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Epidemiology of pericardial effusions at a large academic hospital in South Africa

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SUMMARY

The aim was to establish the prevalence of large pericardial effusions in the Western Cape Province of South Africa, and to determine the incidence of various types of effusions. A total of 233 patients presented with large pericardial effusions. Each patient underwent tests for HIV, sputum smear and culture, blood culture, blood biochemistry and serological testing. Tuberculous pericardial effusions were diagnosed according to pre-determined criteria. Eighty-four patients (36·1%) were found to be HIV positive; 81 of these (96·4%) had tuberculous pericarditis. More than 65% of the study population was aged between 15 and 39 years. The prevalence of HIV amongst unemployed individuals was 49·0% compared to 30·0% amongst employed individuals. Tuberculous pericarditis was the most common cause of pericardial effusions (69·5%, $n=162$). It was concluded that tuberculosis (TB) is a leading cause of pericarditis in this province of South Africa. The prevalence of TB confounded by HIV co-infection is steadily increasing, burdening the health-care facilities.

INTRODUCTION

Tuberculosis (TB) is a leading cause of pericarditis in South Africa and a number of other developing countries [1, 2]. This is in contrast to first-world countries where TB is responsible for less than 4% of acute pericarditis [1].

In spite of economic developments and the availability of effective chemotherapy, the burden of TB is increasing. This increase has been partially attributable to the spread of human immunodeficiency virus (HIV) and is characterized by an increasing proportion of extrapulmonary cases [3]. Estimates by the Medical Research Council National Tuberculosis Research Programme put the burden of TB in South Africa for 2001 at 323 342 new cases, 41·1% of which were infectious and 52·5% of which were also HIV positive (+) [4].

The purpose of this study was to establish the prevalence of large, clinically significant pericardial effusions in the Western Cape Province of South Africa. Furthermore, we wanted to determine the incidence of various types of effusions, in particular tuberculous pericarditis in relation to demography, potential risk factors of lifestyle and HIV co-infection.

METHODS

A prospective study was carried out at Tygerberg Hospital, South Africa. Patients presenting with large pericardial effusions between February 1995 and June 2001 were enrolled. All patients gave written informed consent for participation in the study which was approved by the Ethics Committee of Stellenbosch University.

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A pericardial tap was performed under echocardiographic guidance through a pigtail catheter and fluid sent for biochemistry, microbiology, cytology and differential white cell count. Each patient also underwent tests for HIV. Patients were allocated to diagnostic groups based on pre-determined criteria. Pericardial effusions were considered to be tuberculous in origin when diagnosed by one or more of the following criteria: (i) isolation of *Mycobacterium tuberculosis* from the drained pericardial effusion or pericardial biopsy specimen; (ii) demonstration of granulomatous inflammation on histopathological examination of the pericardial biopsy sample; (iii) presence of a lymphocytic pericardial exudate together with adenosine deaminase (ADA) level $\geqslant 40$ U/l; (iv) presence of a lymphocytic pericardial exudate associated with clinical features and a good response to anti-tuberculous chemotherapy; and/or (iv) presence of a lymphocytic pericardial exudate with a positive sputum ZN stain and/or TB culture.

Statistical analysis

Statistical analysis of interval variables was performed using the Mann–Whitney *U* test and expressed as mean [standard deviation (S.D.)]. Non-parametric data were analysed using the Kruskal–Wallis one-way ANOVA and χ^2 tests. These data were expressed as median (range). A *P* value $<0{\cdot}05$ was considered statistically significant.

RESULTS

A total of 233 consecutive patients were enrolled. Eighty-four patients (36·1%) were HIV+; 81 of these (96·4%) had tuberculous pericarditis, two (2·4%) had septic pericarditis and one (1·2%) had a uraemic pericarditis, probably secondary to HIV-associated renal disease. Only two patients were not tested for HIV; these were classified as HIV negative (−) for the purposes of this study.

Demographic data

There were 132 males (56·7%) and 101 females (43·3%) that presented with large pericardial effusions. The majority of patients were black ($n=121$, 51·9%), followed by patients of mixed racial ancestry ($n=101$, 43·3%). Only 4·7% of the study population was Caucasian ($n=11$). There was a high rate of HIV infection amongst black patients; 55·6% ($n=30$) of black females were HIV+, compared to 13 females (27·7%) of other ethnic origin; 43·3% ($n=29$) of black males were HIV+ compared to 18·5% ($n=12$) of males of other ethnic origin. There was only one white male who was HIV+. The prevalence of HIV co-infection increased from year to year, beginning with 10 cases in the first year of the study and amounting to 19 cases in 2000.

The age at presentation ranged from 13 to 85 years, the mean (S.D.) was 38·0 (14·6) years. More than 65·0% of the study population and 84·5% of the HIV+ individuals were aged between 15 and 39 years. The mean (S.D.) age of the HIV+ patients was significantly lower ($P<0{\cdot}05$) than the HIV− patients [31·9 (8·4) years *vs.* 41·6 (14·1) years]. In addition, HIV+ females were significantly younger than their HIV+ male counterparts [29·2 (7·2) years *vs.* 34·0 (9·1) years, ($P<0{\cdot}05$)].

Social history data

Thirty-seven patients (15·9%) had previously received anti-tuberculous therapy. Of the 84 HIV+ patients, 9·5% had previously had TB, compared to 19·5% of HIV− patients. Fifty-three individuals (22·7%) gave a history of a positive TB contact, including 23 of the 84 HIV+ patients (27·4%) and 30 of the 149 HIV− patients (20·1%).

Only 80 individuals (including five housewives) were employed (34·3%), whereas 115 patients (49·4%) were unemployed; a further 15 patients were students (6·4%), 13 received a state pension (5·6%) and 10 received a state disability grant (4·3%). A total of 54·9% of individuals in the 15–49 years age groups were unemployed. The prevalence of HIV amongst unemployed individuals was 49·0% compared to 30·0% amongst employed individuals. 65·0% of HIV+ patients were unemployed, whereas 31·0% of the HIV-infected were employed and 4·0% were students. The difference between employment status in HIV+ and HIV− patients was statistically significant ($P<0{\cdot}005$). The majority of unemployed HIV+ individuals had never been employed and their unemployment status was not the result of being ill due to HIV infection.

The majority of patients categorized as employed were in the low-income brackets of less than R6868 ($\approx$US$ 1000) per year. Only 24 (10·3%) patients earned more than R6868 per year, including three patients who earned more than R52801 per year. None of these patients were infected with either HIV or TB.

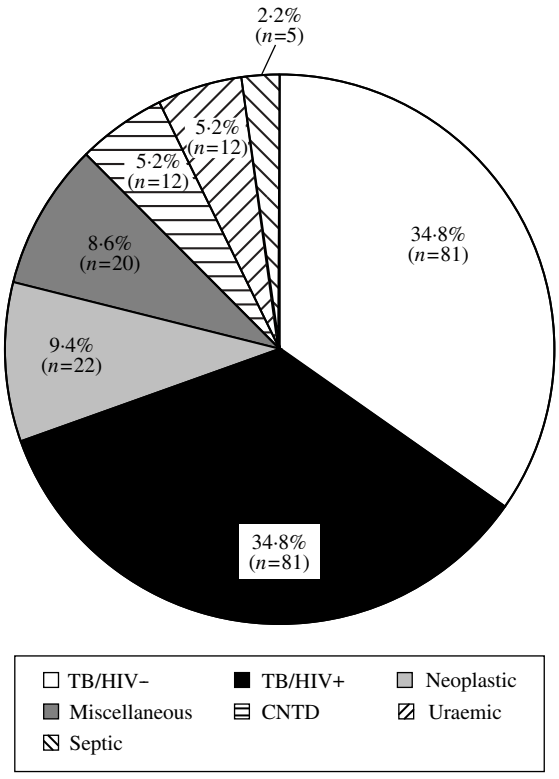

Fig. Aetiological causes of large pericardial effusions. TB/HIV−, HIV-negative tuberculous pericarditis; TB/HIV+, HIV-positive tuberculous pericarditis; CNTD, connective tissue disease.

Aetiology of large pericardial effusions

Tuberculous pericarditis was the most common cause of pericardial effusions (69·5%, $n=162$), while malignancy accounted for 9·4% ($n=22$) of all effusions. The aetiological data are presented in the Figure. The group of 'miscellaneous' effusions ($n=20$) included the following: idiopathic ($n=7$), post-traumatic ($n=5$), post-surgical ($n=2$) and multifactorial/uncertain, including congestive cardiac failure and underlying sepsis ($n=6$).

The incidence of the various types of pericardial effusions differed according to age. TB was the most common cause of pericardial effusions in all age groups, but its prominence decreased in those older than 50 years. It accounted for 83·0% of all pericardial effusions in the 15–29 years age group and for 78·0% of those aged 30–39 years. The HIV prevalence in these TB patients was found to be 57·6% and 69·4% respectively. This strong correlation with HIV diminished with increased age; the prevalence of HIV among tuberculous effusions was 44·0% in the 40–49 years age group, 12·5% in the 50–59 years group and 0% in the $\geqslant 60$ years age group. Most patients who presented with malignancy were in the 50–59 years age group, where it accounted for 32·0% of cases.

TB was the most prevalent cause for pericardial effusions amongst the lower socio-economic groups, accounting for 52·5% ($n=53$) of effusions from patients of mixed race and 90·1% ($n=109$) of effusions from black patients. Amongst the males, TB was the aetiological agent in 75·8% ($n=100$) of pericardial effusions, whereas TB accounted for 61·4% ($n=62$) of pericarditis amongst the females. Half of all tuberculous effusions occurred in individuals that were co-infected with HIV, and 96·4% of the 84 HIV+ individuals required pericardiocentesis because of TB ($n=81$). Of note was the difference observed between females with tuberculous effusions and their male counterparts with regards to HIV. In the female TB group, 67·7% of those affected were HIV+, whereas in the male TB group, only 39·0% were co-infected with HIV.

Malignancy (18 out of 22 malignant effusions) and connective tissue disease (CNTD, 10 out of 12 patients with CNTD) were more frequently diagnosed in individuals of Caucasian or mixed racial ancestry. Nine cases of CNTD (75·0%) were diagnosed in women, whereas uraemic pericarditis was seen more frequently in males ($n=7$, 58·3%).

Tuberculous pericarditis

TB accounted for 69·5% of the 233 effusions ($n=162$), including 100 (61·7%) males and 62 (38·3%) females. Eighty-one patients (50·0%) were HIV+, including 42 females (51·9%) and 39 males (48·1%). Of the HIV− tuberculous patients, a significantly higher proportion ($P<0·05$) was male (75·3%) than female (24·7%).

The mean (S.D.) age at presentation differed significantly between HIV+ and HIV− patients with TB [31·9 (8·4) years *vs.* 39·7 (15·9) years, ($P<0·05$)]. The difference in age was most striking among the group of black females, in whom the mean (S.D.) age at presentation was 44·7 (16·1) years in HIV− patients compared to 29·3 (7·8) years in HIV+ patients.

The 1-year mortality rate in this group of patients was 17·3%, and was significantly higher in the HIV+ patients (22·2%) compared to those not infected with HIV (12·3%).

Malignant pericardial effusions

Twenty-two patients had pericardial effusions due to an underlying malignancy. The majority of these

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patients had bronchus carcinomas ($n=7$), including small cell carcinoma ($n=1$), squamous cell carcinoma ($n=1$) and unspecified bronchus carcinoma ($n=5$). Haematological malignancies accounted for three effusions, including T-cell lymphoma ($n=1$), diffuse large cell lymphoma ($n=1$) and chronic myelomonocytic leukaemia (CMML, $n=1$). Another patient known to have B cell lymphoma developed a pericardial effusion secondary to septicaemia and complicated by uraemia; this patient was included under the miscellaneous group. Other malignancies associated with pericardial effusions include adenocarcinoma ($n=3$), breast carcinoma ($n=2$), cervical cancer ($n=1$), neuroendocrine tumour ($n=1$), thymoma ($n=1$), neuroblastoma ($n=1$), multicentric liver carcinoma ($n=1$), mesothelioma ($n=1$) and unspecified ($n=1$). The mean (S.D.) age of this group was 49·7 (13·8) years; 14 of the 22 patients (63·6%) were >50 years of age.

Despite the high prevalence of HIV in the study population, none of these patients were co-infected with HIV. In addition, none of the other classically HIV-associated malignancies (such as Kaposi's sarcoma and anal carcinoma) were found. Twenty (out of 22) patients with neoplastic pericardial effusions died within 1 year of diagnosis; the 1-year mortality rate for this group was 90·9%.

Pericarditis associated with CNTD

Twelve patients had underlying CNTD, including systemic lupus erythematosus (SLE, $n=7$), scleroderma ($n=1$), mixed connective tissue disease (MCTD, $n=1$), rheumatoid arthritis (RA, $n=1$) and acute rheumatic fever (ARF, $n=2$). Although not classical CNTD, ARF and RA were included in this group, as these diseases may have similar presentations to SLE with regards to constitutional symptoms and involvement of the joints and pericardium. The two patients with ARF were 13 and 15 years old respectively, while the male patient with RA was 64 years old.

The mean age (S.D.) at presentation for this group was 32·6 (14·8) years and the mortality was 33·3%. None of the deaths (three patients with SLE and one with RA) were clearly attributable to the pericardial disease *per se*.

Septic pericarditis

Only five of the 233 patients (2·1%) were diagnosed with septic pericarditis, four of whom were immunocompromised: two were infected with HIV, one had underlying B-cell lymphoma and the fourth patient was a known diabetic with a history of chronic alcohol abuse. In three of these cases, the diagnosis was based on positive cultures: *Staphylococcus aureus* ($n=2$) and Group B *Salmonella* species ($n=1$). The remaining two cases had negative cultures, probably attributable to the fact that both were receiving treatment with broad spectrum antibiotics. The mean (S.D.) age of this diagnostic group was 43·0 (25·6) years. The 1-year mortality rate for this group was 80·0%, and 100·0% in those infected with HIV.

Uraemic pericarditis

Twelve patients were classified as having uraemic pericarditis, one of whom was HIV+ with no evidence of opportunistic infection or TB. The mortality in this group was high (42·0%), and all the deaths occurred in males of mixed racial ancestry. The mean age (S.D.) at death was 50·2 (13·7) years.

Miscellaneous group

In seven patients, large effusions followed cardiac trauma or pericardiotomy, including sustained blunt trauma secondary to motor vehicle accidents ($n=2$), previous stab wounds to the chest ($n=3$), post-aortic valve replacement surgery ($n=1$) and coronary artery bypass grafting ($n=1$). Five additional patients had large pericardial effusions that appeared to be idiopathic in nature.

DISCUSSION

Pericardial effusions can result from a number of disease processes. The clinical presentation can be variable, ranging from asymptomatic effusions discovered incidentally by chest X-ray to life-threatening emergencies associated with cardiac tamponade [5]. Numerous studies have reported on the aetiologies of pericardial effusions [5–7]; however, the majority are retrospective reviews undertaken in first-world countries and suffer from inconsistencies and lack of thorough evaluation inherent in such a study method.

The incidence of the various types of pericardial effusions at Tygerberg Hospital differs significantly from developed countries. TB, which accounts for less than 4% of all cases in first-world countries [1], was the most prevalent cause in this study accounting for

69·5% of all pericardial effusions. It was especially significant amongst blacks and patients of mixed racial ancestry, accounting for 90·1% and 52·5% of all effusions respectively. TB was diagnosed in only one Caucasian patient. Conversely, pericardial effusions of non-tuberculous origin were seen more frequently in Caucasians (90·9% of effusions) and to a lesser extent in those of mixed racial ancestry. These data confirm previous reports indicating significant ethnic differences in the incidence and prevalence of TB in South Africa [8, 9]. There are, however, no data indicating that certain ethnic groups have increased genetic susceptibility to activation of latent tuberculous infection. A study performed in Puerto Rico, which involved following up a large number of persons in a BCG vaccination trial, showed no major differences in the incidence of TB between black and white tuberculin reactors [10].

Although not excluding the possibility of genetic factors, this present study demonstrates clearly that socio-economic factors contribute significantly to the racial distribution observed. TB is more prevalent in poor nations, especially affecting individuals living in poverty. In the present study only 5·8% of African blacks had an individual income in excess of R6868 ($\approx$US$ 1000) per annum. Although total household income was not specified, the impression was that this would not have been much higher. In keeping with these results and according to data contained in the income and expenditure survey, black households are the poorest in the Western Cape Province [11, 12]. Other indicators of deprivation, such as access to drinking water and sanitation, also suggest a relationship between race and socio-economic status. In the Western Cape, 37·0% of black households, compared to 77·0% of mixed and 99·0% of white households, have running tap water inside their dwelling; flush toilets are found in almost all white (99·0%) households, but in only 68·0% of mixed and 30·0% of black households [11, 12]. The correlation between poverty and TB is probably based on the two most important elements of tuberculous disease; first, the risk of becoming infected, and second, the inactivity of the cellular immune system associated with poor nutrition, alcohol abuse and the feeling of hopelessness, which are all prevalent in impoverished communities. The high risk of infection is due to the late diagnosis of smear-positive individuals (source), and the proximity and frequency of exposure related to the sharing of sleeping areas in overcrowded households [13].

The risk of TB is now confounded by HIV co-infection [3, 14, 15]. In this study 36·1% of the study population was HIV+, whereas the seroprevalence amongst those with TB was 50·0% ($P<0·05$). Of the 84 HIV+ individuals in the study, 94·6% presented with tuberculous pericarditis and only 5·4% with other pericardial disease. This finding of dual infection is a major problem in sub-Saharan Africa. The World Health Organization (WHO) estimated that of the 9·4 million people with dual infection of TB and HIV, 6·6 million (70·0%) live in sub-Saharan Africa [16, 17]. In South Africa, the incidence rate of TB is 686/100 000 per year, of which 52·5% are estimated to be co-infected with HIV [4]. In the Western Cape, the TB incidence is estimated to be 932/100 000 per year, but the HIV prevalence (36·5%) is surprisingly lower than the national average [4].

HIV, due to its ability to destroy the immune system, has frequently been implicated as a principal cause for the recent resurgence of TB worldwide. Furthermore, in many developing countries, TB has now emerged as the most common opportunistic disease associated with HIV infection [3]. In our study group, 50·0% of all patients presenting with tuberculous pericardial effusions were HIV+. The difference in age between the HIV+ and HIV− TB groups was statistically significant ($P<0·005$), the mean (S.D.) ages of the two groups being 31·9 (8·4) years and 39·7 (15·9) years respectively. In this study, the highest prevalence of HIV was found in those that are most severely socio-economically deprived, namely African black females.

In addition to an association between ethnicity and HIV infection, this study revealed a statistically significant association between unemployment and HIV infection. The overwhelming majority of those who were unemployed had never been employed; the high level of unemployment was thus not due to the effects of HIV disease. Overall, the level of unemployment observed in our study population was significantly higher than the official 19·0% unemployment level for this province [12]. Differences with regards to both population group and gender have been described in Western Cape unemployment patterns. In 1995, 45·0% of black women were unemployed compared to 23·0% of black men; in comparison, 14·0% of white females and only 3·0% of white men were unemployed respectively [11]. In keeping with previous studies, the majority of unemployed individuals were in the 15–34 years age group [12]. It is, however, important to note that although blacks are most

severely affected by poverty (and dual infection), it should not distract from the high degree of unemployment and poverty experienced by people of mixed racial background.

A previous history of TB did not contribute significantly to the development of tuberculous pericarditis in patients with HIV. This finding could be interpreted to mean that previous infection had indeed occurred less frequently in those with HIV co-infection and that tuberculous pericardial disease occurs in these patients as part of rapidly progressive primary disease. Alternatively, it could mean that the diagnosis of TB was made less frequently in the HIV+ group of which the majority were blacks – many of whom who had grown up in the Eastern Cape with poor access to health services. In this group, the pericardial effusion could have occurred as a result of reactivation of previously undiagnosed disease. Patients with HIV co-infection were also significantly younger than the HIV− patients and extrapulmonary TB is more likely to occur during a first (potentially diagnosable) episode of tuberculous disease in those infected with HIV.

Tobacco smoking and alcohol abuse were not encountered more frequently in patients with tuberculous compared to non-tuberculous effusions. The data must, however, be reviewed cautiously because data were not collected from a matched group of controls. A study performed in Shanghai found the incidence of TB higher (relative risk 2·2) among smokers than non-smokers after adjustment for age, sex, type of work, history of contact, and area of housing [18]. The high level of alcohol abuse is particularly disturbing. A case-control study conducted in Mamre in the Western Cape found an association between alcohol problems in the household and TB with an odds ratio adjusted for employment status of 2·2 [19].

It is thus, not sufficient to state that TB is caused by *M. tuberculosis*. The association between poverty and TB has long been recognized, both locally and internationally [20, 21]. The multifactorial conditions resulting in tuberculous disease involve an interaction between agent, host and environment. There are risk factors associated with becoming infected, and others that determine the breach in the cellular immunity that allows infection to progress to disease. South African statistics have for many years indicated major ethnic differences in the prevalence of TB infection, and similar differences are seen in the incidence (notification rate) of TB, suggesting that the latter are due mainly to differences in the risk of infection.

The steady rise in HIV prevalence observed in this study does not only reflect progressively increasing numbers of new cases of HIV infection, but also demonstrates how the maturation of the HIV epidemic plays out clinically. After initial infection, the human immune system becomes increasingly destroyed and the longer the epidemic lasts, the more clinical cases of HIV-associated disease will be seen. This has ominous social, medical and economic implications for the country and in particular, the Western Cape, and places considerable pressure on the existing fragile and overstretched health services in sub-Saharan Africa where more than 70·0% of the world's infection with HIV and TB occurs [3, 4].

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