Netherlands
The Journal of Medicine
PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

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BIOSIS DATABASE; EMBASE/EXCERPTA MEDICA; INDEX MEDICUS (MEDLINE)

Cover
Etching by Jops Jacobs, for details on the artist, her work, and how to order see page 339.

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Subscription fee
The annual subscription fee within Europe is € 650,00, for the USA € 665,00 and for the rest of the world € 675,00. Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis.

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EDITORIAL

Osteoporosis: disease, risk factor or hype?

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INTRODUCTION

The time for osteoporosis has come. In a recent editorial it was estimated that 'the disease of the 21st century' will increase more than twofold within this period.[1] Until recently, healthcare providers have shown little interest in osteoporosis. The magnitude of the problem was not recognised; back pain and hip fractures were not considered sensational complaints or major events. The pathogenesis of bone fragility was largely unknown and difficult to study.[2] Fractures observed on radiographs of the lumbar or thoracic spine were supposed to be the inevitable consequence of old age. Moreover, bone density could not be measured in a reliable way, and treatment showed no direct clinical results; it was merely confined to the prevention of new fractures. Some, but not all of this, has now changed.

EPIDEMIOLOGY

Public awareness has grown enormously, although the hype in the USA about screening and the use of calcium-enriched milk or oestrogens under the motto 'remain forever young' is not encountered in the more reserved Dutch society. Yet osteoporotic fractures are frequent and still their number increases: worldwide from an estimated 1.7 million in 1990 to a projected 6.3 million hip fractures in 2050.[3] Hip fractures are an important cause of disability; more than half of the patients with hip fractures become dependent. Up to 20% more women die than expected for their age within the first year after a hip fracture due to complications related to immobility and hospital admission.[4] Altogether, fractures in the USA cost around US$ 20 billion a year, with hip fractures accounting for over a third of the total.[5]

RISK FACTORS

As already stated, osteoporosis is a heterogeneous disorder with multiple causes, and risk factors with a different relative importance. Independent of bone mineral density (BMD), previous fractures, premature menopause, hypogonadism, age, current use of drugs (anticonvulsants, corticosteroids, long-acting benzodiazepines or antihypertensives), disability, history of maternal hip fracture and previous hyperthyroidism are all predictors for hip fractures. This is especially so in Caucasian women in the northern countries. Although these risk factors are well established, there is no evidence-based search strategy that identifies individuals at high risk.[6] The epidemiology of vertebral fractures is even less well established. First there is no universally accepted definition; a substantial proportion escape clinical diagnosis,[7] only about a third come to medical attention and less than 10% require admission.[8]

DIAGNOSIS

Diagnostic methods have improved dramatically in the past decade.[9] Especially BMD can be measured quite accurately with a precision of <3%. Quantitative Digital Radiography (QDR), also known as dual energy X-ray absorptiometry (DEXA), is the method of choice. By WHO criteria, osteoporosis is defined as a BMD of more than 2.5 SD below the average value for pre-menopausal women (T score <-2.5 SD) and osteopenia as a T score between <-1 and ≥-2.5. Measurement at the hip is the gold standard in terms of site, since it has the highest predictive value for hip fracture[10] and predicts risk of all fractures as well. Prospective studies with QDR show that the risk of fracture about doubles for each SD reduction in BMD.[10]

PREVENTION AND TREATMENT

There are no highly effective strategies for treatment and, to a lesser extent, for prevention. Preventive measures include adequate calcium intake and regular walking exercise. Measures to reduce the risk of falls in the elderly are of major importance as 90% of hip fractures result from a simple fall.
Four antiresorptive drug regimens are currently approved in the Netherlands: calcium, oestrogen (including the oestrogen receptor modulator raloxifene), vitamin D and bisphosphonates, while calcitonin still has not met with the great expectations of the past.
Oestrogens retard postmenopausal bone loss, but may have serious side effects, such as venous thrombosis and an increased risk of breast, endometrial and ovarian cancer.[11] This risk of cancer is the reason why many women choose for bisphosphonates whose main side effects are gastrointestinal. Especially the once-weekly 70 mg alendronate is an attractive alternative as it might improve long-term compliance.[12]
Bone formation stimulating regimens such as sodium fluoride, a low dosage of the 1-34 synthetic fragment of parathyroid hormone and the use of anabolic steroids are still under debate.

SOME PERSONAL REMARKS TO END WITH

In my opinion, the WHO terminology is somewhat inconsistent. In accordance with, for example, the relation between the risk factor high blood pressure and the disease cerebrovascular accident, it seems logical to me to define osteopenia in terms of BMD as a risk factor for osteoporotic fractures. To define osteoporosis as a disease state on the basis of BMD assessments has the danger of medicalising a significant proportion of women.

In this issue of the Journal two articles on osteoporosis are included. First, the primarily methodological manuscript by Boers that deals with the implications of non-inferiority of drugs for trial design.[13] Because osteoporosis is used as an example, the article gives a nice overview of recent trials with alendronate, risedronate, parathyroid hormone and raloxifene.
Second, a treatment study that compares monthly intravenous administration of pamidronate with oral alendronate.[14] Because of the study design (an open, retrospective study with BMD as an endpoint in a small group of patients) no major conclusions can be drawn. Yet intravenous pamidronate could be an alternative in non-compliant patients or in patients who cannot tolerate an oral bisphosphonate.

Recently, the second revised guideline regarding osteoporosis was published by the Dutch Institute for Healthcare Improvement (CBO).[15] The guideline is of excellent quality: the multiprofessional committee of opinion leaders joined by a representative of the patients has documented all recommendations according to the level of evidence derived from literature. An efficiency analysis has also been performed. Hopefully, the document will end the dispute between two recently published guidelines that contradict each other, one by the Dutch College of General Practitioners[16] and one by the Dutch Health Council.[17]
In the recent CBO guideline, screening of the general population is discouraged. Case finding by QDR (preferred above CT for practical reasons) is advised in selected patients: women above 50 years of age with a recent fracture; women of over 60 years with three combined risk factors (positive family history, low body weight and severe immobility) and women (of any age) with a vertebral fracture. In general, follow-up measurements are not recommended.
As an important preventive measure, weight-bearing physical exercise is mentioned. In the first year after menopause, oestrogens (combined with progestogens), tibolone and raloxifene may be considered. Treatment with bisphosphonates for a maximum of five years is advised in patients treated with corticosteroids, postmenopausal women with one or more osteoporotic fractures, or men and women with an increased risk and a T score <-2.5.
Considering the whole guideline the most surprising recommendation to me was the preference for tibolone and raloxifene. In the studies with tibolone only bone mass was used as an endpoint. The studies with raloxifene are rather weak while long-term safety data regarding the risk of endometrial or breast cancer are not available.

Finally, I am not convinced that osteoporosis of the vertebral spine deserves the attention obtained recently. The burden of disease, even if a fracture occurs, is moderate. The effects of long-term treatment in relation to side effects and the results of widespread medicalisation have not been studied properly. Pressure and major interest from the pharmaceutical companies that have their eye on a new large and rapidly expanding market facilitates all kinds of trials from which major conclusions are drawn. I was perplexed by a statement in the abstract of an overview article on the treatment of osteoporosis: 'nasal calcitonin greatly reduces the risk of vertebral fractures'.[18] In the first paragraph of the same article the antifracture efficacy is only indicated as 'some evidence', while the cited four studies regarding its use show major weaknesses. It reminded me of an occurrence some twelve years ago. At that time I took part in a double-blind, randomised multicentre trial comparing intranasal calcitonin with placebo in patients with osteoporosis. The trial was prematurely terminated because of side effects and insufficient improvement. All support was withdrawn

and it was never published. When I looked up the old study data, I noticed that the author of the overview article had been the consultant for the pharmaceutical company involved. The message? Beware of publication bias.

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EMEA guidelines for trials in osteoporosis: design implications

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ABSTRACT

The design, execution and interpretation of trials that do not contain a placebo arm are a challenge. These issues are briefly discussed in the context of the new European guidelines for the study of drugs for the indication prevention and treatment of postmenopausal osteoporosis.

INTRODUCTION

The new EMEA (European Medicines Evaluation Agency) guidelines for agents active in the treatment and prevention of osteoporosis have important implications for the design of future trials.[1] The 'Group for Respect of Ethics and Excellence in Science' (GREES), an informal 'think tank' that includes scientists, regulators and industry scientists, met to discuss these implications.[2] Part of these discussions was devoted to the concept and challenges of non-inferiority trials, especially in terms of definition of non-inferiority, design issues, the situation in osteoporosis, and the consequences for sample size. These issues are briefly reviewed. It is important to realise that there are important ethical issues around the choice of the comparator in a trial. A placebo comparator provides the most robust evidence of efficacy, but is unacceptable when effective therapy already exists, especially in patients at high risk. In such a situation demonstrating superior efficacy against established treatment seems reasonable. However, such a requirement will limit development of new agents. In most diseases we need several active agents as alternatives, preferably with different modes of action and side effect profiles. To enable the development of these alternatives, non-inferiority trials must be considered.

THE CONCEPT OF NON-INFERIORITY

Classical trial design and frequentist statistics revolve around the null hypothesis of no difference, a hypothesis we will try to reject with the data in hand, allowing a certain error level (alpha level, type I error). This chosen level (usually 5%) indicates we are willing to reject the null hypothesis of no difference, and accept the alternative hypothesis of a difference (of unspecified magnitude and direction) despite a small chance (5%) that in fact no difference exists. The other error (type II error) is committed when we declare no difference when in truth a difference does exist. The level of beta, usually set at 10 or 20%, governs the chance of this error occurring. The inverse of beta is the power of a study. When set at a certain desired level, this power determines the required sample size given a minimum difference we want to detect and the level of uncertainty around the measure we are using.

The limitations of this tradition are well known.[3] They become more evident when we try to design a study that tries to prove equivalence or non-inferiority between two agents. Equivalence is a two-sided concept whereas non-inferiority is one-sided, but both require an explicit definition of what constitutes a minimum clinically important difference. In equivalence we want the statement 'A is not better or worse than B to a relevant degree'; likewise, in non-inferiority we want the statement 'A is not worse than B to a relevant degree'. Here, we will focus on non-inferiority. Once we have defined this minimum clinically relevant difference, we can almost proceed in the classical fashion described above. Other approaches, e.g. Bayesian, may be more acceptable from a methodological point of view,[4] but such methods are still regarded with suspicion by regulatory

agencies. Proceeding in the classical, frequentist fashion we have to recognise the perspective has now changed. Where in normal trial design the null hypothesis states no difference between the treatment arms (e.g. A is no different from placebo), a conservative approach to non-inferiority would be to define the null hypothesis as: 'this new drug (A) is inferior to the active comparator (B) to a relevant degree'. We would only reject this hypothesis (and conclude non-inferiority) on the basis of sufficient evidence. So, in the case of non-inferiority, what was classically the null hypothesis now becomes the alternative hypothesis, and vice versa. If we now proceed to analyse the non-inferiority trial in the classical way (for the moment disregarding the switch of the hypotheses), the rejection of the hypothesis of no difference will, as always, depend on the chosen alpha level. However, the lower the alpha level, the greater the chance we cannot reject the hypothesis of no difference, which would lead to a conclusion of non-inferiority. Thus, an argument can be made to increase the alpha level (e.g. to 10%, corresponding to a one-sided alpha of 5%), increasing the likelihood of rejecting this hypothesis, and forcing the assumption that the new drug is actually inferior. Obviously this should only be done when the new drug performed worse than the active comparator. In effect, we are performing a one-sided test, which can only 'prove' non-inferiority, never superiority. Thus, non-inferiority trials can be analysed in the classical way, but designs that are conservative in a normal set-up become non-conservative when non-inferiority is claimed.

DESIGN ISSUES IN TRIALS WITH AN ACTIVE COMPARATOR

Recent commentaries have outlined the most important issues in trials that compare two active treatments. These include the choice of the active control, the determination of the acceptable margin of inferiority, the choice of the parameter of comparison, and the quality of trial conduct.[5] The choice of the active comparator is obviously essential. This drug must have a well-established, predictable and quantifiable effect that is clinically relevant. Ideally this effect must be proved constant across different populations of interest. The margin of inferiority will be discussed below. As a rule, the parameter of comparison should be appropriate and fair in terms of relative sensitivity to the effects of the study and control treatments. To compare drug effects, it is essential to consider the sensitivity of the endpoints to the mechanism, onset and duration of drug effects. In the guidelines, radiological fractures of the spine, clinical fractures of the hip, and bone density are the principal measures. Interestingly, despite many large trials there is still no common reference standard for the measurement of (radiological) vertebral fractures, in contrast to the other measures. Finally, trial conduct is even more important in the setting of non-inferiority trials than in normal trials. Poor conduct usually biases against finding differences; in non-inferiority trials this would increase the chance of declaring non-inferiority for the new agent. Impeccable design and execution is mandatory. Important issues include randomisation, blinding, handling of co-interventions, contamination (crossing over), and compliance. As discussed below, adequate sample size given the expected results of the chosen outcome in the comparator is essential because low power implies more difficulty in detecting existing differences.

SITUATION IN OSTEOPOROSIS

Treatment of osteoporosis

In the highest risk group (women with documented vertebral fractures) an informal review of several recent large trials yields an incidence of (new) vertebral fracture (over three years) that ranges between 14 and 29% for placebo, versus 3 and 18% for the active drug (*table 1*).[6-12] In patients with only a bone mass T score below -2.5 (but no fractures), there is less evidence, and these percentages are much lower: approximately 4 and 2%, respectively. Finally, for hip fractures percentages range between 1 and 5% for placebo, versus 1 and 4% for the active drug. As discussed elsewhere, these findings would support limiting non-inferiority trials to the highest risk subgroup. In this subgroup placebo-controlled trials are deemed unethical, as several active drugs have shown to reduce the risk of subsequent fracture by 50% or more, and the rate of fracture in the treated group remains high.

Prevention of osteoporosis

Following the guideline, results of bone mass comparisons were only tabulated in prevention studies (*table 2*). In these studies, the change in vertebral bone mass over three years ranged between -1 and 2% in placebo, versus 1 and 8% in actively-treated groups. There was little evidence available for the hip.

SAMPLE SIZE CONSIDERATIONS

Sample size is dependent on the minimum clinically relevant difference, the margin of error around the measurement of this difference, and the chosen alpha and beta levels. When rates are compared, the margin of error is dependent on the base rate in the control group. For continuous measures such as bone mass, a standard deviation of the difference must be available. For the treatment of osteoporosis, calculations have been made for base rates

Table 1

Review of three-year fracture rates (percentage of patients with new fractures) in major trials of postmenopausal osteoporosis treatment/prevention

A. SPINE RISK PROFILE	TRIAL (REFERENCE)	PLACEBO	MAXIMUM EFFECT IN ACTIVE GROUP
Existing fracture	FIT-1[6]	15.0	8.0
	MORE[8]	21.2	10.7
	VERT/USA[9]	16.3	11.3
	VERT/EU/Austr[10]	29.0	18.1
	PTH[12*]	24.5	7.5
Bone mass <-2.5	FIT-2[7]	4.4	2.2
No fracture	MORE[8]	4.5	2.8
Bone mass -2.5 < # <1.0	FIT-2[7]	1.5	1.1
B. HIP RISK PROFILE	**TRIAL (REFERENCE)**	**PLACEBO**	**MAXIMUM EFFECT IN ACTIVE GROUP**
Existing (vertebral) fracture	FIT-1[6]	2.2	1.1
	MORE[8]	0.7	0.8
	VERT/USA[9]	2.3	1.7
	VERT/EU/Austr[10]	2.7	2.2
	PTH[12*]	1.3	0.8
No fracture	Ris Hip all[11]	3.9	2.8
Bone mass <-2.5	Ris Hip <80	3.2	1.9
1 nonskeletal risk factor or bone mass <-2.5	Ris Hip >=80	5.1	4.2
Bone mass <-2.5	FIT-27	1.7	0.8
Bone mass -2.5 < # <1.0	FIT-27	0.4	0.8

*A = new vertebral fractures (on radiographs), B = hip fractures, * = three-year rates extrapolated from 18-21 month data.*

between 0.5 and 20%, for two-sided alpha levels of 5 and 10%, and for power levels of 80 and 90% (*figure 1*). It is evident that to obtain feasible sample sizes the base fracture rate should be above 10% over three years. Lower sample sizes are obtained when the limit of non-inferiority is not set too strictly. For example, if 20% worse than the control group is acceptable, at 10% fracture rate in the control group, the study drug would be deemed inferior if the rate was above 12%. At a power of 90% and a one-sided alpha of 2.5% (two-sided alpha of 5%) this would lead to a sample size of 5134 per group, and 4183 at a one-sided alpha of 5% (see example line in *figure 1*, bottom). A higher alpha will decrease sample size, and is defensible because it will increase the chance of declaring inferiority. Finally, limiting the required power to 80% has important effects. For example, a power of 80% and a one-sided alpha of 5% would lead to a sample size of 3019 (see example line in *figure 1*, top). However, this may not be acceptable because it increases the chance of declaring non-inferiority.

For the prevention of osteoporosis the outlook is more favourable (*figure 2*). Apart from the factors mentioned above, in studies of bone mass the SD of difference plays a major role. Great attention to precision will lead to major savings in sample size, as shown when the SD is reduced from 10 to 5%. For example, if the expected increase in bone mass in the active control group is 4% over three years, we want our new drug to show increase of at least 3.2% (no more than 20% worse compared with control). At a power of 80%, a one-sided alpha of 5% and a SD of 10%,

Table 2

Change in bone mass in major trials of postmenopausal osteoporosis prevention

SITE	TRIAL (REFERENCE)	PLACEBO	MAXIMUM EFFECT IN ACTIVE GROUP
Spine	MORE[8]	0.3	3.0
	FIT-2[7]	1.5	8.3
	VERT[9]	1.1	5.4
Hip neck	MORE	-1.1	1.0
	FIT-2	-0.8	3.8
	VERT	-1.2	1.6
Hip total	FIT-2	-1.6	3.4
Hip troch	FIT-2		difference 6.8
	VERT	-0.7	3.3

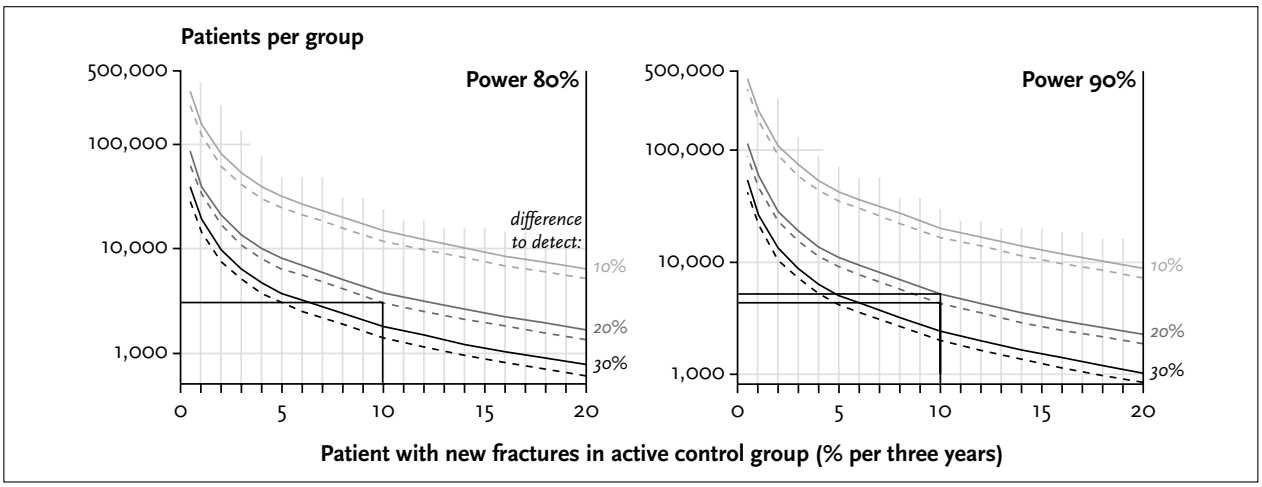

Figure 1

Sample sizes per group in non-inferiority trials with fractures as endpoint

Curves indicate required sample size to detect a difference between the active control group showing a three-year fracture rate between 0 and 20% (x-axis), and an experimental group showing a fracture rate that is at least 10% (light grey), 20% (dark grey) or 30% (black lines) worse. Continuous lines: one-sided alpha level of 2.5%; dashed lines: one-sided alpha level of 5%. Top panel: power 80%; bottom panel: power 90%.

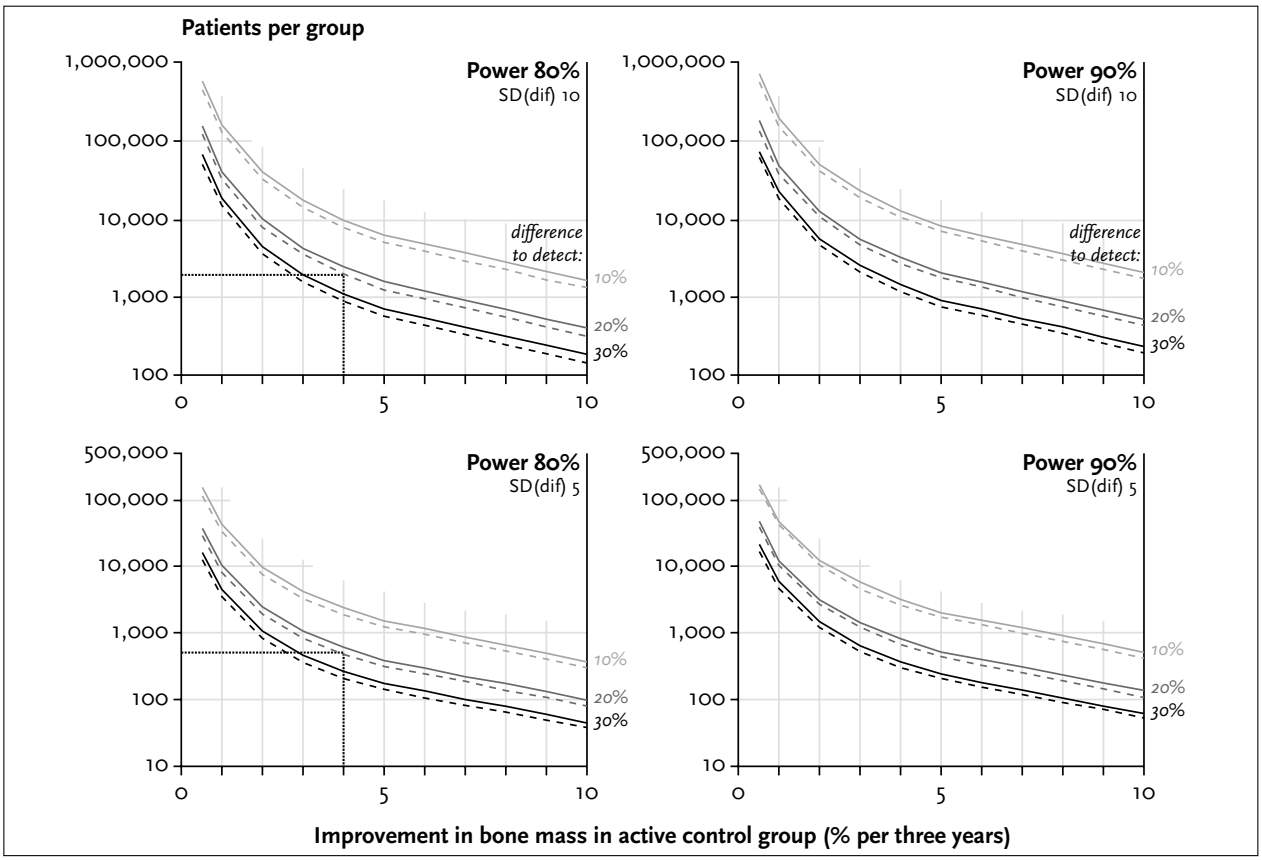

Figure 2

Sample sizes per group in non-inferiority trials with bone mass as endpoint

Graph layout as in figure 1. X-axis now describes the expected improvement in bone mass over three years in the active control group. Again, the difference to detect is expressed as a percentage of this improvement (e.g., expected improvement in control, 5%; 20% inferior in experimental group equals an expected improvement of 4%). Left panels: power 80%; right panels: power 90%. Top panels: standard deviation of difference [SD (dif)] estimated at 10 (percentage units of initial bone mass); bottom panels: SD (dif) estimated at 5.

each group needs 1925 patients. When the SD is reduced to 5%, the group size is 857 (see example line, *figure 2*, left).

CONCLUSION

In conclusion, the advances in therapy of osteoporosis have made it more difficult, and in some instances unethical, to perform placebo-controlled trials. The design and execution implications of non-inferiority trials require careful attention.

NOTE

A summary of this work was included in the GREES report.[2]

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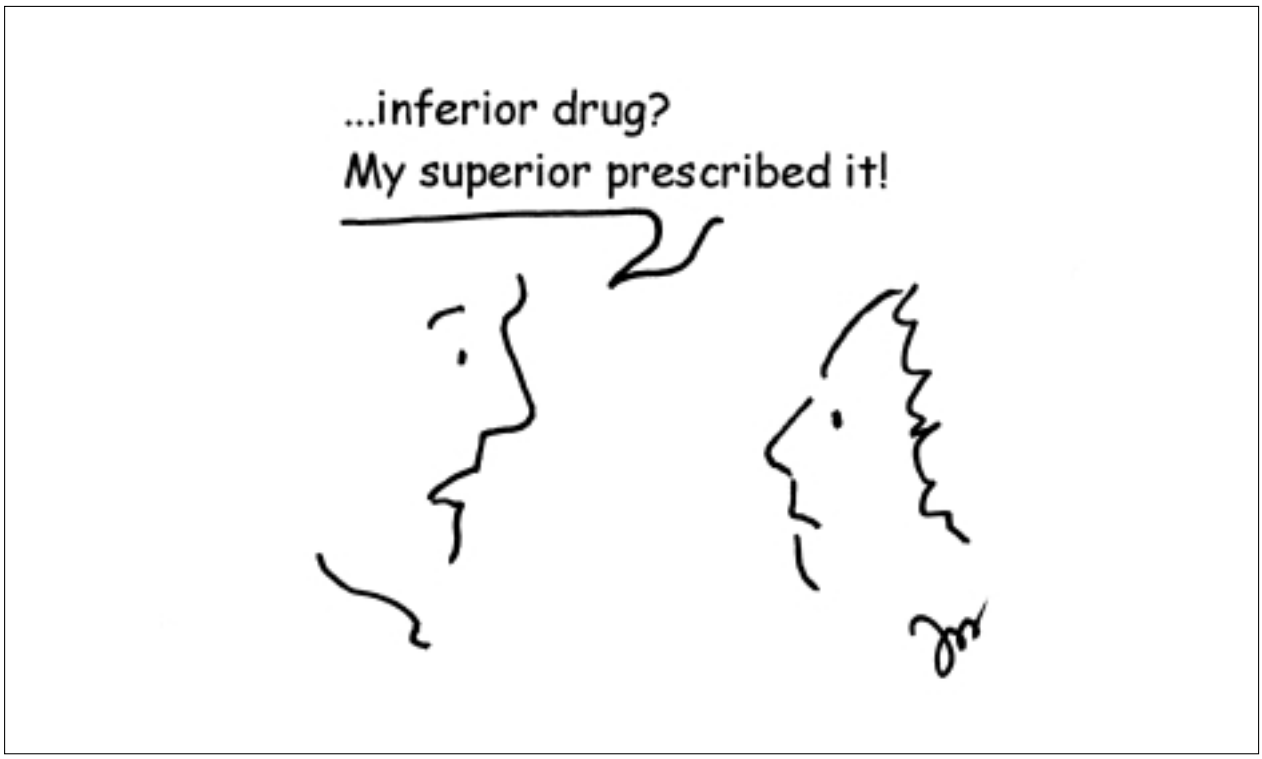

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Intravenous pamidronate compared with oral alendronate for the treatment of postmenopausal osteoporosis

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ABSTRACT

There are several options for the treatment of osteoporosis in postmenopausal women.

One of the options is treatment with bisphosphonates, which are very potent inhibitors of osteoclast-mediated bone resorption *in vitro* and *in vivo*. The most potent bisphosphonates have a nitrogen side chain and can be given orally or intravenously (i.v.). In the present study we evaluated retrospectively the effect of intravenously administered pamidronate (60 mg monthly) in comparison with oral alendronate with regard to bone mineral density (BMD) and vertebral fractures.

A total of 117 consecutive women aged 46 to 78 years were seen in the outpatient clinic because of postmenopausal osteoporosis. Three-year follow-up data were available for a total of 45 patients treated with pamidronate i.v. and 40 patients on alendronate for at least three years. In the pamidronate group mean T score of lumbar spine BMD increased from -3.49 ± 0.72 to -2.81 ± 0.74 SDs after three years of treatment ($p<0.001$). In the 40 patients treated with alendronate we observed an increase in the T score from -2.95 ± 0.67 to -2.33 ± 0.74 SDs ($p<0.001$) during the same observation period.

X-rays of the lumbar and thoracic spine were analysed from 25 patients in each group who had been treated for at least three years. At baseline nine patients (36%) in the pamidronate group had one or more vertebral fractures compared with seven patients (28%) in the alendronate group. After three years of treatment no new fractures were observed, while only three women in the pamidronate group and two in the alendronate group showed a deterioration of one or more pre-existing vertebral fractures (p=ns between groups).

This retrospective analysis demonstrates that monthly intravenous administration of pamidronate is at least as good as alendronate taken orally in the treatment of women with postmenopausal osteoporosis, with regard to improvement of bone mineral density of the lumbar spine. We conclude that it is a good alternative for the more widely used oral bisphosphonates as it is effective, well-tolerated and easy to administer.

INTRODUCTION

Postmenopausal osteoporosis is a major healthcare problem that results in substantial morbidity and mortality.[1-4] Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.[1]
During adult life, bone is continuously remodelled, resorbed by osteoclasts and new bone formed by osteoblasts. In young adults remodelling is near-perfectly coupled so that the overall rate of resorption is almost exactly matched by the overall rate of formation. Following the menopause, however, the volume of bone resorbed exceeds the volume of new bone formed, leading to osteopenia and osteoporotic disease. Progressive bone loss is almost universal in women after the age of 35 years. The rate of loss is accelerated during

the early postmenopausal period, particularly at skeletal sites with a high proportion of trabecular bone.
As a consequence, women have an average lifetime risk of approximately 50% for developing at least one osteoporotic fracture and a risk of 15% for experiencing a hip fracture.[5,6] These fractures are associated with a high morbidity and a high mortality, as well as a marked reduction in the quality of life and high costs of treatment.
There are several options for the treatment of osteoporosis in postmenopausal women. Compounds that inhibit bone resorption, i.e. osteoclastic activity, are attractive pharmacological candidates. One of the options is treatment with bisphosphonates. These are analogues of inorganic pyrophosphate and very potent inhibitors of osteoclast-mediated bone resorption *in vitro* and *in vivo*.[7] The most potent bisphosphonates have a nitrogen molecule in the side chain (e.g. pamidronate and alendronate) and can be given orally or intravenously (i.v.). Oral administration may cause serious side effects, especially in the digestive system.[8-10] Although there are several risk factors for fractures, reduced bone mineral density (BMD) is the strongest predictor.[11] Thus, one of the goals of pharmacological treatment in women with postmenopausal osteoporosis is to reduce the risk of fractures by increasing bone mass of normal quality. Most of the clinical studies with bisphosphonates have investigated the abilities of a specific compound with regard to inhibition of mineral loss and fracture incidence in comparison with placebo. Almost all known bisphosphonates show more or less advantages with regard to the previously mentioned parameters if compared with placebo treatment or just calcium (and sometimes vitamin D) supplements. Intermittent intravenous regimens with bisphosphonates are being explored as alternatives to oral regimens. In the present study we evaluated retrospectively the effect of i.v. administered pamidronate in comparison with oral alendronate with regard to BMD and vertebral fractures. The decision to start therapy was made by the treating physician together with the patient in the outpatient clinic, so this paper describes the effects of these treatments in real life. Intravenous pamidronate was chosen because some patients prefer this way of administration, because it is easy to administer and avoids (worsening of) gastrointestinal complaints or gastrointestinal side effects of oral bisphosphonates. Furthermore, experiences from clinical practice as well as one paper[12] have suggested that intravenous pamidronate may lead to more rapid reduction in pain.

METHODS

Study population

A total of 117 consecutive women aged 46 to 78 years were seen in the outpatient clinic because of postmenopausal osteoporosis. The same physicians (A.C. Heijckmann and J.R. Juttmann) followed all patients in one hospital. The diagnosis was based on BMD measurements of the lumbar spine, while other causes of osteoporosis were excluded. We used the criteria of the World Health Organisation,[13] so all patients had a BMD value more than 2.5 SD below the adult peak bone mass. They were started on i.v. pamidronate (n=67) or alendronate (n=50), and continued this therapy for at least one year. At the start of treatment all patients were at least five years postmenopausal. Pamidronate was given to patients primarily if no daily oral medication was desired or needed, and also to some subjects who experienced gastrointestinal side effects after a short one to three weeks' period of alendronate use and to patients who experienced severe low back pain. None of the women were on hormone replacement therapy (HRT) during this study. Due to the retrospective nature of our study, previous HRT use could not be ascertained fully.

Oral calcium supplements were given (500-1000 mg/day) if the dietary history indicated that daily calcium intake was less than 1000 mg. No other medication with a possible effect on bone metabolism (e.g. vitamin D, corticosteroids) was used. Vitamin D levels were not measured routinely before or during this treatment.

Treatment

Patients in the pamidronate group received 60 mg of this drug by intravenous infusion once monthly. Pamidronate was dissolved in 500 ml saline, which was infused over a period of three hours in an outpatient clinic setting. Patients on alendronate took one 10 mg tablet orally once a day, in the morning, 30 minutes before breakfast.

Endpoints

Our clinical protocol describes that BMD of the lumbar spine is measured yearly with a Hologic 2000 BMD measuring machine following standard procedures. X-rays of the spine were also taken every year. In July 2001 we retrospectively evaluated the data of all patients who had been treated for osteoporosis in our clinic with alendronate or pamidronate i.v. during the last five years. An aselect sample of 25 patients from each group was drawn to assess lumbar and thoracic spine X-rays and evaluate possible new vertebral fractures. A vertebral fracture at baseline was defined as a reduction of either the posterior, anterior or middle height of the vertebra of at least 20% with an absolute infraction of 4 mm compared with one of the adjacent vertebra. A new fracture was defined as a reduction of at least 20% with an absolute decrease of at least 4 mm of either the posterior, anterior or middle height of the same vertebra at baseline.

Statistical analysis

A descriptive statistics report was created using SPSS (version 11.01 for Windows™). Independent two tailed t-tests

were performed to test for significance between the two groups (pamidronate versus alendronate). Analyses for trend and paired t-tests were performed to test for the significance level within the group, testing interval 0 versus 1, 2 and 3. P values <0.05 were considered to be statistically significant.

RESULTS

Table 1 depicts some of the baseline data. Full data were available for a total of 45 patients who were treated with pamidronate i.v. for at least three years. Their mean age at start was 66.6 ± 8.4 years and their average BMD at the lumbar spine was 0.69 ± 0.08 g/cm². The 40 patients who were treated with alendronate for at least three years were slightly younger (age 61.2 ± 9.9 years), and had a slightly higher BMD (0.75 ± 0.07 g/cm², p<0.05 versus the pamidronate group).
The mean T score had increased by 0.67 (from -3.49 ± 0.72 to -2.81 ± 0.74) after three years of treatment in the pamidronate group (p<0.001). The alendronate-treated patients showed an increase of 0.62 (from -2.95 ± 0.67 to -2.33 ± 0.74, p<0.001) during the same observation period (*table 2*).
As there was a difference in BMD at baseline between the two groups, we also assessed the percentual change over time, which was not different between the two groups (*figure 1*).

Table 1
Baseline characteristics of the patients with a complete three-year follow-up

	PAMIDRONATE	ALENDRONATE
Number	45	40
Age	66.6 ± 8.4*	61.2 ± 9.9
BMD lumbar spine (g/cm²)	0.69 ± 0.08*	0.75 ± 0.07
T score (SDs)	-3.49 ± 0.72*	-2.95 ± 0.67

* *P<0.05 pamidronate versus alendronate.*

Additional analysis of the cohort of patients who completed four years of treatment indicates that both patient groups showed a further small increase in BMD from year 3 to year 4. In 20 patients on pamidronate mean BMD increased from 0.76 ± 0.07 g/cm² to 0.78 ± 0.07 g/cm², and in the 19 subjects on alendronate it increased further from 0.78 ± 0.10 g/cm² to 0.80 ± 0.10 g/cm² (both p<0.001).

X-rays of the lumbar and thoracic spine were analysed from 50 patients treated for at least three years (25 in each group). At baseline nine patients (36%) in the pamidronate group had one or more vertebral fractures compared with seven patients (28%) in the alendronate group. After three years of treatment only three women in the pamidronate group and two in the alendronate group showed a deterioration of one or more pre-existing vertebral fractures. There were no new fractures in either group (*table 3*).

Pamidronate was well tolerated. A few patients developed the expected flu-like symptoms, but only from the first administration of the drug.

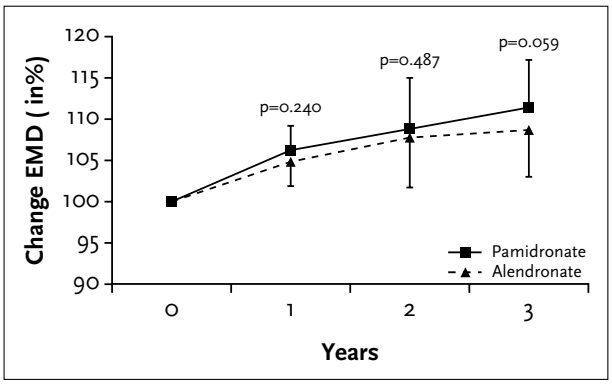

Figure 1
Percentage change BMD (pamidronate versus alendronate)
There was no significant difference between the two treatment groups. However, there was a statistical difference (p≤0.001) in BMD increase between every year in the same group.

Table 2
BMD and T scores in the pamidronate-treated (n=45) and the alendronate-treated group (n=40), observation period up to three years

	START		THREE YEARS	
	PAMIDRONATE	ALENDRONATE	PAMIDRONATE	ALENDRONATE
BMD	0.69 ± 0.08*	0.75 ± 0.07	0.77 ± 0.08* $	0.82 ± 0.08$
T score	-3.49 ± 0.72*	-2.95 ± 0.67	-2.81 ± 0.74* $	-2.33 ± 0.74$
Delta T	-	-	0.67 ± 0.35#	0.62 ± 0.37
Increase BMD in %	-	-	11.6 ± 6.5#	9.3 ± 5.8

* *P<0.05 pamidronate versus alendronate,* # *p=ns pamidronate versus alendronate,* $ *p≤0.001 three years versus start.*

Table 3
Fracture incidence in both groups

	NUMBER ANALYSED	NUMBER WITH VERTEBRAL FRACTURES AT BASELINE	NUMBER WITH DETERIORATION OF FRACTURES AFTER THREE YEARS	NEW FRACTURES
Pamidronate	25	9 (36%)*	3	0
Alendronate	25	7 (28%)	2	0

* *P=ns.*

DISCUSSION

This analysis demonstrates that monthly intravenous administration of pamidronate is at least as good as alendronate taken orally in the treatment of women with postmenopausal osteoporosis, with regard to improvement of bone mineral density of the lumbar spine. We observed an increase in BMD of 11.6% in the pamidronate group compared with 9.3% in the alendronate group, which is not statistically significant. Possibly this difference can be explained by a lower baseline BMD of the pamidronate group. The increase in BMD corresponds well with data described in the literature on the general effects of the more frequently used oral bisphosphonates. For alendronate the average was 9% after three years of treatment.[14] Reid *et al.* found an increase in lumbar spine BMD of 9.4% in 48 postmenopausal women treated with pamidronate 150 mg/day orally.[15] In a recent Dutch study in 78 postmenopausal women and 23 men with at least one vertebral fracture, an increase of 14.3% of BMD of the spine was found after five years of treatment with oral pamidronate.[16] Only limited results of intravenous administration of pamidronate are available. Also, several different doses, regimens and intervals were employed,[17,18] which makes the comparison of these studies difficult. Krieg *et al.* treated 11 patients with intravenous pamidronate (60 mg every three months) for osteoporosis after heart transplantation (mean BMD 0.809 ± 0.017 g/cm^2), and showed an increase in BMD at the lumbar spine of 14.3% after three years of treatment.[17] Younes *et al.* treated 20 patients with osteopenia and osteoporosis with 30 mg pamidronate intravenously every three months and found a significant increase in bone mineral density after 14 months.[19]
In our small group of patients for whom a four-year follow-up was available, we still found a small increase in BMD between year 3 and 4, in both groups. A similar continued positive effect of bisphosphonates was previously reported by Tonino *et al.* who found a still further increase in BMD amounting 0.8% a year, even in years 5 and 6.[20] No striking difference in fracture incidence was noticed between the two groups before and during treatment, although we realise that the groups investigated are too small to draw firm conclusions on this aspect.

In the FIT (Fraction Intervention Trial) study[21] the effect of alendronate on fracture incidence was studied. A new vertebral fracture was defined as a decrease of 20% and at least 4 mm in the height of any vertebral body from baseline to end of the study. In the group with existing vertebral fractures at baseline they found an annual incidence for a radiological vertebral fracture from 2.61% in the alendronate group versus 5.01% in the placebo group. In our present study, after three years of treatment we did not find any new fractures; in 12% of pamidronate users a deterioration of fractures was seen compared with 8% in the alendronate group.

We conclude that intravenous administration of pamidronate is a good and attractive alternative for the more widely used oral bisphosphonates, as it is effective, well-tolerated and easy to administer. We are currently performing a prospective evaluation of this treatment with a more systematic evaluation of pain symptoms.

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Netherlands
The Journal of Medicine

Clinical and radiological evolution in patients with pulmonary Langerhans' cell histiocytosis

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ABSTRACT

Background: Pulmonary Langerhans' cell histiocytosis (LCH) is a diffuse, smoking-related lung disease characterised pathologically by proliferation of abnormal Langerhans' cells, cyst formation and vascular abnormalities, and physiologically by a decreased diffusing capacity. The aim of this study was to describe our experience with pulmonary LCH at our institution during the past 30 years, with particular reference to diagnosis and long-term outcome.

Patients and methods: Seven patients, two men and five women, mean age 33 years (range 26-49 years), who had been evaluated for pulmonary LCH, were retrospectively studied. All available clinical, diagnostic and pathological data were included.

Results: The patients presented with symptoms of dyspnoea, cough, pleuritic pain, anorexia and fatigue. Chest X-ray and high-resolution computed tomography (HRCT) showed bilateral nodular and cystic lesions, with a predilection for the middle and upper lung zones. In the majority of patients, lung function tests showed a decrease in diffusing capacity. In six patients the diagnosis of pulmonary LCH was made after immunohistochemical examination of an open lung biopsy specimen. In one patient a confident diagnosis was made radiologically.

During serial follow-up, median seven years (range 1-28 years), three patients stopped smoking and in four patients the tobacco consumption remained unchanged. For the whole group the evolution was benign, with all patients being asymptomatic or showing improvement in symptoms and regression of radiological signs.

Conclusion: Radiographic studies often provide clues to the diagnosis, but may not obviate the need for open lung biopsy in the majority of cases. Our study shows that irrespective of smoking cessation, spontaneous regression of symptoms and radiological signs and long-term survival are possible.

INTRODUCTION

Pulmonary Langerhans' cell histiocytosis (LCH) appears to be primarily a reactive process in which non-lethal, non-malignant clonal evolution of LCH cells may arise in the setting of non-clonal LCH hyperplasia. Several organs may be involved in LCH. The term pulmonary LCH is used to refer to disease in adults that affects the lung, either in isolation or in addition to other organ systems. The natural history of pulmonary LCH is variable, difficult to predict and ranges from spontaneous resolution to progressive respiratory insufficiency and death, even after many years of apparent clinical stability.[1] Since 1951, when two patients were reported with exclusively pulmonary LCH, more than one hundred cases have been reported.[2] Recently, three review articles were published.[3-5] However, the diagnosis is not readily recognised by all clinicians and pathologists. It has been suggested that smoking may play a role in causing LCH, because more than 90% of the patients with this disease are or have been smokers.

The purpose of this study was to review a personal experience with pulmonary LCH, and describe the spectrum of the disease in terms of clinical presentation, pathological manifestations, diagnostic findings, and course.

PATIENTS AND METHODS

During the last 30 years, the diagnosis of pulmonary LCH was made in seven patients at our institution. There were two men and five women, whose ages ranged from 26 to 49 years, with a mean of 33 years, at the time of diagnosis (*tables 1* and *2*). We retrospectively reviewed the records of these patients, including all available clinical, diagnostic and pathological data. Clinical follow-up ranged from 1 to 28 years, with a median of seven years.

RESULTS

The results of the clinical, radiographic and pathological data and the results of the lung function tests at the time of first presentation and last follow-up are outlined in *tables 1, 2* and *3*.

Clinical presentation

All patients had symptoms for between two to three months before they were admitted to hospital.

Almost all patients complained of dyspnoea and cough. A few of them had symptoms including pleuritic pain, anorexia and fatigue (cases A, B, C and E). Patient F had a bone lesion in the right femur. All patients had a history of smoking. There was no relation with occupation, hobbies or contact with pets, including birds. There was no history or evidence of exposure to medications, tuberculosis contact or recent travel. Previous medical histories were unremarkable.

Radiology

A chest radiograph was performed in all patients. On the chest X-ray six patients had bilateral nodular abnormalities in the upper lobes, one of them also had increased interstitial markings, and patient D had increased interstitial markings with reticulation. A high-resolution computed tomography (HRCT) of the thorax was carried out in five patients. The HRCT showed cysts and/or nodules in the lungs, with a predilection for the middle and upper lung zones in these patients.

Lung function tests

Lung function, including volumes (vital capacity: VC), forced expiratory volume in 1 second (FEV_1), total lung capacity (TLC) and diffusing capacity (DL_{CO} and K_{CO}), was measured according to the guidelines of the European Respiratory Society (ERS) and expressed as obstructive (low FEV_1 and low FEV_1/VC ratio) or restrictive syndrome (low TLC).[6-7]

Table 1
Clinical and diagnostic features of the seven patients at time of presentation

PATIENT	AGE AT TIME OF DIAGNOSIS	SEX	TOBACCO USE	SYMPTOMS	CHEST RADIOGRAPH	HRCT	OPEN LUNG BIOPSY	BAL	TRANSBRONCHIAL BIOPSY	DIAGNOSIS DEFINITIVE?
A	29	F	10 py	Cough, anorexia	Diffuse nodular opacities upper lobes	Multiple micronodules with central cavities	LCH	N	ND	Definitive LCH
B	49	M	40 py	Dyspnoea, cough, pleuritic pain	Diffuse bilateral nodular shadows	Multiple thin-walled cysts upper lobes and middle lobes	LCH	N	ND	Definitive LCH
C	49	F	5 py	Dyspnoea, cough, fatigue	Diffuse nodular opacities upper lobes	Diffuse increased interstitial markings with macro- and micronodules	LCH	N	ND	Definitive LCH
D	34	F	15 py	Dyspnoea, cough	Diffuse bilateral increased interstitial markings with reticulation	Bilateral thin-walled cysts with some micronodules upper lobes	LCH	N	ND	Definitive LCH
E	33	F	8 py	Dyspnoea, cough, pleuritic pain	Bilateral increased interstitial markings with nodules	Bilateral increased interstitial markings with small cysts	NP	N	ND	Presumptive LCH
F	26	M	10 py	Dyspnoea, cough	Bilateral nodular opacities upper lobes	NP	LCH	NP	NP	Definitive LCH
G	31	F	5 py	Dyspnoea, cough	Bilateral nodular opacities upper lobes	NP	LCH	NP	NP	Definitive LCH

HRCT = high-resolution computed tomography, py = pack years, LCH = Langerhans' cell histiocytosis, BAL = bronchoalveolar lavage, N = normal, NP = not performed, ND = not diagnostic.

The diffusing capacity was expressed as percentage of predicted.
At the time of diagnosis four patients had a normal lung function, two (cases E and F) had an airway obstruction and one (case A) an obstructive and restrictive pulmonary function (*table 2*). The majority had a decreased diffusing capacity.

Bronchoalveolar lavage (BAL)
Lavage with 4 x 50 ml saline was performed in five patients. The differential cell counts of the BAL fluid showed normal results.[8] Neither microbiological agents nor other foreign substances were found. We could not demonstrate any sign of malignancy.

Histology
Transbronchial biopsies were performed in five patients and showed no specific abnormalities on immunohistochemical examination.
Six patients underwent an open lung biopsy. In these patients the diagnosis of pulmonary LCH was made after immunohistochemical examination of the biopsy specimen, which confirmed the presence of Langerhans' cells based on their morphology and immunophenotype (S100, CD1a, CD68 positive). None of the specimens were examined for the presence of Birbeck granules by electron microscopy. Patient F also had a histopathologically proven bone lesion of LCH.

Table 2
Pulmonary function test results at time of presentation and at time of last follow-up

PATIENT		DL_{CO} (PREDICTED)	K_{CO} (PREDICTED)	FEV_1 (L (PREDICTED))	FEV_1/VC (%)	TLC (L (PREDICTED))
A	Presentation	73	75	2.5 (3.7)	62	5.2 (6.0)
	Follow-up	109	93	2.1 (3.6)	48	8.0 (6.0)
B	Presentation	85	100	3.3 (3.3)	86	5.7 (6.3)
	Follow-up	73	77	3.1 (3.1)	80	5.7 (6.3)
C	Presentation	54	55	2.8 (2.7)	84	5.3 (5.2)
	Follow-up	62	60	3.1 (2.7)	79	Unknown
D	Presentation	88	93	3.3 (3.5)	83	5.7 (5.9)
	Follow-up	84	88	3.4 (3.4)	80	6.1 (5.9)
E	Presentation	46	49	2.7 (3.2)	69	5.1 (5.4)
	Follow-up	45	47	2.0 (3.1)	58	5.4 (5.4)
F	Presentation	100	100	2.5 (3.2)	62	6.1 (6.0)
	Follow-up	100	100	2.0 (3.2)	50	6.2 (6.0)
G	Presentation	62	Unknown	2.2 (2.8)	84	5.1 (5.4)
	Follow-up	56	56	1.6 (2.6)	50	6.0 (5.4)

DL_{CO} and K_{CO} = lung diffusing capacity of carbon monoxide, FEV_1 = forced expiratory volume in 1 second, VC = vital capacity, TLC = total lung capacity.

Table 3
Clinical and radiological features of the seven patients at time of last follow-up

PATIENT	FOLLOW-UP (YEARS)	SMOKING CESSATION?	TOBACCO USE	RESOLVEMENT OF SYMPTOMS?	REMISSION ON HRCT AND CHEST X-RAY?
A	7	Yes	10 py	Complete	Complete
B	5	No	49 py	Complete	Complete
C	1	Yes	5 py	Complete	Partial
D	4	Yes	15 py	Complete	Partial
E	7	No	12 py	Complete	Complete
F	22	No	32 py	Partial	Complete
G	28	No	15 py	Partial	Partial

HRCT = high-resolution computed tomography, py = pack years.

Treatment

All patients were advised to stop smoking. Patient F, who also had an extrapulmonary manifestation of LCH, received corticosteroid therapy for one year and furthermore the bone lesion was removed surgically.

Outcome

During serial follow-up three patients stopped smoking and four continued.

In the patients who continued smoking, the tobacco consumption remained unchanged throughout the years. Two patients were symptom-free after a period of three months and two patients showed stabilisation of symptoms during follow-up. In this group, patients B, E and F had complete radiological remission, confirmed both on chest radiography and HRCT, after a median follow-up of ten months and patient G showed a stabilisation of the radiographic abnormalities. The lung function showed slow progressive airway obstruction in patients E, F and G and was still normal in patient B. The diffusing capacity decreased in patient B, was stable in patients E and G and was still normal in patient F.

In the non-smokers group all patients were symptom-free after a mean follow-up of three months. In this group patient A had a complete radiographic remission and patients C and D showed an improvement in the radiological abnormalities. The pulmonary lung function was still normal in patients C and D after serial follow-up and showed a progressive airway obstruction with the occurrence of hyperinflation in patient A. The diffusing capacity improved in patient C, improved to a normal value in patient A and was still normal in patient D.

For the whole group the evolution was benign, with all patients being asymptomatic or showing improvement of symptoms. Spontaneous regression of symptoms and radiological signs occurred in most cases.

DISCUSSION

Incidence, age at diagnosis, aetiology

The precise incidence and prevalence of LCH are unknown. The incidence is probably underestimated. The relative frequency in men and women is controversial. Most patients are 20 to 40 years of age. The overwhelming majority of patients have a history of smoking. Little is known about the aetiology and pathophysiology of pulmonary LCH. It is assumed that smoking is a major risk factor for LCH.[1,9-11] Cigarette smoking is associated with the induction of several immune mechanisms, which may be responsible for the local accumulation of Langerhans' cells on the epithelial surface of the lower respiratory tract and the subsequent development of lung injury.[12-18] Besides, there is evidence implicating the role of genetic and additional environmental factors.[19-21]

Pathology, BAL findings

Histologically, pulmonary LCH begins as a proliferation of Langerhans' cells along the small airways and the pulmonary blood vessels.[21] The cellular lesions expand to form nodules. The nodules include Langerhans' cells (LHC), eosinophils, lymphocytes, plasma cells, fibroblasts and pigmented alveolar macrophages.[21,22] With progression fibrotic nodules are identified, which may connect with other nodules to form a honeycomb-like structure. At the end stage the histological findings consist of fibrosis and honeycombing, without features of LCH. The LHC can be characterised by their morphology (nuclei with fine chromatin and grooves of folds), immunophenotype (S100, CD1a, CD68 positive) and ultrastructure (cytoplasmic Birbeck granules) (*figure 1*).[23,24] Differential cell counts of the BAL may reveal a moderate increase in the percentage of neutrophils and eosinophils above that seen in smoking control subjects. The proportion of lymphocytes is normal or reduced and the CD4/CD8 ratio is decreased, as in cigarette smokers.[11] In our study the differential cell counts of the BAL were normal in five cases.[8] Immunohistochemical confirmation of the diagnosis may be obtained by BAL, transbronchial lung biopsy or surgical lung biopsy. The presence of more than 5% CD1a-stained cells in the BAL makes the diagnosis of pulmonary LCH very likely.[25-28] The test, however, has quite a low sensitivity (<25%).[4] As transbronchoscopic biopsy has a poor sensitivity, the usual procedure to obtain sufficient specimens of lung tissue for pathological interpretation is open lung biopsy.[29] In our study the diagnosis was made by open lung biopsy in six patients.

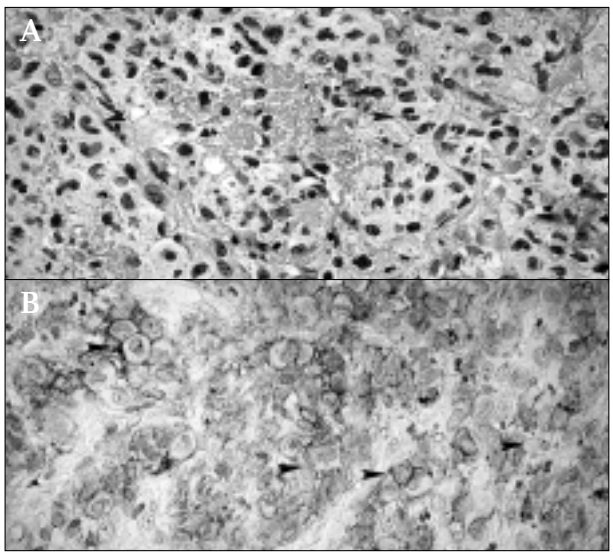

Figure 1

Details of the cellular infiltrate in lesions of pulmonary LCH (115x), including Langerhans' cells with the typical delicate and folded nuclei (panel A, haematoxylin and eosin chain) and the presence of the CD1a antigen on the cell surface (panel B)

Clinical signs, pulmonary function tests

Our study confirms that patients with LCH usually present with a non-productive cough, dyspnoea on exertion or chest pain.[13] Fever, weight loss, haemoptysis and wheezing are occasionally noted, and spontaneous pneumothorax occurs in about 10% of patients.[9,10] Bone involvement, presenting in one patient in our series, is found in a minority of cases in which there is lung disease.[9,10] Less commonly associated findings are posterior pituitary involvement with diabetes insipidus and skin involvement.[9,10,30] Up to 25% of patients are asymptomatic at presentation.[10] Development of dissemination after the initial diagnosis of pulmonary LCH is very rare.

The physical examination can be normal, but decreased breath sounds and rates are common.

Individuals with LCH often present to medical attention with abnormal lung physiology. The most sensitive parameters in early disease are the pulmonary diffusing capacity and arterial blood gases at rest and/or during exercise.[31] At time of presentation, the results of pulmonary function tests are either normal or demonstrate mild obstructive, restrictive or mixed abnormalities.[10]

Radiological findings

In most patients, the chest radiograph shows typically diffuse, symmetrical micronodular, reticulonodular and interstitial abnormalities, predominating in the upper and middle lobes (*figure 2*).[10,31,32] HRCT has proved to be of considerable value in the diagnosis of pulmonary LCH and allows a precise identification of both nodular and cystic lesions.[33] The combination of diffuse, irregularly shaped cystic spaces with small peribronchial nodular opacities, predominantly in the middle and upper lobes, allows the clinician to make a diagnosis of LCH without open lung biopsy (*figure 3*).[31,33,34] We agree that the diagnosis can be strongly suggested radiologically, but diseases that may resemble pulmonary LCH, such as sarcoidosis, tuberculosis, lymphangioleiomyomatosis, chronic hypersensitivity pneumonitis and idiopathic pulmonary fibrosis, need to be excluded by histopathological analysis of an open lung biopsy specimen.

Treatment, outcome, follow-up

Because of the rare occurrence and the high rate of spontaneous remissions of the disease, there are no reliable data on the efficiency of the various treatment regimens. It appears reasonable to stop smoking, but there are no conclusive data on the effect of this measure. In most patients this advice leads to stabilisation of symptoms.[35,36] A few reports also document objective radiographic and physiological improvement in lung function after smoking cessation.[35,36] In one study, continuation of tobacco consumption was not associated with diminished survival.[37] In the study by Friedman *et al.* there was no evidence that a longer

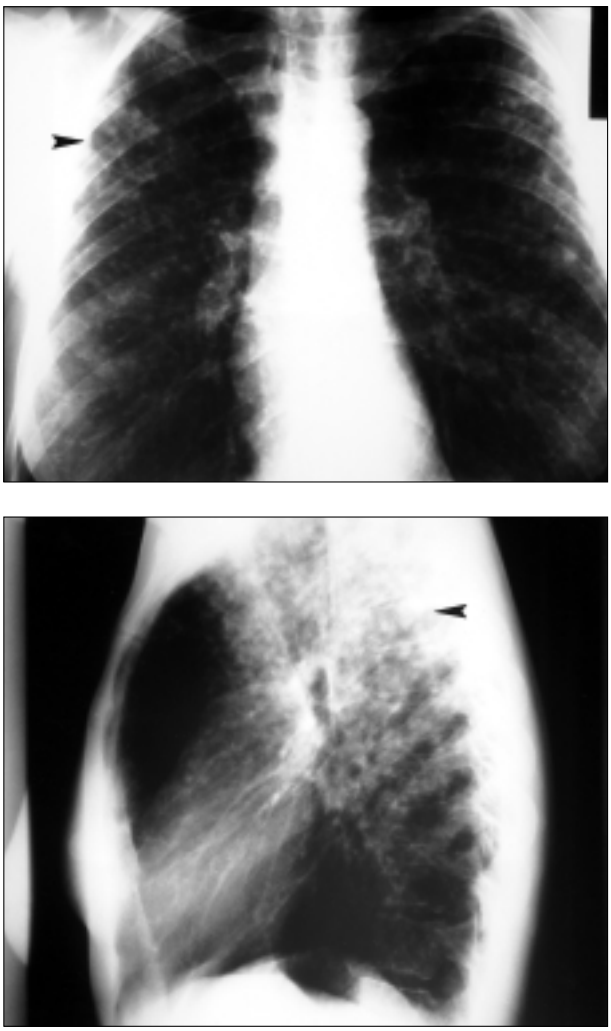

Figure 2

Posterior-anterior and lateral chest radiograph of a patient with pulmonary LCH, showing multiple small nodules with a predominantly upper and middle lobe distribution

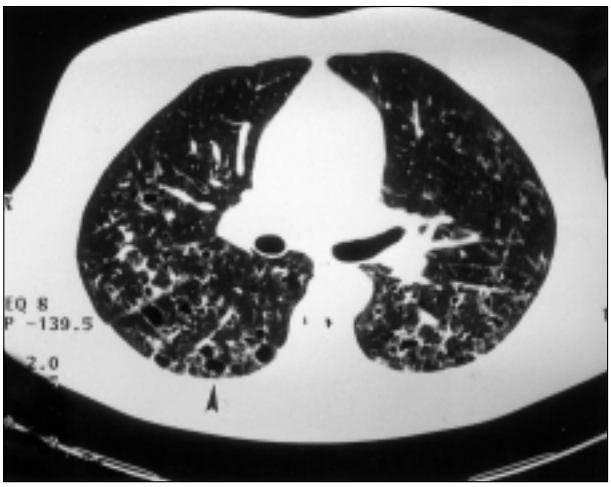

Figure 3

High-resolution computed tomographic scan of the chest in pulmonary LCH, showing a typical combination of cystic and nodular changes

or heavier smoking history predisposed to more severe disease.[10] Irrespective of smoking cessation, we found a complete or partial improvement in symptoms and radiographic data in almost all patients with pulmonary LCH. Results of prospective treatment with systemic corticosteroids are fairly encouraging.[31]
This treatment should generally be attempted only after smoking cessation has been achieved and progression of symptoms or disease occurs. Corticosteroids in combination with cytostatics were tried, but the usefulness of this therapy could not be demonstrated as in generalised disease.[31]
Lung transplantation may be proposed as an efficient treatment for end stage LCH, although there is a risk of recurrence of the disease when systemic disease is present or when patients continue smoking.[38]
The natural history of pulmonary LCH is variable, difficult to predict and ranges from spontaneous resolution to progressive respiratory insufficiency and death, even after many years of apparent clinical stability.[1] Therefore patients with pulmonary LCH require long-term follow-up to detect potential disease progression and relapse. In the majority the course is generally benign.[10] Our study confirms that long-term survival is possible for pulmonary LCH patients. Controversy remains about which tests are most effective for judging natural progression of interstitial lung disease in general or assessing therapeutic improvement. Simple lung function tests may be the best to follow, but improvement is rarely dramatic.[39] Yet follow-up revealed that even in cases of radiological remission there is usually a persisting disturbance of gas exchange and lung perfusion, suggesting that healing as a rule leaves scars and is not complete.[31,40] This finding is also in accordance with our study results: an improvement in radiographic data was not always associated with a normalisation of the diffusing capacity. HRCT scans are helpful in evaluating the histopathological activity of pulmonary LCH and are being used widely.[41]

CONCLUSION

Pulmonary LCH is a diffuse, smoking-related lung disease characterised pathologically by proliferation of abnormal Langerhans' cells, cyst formation and vascular abnormalities, and physiologically by a decreased diffusing capacity. The diagnosis should be considered when a middle-aged smoker presents with aspecific pulmonary symptoms, symmetrical interstitial abnormalities in the upper and middle lobes on the chest X-ray and a decreased diffusing capacity. We have described our experience with seven patients with pulmonary LCH and support the view that although the HRCT scan often provides clues to the diagnosis, there is still a need for bioptical clarification of the diagnosis of pulmonary LCH, especially in those patients in whom other differential diagnoses cannot be excluded with certainty based on clinical-radiological findings.

We conclude that irrespective of smoking cessation, long-term survival with an improvement in symptoms and radiological signs is possible for pulmonary LCH patients.

ACKNOWLEDGEMENT

The authors wish to thank J.A.M. van der Palen, and J.G. Somsen.

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CASE REPORT

Tuberculous dacryoadenitis: a rare manifestation of tuberculosis

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ABSTRACT

A 41-year-old Somalian female inhabitant of the Netherlands presented with malaise and cervical lymph node swelling. Enlarged mediastinal, hilar and abdominal lymph nodes were found on CT scan. Subsequently the left lacrimal gland became swollen, accompanied by periostitis of the lateral orbit margin. *Mycobacterium tuberculosis* was cultured from lymph node tissue and the diagnosis of tuberculous dacryoadenitis with periostitis was made on CT images and histology. All lesions responded well to tuberculostatic treatment. Although tuberculous dacryoadenitis is a very rare manifestation of tuberculosis, it is still important to recognise this presentation, especially since the incidence of tuberculosis continues to increase in Western countries.

INTRODUCTION

Tuberculosis is still the leading cause of infectious deaths on a worldwide basis.[1] In many countries in Western Europe and the United States there has been a resurgence of tuberculosis since 1985. This increase is almost entirely due to tuberculosis in people born outside these Western countries; this group accounts for 40 to 50% of all cases of tuberculosis in the Western world.[2] The HIV epidemic is a major factor in the increasing incidence of tuberculosis, since HIV infection is the most important known risk factor for reactivation of latent tuberculosis infection.
In the light of this, it is of great importance for physicians, especially in the West, to be conscious of rare manifestations of tuberculosis besides the frequently observed pulmonary and generalised lymph node tuberculosis. In this case report we present a Somalian patient with lacrimal gland and orbital involvement of tuberculosis.

CASE REPORT

A 41-year-old Somalian woman, who had been living in the Netherlands for two years, presented at the internal medicine outpatient clinic with abdominal pain, nausea and anorexia. Her weight had decreased by about 10 kg in the past six months. She had no complaints of night sweats or fever. Six months earlier she had been treated with antibiotics and a proton pump inhibitor for a *Helicobacter pylori*-positive duodenal ulcer. This resulted in a clinical response of only short duration. Physical examination showed an adipose woman with two slightly enlarged cervical lymph nodes and epigastric pain on palpation. Further examination was unremarkable.
Blood tests demonstrated microcytic red blood cells (MCV 79 fL), without anaemia, and slightly elevated amylase of 290 U/L (normal <220 U/L), alkaline phosphatase of 133 U/L (normal 120 U/L) and γ-glutamyltransferase of 64 U/L (normal 45 U/L). ESR was 20 mm in the first hour and the white blood cell count was 4.4 x 10^9/L with a normal differentiation.
A gastroduodenoscopy was carried out, showing *Helicobacter*-negative bulbitis. Enlarged mediastinal and hilar lymph nodes were seen on chest X-ray and abdominal ultrasound revealed abdominal lymphadenopathy. Chest and abdominal CT scans could confirm these findings. A tuberculin skin test was positive (32 x 29 mm). Bronchial secretions did not show any acid-fast bacilli.

A biopsy of one of the pathological cervical lymph nodes was ordered. In the mean time, our patient developed a non-tender swelling of the left orbital margin and she complained of diplopy, vertigo and headache. She had no excessive tear production, orbital oedema or redness. The neurologist and the opthalmologist found no signs of cerebral or ocular involvement. A CT scan of the cerebrum and skull demonstrated swelling of the left lacrimal gland accompanied by soft tissue swelling outside the skull on the temporal side and bone destruction of the lateral orbit margin. Involvement of the cerebrum was suspected (*figures 1a* and *b*).

Differential diagnosis at this time consisted of tuberculous lacrimal gland involvement, lacrimal gland carcinoma and benign mixed tumour of the lacrimal gland. A biopsy showed a granuloma with Langhans'-type giant cells; cultures remained sterile. A cervical lymph node biopsy showed acid-fast bacilli and cultures revealed *Mycobacterium tuberculosis*. Sputum cultures also revealed *M. tuberculosis*, which was sensitive to all the common antituberculous drugs. In the mean time polymerase chain reaction (PCR) of the sputum for *M. tuberculosis* complex turned out to be positive. Thus, the final diagnosis was generalised lymph node and pulmonary tuberculosis with tuberculous dacryoadenitis, although a PCR of the lacrimal gland tissue was negative. The HIV test was also negative.

After the diagnosis was made on the acid-fast strains of the lymph node biopsies, the patient started treatment with a four-drug tuberculostatic regimen: pyrazinamide and ethambutol during the first two months, and isoniazid and rifampicin during a total of six months. Signs and symptoms resolved completely within a few weeks.

DISCUSSION

Dacryoadenitis is an inflammation of the main lacrimal gland. Pyogenic bacteria such as *S. aureus* and streptococci are the most common causes of the acute infection. Chronic infections of the lacrimal gland occur in tuberculosis, syphilis, leprosy, cysticercosis and schistosomiasis.[3] Dacryoadenitis is a rare manifestation of tuberculosis. It was first described by Abadie in 1881.[4] Since 1970, nine cases have been mentioned in the English literature.[5-11] In a study investigating ocular involvement in 1005 patients with active systemic tuberculosis, no lacrimal gland involvement was observed.[12] A series of 10,542 cases of tuberculosis demonstrated an incidence of ocular tuberculosis of 1.4%, but again no cases of dacryoadenitis were encountered.[13] Females in endemic areas aged between 35 and 50 years are predominantly affected by this manifestation, although it has been described in children.[7,11] It is most often found years after an old pulmonary or lymph node tuberculosis has resolved. It may, however, exist in newly diagnosed tuberculosis, even as the presenting symptom.

As in our patient, the presenting symptom is usually a painless swelling of the eyelid, mimicking a benign mixed tumour of the lacrimal gland. There may be periostitis of the orbit.

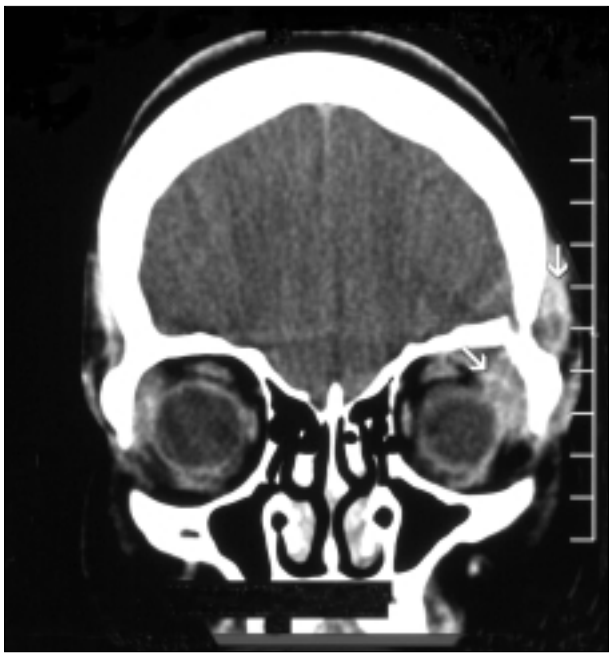

Figure 1a
Swelling of the left lacrimal gland caused by a tuberculous dacryoadenitis (left thin arrow), accompanied by soft tissue swelling outside the skull on the temporal side (right thick arrow)

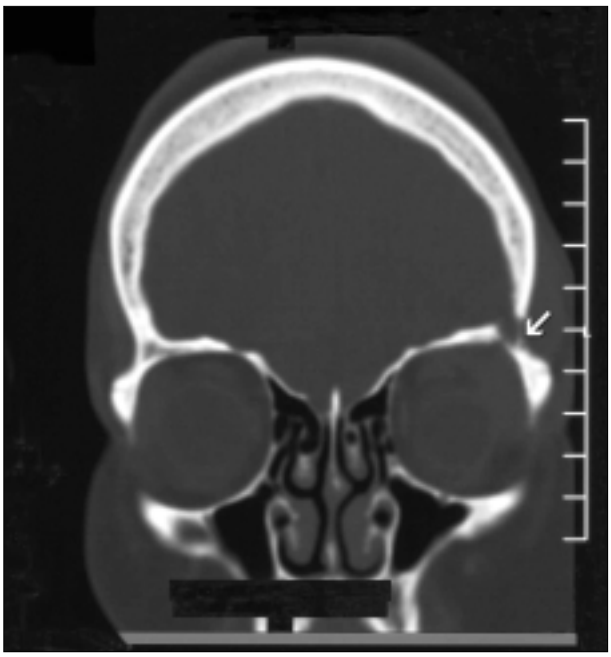

Figure 1b
The same CT scan in bone setting, showing bone destruction of the left superolateral margin of the orbit (arrow)

The spread of *M. tuberculosis* to the lacrimal gland is thought to be mainly haematogenous. Local spread with conjunctival tuberculosis as the source may be possible.[9] Isolation of *M. tuberculosis* is required for the definite diagnosis, but positive cultures from lacrimal gland secretions or from fine-needle aspirations are extremely rare. Histopathological examination shows a typical granuloma, and this usually leads to the diagnosis, especially when other features of tuberculosis are present. Two histological types of dacryoadenitis can be distinguished, the sclerotic and the caseous type, the latter being extremely rare.[14] The use of PCR for *M. tuberculosis* complex on tissue of the lacrimal gland in cases of tuberculous dacryoadenitis is not mentioned in the literature. In our patient it turned out to be negative. We speculate that tuberculous dacryoadenitis is a paucibacillary infection, comparable with cutaneous tuberculosis and tuberculids, in which the immunological reaction to the infection plays a crucial role. In individuals with highly suspected cutaneous tuberculosis, PCR for detection of *M. tuberculosis* is positive in 54 to 60%.[15,16]
A combination of surgery and antituberculous drugs was reported successful in literature in the past, but nowadays antituberculous drug treatment is adequate and the prognosis is excellent.[5,6,17]
We believe that the differential diagnosis in patients with enlargement of the lacrimal apparatus should also contain tuberculous dacryoadenitis, especially when originating from endemic areas. The need for knowledge about rare manifestations of tuberculosis is becoming greater since the incidence of tuberculosis is increasing due to HIV infection and immigration of people from endemic areas to Western countries. Histopathology will usually lead to the diagnosis, while cultures rarely become positive for *Mycobacterium tuberculosis*.

ACKNOWLEDGEMENT

The authors would like to thank Prof J.W.M. van der Meer, internist, for his helpful suggestions.

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Netherlands
The Journal of Medicine

CASE REPORT

Adult T-cell leukaemia and lymphoma: report of two cases and a brief review of the literature

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ABSTRACT

Human T-cell lymphotropic virus type 1 (HTLV-1) can cause adult T-cell leukaemia/lymphoma (ATLL). Two patients originating from the Caribbean area with ATLL are described. The first patient developed respiratory insufficiency due to acute T-cell leukaemia. The diagnosis was suspected because of characteristics of abnormal lymphocytes in the blood smear. The second patient had lymphadenopathy and developed severe hypercalcaemia. Both patients were typical cases of ATLL. The pathogenesis, clinical manifestations, pitfalls and treatment of this intriguing disease are discussed.

INTRODUCTION

Infection with human T-cell lymphotropic virus type 1 (HTLV-1) may cause a distinctive malignancy, adult T-cell leukaemia/lymphoma (ATLL). The clinical features of ATLL can be divided into four different subtypes; acute, chronic, smouldering, and a lymphoma type. This HTLV-1-associated malignancy occurs mainly in Japan, the Caribbean area, Africa and parts of South America. This disease is rare in Europe. We describe two patients originating from the Caribbean with ATLL, one suffering from an acute T-cell leukaemia and the other from the lymphoma type. We also discuss the possible pitfalls of this disease, such as hypercalcaemia and infection with *Strongyloides stercoralis*.

CASE REPORT

Patient 1

A 36-year-old female was admitted to the pulmonary department of our hospital because of rapidly progressive shortness of breath. She was born in French-Guyana and had never been ill before. On physical examination she was tachypnoeic with a breathing rate of 30/min. Physical examination of the chest revealed no abnormalities. The temperature was 38 °C, no lymph nodes were palpable, and liver and spleen were not enlarged. Laboratory examination showed lymphocytosis (leucocytes 34 x 10^9/L, with 32% atypical lymphocytes), elevated LDH 2684 U/L (normal value 450 U/L), and hypoxaemia; pH 7.42, pO_2 41.9 mmHg, pCO_2 32 mmHg, O_2 saturation 79%. Chest X-ray showed fine reticular infiltrates of both lungs. She was treated for atypical pneumonia with intravenous erythromycin, oxygen and inhalation treatment with salbutamol and ipratropium. HIV serology proved to be negative. Two days later she was transferred to the intensive care unit for mechanical ventilation because of respiratory insufficiency. A bronchoscope showed no abnormalities, but lavage showed atypical lymphocytes. The next day, the haematologist was asked to look at the blood smear, which showed typical cleaved and cerebriform lymphocytes (*figures 1* and *2*). The diagnosis of HTLV-1 infection with acute T-cell leukaemia was suspected and immediately confirmed by immunological typing of these lymphocytes; CD3/CD4 positive, CD8 negative, CD5 positive, CD25 positive and CD7 negative. Antibodies to HTLV-1 were positive. She was treated with CHOP chemotherapy (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² and prednisolone 100 mg) and improved dramatically. After four days she could be transferred to the haematology department for further treatment.

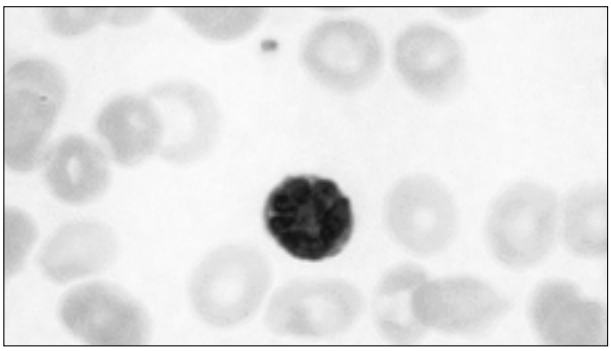

Figure 1
Cerebriform lymphocyte in the pheripheral blood of patient 1

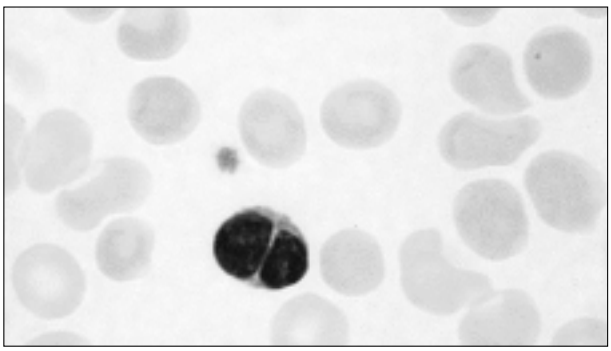

Figure 2
Cleaved lymphocyte in the peripheral blood of patient 1

Microbiological examination of the stool showed *Strongyloides stercoralis* for which she was successfully treated with ivermectine. She received cotrimoxazole (480 mg/day) as prophylaxis for *Pneumocystis carinii* pneumonia. The ATL was treated with six cycles of CHOP chemotherapy resulting in a clinical remission. Eleven months later the ATL relapsed, showing a rise in leucocyte count from 4.8 to 40.9 x 10^9/L with 88% lymphocytes, hypercalcaemia (calcium 2.91 mmol/L) and serum LDH elevated to 1454 U/L. No lymph nodes were palpable. The hypercalcaemia was treated with intravenous pamidronate. The ATL was treated with another two cycles of CHOP chemotherapy, followed by DHAP (dexamethasone, high ARA-C, cisplatinum), zidovudine/interferon-alpha, and fludarabine, respectively. Despite these efforts she died of refractory disease four months after the relapse. Her identical twin sister also appeared to be HTLV-1 positive, without any symptoms.

Patient 2

A 64-year-old man from Surinam was admitted to our outpatient clinic because of lymphadenopathy. Ten days previously he had noticed enlarged axillary and inguinal lymph nodes. He had no complaints of weight loss, night sweats or fever. On physical examination he appeared well, and had axillary and inguinal lymph nodes between 2 and 5 cm in diameter. Liver and spleen were not enlarged.

Laboratory examination showed no abnormalities, except for an elevated LDH of 589 U/L (normal value <450 U/L). Serum calcium was normal (2.42 mmol/L). Chest X-ray and sonography of the abdomen were normal. HIV serology was negative. Cytological punctures of different lymph nodes showed small lymphocytic cells between large atypical lymphoblasts with high mitotic activity. These cells were positive for CD3, CD4, HLA-DR and negative for CD7, CD8 and CD25. Bone marrow examination showed normal red, white, and megakarocyte distribution but with clusters of lymphocytes with identical immunological markers. A T-cell non-Hodgkin's lymphoma was suspected and HTLV-1 serology was performed, which proved to be positive. Before we could discuss these results with the patient, he was admitted to hospital because of severe somnolence. This was due to severe hypercalcaemia (serum calcium 4.52 mmol/L, albumin 32 g/L and LDH 1484 U/L). He was treated with intravenous pamidronate, resulting in an improvement in his clinical condition. It was concluded that this patient had an HTLV-1-associated T-cell NHL, stage 4A, and treatment with CHOP chemotherapy was started. Cotrimoxazole 480 mg daily was given for *Pneumocystis carinii* prophylaxis. *Strongyloides stercoralis* was not found in the stools of this patient. After six cycles of CHOP chemotherapy, physical examination and CT scan analysis showed a complete remission. Two months after the last cycle of chemotherapy, the disease relapsed with enlarged lymph nodes, elevated calcium level of 4.28 mmol/L and elevated LDH 680 U/L. Again he was treated with pamidronate and chemotherapy (dexamethasone, high-ARA and cisplatinum). Because of the minor response after two cycles of DHAP, zidovudine/interferon was given. Due to intolerance of this combination and because of severe pancytopenia, the latter treatment was stopped and fludarabine 25 mg/m^2 for five consecutive days was given. During this treatment he developed skin lesions with nodules and papules in the neck region and he became somnolent, which turned out to be due to involvement of the central nervous systems, which was apparent from the presence of malignant lymphocytes in the cerebrospinal fluid. Following the wish of the patient and his family, all treatment was stopped and he died soon afterwards.

DISCUSSION

Epidemiology and pathogenesis

Adult T-cell leukaemia/lymphoma (ATLL) was first reported in Japan in 1977.[1] ATLL is associated with the human T-lymphotropic virus type 1 (HTLV-1). HTLV-1 is an RNA-containing retrovirus, which is endemic in Japan, parts of South America, the Caribbean and areas of Central and West Africa. Our two patients originated from French-Guyana and Surinam, respectively.

In endemic areas of Japan, antibodies to HTLV-I are found in up to 37% of healthy adults.[2] However, only about 3% of carriers develop ATLL. ATLL only occurs in adults. The age of onset ranges from 24 to 85 years, with an average of 58 years. The aetiological association of HTLV-I and ATLL is based on a series of findings. First, areas of high incidence of ATLL correspond with those of high prevalence of HTLV-I infection. Second, all patients with ATLL have antibodies against HTLV-I. Third, HTLV-I proviral DNA can be found in ATLL neoplastic cells. Finally, HTLV-I immortalises human CD4 T cells.[3,4]

The incubation period of ATLL is long, ranging from 10 to 30 years, although ATLL acquired from blood transfusion may occur after a shorter period.[5]

HTLV-I is not easily transmissible, since cell-cell contact is generally required. Two major transmission routes have been described. One is vertical transmission from mother to child via HTLV-I positive lymphocytes in breast milk. The second important route is horizontal transmission through sexual contact, frequently from husband to wife, rarely from wife to husband. Virus-positive lymphocytes have been detected in semen of seropositive men. Two other transmission routes of HTLV-I are blood products containing infected T cells and intravenous drug abuse. In the Netherlands, every year 3 to 15 healthy blood donors are found to have antibodies against HTLV-I.[6]

Most of the effects of HTLV-I infection have been attributed to the HTLV-I-encoded protein Tax (trans-activator of X). This protein is a key regulator for immortalisation, transformation, and oncogenesis of the HTLV-I-infected lymphocytes through its interaction with many cellular proteins. Most of these proteins, including Tax, are not expressed at detectable levels in cells in ATLL. Their role in the leukemogenic process must therefore be limited to the early stages.[7,8]

Human T-lymphotropic virus type 2 (HTLV-II) was isolated in 1982 by Kalyanaraman from a patient with an unusual T-cell variant of hairy cell leukaemia. It has subsequently been isolated only rarely in lymphoid neoplasia, but is prevalent in intravenous drug abusers.[9]

CLINICAL MANIFESTATIONS

Four clinical subtypes of ATLL have been proposed.[10] First, the acute leukaemia type, representing 57% of the patients, in which a leukaemic manifestation of the disease is seen (patient 1). Hypercalcaemia and elevated LDH levels are common. Second, a lymphoma type (about 19% of the patients) without lymphocytosis and with histologically proven lymphadenopathy with or without extranodal lesions (patient 2). Third, a chronic type (about 19% of the patients) with more than 3.5 x 10^9/L T lymphocytosis, LDH value up to two times the normal upper limit, and no hypercalcaemia. Lymphadenopathy and involvement of liver, spleen and lung may be present. Finally, the smouldering type, representing the remaining patients, with a normal lymphocyte count, but with at least 5% abnormal T lymphocytes in peripheral blood, no hypercalcaemia, LDH value of up to 1.5 times the normal upper limit, and no lymphadenopathy or liver and spleen involvement.

The most common physical findings at presentation are lymphadenopathy, skin lesions, hepatomegaly and splenomegaly. Rapid development of diffuse peripheral lymphadenopathy without mediastinal involvement, as in our second patient, is typical. The skin lesions in ATLL are variable, including nodules and papules as in patient 2, localised erythema and plaques, and generalised erythroderma. A biopsy of skin lesions usually reveals dermal or epidermal infiltration of malignant T cells. The skin lesions in ATLL often resemble mycosis fungoides, a low-grade cutaneous T-cell lymphoma. Characteristically, mycosis fungoides progresses from an eczematous stage to plaques and finally to tumours. Circulating lymphocytes with cleaved or cerebriform nuclei are highly suggestive of ATLL (*figures 1* and *2*). This emphasises the importance of examination of the blood smear. The surface phenotype of ATLL cells characterised by monoclonal antibodies is CD3-positive, CD4-positive, CD7-negative, CD8-negative, and CD25-positive.[2] These findings suggest that ATLL cells originate from the CD4 subset of mature T cells.

Elevated serum calcium levels are seen in most patients with aggressive disease. Our two patients also developed this complication. Parathyroid-hormone-related protein (PTHrP), probably induced by Tax protein, is released from ATLL cells in patients with hypercalcaemia and stimulates osteoclasts.[11] There is a much lower rate of replication of HTLV-I than of HIV. HTLV-I can impair the immune response, but less dramatically than HIV. Opportunistic infections are frequent in patients with ATLL. The spectrum of agents that cause these infections is similar to that seen in AIDS, including protozoa, fungi and viruses. Strongyloidiasis (as in patient 1) is frequent and may be associated with hyperinfection and gram-negative bacteraemia, which is often fatal.[12] Other diseases associated with HTLV-I infection are HTLV-I uveitis and tropical spastic paraparesis with hyperreflexia, urinary bladder disturbances and muscle weakness.[2]

PROGNOSIS AND TREATMENT

Survival of patients with acute and lymphoma types of ATLL is poor, being 6.2 months for acute type, 10.2 months for lymphoma type and 24.3 months for chronic type ATLL. Several features were found to be predictive of shortened survival: poor performance status, age >40 years, hypercalcaemia, high lactate dehydrogenase, and increased

tumour bulk.[10] There is no consensus on the best available therapy for ATLL. For acute and lymphoma type ATLL, combination chemotherapy can be effective. Complete response rates of 30 to 40% are reported with different combinations of drugs (CHOP, MACOP-B, PROMACE), but no one regimen appears superior.[10,12] Although these combinations of chemotherapy have improved response rates, this has not translated into increased survival due to early relapse. Autologous and allogeneic bone marrow transplantation have been reported with little success.[13,14] The combination of zidovudine and interferon-alpha has activity against ATLL, even in patients in whom prior cytotoxic therapy has failed. With oral zidovudine (200 mg five times daily) and interferon-alpha (five to ten million units daily) subcutaneously, responses were achieved in 50 to 60% of the patients.[15,16] Profound pancytopenia is the major toxicity of this combination treatment in these high doses. We encountered such side effects in patient 2.

Central nervous system involvement may develop in as many as 10% of patients with ATLL.[17] Meningeal relapse after initial treatment may occur in patients not receiving prophylactic intrathecal therapy. Therefore, it is recommended that the cerebrospinal fluid is analysed at diagnosis and CNS prophylaxis is given to all patients with acute and lymphoma-type ATLL. Our two patients did not receive CNS prophylaxis, and in patient 2 meningeal involvement occurred at the end of the disease.

Prevention of infection is extremely important during treatment of ATLL. Prophylactic use of cotrimoxazole is now routine, but antifungal and antiviral agents should be considered in all patients with acute or lymphoma-type ATLL. Stools from all patients should be screened at diagnosis and any patients positive for *Strongyloides* should be treated appropriately.[10] In the first patient *Strongyloides* was found and was successfully treated with ivermectine.

Treatment of patients with ATLL remains disappointing. The best treatment is prevention of infection with HTLV-1. The most important way to achieve this is to discourage breastfeeding by women positive for HTLV-1 antibodies. We assume that the first patient and her identical twin sister were infected by breast milk. Because only a minority (<5%) of the HTLV-1 carriers develop ATLL, prophylactic antiretroviral treatment is not recommended at this moment. In most Western countries all donated blood is tested for HTLV-1 antibodies. No transfusion recipients have seroconverted since screening started, even among patients who have received many transfusions.

In summary, the blood smear remains a simple and effective examination, but is often undervalued. Severe hypercalcaemia can be one of the major symptoms of ATLL, especially in the acute and the lymphoma type. Stools of all patients with ATLL should be examined for *Strongyloides*. Finally, analysis of the cerebrospinal fluid in all patients with acute and lymphoma type ATLL is recommended at diagnosis, and these patients should be given CNS prophylaxis.

ACKNOWLEDGEMENT

The authors wish to thank Mr. W. de Vries of the Special Haematology laboratory for providing the figures.

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Netherlands
The Journal of Medicine

How to diagnose cardiac tamponade

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ABSTRACT

Malignant pericardial effusion is a potentially fatal complication of malignancy unless recognised and treated promptly. Patients with this condition are often difficult to diagnose. Physical examination, chest radiography and electrocardiography have poor diagnostic values in identification of patients with pericardial effusion.
Echocardiography, which allows rapid confirmation of the presence of an effusion and precise assessment of its haemodynamic impact, is the gold standard for diagnosis.

INTRODUCTION

The incidence of malignant involvement of the pericardium has been reported to range from 0.1% in some clinical series to as high as 21% in autopsy series.[1,2] These figures suggest that malignant pericardial effusion (MPE) is often not suspected clinically. This is explained by the non specificity of the early symptoms and signs.[1] Frequently there is concomitant pulmonary involvement associated with the malignancy and symptoms may often be attributed to pulmonary disease rather than cardiac disease, resulting in a diagnostic pitfall.[1,2] However, pericardial effusion may quickly progress to cardiac tamponade. Cardiac tamponade is a life-threatening condition and accurate diagnosis and prompt intervention are necessary.[1-6] Echocardiography can accurately detect and quantify the size of pericardial effusion and can assess the haemodynamic impact.[4-6] However, this technique is relatively expensive and is often not feasible as a screening test for pericardial effusion. In contrast anamnesis, physical examination, chest radiography and electrocardiography are inexpensive and are easily performed. We will describe a patient with disseminated breast cancer who had symptoms of dyspnoea and orthopnoea, which in the first instance were attributed to a pleural effusion suggestive of a malignant pleural effusion. However, an MPE was finally diagnosed. The diagnostic value of anamnesis, physical examination, chest radiography, electrocardiography and echocardiography will also be discussed.

CASE REPORT

A 35-year-old woman with disseminated breast cancer presented for the second time within one week with dyspnoea on exertion and orthopnoea. She had a one-year history of breast cancer with liver and bone metastasis, which had been treated with anthracycline-based polychemotherapy and irradiation to the breast, followed by hormonal treatment (Tamoxifen). On her admission six days earlier, the jugular venous pressure was not elevated and a pulsus paradoxus was not heard. Slight pitting oedema of the ankle was noticed. The chest radiography showed a right-sided pleural effusion. The patient was treated with pleural drainage for suspected malignant pleural effusion, resulting in a decrease in the dyspnoea. An electrocardiogram (ECG) was not carried out.
However, the dyspnoea returned, accompanied by increasing circumference of her abdomen and ankle oedema. Physical examination showed a woman in moderate respiratory distress. Her blood pressure was 130/90 mmHg with a pulse rate of 84 beats a minute. A pulsus paradoxus of 30 mmHg was found. The jugular venous pressure

was increased and the heart sounds were soft. Signs of bilateral pleural effusion were found. There were signs of ascites and pitting ankle oedema on both sides. Chest radiography showed bilateral pleural effusion. The cardiac silhouette could not be evaluated because of the pleural effusion. The ECG showed a sinus tachycardia with a QRS electrical alternans (*figure 1a*). Due to suspicion of pericardial effusion with cardiac tamponade, echocardiography was performed, showing a pericardial effusion of 3 cm in diameter and a 'swinging heart' (*figures 2a* and *b*).

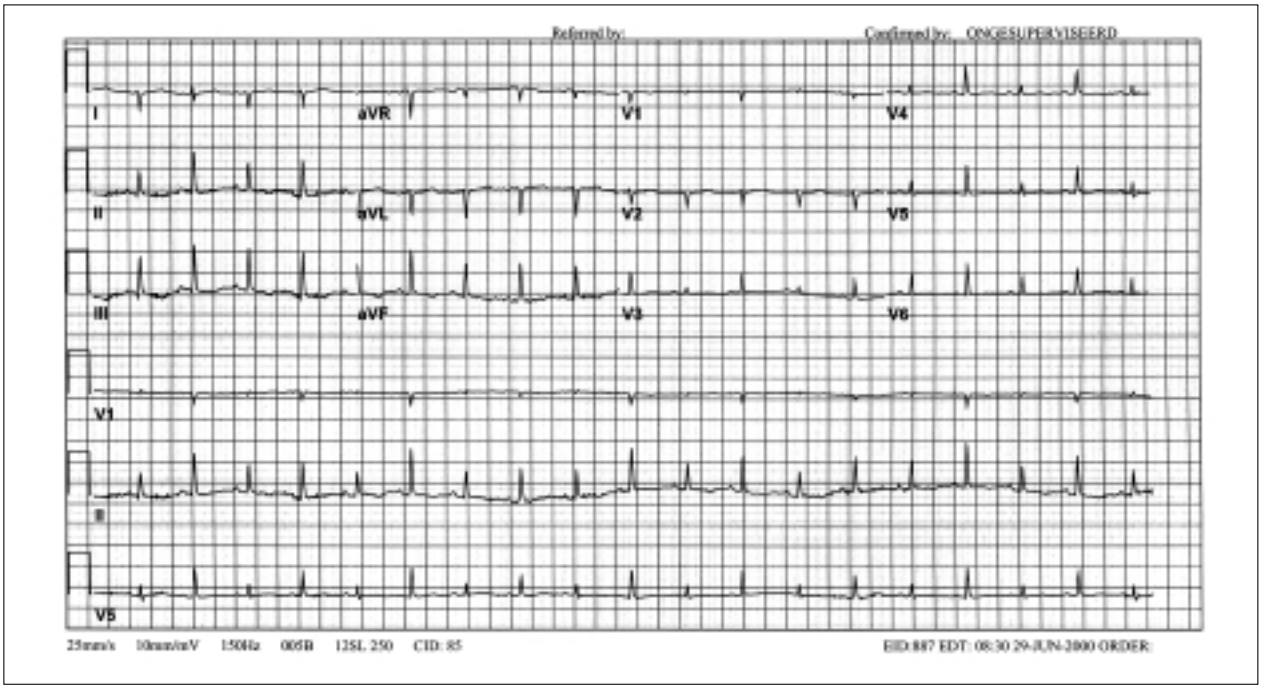


Figure 1a
Electrocardiogram on admission, showing a sinus tachycardia with a QRS electrical alternans

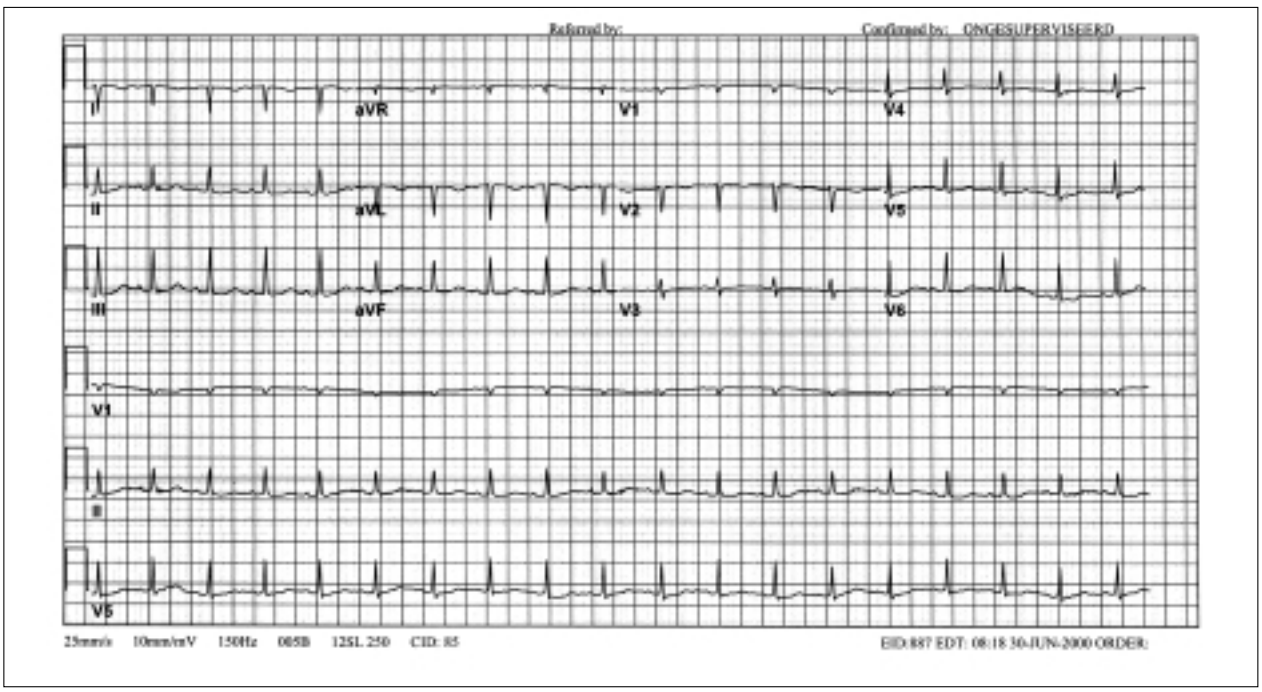
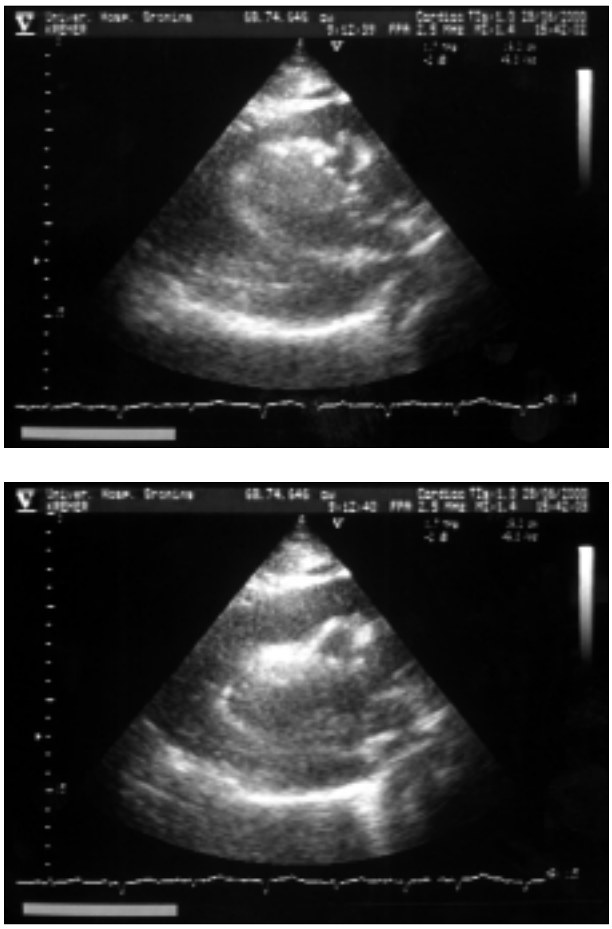


Figure 1b
Electrocardiogram after pericardiocentesis showing disappearance of the QRS electrical alternans

Pericardiocentesis, with the removal of 2000 ml of haemorrhagic fluid, resulted in clinical improvement and immediate disappearance of the electrical alternans (*figure 1b*). Cytological examination of pericardial fluid confirmed the diagnosis of malignancy. The pleural fluid tested negative. The pericardiocentesis was followed by pericardial sclerosis with thiotepa (15 mg).
Because of a diminished left ventricular ejection fraction (50%) on thallium scintigraphy, probably due to the previous anthracycline-based chemotherapy and breast irradiation, ACE inhibition, β-blockade and diuretic therapy were started. Second-line hormonal therapy was also commenced. Two weeks after discharge dyspnoea, ascites and ankle oedema had disappeared.

DISCUSSION

Our case is a presentation of cardiac tamponade and illustrates some of the clinical and ECG signs of tamponade. However, most patients do not have classical features of tamponade.[1-7] Cardiac tamponade is therefore often difficult to diagnose without performing echocardiography. We will discuss the values of the anamnesis, physical examination, chest radiography and ECG in diagnosing cardiac tamponade.



Figures 2a and b
Echocardiography showing a pericardial effusion and a 'swinging heart'

Cardiac tamponade refers to cardiac compression caused by an accumulation of pericardial fluid that leads to increased intrapericardial pressure, progressive limitation of ventricular filling, and reduction of stroke volume and cardiac output. Cardiac tamponade is not an all-or-nothing phenomenon. A spectrum of abnormal haemodynamic changes associated with this condition has been identified with echocardiography. The term cardiac tamponade is generally been used to convey the presence of cardiac compression accompanied by overt clinical manifestations. With echocardiography, detection of the haemodynamic impact of an effusion is possible even in situations where overt clinical signs are absent. This is often called 'echocardiographic evidence of tamponade'.[4-6]

Classically, clinical features of tamponade include dyspnoea, pulsus paradoxus, tachycardia, increased jugular venous pressure and hypotension. They are the result of the haemodynamic impact of the effusion. Large effusions that accumulate over an extended period of time, permitting stretching of the parietal pericardium, may be associated with minimal or no symptoms. In contrast, as little as 50 ml of fluid entering the pericardial space rapidly may impair cardiac filling sufficiently to produce marked haemodynamic compromise. Both the volume of fluid and the distensibility of the pericardium contribute to the haemodynamic impact of the effusion.[4-6,8]
Patients often do not have symptoms because of the insidious development of pericardial effusion, for instance in cancer patients. If there are symptoms they are frequently non-specific respiratory problems such as dyspnoea and cough and, in the case of a malignancy, are frequently falsely attributed to pulmonary involvement of the malignancy.[1]

The value of the pulsus paradoxus (>10 mmHg) in the diagnostic work-up of cardiac tamponade has been evaluated.[7,9-11] Positive predictive values (PPV) are between 81 and 97% with prevalence values of 30 to 49%. Negative predictive values in the same population are between 77 and 92%. When the prevalence decreases, PPV will also decrease. Also, it is disputable whether a false-negative percentage of up to 13% is acceptable for deciding against further investigation.
Pulsus paradoxus may be absent during tamponade because of atrial septal defect, severe aortic stenosis, left ventricular dysfunction, or decreased intravascular volume (low-pressure tamponade). Conversely, pulsus paradoxus can be found in patients without tamponade as a result of acute or chronic obstructive airway disease, pulmonary

embolism, tension pneumothorax, large pleural effusions, right ventricular infarction, restrictive cardiomyopathy, extreme obesity, or tense ascites.[4-6,11]
There have also been reports that the diagnosis of cardiac tamponade was suspected on the basis of other clinical signs, before measuring the pulsus paradoxus.[7,9-11]
Finally, measurement of the pulsus paradoxus is not always easy. About 13% of medical students are able to measure the pulsus paradoxus correctly. For fellows and medical specialists, the values are reported at 23% and 57%, respectively.[12]

Evaluation of the jugular venous pulse (JVP) provides important information about pressure in the right atrium. It is an estimate of central venous pressure (CVP). The clinical evaluation of the JVP can be useful whenever intravascular volume status, ventricular function, valvular disease, or pericardial constriction is in question. However, this examination may be difficult for different reasons, for example due to a short or fat neck or distinguishing arterial (carotid) from venous (jugular) pulsation. In a study of 62 patients undergoing right heart catheterisation, the sensitivity of the clinical examination for identifying low (<0 mmHg), normal (0-7 mmHg) or high (>7 mmHg) CVP was 0.33, 0.33, and 0.49, respectively. The specificity was 0.73, 0.62, and 0.76, respectively. These data show that not finding or finding an abnormal CVP does not necessarily confirm that the CVP is really normal or abnormal.[13]
CVP was also assessed in 50 intensive care patients. In this population a clinically assessed low CVP increases the likelihood that the measured CVP will be low by 3.4. A clinically assessed normal CVP does not increase or decrease the likelihood (Likelihood Ratio (LR) 1.0) that the measured CVP will be low, and no patients clinically assessed as having a high CVP had a low measured CVP (LR 0). Clinical assessment of a high CVP increases the likelihood that the measured CVP will be high by 4.1. Clinical assessment of a normal CVP decreases the likelihood that the measured CVP will be high by 0.8. Clinical assessment of a low CVP makes the probability of finding a high CVP unlikely (LR 0.2). These data demonstrate that clinical assessments of a normal CVP are truly indeterminate with LR approaching 1.0 (provides no information because they neither increase nor decrease the probability of an abnormal CVP).[14] There is no mention in the literature of a study about clinical assessment of the CVP and constrictive pericarditis so the value of the clinically assessed CVP in our patient is indeterminate.

Chest radiography may suggest pericardial effusion because of an enlarged cardiac silhouette or an unexplained increase in transverse cardiac diameter.[6] Differentiation between four chamber dilatation and a large effusion is difficult, while small pericardial effusions may not be apparent.[6] Eisenberg found that chest radiographic signs were unreliable in either confirming or excluding the presence of pericardial effusions.[15] In the case of a co-existing pleural effusion, the cardiac silhouette is often not seen.[1]

The ECG may provide additional clues, such as the findings of a low voltage (total amplitude of the QRS complexes in each of the six limb leads is 5 mm – 0.5 mV – or less). Or it may provide an electrical alternans (cyclic beat-to-beat shift in the QRS axis), which was found in our patient. Although these signs are specific, they are not sensitive in diagnosing pericardial effusion (specificity: 89 to 100%; sensitivity: 1 to 17%) or cardiac tamponade (specificity: 86 to 99%; sensitivity: 0 to 42%).[2,3] Consequently, although the presence of a low voltage or an electrical alternans is suggestive of pericardial effusion, its absence does not rule out an effusion.
Other causes of a low voltage include chronic obstructive pulmonary disease, pleural effusion, pneumothorax, cardiomyopathy and obesitas. Low voltage can also be found after open heart surgery. Besides in pericardial effusion, electrical alternans has also been reported in a number of other clinical settings including supraventricular and ventricular tachycardias, electrolyte abnormalities, hypothermia, prolonged QT syndromes, bradycardia, and ischaemic cardiac disease.[2,3,16]

Echocardiography is the imaging technique of choice for detecting a pericardial effusion with a high sensitivity and specificity (78% and 100% respectively).[6] An echo-free space between parietal and visceral pericardium that persists throughout the cardiac cycle is the diagnostic feature. Moreover, the volume and distribution of the effusion can be assessed. Morphological features suggestive of tamponade physiology (swinging heart, right atrial collapse, right ventricular diastolic collapse, left atrial collapse, left ventricular collapse, marked inspiratory changes in ventricular dimensions, marked respiratory variation in Doppler velocities, and inferior vena cava plethora) are easily confirmed.[4-6]
In conclusion, cardiac tamponade is a condition that is difficult to diagnose without echocardiography. The symptoms are non-specific and, in the case of co-existing pleural effusion, can be falsely attributed to pulmonary problems. Physical examination, chest radiography and ECG have poor diagnostic values. Our patient was misdiagnosed as only having pleural effusion as the cause of her symptoms. Only the signs found at the second admission raised the suspicion of a pericardial effusion. It is emphasised that in patients with a history of a malignancy and symptoms of dyspnoea, malignant pericardial effusion should be considered. Echocardiography can provide a rapid confirmation of the presence or absence of pericardial effusion, as well as precise haemodynamic assessment, allowing the most appropriate management decision to be taken.

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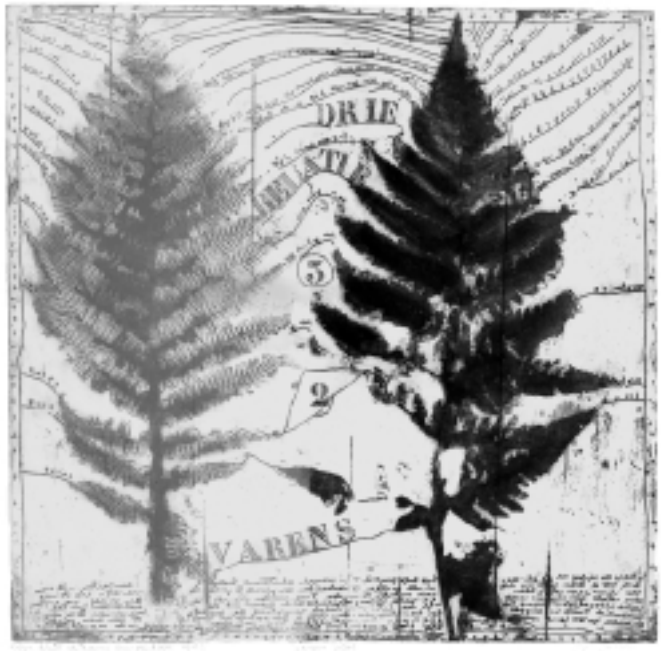
ABOUT THE COVER

Varens 2001

Jops Jacobs



This month's cover shows an etching by Jops Jacobs. Jops (1947) originally attended training school for handicraft teachers in Eindhoven. Between 1972 and 1992 she gave workshops in Graphic Art in Havelte and Arnhem. She exhibits her work at several individual and group exhibitions in the Netherlands. In 1996, 1998 and 2000 she made a Calendarium Linneas. These calendars consisted of twelve impressions of leaves. Nature is the starting point and foundation of her life and art. Her lifelong fascination with the secret life of plants resulted in a body of work with an almost exclusively botanical content. She uses impressions of leaves in 'vernis mou' as the basis of her etching technique and makes prints on handdipped paper in striking and vivid colours. A limited edition of original prints (size 60 x 60 cm) of this month's cover is available at a price of € 200. You can order the print at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.

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The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

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[3.] Powell LW, Isselbacher KJ. Hemochromatosis. In: Harrison's Principles of Internal Medicine, 15th Edition, Braunwald E, Fauci AS, Kasper DL, et al. (eds). New York: McGraw-Hill; 2001. p. 2257-61.

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