and facilities for their documentation. All cases with confirmed low CD4+ counts should be evaluated by clinical assessment and functional immunological and virological investigations. Only those with significant evidence of underlying generalised immunodeficiency require specific management measures but, in view of the uncertainty about longer term outcome, all should be observed until investigations normalise. The current CDC definition of idiopathic CD4+ T lymphocytopenia does not specify recommended time intervals between counts before case registration. In view of the

Table V. CD4 sequestration syndromes

Source	Sex	Age	HIV risk	Clinical problem	CD4 count (per mm³)*
Goodrich *et al.* (1993)	M	48	No	contact dermatitis	48
Griffiths, Stevens & Cooper (1994)	M	68	No	erythroderma, cutaneous T cell lymphoma	30
	M	63	No	atopic dermatitis	40
	M	37	No	erythroderma, psoriasis	<400
Grossman *et al.* (1994)	M	39	HS	mycosis fungoides	40
Levine *et al.* (1994)	F	42	No	common variable immunodeficiency, cutaneous granulomata	400

*Lowest reported CD4 count.

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dynamic nature of blood lymphocyte populations, a revision of the case definition is required to take account of the secondary reduction in blood CD4 cells that can occur as a result of infection or inflammation. Since blood CD4 populations do not necessarily reflect changes in secondary lymphoid organs, information is required about the numbers and functional capacity of CD4 lymphocytes in the lymph nodes and spleens of some of these patients.

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