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EDITORIAL

The truth in reviews

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In this issue of the Journal, a critical appraisal of the value of population screening for breast cancer is published. This paper by Van Veen and Knottnerus, secretary and chairman of the Health Council of the Netherlands, respectively, reviews the available evidence for the benefits of such screening.[1] The review of the literature was undertaken by a committee of the Council, in reaction to the Cochrane review by Olsen and Gøtzsche, recently published in The Lancet.[2] This review by the Danish scientists heavily criticised the available studies, and reached the disturbing conclusion that breast cancer screening has more drawbacks than proven benefit.

The publication received much attention in the media, and at that time prompted the Dutch Minister of Health, Dr Els Borst, to ask the National Health Council for advice. It is intriguing that the apparently unbiased expert committee of the Council reaches a more balanced view on the benefits of this population screening.

In a broader context, the divergent conclusions of both systematic reviews are interesting.

Exactly 30 years ago, the British epidemiologist, Dr Archie Cochrane, published his seminal book 'Effectiveness and efficiency. Random reflections on health services'[3] and this marked the starting point of what is now called systematic reviews. Cochrane proposed that reviews of research evidence should be prepared systematically and that they must be kept up-to-date using new evidence. The aim was and is to identify the good and bad effects of health care in order to serve those that make use of it optimally. In addition, the systematic review of previous research is necessary to plan new research, and to avoid missing promising leads and performing research based on questions that have already been answered.

In the course of the past 30 years, reviews by the Cochrane Collaboration have become leaders in medical practice and clinical research. The exact way the Cochrane Collaboration is organised is beyond the scope of this editorial, but I recommend the reader to visit the Cochrane website at: www.Cochrane.org. 'Cochrane' has become synonymous to 'quality' to such an extent that many professionals and laymen perceive the products as infallible. The divergent conclusions reached regarding breast cancer screening between the Danish Cochrane review and the Dutch expert committee are an eye-opener. It certainly reminds us to remain critical also in an evidence-based arena, and it tells us that it is allowed to challenge a Cochrane review.

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REVIEW

Glucose and cardiovascular risk

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ABSTRACT

The American Diabetes Association and the World Health Organisation have recently redefined the spectrum of abnormal glucose tolerance. The criteria for diabetes mellitus were sharpened and impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) were classified as intermediate stages between normal glucose homeostasis and diabetes, based on fasting and challenged glucose levels, respectively. Criteria were established for 'the metabolic syndrome', as a cluster of cardiovascular risk factors that frequently coincides with the abnormal glucose tolerance state. The extent to which the glucose level itself should be regarded as a cardiovascular risk factor is the subject of ongoing debate. Recent research suggests that cardiovascular risk is related to the plasma glucose level even in the normal range of glucose concentrations. The impact of glucose in relation to cardiovascular events is discussed in this review.

INTRODUCTION

Diabetes mellitus, in particular type 2, is well recognised for its association with cardiovascular disease. Mortality risk from coronary and cerebral vascular incidents in diabetics is about fivefold higher than in non-diabetics.[1-3]

The risk of myocardial infarction and cardiovascular death in diabetics is as high as in non-diabetics with previous coronary heart disease.[4] This can partly be attributed to other risk factors that frequently accompany the condition, such as visceral obesity, dyslipidaemia and hypertension.[5,6]

Recent population studies suggest that plasma glucose levels are related to cardiovascular disease without a threshold. The topic of glucose as a cardiovascular risk factor is discussed in this review with emphasis on the epidemiological evidence in subjects with glucose intolerance.

DECREASED GLUCOSE TOLERANCE

The observation that microvascular complications can occur at lower fasting levels of glucose than formerly assumed motivated the American Diabetes Association (ADA) to redefine disturbed glucose metabolism at lower fasting serum glucose levels, while skipping the post-challenge criteria. Plasma glucose values of 7.1 mmol/l and higher were defined as 'diabetes mellitus' and values between 6.1 and 7.0 mmol/l as 'impaired fasting glucose' (IFG).[7] The World Health Organisation (WHO) agreed with the lower fasting criteria, but maintained the additional criteria of two hours post 75 grams glucose loading values, which define glucose levels between 7.8 and 11.1 mmol/l as 'impaired glucose tolerance' (IGT) *(table 1)*.[8] IFG and IGT are thus defined as two phenomena of decreased glucose tolerance, which can occur together or on their own.
The topic of glucose as a cardiovascular risk factor cannot be discussed without considering insulin. There is a continuous sequence of insulin resistance with normal glucose levels, IFG and IGT, and finally manifest type 2 diabetes mellitus. All of these are characterised by inadequate high plasma glucose levels relative to the insulin levels.[9] Resistance to non-glucose mediated effects of insulin is part of the increased cardiovascular risk. In particular a disturbed fat

Table 1
WHO definitions of normal and disturbed glucose metabolism[8]

FASTING PLASMA GLUCOSE (MMOL/L)	2 HOURS POST-LOAD PLASMA GLUCOSE (MMOL/L) (75 G GLUCOSE)		
	<7.8	7.8-11.1	≥11.1
<6.1	Normal	IGT[b]	Diabetes
6.1-7.0	IFG[a]	IFG[a] + IGT[b]	Diabetes
≥7.0	Diabetes	Diabetes	Diabetes

[a] = *impaired fasting glucose,* [b] = *impaired glucose tolerance.*

metabolism is associated with insulin resistance. Insulin stimulates endothelial-derived lipoprotein lipase, which catalyses the metabolism of postprandial triglycerides and impairs the activity of hormone-sensitive lipase, which is the rate-limiting enzyme in fat cell lipolysis. Resistance to these effects may induce an increase in the levels of triglycerides and free fatty acids (FFA) both in the post-prandial phase and in the fasting state. Glucose and FFA might compete for the same cellular clearance pathways and hyperglycaemia will therefore result in impaired clearance of FFA and vice versa.[10] The role of insulin in very-low-density lipoprotein (VLDL) production in the liver is complex. While acute hyperinsulinaemia seems to suppress VLDL formation, the chronic hyperinsulinaemic state is associated with impaired suppression contributing to hypertriglyceridaemia.[11] As a counterpart of high triglyceride levels, low levels of HDL cholesterol and changes of LDL cholesterol to more atherogenous small dense particles are seen in insulin resistance.[12] The importance of high triglycerides and low HDL cholesterol as independent risk factors of cardiovascular disease has been proven in population studies.[13,14]

The association of abnormal glucose response to insulin and dyslipidaemia as part of a combined cardiovascular risk syndrome has been acknowledged for more than a decade[5,6] and has recently been defined by the WHO as 'the metabolic syndrome' (*table 2*).[8] Several mechanisms of the development of the clinical entity of insulin resistance characterised by high serum levels of insulin frequently accompanied by the metabolic syndrome are described, but a detailed discussion of these is out of the scope of this review.[15]

GLUCOSE AND CARDIOVASCULAR RISK IN TYPE 2 DIABETES MELLITUS

Several studies have addressed the question whether glucose is an independent cardiovascular risk factor in manifest type 2 diabetes. In the Cardiovascular Health Study fasting glucose levels appeared to be only weakly associated with coronary heart disease in elderly diabetics during a six-year follow-up.[16] In a Finnish cohort study in elderly patients with type 2 diabetes, the incidence of stroke was more strongly correlated with fasting glucose than post-challenge glucose, and coronary heart disease was only associated with glycated haemoglobin (HbA1c).[17,18] The Diabetes Intervention Study examined the association between cardiovascular risk and fasting and postprandial glucose levels.[19] From this study in 1139 newly diagnosed patients with a follow-up of 11 years, it appeared that postprandial glucose levels were associated with an increased risk of myocardial infarction and death, whereas fasting glucose levels were not. Observational studies, however, give no answer to the question whether manipulation of the observed associated factor influences clinical outcome. The key intervention study of recent years that explored the effect of tight glucose control on cardiovascular risk was the United Kingdom Prospective Diabetes Study (UKPDS).[20] In the original analysis of this study, no statistically significant reduction of tight glucose control on cardiovascular mortality could be demonstrated when mean fasting glucose or HbA1c in the intensively treated and conventionally treated groups were compared. A later cohort analysis, however, showed that each reduction of 1% in HbA1c resulted in 14% decrease in the incidence of myocardial infarction, interestingly without a lower threshold of

Table 2
The metabolic syndrome in diabetes mellitus, impaired fasting glucose or impaired glucose tolerance according to the WHO definition[8,a]

Hypertension	Systolic ≥140 mmHg and/or diastolic ≥90 mmHg
Central obesity	Body mass index (kg/m^2) >30 and/or waist-to-hip ratio >0.90 (men) or >0.85 (women)
Microalbuminuria	Urinary albumin excretion ≥20 mcg/min or albumin: creatinine ratio ≥2.5 mg/mmol
Dyslipidaemia	Triglycerides >1.7 mmol/l and/or HDL cholesterol <0.9 mmol/ in men and <1 mmol/l in women

[a] = *two of the criteria present.*

HbA1c.[21] One could argue that not the glucose per se, but the insulin is in fact the related factor. A remarkable finding in this respect is the observation that metformin rather than sulphonylureas resulted in reduction in mortality.[22] An important difference between these two classes of medication is that the former does not increase insulin levels while the latter does.

GLUCOSE INTOLERANCE AND CARDIOVASCULAR RISK

Several older population studies addressing cardiovascular risk factors in the general population have shown the importance of decreased glucose tolerance as a risk factor for coronary heart disease.[23-26] In the Zutphen Study, as part of the Seven Countries Study, post-challenge hyperglycaemia appeared to be a greater risk factor for ischaemic heart disease than fasting glucose. A continuous risk gradient of glucose to cardiovascular disease has already been suggested in this study.[23] Not all of these studies, however, were conclusive with respect to the cardiovascular risk of glucose levels in the near normal range.[27] Population studies considering the association of near normal glucose and stroke also gave conflicting results.[23,28] Coutinho *et al.*[29] conducted a meta-analysis of 20 population studies that assessed the relationship between cardiovascular risk and glucose in non-diabetic subjects published between 1966 and 1996. This meta-analysis is confined to studies that were conducted before the WHO redefined the criteria of disturbed glucose metabolism. Different definitions of glucose intolerance were used, including glucose levels that would implicate manifest diabetes under the new criteria. In a total of 95,783 individuals (94% men) 3707 fatal and non-fatal cardiovascular events, including stroke, were recorded during 12.4 years. There was an exponential relationship between the risk of cardiovascular incidents and both fasting and post-loading glucose levels starting in the normal range of glucose levels. Extrapolating the glucose values to the current WHO cut-off levels of glucose intolerance, the relative risks of cardiovascular incidents were 1.33 (95% CI 1.06-1.67) at a fasting glucose level of 6.1 mmol/l and 1.58 (95% CI 1.19-2.10) at a challenged glucose level of 7.8 mmol/l, which are threshold values of IFG and IGT, respectively.

Using the adjusted WHO criteria for IFG and IGT, studies from different continents are available. In the USA, the Cardiovascular Health Study,[30] considering cardiovascular risk factors in people aged 65 years and older, showed that cardiovascular disease was related to both fasting and post-challenge glucose (*table 3*). In the younger population of the NHANES Study in the USA,[31] consisting of 3092 adults aged between 30 and 74 years, an increased relative risk of all-cause mortality of 1.6 (95% CI 1.0-2.6) was documented in subjects with newly diagnosed diabetes mellitus based on the criterion of isolated post-challenge hyperglycaemia (glucose ≥11.1 mmol/l), whereas the relative risk of death in those with known diabetes mellitus was 2.1 (95% CI 1.4-3.2). Mortality was also increased in those with IGT showing a relative risk of 1.3 (95% CI 1.0-1.6). Although cardiovascular death made the burden of the increased risk statistical, significance was not reached when corrections were made for confounding factors such as smoking, blood pressure, cholesterol, body mass index and socioeconomic status in those with IFG and IGT. The absolute number of subjects with isolated IFG in this study, however, was rather small (*table 3*).
In Europe, the DECODE study group[32] assessed the risk of death in relation to glucose levels in an analysis of 13 prospective European cohort studies including a total of 18,048 men and 7316 women. Nearly one third of 2411 individuals who had IFG following the ADA criteria also had IGT according to the WHO criteria. Yet only a quarter

Table 3
Relative risks (RR) and 95% confidence interval of ischaemic cardiovascular disease (including stroke) and death in subjects with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)

STUDY	POPULATION (N)			FOLLOW-UP	CARDIOVASULAR DISEASE/DEATH	
	Total	IFG	IGT	Years	IFG	IGT
Cardiovascular Health Study[30,a]	4515	582	1264	Mean 5.9	1.39 (1.09-1.77)	1.23 (1.01-1.98)
NHANES II[31,b]	3092	9	503	Mean 16	1.02 (0.79-1.32)	1.07 (0.78-1.46)
Funagata[34,b]	2806	155	382	Mean 8	1.14 (0.35-3.73)	2.22 (1.08-4.58)
DECODE[32,c,d]	25,364	2411	2766	4.8-10	1.60 (1.04-2.47)	1.59 (1.38-1.82)[e]
Mauritius, Fiji, Nauru[33,b,d]	9179	142	243	5-12	1.3 (0.5-3.6)[f] 1.4 (0.5-4.0)[g]	2.3 (1.2-4.2)[f] 2.6 (1.3-5.1)[g]

[a] = endpoint: clinical cardiovascular disease, [b] = endpoint: cardiovascular death, [c] = endpoint: all-cause mortality, [d] = meta-analysis, [e] = RR combined IFG/IGT: 1.59 (1.05-2.41), [f] = men, [g] = women.

of the 2766 individuals with IGT also had IFG. So, isolated IGT appears to be far more common than isolated IFG. The clinical importance of IGT was, moreover, illustrated by the statistically more powerful relative risk of death in IGT compared with IFG (*table 3*). Also outside of Europe and the USA the cardiovascular risk of IGT has been acknowledged as demonstrated in the pooled population studies of Mauritius, Fiji and Nauru[33] and in the Funagata Study in Japan,[34] both indicating an increased relative risk of cardiovascular death in IGT, but not in IFG (*table 3*).
In vivo studies on the relation between glucose and arterial wall thickness also point to the importance of postprandial hyperglycaemia. This has been illustrated in studies measuring carotid medial intima thickness, which seems to be more closely related to post-challenge glucose levels than to fasting glucose.[35,36]
It therefore appears that post-challenge glucose levels, which could be regarded as a surrogate for postprandial glucose levels, are better at predicting cardiovascular disease than fasting glucose levels.

NORMAL GLUCOSE AND CARDIOVASCULAR RISK

Recently, a sub-report of the Botnia Study was published. In this study the occurrence of the metabolic syndrome according to the WHO definition was studied systematically in relation to glucose tolerance and cardiovascular risk in 4483 relatives of subjects with known type 2 diabetes.[37] Up to a threefold increased risk for coronary heart disease and stroke was observed in subjects with IFG and IGT. Most remarkable was the finding that the risk was increased even in subjects with insulin resistance who still had glucose levels in the normal range. The best predicting factor in these subjects, however, was the presence of the metabolic syndrome.

In the Hoorn Study the relative risk of cardiovascular mortality started to be significant from a fasting glucose level of 6.1 mmol/l onwards.[38] Both post-loading glucose and HbA1c showed a linear correlation to cardiovascular risk, even in the non-diabetic range. A response above two standard deviations of the normal population in a two-hour post-loading test was related to an increased relative risk of all-cause mortality and cardiovascular mortality in the range of 2.2 to 3, respectively. In contrast to these figures, when analysed separately, the increased relative risk of cardiovascular mortality in subjects with IGT and/or IFG did not reach statistical significance.[39]
The Norfolk Study, a prospective study in 4662 men aged between 45 and 79 years, showed a linear correlation between ischaemic cardiovascular disease and death which continued in the normal range of HbA1c. An increase of 1% HbA1c was associated with a 28% increase in death throughout the whole range of HbA1c levels. The relative risk for ischaemic cardiovascular disease gradually increased from individuals with HbA1c levels beneath 5% to more than 5% in individuals with HbA1c levels above 7%. The adjusted relative risk of glucose levels for cardiovascular disease was even greater than the risk of cholesterol.[40]

These findings correspond with the results from the UKPDS, which showed a continuous increase in risk of both myocardial infarction and microvascular complications in type 2 diabetes with increasing HbA1c levels from the lowest level of about 5.5 onwards, notably without a threshold.[41] From all of these studies it is suggested that the association between glucose and cardiovascular risk is continuous without a lower threshold. However, there are limits to the benefit of low glucose levels. This has been illustrated in a large cohort study showing a U-shaped relation between fasting plasma glucose and cardiovascular disease. After a decline at lower glucose levels the risk of coronary heart disease and all-cause mortality began to increase again below glucose levels of 4.5 mmol/l.[42]

GLUCOSE AND OTHER RISK FACTORS

In the cited population studies concerning glucose and cardiovascular risk the data were corrected differently for confounding factors. In most of these studies insulin levels were not measured. In the already mentioned Botnia Study the correlation between insulin levels and cardiovascular morbidity in subjects with insulin resistance was of borderline significance.[37] Also in a meta-analysis of studies linking insulin levels to ischaemic cardiac disease, defined as myocardial infarction, death or ECG abnormalities, hyperinsulinaemia appeared to be only a weak risk factor.[43] In a case-control study of 66 non-diabetic subjects aged below 55 years with premature cardiovascular disease, the association between insulin levels and coronary artery disease disappeared when parameters were corrected for body mass index.[44] In a study of subjects who recently developed impaired glucose tolerance, fasting insulin levels were negatively correlated with changes in distensibility and compliance of the carotid artery in men, but not in women.[45]
In insulin resistance other, not glucose-related, metabolic disturbances could be incriminated in the cardiovascular risk. Many pathways involved in the cardiovascular damage in insulin resistance have been suggested, such as disturbances in the clotting system, endothelial dysfunction and proinflammatory mediators.[46-49] The apparent risk of postprandial hyperglycaemia, which seems to imply a greater cardiovascular risk than fasting hyperglycaemia, has focussed the attention to the postprandial sequelae of insulin resistance. High postprandial glucose levels in

insulin resistance are associated with high serum levels of free fatty acids.[10] Insulin levels following glucose challenge correlate well with post-challenge remnant lipid levels in subjects with IGT, suggesting that postprandial dyslipidaemia might be the mediating factor in the cardiovascular sequelae and not glucose or insulin per se.[50] In the Botnia Study about 50% of the subjects who were classified as IFG and/or IGT also had the metabolic syndrome. The occurrence of this syndrome was highly predictive for both coronary heart disease and stroke in these patients.[37] Analysis of the individual components of the metabolic syndrome in relation to cardiovascular risk in subjects with manifest type 2 diabetes showed that the presence of dyslipidaemia, notably hypertriglyceridaemia, was by far the most indicative predictor of coronary heart disease, while the predicting effect of HbA1c was only borderline.[51]

DISCUSSION

What we have learned from the population studies in recent years is that insulin resistance, IFG, IGT and diabetes mellitus type 2 form a continuous sequence of risk for cardiovascular disease. Especially postprandial glucose is a predictor for both coronary and cerebral ischaemic incidents. The appreciation to which extent glucose itself is important in the mechanism of cardiovascular pathology has not been fully elucidated at this moment. Subjects with glucose intolerance frequently cluster other cardiovascular risk factors.[37,52] The components of the metabolic syndrome in subjects with glucose intolerance appear to be strongly related to this increased risk. On the other hand, the vast majority of subjects known to have multiple metabolic cardiovascular risk factors appear to be insulin resistant, especially those with high triglycerides and low HDL cholesterol levels.[53] In particular, postprandial hypertriglyceridaemia could be incriminated as a mediator of the increased cardiovascular risk of IGT.[50] As we have learned from the UKPDS, effective reduction of cardiovascular risk in type 2 diabetes mellitus requires treatment of coexisting risk factors. Tight blood pressure control reduces both microvascular and macrovascular complications, in particular stroke.[54] The treatment of dyslipidaemia in diabetes mellitus primarily for the prevention of ischaemic cardiac events is useful. This topic was recently reviewed in this journal.[55] The same seems to be true for glucose intolerance, although there are only few data available.[56] Since glucose and triglycerides are so strongly interrelated, postprandial hyperglycaemia could only be a marker of postprandial hypertriglyceridaemia. This would imply that the increased cardiovascular risk of postprandial hyperglycaemia is mediated by an increased triglyceride level after a meal and not by the glucose level per se. That the lowering of glucose nevertheless has a beneficial effect not only on microvascular diabetic complications, but also on cardiovascular disease, is illustrated by the inverse relation between HbA1c and myocardial infarction in the UKPDS.[21] Since the association of glucose and cardiovascular risk starts at glucose levels in the normal range and gradually increases, it could be of paramount importance to prevent glucose intolerance and consequent progression to manifest diabetes. In the Hoorn Study the odds ratios for developing diabetes mellitus (WHO criteria) were 10, 10.9 and 39.5 for individuals with IFG, IGT and the combination of both, respectively.[57] Moreover, features of the metabolic syndrome are highly predictive for developing IGT and diabetes.[58] The Finnish Diabetes Prevention Study showed that in subjects with IGT the development of manifest diabetes could be effectively prevented by dietary intervention consisting of lowering the intake of saturated fat and relatively enriching the food with monounsaturated fatty acids, fruits, vegetables and fibre in combination with daily moderate exercise.[59] In the Diabetes Prevention Programme, lifestyle intervention proved to be more effective in preventing progression of IGT to manifest diabetes than treatment with metformin.[60]

Lifestyle interventions with diet and exercise combine the beneficial effects on glucose levels and the metabolic syndrome. This has been demonstrated in subjects with IGT, showing that remnant hyperlipidaemia and insulin levels improve with diet and exercise.[50,61] In the Malmö Prevention Trial, men with IGT who could stick to a lifestyle programme normalised their life expectancy during a follow-up time of 12 years in contrast to those with IGT who were treated routinely.[62] This improvement of outcome coincided with improvement of features of the metabolic syndrome.

If prevention of postprandial hyperglycaemia is indeed more important than fasting hyperglycaemia with respect to cardiovascular risk, new glucose-lowering therapies, both orally and insulin derived, may have promising perspectives. The new class of carbamoylmethyl benzoic acid derivatives, such as repaglinide, has a rapid and short-acting profile which effectively lowers postprandial glucose.[63] The thiazolidines are a new class of drugs that activate the peroxisome proliferator-activated receptors and appear to improve insulin action in subjects with type 2 diabetes mellitus. Moreover, thiazolidines might have several non-insulin-related potential beneficial effects on cardiovascular risk factors.[64] Thiazolidines might also improve insulin sensitivity in insulin-resistant subjects without diabetes. In a 12-week double-blind randomised trial it was shown that rosiglitazone improves insulinaemic responses to both oral glucose load and to mixed meal.[65] Finally, the combination of metformin and thiazolidines may facilitate insulin action.[66]

Insulin analogues, also when used in mix forms in type 2

diabetes, may effectively improve postprandial glucose excursions.[67] For all of these new classes of antidiabetic therapies it remains to be proven in clinical trials that the prevention of cardiovascular disease is indeed better than with the classical drugs.

The most challenging consequence of recent epidemiological research is the exact characterisation of the impact of glucose lowering with respect to cardiovascular risk. First of all, it needs to be further elucidated whether glucose per se is the risk factor, or whether it is just a marker of underlying mechanisms. And if glucose turns out to be a gradual risk factor starting even in the normal range of glucose levels, then primary and secondary trials are needed, just as those carried out on cholesterol. From these trials it should become clear what the relative effects are of both glucose and insulin levels, and of the different components of the metabolic syndrome.

The next question is how to find people at risk, especially those with postprandial hyperglycaemia. Isolated IGT is far more common than isolated IFG and the cardiovascular risk seems to be of greater importance in the former than in the latter. By definition, however, IGT can only be detected by glucose tolerance testing. Obviously, we should be aware of the clinical presentation of the insulin resistance syndrome with its visceral obesity, hypertension and dyslipidaemia. In people with the well-known metabolic cardiovascular risk factors, especially the combination of high triglycerides and low HDL cholesterol is highly associated with insulin resistance and IGT. [53] Without glucose challenging, however, these types of glucose intolerance are not detected. Several years ago we abandoned the oral glucose tolerance test (OGTT) as a routine test in clinical practice. Is it reasonable to reintroduce the OGTT in the year 2002 as first-line diagnostic step in people we consider they may have the metabolic syndrome?[68]

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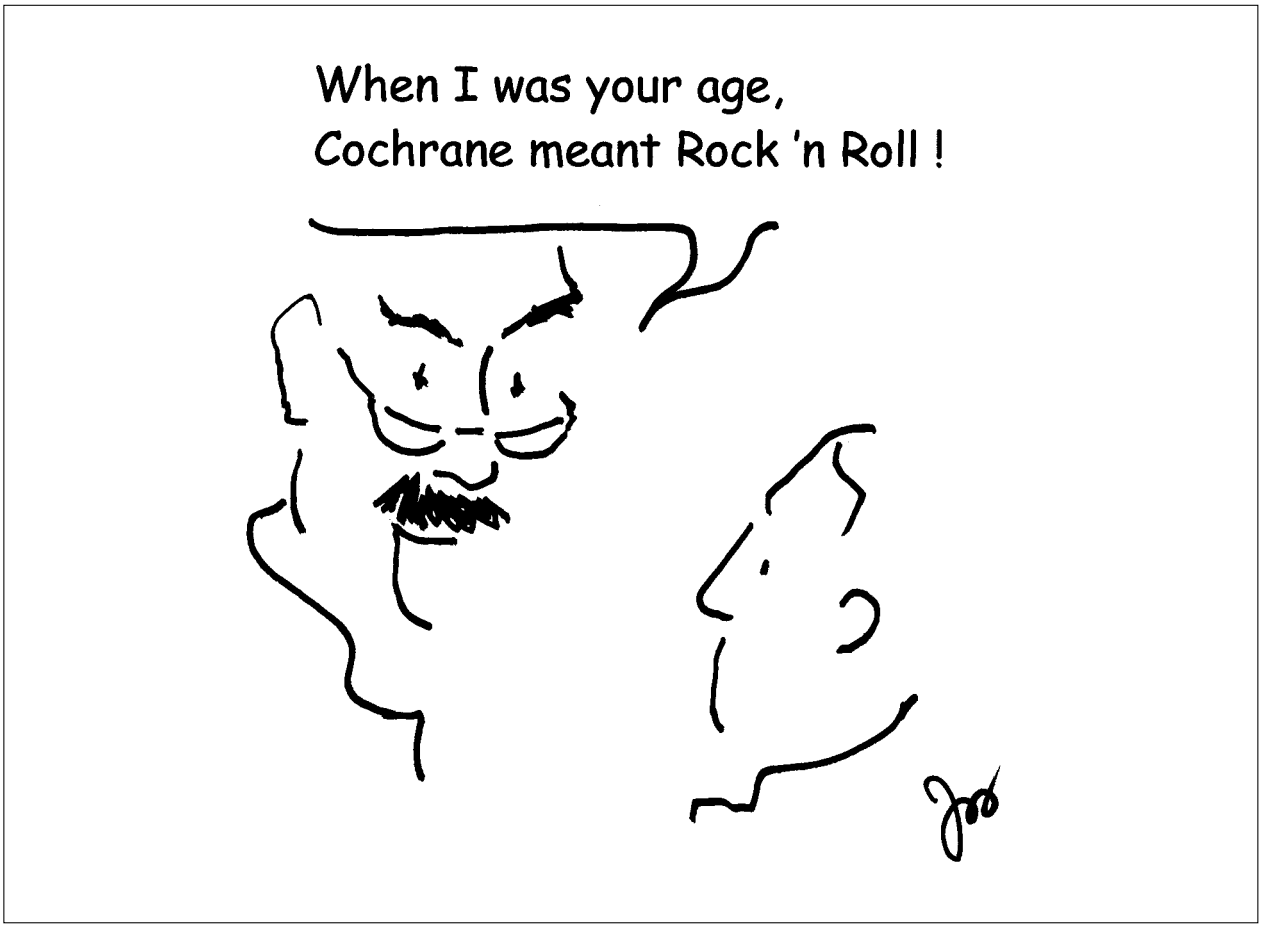

Fuchs, et al. Glucose and cardiovascular risk.

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REVIEW

The evidence to support mammography screening

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ABSTRACT

A recent Cochrane review claimed that mammography screening did not save lives and could actually be harmful. In an advisory report to the Dutch government, a committee of the Health Council of the Netherlands concludes that the Cochrane review does not nullify the evidence supporting breast cancer screening programmes for women aged 50 or over. Except for one flawed trial, the committee found no convincing arguments to exclude four out of the six other eligible trials entirely or partially from the analysis. The committee considers the reviewers' conclusions that breast cancer mortality as an outcome is unreliable (biased in favour of screening) and must be replaced by overall mortality to be too extreme. In the committee's view, breast cancer mortality is an important outcome. However, this outcome should be considered in conjunction with all-cancer mortality and all-cause mortality when interpreting the results of screening trials (or observational studies).

INTRODUCTION

A recent Cochrane review concluded that 'the currently available reliable evidence does not show a survival benefit from screening for breast cancer'.[1] This conclusion attracted considerable publicity in medical journals and the lay press. Hoping to eliminate confusion on this issue, the Dutch Minister of Health asked the Health Council of the Netherlands to advise her whether the Cochrane review nullifies the rationale of the ongoing screening programme for women aged 50-75. The committee that prepared the report re-examined the original studies and held a hearing that was attended by experts either involved in or opposed to breast cancer screening. This article summarises the advisory report[2] that was issued on 7 March 2002, focusing on two features: the methodological quality of the reviewed studies, and the reliability of breast cancer mortality as an endpoint.

METHODOLOGICAL QUALITY

The Cochrane review,[1] conducted by Olsen and Gøtzsche from the Nordic Cochrane Centre, Copenhagen, assessed the results of the seven eligible randomised controlled trials (RCTs) of screening mammography. These RCTs were started between 1963 and 1982, involved half a million women, and were concluded more than ten years ago.
The reviewers used the following quality criteria:

- randomisation was adequate and led to comparable groups;
- post-randomisation exclusions were few or unbiased;
- reliable outcome data were available.

On the basis of these assessments the reviewers classified the quality of the available data into four groups: high, medium, poor and flawed.
Two RCTs (Edinburgh and the HIP Trial in New York) were judged to be flawed and therefore not suitable for use in the meta-analysis. This was because the intervention groups (those invited for screening) and control groups (those not invited) were considered not comparable at entry or for analysis of the results.
Women whose breast cancer was diagnosed before randomisation were subsequently excluded from analysis, because

they could not benefit from screening. On the basis of successive publications, the reviewers calculated that in the HIP Trial, 853 women were excluded after allocation to the intervention group, while only 336 women were excluded from the similar-sized control group (31,092 women aged 40-64 years). This differential exclusion would be expected to create bias in favour of screening. The reviewers were also critical of the cause of death assessment. Cases considered dubious (71 from the intervention group and 73 from the control group) were reassessed blindly. Based on the classification in the control group, there were 21 fewer cases classified as breast cancer deaths in the intervention group than expected. Differential misclassification might therefore be responsible for approximately half of the reported mortality benefit (44 deaths), the reviewers claim.
The RCT in Edinburgh also involved women aged 40-64, who were patients at 87 group practices. These practices were allocated randomly to the intervention and control groups, taking account of the number of GPs in each practice. This so-called 'cluster randomisation' led to a situation whereby the intervention group contained twice as many women of higher socioeconomic status (SES) as the control group (53% as opposed to 26%).
The reviewers rated the quality of three Swedish RCTs (Two-County, Stockholm and Göteborg) poor. The Two-County Trial (Kopparberg, Östergötland) was singled out for particular criticism because of an alleged lack of clarity regarding the cluster randomisation, the date of entry into the trial, and the number of women randomised. According to the reviewers, the randomisation procedure may have been seriously flawed. They put forward three arguments to justify their assessment:

- breast cancer mortality in the control group in Kopparberg was higher than in the Östergötland control group (0.0021 *versus* 0.0012, p=0.002);
- there was an excess of post-randomisation exclusions in the Kopparberg control group;
- there was a difference in age distribution between the intervention and control groups (+0.45 years in Kopparberg and -0.27 years in Östergötland).

Two individually randomised trials (Canada and Malmö) were classified as of medium quality. In the Canadian RCT, no women had to be excluded because of previously detected breast cancer; the trial recruited volunteers, and all were asked about their history when invited to consent to participation in the trial. In Malmö, some women were excluded but this was deemed unbiased since this step involved an official source, namely the cancer registry.
Results from the different quality groups should not be combined, the reviewers claim. The 'medium-quality' trials failed to find a statistically significant effect of screening on breast cancer mortality, whereas the three 'poor-quality' trials found a marked effect. The difference between the two effect estimates is significant. This statistical heterogeneity is described as very rare and a strong warning signal that something is wrong. The explanation in such cases, the reviewers claim, is generally methodological. The difference between the two effect estimates (RR = 0.97 and 0.68, respectively after 13 years for women aged 40-74 at entry) is in good agreement with the results from empirical, methodological research.

The committee's view

The committee feels that the criticism of the HIP Trial is partly justified. However, the claim of differential exclusion was dealt with by one of the investigators involved.[3] After an interval (there was no cancer registry), it was apparent that all deaths from breast cancer were identified in both study groups; identification of the date of diagnosis was then possible from hospital records. In the Edinburgh Trial the study groups were not comparable in terms of SES. Since there is a correlation between SES and both breast cancer risk and overall mortality, the differences in SES are likely to have influenced the trial results, as the researchers themselves noted, tending to *under*estimate the effect of screening.[4]
The decision to also omit three Swedish trials from meta-analysis is critical in relation to the Cochrane review's conclusions regarding the benefit of breast cancer screening. Where women over the age of 50 are concerned, the 'poor-quality' trials yield a statistically significant reduction in breast cancer mortality by 31%, RR = 0.69 (0.55-0.86), whereas the 'medium-quality' trials failed to do so: RR = 0.88 (0.64-1.20) after seven years.
The reviewers' conclusion that the two categories of trials are heterogeneous is partly based on a statistical test, combining data on women under 50 and over 50. These data should have been analysed separately because the benefit of mammography remains uncertain in women under 50. Moreover, heterogeneity may be attributable to methodological shortcomings, but just as well to clinical heterogeneity (a difference in characteristics such as the nature and intensity of the intervention or the nature of the trial population) or to some unknown coincidental phenomenon.[5] The various trials were, for example, clinically heterogeneous in terms of the so-called control rate. The stage distribution in the Canadian Trial control group was more favourable than that in the control groups of the Swedish trials.[6] Other factors, such as differences in attendance rates, in the quality of the mammography, in the film reading, or in the diagnostic work-up can also account for the observed difference between the two effect estimates.[7] The reviewers did not take these factors into account.

Moving on to the question of randomisation in the trials considered, it should be said at the outset that randomisation at the individual level is generally preferable to random-

isation at the group level. However, individual randomisation is not always possible or desirable. Cluster randomisation can sometimes be unavoidable for methodological (threat of contamination) or logistical reasons.
The 'poor-quality' trials were cluster randomised. With cluster randomisation, it is more likely that the intervention group and control group will differ in terms of prognostic characteristics such as age, because the number of randomisation units is smaller than would be the case with individual randomisation. In addition, the largest age imbalance, roughly five months in the Two-County Trial, should be considered in the light of the fact that the trial involved women aged 40-74 years at entry. The presence of this age imbalance, therefore, does not mean poor randomisation. Such imbalances are not problematical, provided the analysis is adequate. However, the reviewers used age imbalance as a marker for irregularities in the randomisation process. Where the Two-County Trial is concerned, bias in favour of screening because of poor randomisation is unlikely, since the age imbalance would tend to underestimate the benefit of screening.[8] Also, the comparability of the study groups has been examined in terms of all-cancer mortality and all-cause mortality, excluding breast cancer in both cases. These two basic measures proved to be very similar.[9] In an overview of all four Swedish trials based on individual patient data (a so-called IPD meta-analysis), the cause of death pattern in the intervention groups was, except for breast cancer, very similar to that in the control group.[10]
Another case for poor randomisation, the reviewers stated, is that breast cancer mortality in the Kopparberg control group was higher than in the Östergötland control group. The difference is indeed notable. However, alternative explanations need exclusion first. It may be that the difference in mortality reflects true regional variations in breast cancer mortality. The Swedish trialists should be able to give a decisive answer.
A third case for poor randomisation is an excess of excluded women in the Kopparberg control group. If one calculates the number of exclusions in the way the reviewers indicate (using data from Tabár *et al.*, references 9 and 11), it does indeed appear that the exclusion rate for the Kopparberg control group (264/18,846 = 1.4%) is higher than that for the intervention group (462/39,051 = 1.2%). However, the difference is small, tends to *under*estimate the benefit of screening, and cannot be attributable to differences in the thoroughness of the ascertainment of previous breast cancers, since it involved record linkage to cancer registry data in both cases.[11]

In the committee's view, the Cochrane reviewers' decision to exclude the Edinburgh Trial was justified, because of the baseline imbalance in SES. However, there are no convincing arguments for scoring four other trials much lower on methodological grounds than those in Malmö and Canada. This raises doubts whether the quality criteria have been consistently applied. As a result, five of seven trials are left (completely or partially) outside the analysis.

BREAST CANCER MORTALITY AS AN ENDPOINT

The Cochrane review concludes that breast cancer mortality is an unreliable outcome that is biased in favour of screening. Flaws are attributed to differential exclusion of women with previous breast cancer and to differential misclassification of cause of death.
First, according to the reviewers' calculations on data from the Two-County Trial,[9] mortality from non-breast cancer among breast cancer cases was 2.4 times higher in the intervention groups than in the control groups. Second, referring to data from the Malmö Trial,[12] it is pointed out that 21% of women with breast cancer who died (previously) had another malignancy, creating considerable potential for misclassification bias. Third, the review suggests, belief in the effectiveness of a particular intervention may influence cause of death certification, creating quite a substantial bias in favour of screening. Finally, the authors draw attention to the issue of radiotherapy. Radiotherapy reduces the rates of local recurrence by two-thirds.[13] Early cancers are treated by tumourectomy and radiotherapy. The implication of this, according to the review, is that deaths among women whose breast cancer was detected by screening are more likely to be misclassified than deaths from other causes and that too many deaths in the control group will be classified as breast cancer deaths. Blind (re)assessment of the cause of death, the Cochrane reviewers argue, does not remove the objections to the use of breast cancer mortality as an outcome measure. First, this is because this procedure favours screening. To support this contention, the authors refer to the results of the blind reassessment of cause of death in 144 dubious cases in the HIP Trial. The authors also claim to have found evidence of differential misclassification in the Swedish overview.[14] Blind reassessment of the cause of death resulted in the conclusion that 418 women in the intervention groups (with a total observation period of 1.43 million women-years) died of breast cancer, while the corresponding figure in the control groups (1.14 million women-years) was 425. On the basis of the officially recorded causes of death, the figures were 419 and 409, respectively.[14] The fact that the net 17 reclassifications by the committee was in favour of screening is regarded by the Cochrane review as evidence of bias. Second, blinded cause-of-death assessment will overlook a screening-associated increase in mortality. The finding that post-mastectomy radiotherapy increased vascular mortality[13] is cited as evidence of this source of misclassification.

The committee's view

The reported chance of breast cancer being misclassified as the cause of death ranges from less than 5% to a maximum of 10%.[12-18] The numbers of false-positive and false-negative misclassifications tend to cancel out. Therefore, the overall bias in reporting breast cancer deaths is small.

Misattributions occur most commonly when another cancer is present.[3] The Cochrane reviewers suggest that confusion is quite common, citing data from Malmö in support. These data indicate that 21% of breast cancer patients who die also have another (primary) form of cancer.[12] This figure probably includes second (primary) breast cancers and non-melanoma skin cancers. Such malignancies should be disregarded in this context, since comorbidity of this kind cannot lead to uncertainty regarding the cause of death. Other studies have suggested a much lower percentage than 21, namely 6 to 12%.[15,19] Results of studies on the development of second (primary) tumours following treatment of breast cancer also point to a much lower percentage, about 5%. In the committee's view, the number of dubious cases is modest and cannot be an important source of bias.

The contention that belief in the effectiveness of an intervention is a quite substantial source of bias is derived from a retrospective cohort study.[20] As noted by the original investigators themselves, their work was not intended to test the validity of the information bias hypothesis; this hypothesis emerged from post-hoc subgroup analysis. Data from a trial for the early detection of colorectal cancer cannot be taken to support the alleged information bias either.

Although the validity of breast cancer as a certified cause of death is high, it does not automatically follow that breast cancer mortality, as an outcome in experimental studies is not subject to bias. However, as indicated, the suspicion of differential exclusion in the HIP Trial was refuted by one of the researchers involved.[3] Likewise, exclusion in the Swedish RCTs was performed objectively, by record linkage to the Swedish Cancer Registry.[11] Furthermore, the committee could not find any definite evidence in literature of *differential* misclassification of breast cancer as the cause of death.[12-20] The review suggests that there is definite evidence of differential misclassification occurring. This is a serious issue since, if proven, the resulting bias would account for half of the reduction in breast cancer mortality reported in the Two-County Trial. However, the committee believes that there has been a misunderstanding. The reviewers used data from the Two-County Trial[9] to show that women in the intervention group in whom breast cancer was diagnosed (1295 as compared with 768 women in the control group) had a higher mortality from other malignancies (25 and 6, respectively) and also from all causes other than breast cancer (81 and 34, respectively): RR = 2.4 and 1.4, respectively. The alleged excess rates in the intervention group can, however, at least partially be explained by the fact that screening will result in breast cancer being diagnosed several years earlier than would otherwise be the case. Because of this 'lead time', women in the intervention group who contracted breast cancer were at risk of death several years longer. The Cochrane review does not take account of this. To make a valid comparison, the denominator should not be the number of women with breast cancer, but the number of women-years at risk. When comparison is made on this basis, no statistically significant discrepancy emerges between intervention and control groups in terms of mortality from all causes other than breast cancer.[8,21] The publications are, however, inconclusive with regard to mortality from other forms of cancer among women with breast cancer.

Slippery linkage bias

The Cochrane review rightly states that blind (re)assessment of cause of death does not preclude the possibility of bias. So-called 'slippery linkage bias'[22] is a case in point. Such bias occurs where a 'positive' screening result leads to an invasive or otherwise hazardous intervention, ultimately causing the subject's death, without this being associated with screening. Blinded endpoint committees cannot include such screening-induced deaths, for example deaths following a false-positive screening result.[23] The reviewers claim that greater use of radiotherapy in screened women than in controls is a source of bias of this kind.

The reviewers' assertion that radiotherapy following mastectomy increases vascular mortality, and their expectation that post-mastectomy radiotherapy even *in*creases overall mortality in screened women, is derived from a meta-analysis of 40 radiotherapy trials started between 1960 and 1990.[13] Midway through this period, radiotherapy techniques were improved substantially.[14] For this reason, RCTs were launched to determine the effect of modern locoregional radiotherapy, designed to minimise cardiopulmonary radiation exposure. The findings of these studies demonstrate that in the medium term (median observation period: ten years), modern radiotherapy does not increase vascular morbidity or mortality, and that overall mortality actually declines.[24,25] The ten-year survival rate was 45% in women who had received radiotherapy and 36% in women who had not.[25] A meta-analysis of 18 recent studies reports very substantial benefits in irradiated patients with a decrease of overall mortality by 17%: RR = 0.83 (0.74-0.94).[26] Longer follow-up is required to confirm that excess vascular mortality can be substantially reduced or even avoided.

In any case, it does not strike the committee as likely that any harmful effects of radiotherapy would manifest themselves especially among screened women, as the reviewers assume.

Post-mastectomy radiotherapy is mainly used in women with an increased risk of local breast cancer recurrence (tumour-positive axillary nodes, tumour diameter greater than 5 cm). Screening tends to detect less advanced breast cancer, which can normally be treated without irradiating the lymph nodes in the neck (supraclavicular). In the committee's view, it is not likely that the results of the screening trials started after 1975, except for the HIP Trial, are biased in favour of screening.

The contention that the endpoint committee's reclassification biased the results of the HIP Trial is rejected by one of their members.[3] In his reply,[27] Gøtzsche persisted, claiming that there had been no decline in all-cancer mortality. The committee takes issue with Gøtzsche on this point, however. The power of the trial was not designed to detect differences in all-cancer mortality. Hence, a statistically significant reduction in this outcome cannot be expected. According to the Cochrane review, the HIP Trial yields a relative risk for all-cancer mortality of 0.98 (0.89-1.08) for women aged 40-64. A reduction in all-cancer mortality of this order is consistent with a reduction in breast cancer mortality of 17% after 13 years,[1] as is the 1% fall in the overall mortality: RR = 0.99 (0.94-1.05) after 13 years.[1] The committee feels that serious bias is unlikely. In the Swedish overview, there does appear to be differential misclassification in favour of screening, if one looks at the numbers and the direction in which classifications are shifted. Blind reassessment leads to some revision of the estimated effect: breast cancer mortality appears to decline by 23%, rather than 20%.[14]
Several other studies with data from the Swedish overview have also shown that only marginal differences between the relative risk estimates emerge when using different outcome measures.[10,18] One of the comparisons used 'breast cancer related excess mortality' as an outcome. This analysis does not require cause of death assessment. The basic principle is an indirect standardisation of the total mortality in the breast cancer cases in the intervention and control groups, using national cause-of-death statistics as a reference. This analysis yielded a relative risk reduction of 24% for women aged 40-74 years. This compares with a reduction of 23% obtained by individual cause-of-death assessment by a blinded endpoint committee, and of 20% obtained by record linkage to the Swedish Cause of Death Register.[18] This close concordance argues against serious bias in favour of screening.

The Cochrane review regards overall mortality as the only reliable outcome. This is partly because the authors claim that breast cancer mortality is biased, and partly because the possibility of a screening-associated increase in mortality from other causes should be taken into account. Hence, an effect on overall mortality would need to be shown, according to the reviewers. On the other hand, they concluded that the two 'medium-quality' trials, when combined, failed to show a reduction in overall mortality or in total cancer mortality.

The committee regards breast cancer mortality as an important endpoint. If data from all eligible trials (excluding Edinburgh) are considered, then the relative risk for breast cancer mortality is 0.72 (0.61-0.85) after seven years, and 0.76 (0.67-0.85) after 13 years in women over 50. The Danish authors' contention that overall mortality should be the primary endpoint is not agreed with. It is nevertheless the committee's view that the effect of screening should be assessed not only on the basis of breast cancer mortality, but also in conjunction with total cancer mortality and overall mortality. Those other outcome measures should be considered when interpreting the results of cancer-screening trials,[22] as indeed they normally are.[8-10,13,18,21,24,28] There are good reasons for this. First, such an approach facilitates the identification of any (direct or indirect) adverse effects that screening may have. Second, examination of all-cause mortality in combination with disease-specific mortality can reveal major threats to the validity of an RCT, such as flaws in randomisation and ascertainment of vital status.[4,22] If screening has a beneficial effect on breast cancer mortality, it should also be expected to have a smaller beneficial effect on all-cancer mortality and an even smaller effect on overall mortality. None of the reviewed RCTs showed a statistically significant decline in all-cancer mortality. However, as stated, they were not designed to demonstrate such a decline. The Swedish overview does show a decrease of 2%.[10] It has been suggested that this decrease is too small, and that 30% of all-cancer mortality is attributable to breast cancer.[27,29] The failure to find evidence of a significant reduction in all-cancer mortality is described as 'certainly a cause for concern'.[29] However, one should not overlook the fact that the proportion of all-cancer mortality accounted for by breast cancer will be much lower in a trial population than in the population at large: 11% in the Swedish RCTs and 24% among Dutch women.[10,30] The difference arises because the trials have, rightly, excluded all women with previous breast cancer from analysis. Therefore, a 20% reduction in breast cancer mortality (concerning women aged 40-74) translates into a 2% fall in all-cancer mortality. The non-significant decline referred to in the overview[10] is consistent with this estimate, whereas the figures in the Cochrane review are not. However, these figures have not been broken down according to age. The committee feels it would be instructive to obtain insight into all-cancer mortality among women over the age of 50.
Finally, attention should be given to overall mortality as well. The reviewers abandoned their assertion[31] that mammographic screening causes six times as many deaths as it prevents. In the Cochrane review it is stated

that a screening-associated increase in mortality cannot be excluded.[1] However, if data from all eligible trials (excluding Edinburgh and New York) are considered then the relative risk reduction in overall mortality is 1 to 3% for women aged 50 or over.[2] This is consistent with what might be expected. Among Swedish women aged 40-69, breast cancer deaths constituted 7 to 10% of overall mortality.[8,18] The corresponding percentage in the control groups of the Swedish RCTs was much lower, namely 3.4%[10] because women with previous breast cancer were excluded. Hence, a 20% reduction in breast cancer mortality (or 25% in women over 50) could be expected to reduce overall mortality by about 1%. An update of the Swedish overview (median observation period nearly 16 years) indicates that, among women aged 40-69, overall mortality had declined by 2%: RR = 0.98 (0.96-1.00).[32]

CONCLUDING REMARKS

The committee does not find the Cochrane review's arguments convincing for scoring four of the reviewed trials much lower in methodological quality than two so-called medium-quality trials. The reviewers do not document important bias in favour of screening. The committee judges the conclusion that breast cancer mortality is an unreliable outcome as too extreme. However, the reviewers are right in arguing that the use of breast cancer mortality may cause one to overlook an important harmful (or beneficial) effect of screening on other causes of death. Because of the threat of bias, the committee finds that breast cancer mortality must be interpreted in conjunction with all-cancer mortality and all-cause mortality. They conclude that the Cochrane review does not nullify the scientific basis for breast cancer screening in women aged 50 years or over. This conclusion is in agreement with the results of the updated Swedish overview,[32] published shortly after the advisory report was issued.

NOTE

The authors were the secretary and chair, respectively, of the Health Council's committee that compiled the advisory report. The full report can be downloaded from www.gr.nl or ordered electronically by: order@gr.nl.

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ABOUT THE COVER

'Joyas'

Carole Witteveen

This month's cover shows graphic art entitled 'Joyas' (mixed technique) by Carole Witteveen. Carole works in Nijmegen, the Netherlands. She attended the Academy of Art in Arnhem and the Jan van Eijk Academy in Maastricht. She teaches at the Academy of Art in Arnhem, and exhibited her work at numerous individual and group exhibitions in the Netherlands (Villa Sonsbeek and De Gele Rijder in Arnhem, Galerie Magenta in Nijmegen, Museum Waterland in Hoorn, Purmaryn Grafiek in Purmerend and Kunst in de AA Kerk in Groningen) and abroad (Kunstverein in Basel/Switzerland, Zentrum Artoll in Bedburg-Hau/Germany, Centro La Luz in Santander/Spain, Les Images in Kasteel Brasschaat/Belgium and Kunstraum in Wuppertal/ Germany). She has served on a number of committees for advice and selection of art and participated in the Dutch television programme Kunst te Kijk (Viewing Art). In her work, she wants to depict beauty and desire, metamorphosis and changes, myth and reality; things around us that we see but do not observe. A limited edition of original print of this month's cover (size 65 x 55 cm) is available at a price of € 200. You can order the print at Galerie Unita, Rijksstraatweg 109, 6573CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.

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ORIGINAL ARTICLE

Pathogenesis and treatment of pain caused by skin metastases in neuroendocrine tumours

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ABSTRACT

Background: Prognosis of neuroendocrine tumours has improved during the last decade and one might expect that more patients with (sub)cutaneous metastases will be seen in the future. We investigated the cause of pain in skin metastases and tried to give recommendations about treatment options.

Methods: We compared histology of (sub)cutaneous metastases in four patients, two with severely painful skin lesions and two without pain.

Results: On the pathological slides there were no differences in neuroinvasion, angioinvasion or mitosis between painful and non-painful metastases. However, the painful metastases rapidly multiplied, while the others remained indolent in nature. Pain was very difficult to manage and did not respond to analgesics, irradiation or systemic treatment with interferon or chemotherapy. Local excision was the only successful treatment option.

Conclusion: Histology did not show differences between painful and non-painful skin metastases. Local excision is the treatment of choice.

INTRODUCTION

Neuroendocrine tumours are well known for their metastatic spread to the liver and for the production of vasoactive hormones. Metastases to the skin seem to be a late manifestation of advanced disease, but there are few data in the literature which are limited to single case reports only.[1-4] These metastases may present as painless subcutaneous nodules,[1,4] but sometimes they are extremely painful.[2,3] In the literature this has been explained by invasion of a superficial nerve as seen in one patient.[2] There is no information on treatment options for this type of skin metastases.

Recently confronted with four patients with skin metastases, we explored the hypothesis of neuroinvasion by comparing asymptomatic metastases with extremely painful nodules. Various treatment modalities failed, but local resection led to reasonable palliation.

CASE A

A 39-year-old man presented with pain in the right shoulder and some dyspnoea and wheezing. A pulmonary mass in the right hilum was detected. During surgery the tumour appeared to be irresectable. Histology revealed an atypical carcinoid tumour, which was positive to neuroendocrine markers (chromograninA, synaptophysin). Chemotherapy (cis-platinum plus etoposide) and additional irradiation resulted in stable disease for six months, when liver metastases appeared. Diagnostic ^{111}In-pentetreotide scan as well as ^{131}I-meta-iodobenzyl guanidine (MIBG) scintigraphy were negative and urinary 5-hydroxyindole acetic acid (5-HIAA) excretion was slightly elevated at 68 μmol/24 h (normal ≤40). In the absence of symptoms, an expectative policy was pursued. Eight months later he was referred to our hospital because of pain in the liver, weight loss (11 kg), fever and attacks of severe perspiration. Physical examination revealed an enlarged liver and two painless subcutaneous nodules on the head. His condition deteriorated rapidly in

the following weeks. This was accompanied by clear laboratory changes: alkaline phosphatase 520 U/l (normal 40-120), γ-GT 902 U/l (normal <35), ASAT 61U/l (normal <40) and ALAT 86 U/l (normal <45); the 5-HIAA excretion was elevated to 163 μmol/24 h (*table 1*). Treatment with interferon-α (6 x 10^9 units s.c. three times a week) was initiated. Abdominal pain increased due to progressive liver metastases. Meanwhile, more subcutaneous nodules appeared, which were not painful in contrast to the liver localisation. The pathology of such a skin lesion showed metastasis of atypical carcinoid tumour, close relation with superficial nerves and angioinvasion (*table 2*). Six weeks after the start of interferon the patient died, i.e. two months after the detection of skin metastases and two years after the initial diagnosis.

CASE B

A woman, 38 years of age, presented with watery diarrhoea, malaise and weight loss (5 kg). Physical examination revealed a cardiac murmur, enlarged liver and a subcutaneous nodule in the right buttock. A CT scan of the abdomen showed multiple liver metastases. Liver cytology and histology of the resected subcutaneous lesion matched the diagnosis of low-grade neuroendocrine carcinoma (carcinoid tumour). Immunohistochemistry was positive to chromograninA and synaptophysin. The primary tumour remained unknown. Urinary 5-HIAA excretion was strongly elevated at 1665 μmol/24 h. In addition, ultrasound of the heart revealed some fibrosis of the tricuspid valve. A diagnostic ^{111}In-pentetreotide scan as well as ^{131}I-MIBG scintigraphy were positive with clear retention in the liver metastases. Following treatment with unlabelled MIBG in accordance with a phase II trial,[5] symptoms of diarrhoea and weight loss ceased almost completely, accompanied by a decrease in 5-HIAA excretion. Six months later painful skeletal metastases appeared. Treatment with radiolabelled MIBG[5] resulted in a symptomatic and biochemical response. Diarrhoea and flushes reappeared after five months. Daily injections of octreotide led to symptomatic and biochemical improvement which lasted 17 months when the patient developed an epileptic seizure due to malignant meningitis. At that time she also noticed a recurrent somewhat painful swelling in the scar of the former subcutaneous lesion in the buttock. However, analgesics were not needed. The histology of the subcutaneous lesion (*table 2*) revealed a tumour deposit without clear invasion in blood vessels and superficial nerves. Her condition deteriorated and she died seven months later, three years after the diagnosis of metastatic carcinoid syndrome and the first skin metastases.

CASE C

A 58-year-old woman presented with a palpable mass in the right supraclavicular area due to undifferentiated carcinoma at cytology. Additional investigation did not reveal a primary tumour. Progression was remarkably slow. Eventually three years later an excisional biopsy revealed a low-grade neuroendocrine carcinoma (carcinoid tumour), which was positive to chromograninA and synaptophysin. After two years without symptoms she was referred to our hospital with some dyspnoea and retrosternal discomfort, especially at night. CT scan showed a large irresectable tumour in the upper mediastinum. A diagnostic ^{131}I-MIBG scintigraphy showed a vague retention in the mediastinum, considered too little for a treatment dose of ^{131}I-MIBG. Chemotherapy was given conform a phase II trial with mitoxantrone for one year, resulting in stable disease and improvement of symptoms. Her condition remained stable in the next three years until she noticed several subcutaneous nodules

Table 1
Clinical characteristics of carcinoid patients with subcutaneous metastases

CASE	PRIMARY	METASTASES	SUBCUTANEOUS METASTASES		CARCINOID SYNDROME	URINARY 5-HIAA* (NORMAL <40 μMOL/24 H)	SURVIVAL (MONTHS)	
			Localisation	Pain			Overall	From subcutaneous metastases
A	Bronchial	Liver	Head	-	+	163	24	2
B	Unknown	Liver	Buttock	+/-	+	1665	37	37
C	Unknown	Mediastinum	Head and breast Trunk and axilla	- ++	-	<40	88	40
D	Bronchial	Lung	Trunk Extremities Head and neck	++ ++ ++	-	<40	46	29

* *5-HIAA = 5-hydroxyindole acetic acid.*

(5-15 mm in diameter); most of these lesions were extremely painful (*table 1*). Local excision showed metastases of the formerly diagnosed carcinoid tumour and resulted in instant relief of pain. During the following three years until her death, the major problem was the severe pain from many tiny subcutaneous lesions. The pain did not respond to analgesics, including morphine, and only resection of the lesions was effective. In total 28 metastases were resected. Comparing painless and painful lesions at histology (*table 2*), invasion in nerves was not a consistent finding and did not correlate with the pain sensation of the patient (*figure 1*). Meanwhile, the mediastinal mass showed slow progression, for which she was irradiated, leading to minimal regression. She died seven years after the initial diagnosis and three years after the appearance of the painful subcutaneous metastases.

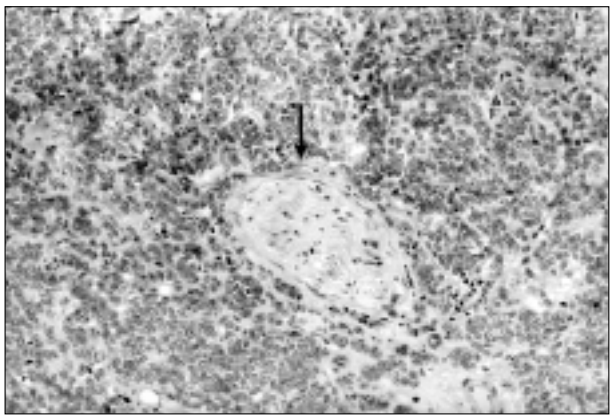

Figure 1
Excisional biopsy of a painless skin metastasis in case C
HE staining, 200x: perineural circular growth of atypical carcinoid around a small nerve bundle (at the arrow).

CASE D

A 68-year-old man presented with coughing and some exercise-induced dyspnoea due to a solitary nodule in the right lung. The lobectomy specimen revealed an atypical carcinoid tumour with sporadic mitoses (diameter 2 cm) without lymph node metastases. The neuroendocrine markers chromograninA and synaptophysin were both positive. Seven months later approximately ten subcutaneous nodules appeared on the lower extremities, trunk and head that were extremely painful, both spontaneously and on pressure (*table 1*). After resection of the largest nodule (3 x 1 x 1 cm) in the left thigh, histology (*table 2*) revealed metastatic atypical carcinoid with three mitotic figures in 2 mm^2 and also patchy necrosis. A nerve was seen close

Table 2
Histological findings in the skin metastases of carcinoid patients

	STROMA	NEUROINVASION	ANGIOINVASION	MITOSES PER 2 MM^2	LOCALISATION	DIAGNOSIS
Case A						
Non-painful head	-	+	+	4	Cutis + subcutis	Atypical carcinoid
Case B						
Non-painful buttock	-	-	-	10	Subcutis	Low-grade neuro-endocrine carcinoma (carcinoid)
Case C						
Non-painful:						Low-grade neuro-docrine carcinoma (carcinoid)
* Head '90	-	+	-	13	Cutis + subcutis	
* Breast '90	-	+	-	6-12	Cutis + subcutis	
Case C						
Very painful:						Low-grade neuro-docrine carcinoma (carcinoid)
* Axillary '89	-	+	-	16	Cutis + subcutis	
* Lumbal '91	-	-	-	14	Cutis + subcutis	
* Back '92	-	+	-	13	Subcutis	
Case D						
Very painful:						Atypical carcinoid
* Thigh	+	-	?	3	Subcutis	
* Head	-	-	+	0	Cutis	
* Axillary	+	-	+	0	Subcutis	

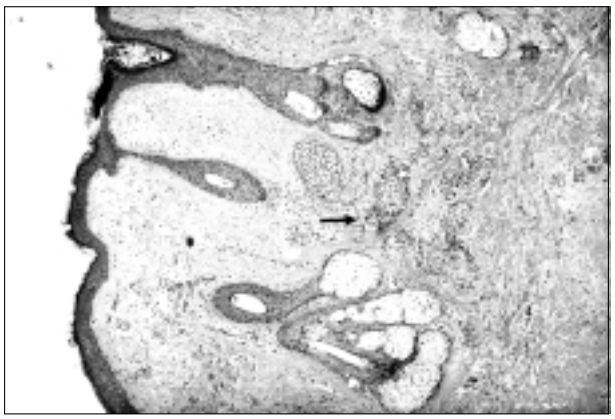

Figure 2

Excisional biopsy of a very small, but extremely painful skin metastasis in case D

Microscopy (HE staining, 50x) revealed a tiny intracapillary carcinoid deposition (at the arrow) not in the presence of a nerve bundle.

to the tumour site, but without clear invasion. The pain was difficult to manage with analgesics, but disappeared after resection. The other lesions were very small ranging from 3 to 5 mm, some hardly palpable but very painful. The resection material showed tiny intracapillary tumour localisations (*figure 2*).

Staging revealed five small lung metastases but no liver metastases. Radionuclide imaging with ^{111}In-pentetreotide and ^{131}I-MIBG was negative. Laboratory tests were within normal limits and urinary 5-HIAA excretion was repeatedly normal. Local treatment by irradiation (4 x 5 Gy) of several skin lesions and systemic treatment with interferon-α did not affect the pain. Within three months of the interferon-α treatment, several new subcutaneous lesions evolved, up to a total of 20 lesions, while the lung metastases remained stable. The only way to effectively treat the extremely painful lesions was local resection.

The patient died 46 months after the initial diagnosis of a carcinoid tumour and 29 months after the appearance of skin metastases.

DISCUSSION

Skin (cutis or subcutis) involvement by metastatic disease is an infrequent phenomenon in carcinoid-like neuroendocrine tumours, in contrast to skin metastases in melanoma and adenocarcinomas, especially breast cancer, colonic cancer or lung cancer.[6] Usually these skin metastases cause only minor problems to the patient, but they implicate a poor prognosis.[7] Such metastases in neuroendocrine tumours have only been reported in single case reports.[2-4] In a compilation of these data[1] six cases with a gastrointestinal primary are reported, two of them suffering from the carcinoid syndrome. A subsequent literature survey[4] described a total of 17 patients, among which the bronchial tree was the main primary origin (n=9).

Out of a total of 86 carcinoid patients treated at our hospital, we detected four patients with skin metastases (*table 1*). The patients with the extremely painful metastases (cases C and D) had a different clinical presentation than the other two (cases A and B): they did not show signs of hormone production. The clinical course was also different over time: the painful metastases were very small and progressive with the appearance of multiple lesions, while the others remained localised and indolent.

An explanation of the pain caused by some skin metastases might be infiltration of nerve bundles by tumour deposits. Although this has been reported in an 80-year-old patient with extremely painful nodules due to a carcinoid tumour, most probably derived from the gastric antrum,[2] in our patients these changes were seen in painful as well in non-painful metastases (*table 2*). Another hypothesis is that various peptide hormones and vasoactive agents, such as serotonin and kallikrain, produced by carcinoid tumours cause local necrosis and fibrosis and hence induce the severe pain. However, this local fibrosis was only seen at histology of the subcutaneous lesions in patient D, who had no clinical or biochemical signs of hormone production. Moreover, patients A and B with carcinoid syndrome did not have pain in the skin metastases. We also examined the histology for vascular obstruction or inflammatory changes as an explanation for the cause of pain, but this could not be found in any of the four patients. Therefore, the pathogenesis of the pain remains unclear.

Treatment of metastatic carcinoid tumours is mainly focused to the palliation of symptoms, usually carcinoid syndrome, for which there are various options: octreotide, interferon-α and MIBG, or combinations.[8] Each treatment modality results in a subjective improvement of 65 to 80% and a biochemical response in up to 50% of the patients, while tumour reduction is only occasionally seen.[5,9] To improve local tumour symptoms as bowel obstruction, pain and fever, tumour reduction is needed, for which medical treatment is inadequate. Data on treatment of painful subcutaneous metastases are lacking. In the patients presented here, medical treatment failed. In contrast, local excision resulted in instant and persisting pain relief.

In conclusion, subcutaneous metastases in metastatic carcinoid tumours may be extremely painful. The pathogenesis of the severe pain encountered in these, often tiny, metastatic deposits remains difficult, as neural involvement was not a consistent finding. In our patients pain was difficult to manage with analgesics, but local excision provided satisfactory long-term palliation. As the prognosis of metastatic carcinoid has improved during the last decade[10] we might expect to see more patients with (sub)cutaneous metastases in the future.

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CASE REPORT

Right aortic arch symptomatic in adulthood

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ABSTRACT

We present a patient with progressive dysphagia and shortness of breath due to a right aortic arch with aberrant left subclavian artery that became symptomatic in adulthood. Diagnosis was made after a delay because the possibility of a congenital anomaly was not considered when the patient presented with dysphagia. A review is given of the incidence, embryology, aetiology, diagnostic evaluation and management, as well as a discussion of other congenital aortic arch anomalies.

INTRODUCTION

Congenital anomalies of the aortic arch are rare and usually recognised in childhood. Some variants can become symptomatic in adulthood due to various mechanisms. Presentation with dysphagia can be the first symptom and recognition in adults is difficult and often delayed, especially when another diagnosis is made.

CASE REPORT

A 67-year-old woman presented with dysphagia and mild dyspnoea on exertion, which had been slightly progressive during the last few years. Her history revealed a hysterectomy, hypertension and insulin-dependent diabetes mellitus, because of which she was seen by an internist. She did not smoke or drink alcohol; her medication consisted of insulin and a calcium antagonist. In 1983 she was first seen with difficulty in swallowing. A gastroscopy at that time showed a small hiatal hernia. Omeprazole was started, which temporarily reduced her symptoms. The blood pressure was well controlled. In the following years there were mild symptoms of dysphagia, which were thought to be due to the hiatal hernia. Several years later, while continuing omeprazole, her symptoms slowly progressed; she described a retrosternal obstruction on swallowing. She also complained of shortness of breath during exercise. There were no other respiratory or cardiac complaints. Physical examination was normal, as were laboratory tests and electrocardiography. Blood pressure was 150/95 mmHg. A chest X-ray demonstrated an abnormal round projection on the right side of the upper mediastinum (*figure 1*); the cardiothoracic ratio was less than 50%. A barium

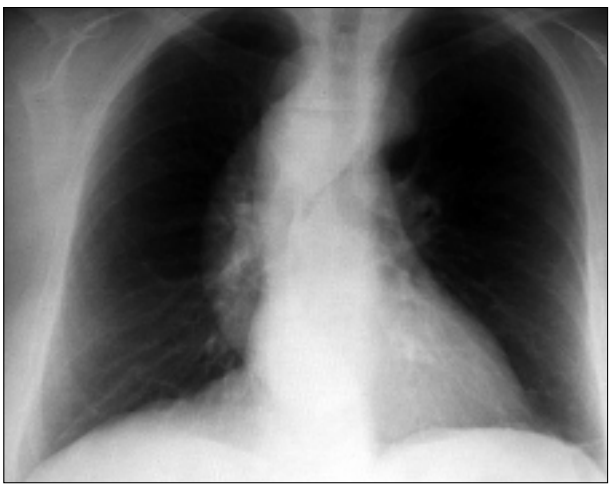

Figure 1
Chest X-ray showing widening of the upper mediastinum

oesophagram revealed anteroposterior indentation on the oesophagus; endoscopy showed a pulsating mass compressing the oesophagus. The combination of chest X-ray and barium oesophagram was suggestive of a vascular anomaly. The exact vascular structure was revealed by multiplanar reconstruction of a CT (*figure 2*) and CT angio with 3D reconstruction (*figures 3* and *4*), confirming the presence of a right aortic arch with aberrant left subclavian artery and ligamentum arteriosum.

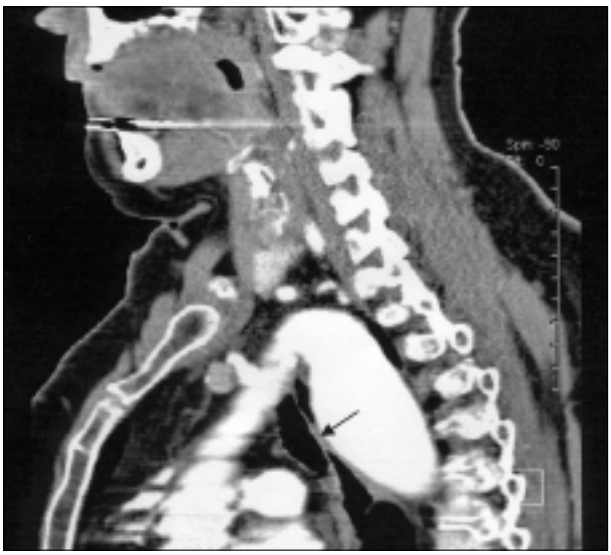

Figure 2
Multiplanar reconstruction of a contrast-enhanced CT showing compression on oesophagus (arrow) by aneurysmatic widening of aorta (max. diameter 4.2 cm)

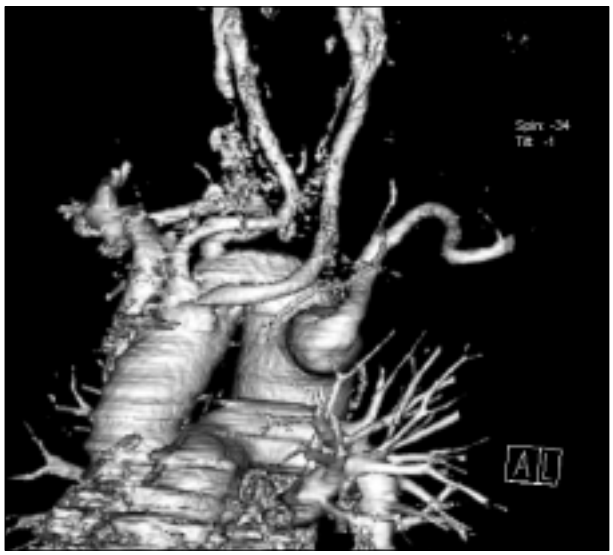

Figure 3
Lateral view (3D reconstruction) of RAA with aberrant LSCA arising from Kommerell's diverticulum

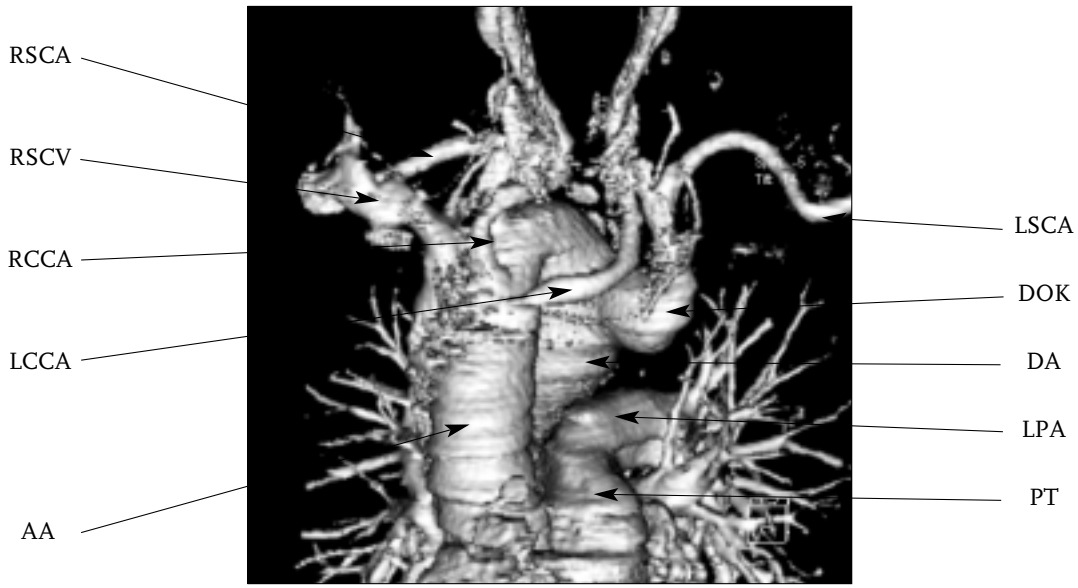

Figure 4
Front view (3D reconstruction) of RAA with aberrant LSCA arising from Kommerell's diverticulum

AA = ascending aorta, DA = descending aorta, DOK = Kommerell's diverticulum, LCCA = left common carotid artery, LPA = left pulmonary artery, LSCA = left subclavian artery, PT = pulmonary trunk, RCCA = right common carotid artery, RSCA = right subclavian artery, RSCV = right subclavian vein.

DISCUSSION

Congenital anomalies of the aortic arch are rare and are mostly found in infants or infancy, with an incidence of 1 to 3% of all congenital heart disease.[1] A vascular ring can be present in certain abnormalities, occurring with an incidence of less than 0.2%, which surrounds the trachea and oesophagus and has the potential to cause symptoms.[2]
At embryological development, six pairs of aortic arches are normally formed during the fourth and fifth week, arising from the aortic sac. During further development the arterial pattern becomes modified and some vessels regress. In a 10 mm embryo the fourth arch persists on both sides. On the left side it forms part of the aorta between the left common carotid and the left subclavian artery. On the right side it forms the most proximal segment of the right subclavian artery; a portion of the right dorsal aorta forms the distal part.
In right aortic arch anomaly (RAA), the left arch atrophies and disappears whereas the right arch persists, contrary to the situation in normal subjects.
Aetiological factors have been recognised as determining this abnormality, including genetic factors (deletion of chromosome 22q11) and haemodynamic factors with a dominant flow on the right side in the embryonic stage.[3,4]
Aortic arch anomalies include double aortic arch (DAA), right aortic arch with aberrant left subclavian artery (LSCA) and ligamentum arteriosum, both forming a vascular ring that surrounds the oesophagus and trachea. DAA is the most common vascular abnormality.[5,6] Other variants include RAA with mirror-image branching, aberrant left pulmonary artery, RAA with isolated LSCA and aberrant right subclavian artery. These abnormalities do not form a vascular ring and are usually asymptomatic.
In RAA the abnormal right aorta may either descend on the right or on the left side of the vertebral column. There are two main types of RAA; type 1 RAA with mirror-image branching where there is no vascular ring present and type 2, as in our case, with an aberrant LSCA, forming a vascular ring by ventral position of the ligamentum arteriosum (*figure 5*).
There is a low prevalence of associated cardiac defects in aortic arch anomalies and if present, the defect is mostly associated with DAA and is usually recognised in childhood.[6] Associated defects include tetralogy of Fallot, pulmonary atresia with VSD and truncus arteriosus.
There are several reports of RAA in adults, often asymptomatic or found at autopsy. Symptoms in childhood are often severe and mainly consist of respiratory distress and difficulty in swallowing, requiring surgery. In adults, dysphagia is the most reported symptom; other symptoms include dyspnoea on exertion, bronchitis, haemoptysis, stridor, hoarseness, wheezing and chest pain. Most patients, however, are asymptomatic.[7,8]
Possible mechanisms why RAA with aberrant LSCA can manifest during adulthood include airway injury by direct aortic compression, transtracheal pressure differences causing narrowing, changes in vertebrae and thoracic skeleton causing limited dimensions of the mediastinum, dilatation of the aorta by ageing, hypertension and atherosclerosis.[2,8] Aneurysmatic dilatation can lead to aortic dissection, especially with pre-existing hypertension.
In RAA with aberrant LSCA, rupture of Kommerell's diverticulum, an aneurysmatic widening of the origin of the LSCA, has also been reported.[9,10]
For diagnostic evaluation a chest X-ray, barium oesophagography, bronchoscopy and echocardiography may raise suspicion of the presence of RAA with aberrant LSCA. Angiography, CT or MRI will generally be needed to demonstrate the exact anatomy. MRI is preferred because it is non-invasive and differentiates best from other vascular anomalies.
Management of RAA with aberrant LSCA in adulthood includes division of the ligamentum arteriosum in symptomatic patients, which can be performed easily via a left thoracotomy. The vascular ring is interrupted, freeing the oesophagus and trachea. Division of the LSCA with reconstruction by re-implantation of the artery is mainly recommended when there is a potential risk of rupture of Kommerell's diverticulum.[5,10,11]
In this case with progressive dysphagia, a delay of diagnosis occurred because a hiatal hernia was thought to be the cause of dysphagia. The possibility of a congenital vascular anomaly was not considered. Because of progression of dysphagia and dyspnoea, further diagnostic procedures were performed. Symptoms became manifest due to

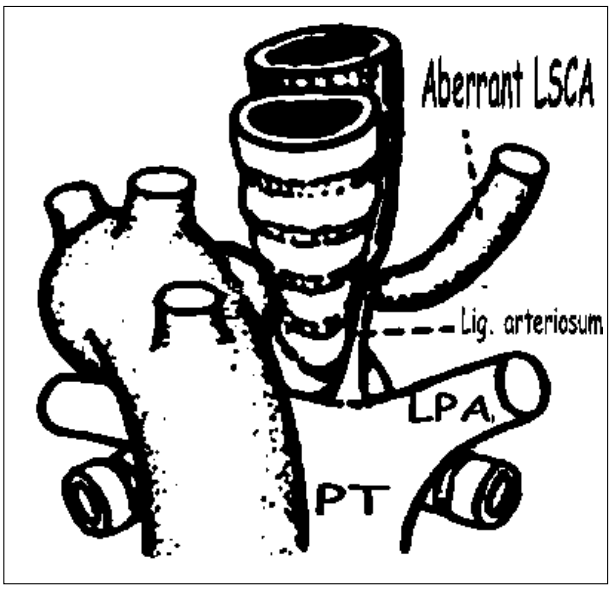

Figure 5
Schematic representation to clarify the aberrant anatomy

dilatation of the aorta, possibly made worse by hypertension. Operative surgery has not yet been performed in this patient.

In case of unexplained dysphagia, vascular anomalies should be considered as a possible cause and the proper diagnosis can be made with CT or MRI. Special attention to treatment of hypertension is necessary in this rare abnormality.

ACKNOWLEDGEMENT

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CASE REPORT

Methotrexate-associated liver toxicity in a patient with breast cancer: case report and literature review

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ABSTRACT

A patient with breast cancer developed severe asthenia, accompanied with progressively increasing transaminases, during adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate and 5-fluorouracil). Additional blood tests and imaging were negative. A liver biopsy revealed a grade II toxic hepatitis. Because methotrexate was suspected to be the cause of the hepatotoxicity, the administration of this drug was stopped and mitoxantrone was given instead. A recovery of clinical symptoms and normalisation of the liver function tests was observed afterwards. In that sense, mitoxantrone appears to be a valuable alternative to methotrexate in cases of hepatotoxicity in patients with breast cancer. An overview of the literature regarding methotrexate hepatotoxicity is presented.

INTRODUCTION

Breast cancer is the most common malignancy among women in Europe. Depending on the stage, the treatment consists of local surgery (tumourectomy or mastectomy with axillary lymph node dissection) with or without post-operative radiotherapy and adjuvant systemic therapies. Several chemotherapeutic agents are used in the adjuvant setting when treating patients with breast cancer. Common chemotherapy combinations are CMF (cyclophosphamide, methotrexate, 5-fluorouracil), AC (doxorubicin, cyclophosphamide), FAC (5-fluorouracil, doxorubicin, cyclophosphamide) and FEC (5-fluorouracil, epirubicin, cyclophosphamide). The most frequently observed toxicities with these treatment schedules are myelosuppression, nausea and vomiting, stomatitis and diarrhoea. The anthracycline-based regimens in particular may induce more severe hair loss and cardiotoxicity.
We describe a patient with breast cancer who developed a toxic hepatitis due to methotrexate within the context of an adjuvant therapy with CMF and give a literature review on methotrexate-induced liver toxicity.

CASE

A 60-year-old woman with a history of asymptomatic cholecystolithiasis complained of a mass in the left breast. She first detected the mass several weeks before admission to the hospital. On clinical examination, a tumour of two centimetres in diameter was indeed palpated in the superolateral quadrant of the left breast, without any suspicion of involved axillary lymph nodes.
Mammography confirmed the presence of a suspicious lesion in the same quadrant. Pre-treatment evaluation consisted of a chest X-ray, bone scan and ultrasound examination of the liver and was considered negative. The tumour marker (CA 15.3) at baseline was within normal limits, as was the kidney function. Before treatment, aspartate aminotransferase (AST) was 25 U/l (normal values 5-40 U/l) and alanine aminotransferase (ALT) 37 U/l (7-56 U/l). Alkaline phosphatases (AP) at baseline were 49 U/l (36-95 U/l), lactate dehydrogenase (LDH) was 443 U/l (313-618 U/l). Gamma-glutamylpeptidase (γ-GT) was slightly increased to 36 U/l (11-29 U/l). No hypoalbuminaemia was present.
A tumourectomy and axillary lymph node dissection were

performed. The pathological examination showed a poorly differentiated ductal adenocarcinoma of 1.7 cm in greatest dimension. One of the 17 removed axillary lymph nodes was involved. Oestrogen and progesterone receptors were absent. Therefore, the diagnosis of a $pT_{1c}pN_{1bi}M0$ breast cancer was made.

Postoperative treatment consisted of irradiation of the breast, the left internal mammary chain and the supraclavicular nodes (50 Gy in 25 fractions with an additional boost on the tumour bed). The planned adjuvant chemotherapy consisted of cyclophosphamide (CTX) 600 mg/m²/day, methotrexate (MTX) 40 mg/m²/day, and 5-fluorouracil (5-FU) 600 mg/m²/day on day 1 and day 8, given every four weeks for six cycles. Corticosteroids were administered before each new chemotherapy cycle.
After two cycles of chemotherapy, the patient complained of asthenia. She stayed in bed several hours a day. There was no fever, nausea, vomiting, abdominal pain, cough or weight loss. Her appetite was normal; oral food intake remained possible. On clinical examination, her general condition was good and no abnormalities were detected. The patient was only taking low doses of benzodiazepines. Blood examination revealed slightly elevated transaminases: AST of 45 U/l and ALT of 64 U/l. The other liver function tests, including γ-GT, were within normal limits. Two more cycles of CMF were administered. A minor weight loss of two kilograms (without nausea or vomiting) and a further deterioration of the liver function tests accompanied them. AST rose to 88 U/l, ALT increased to a value of 98 U/l (*figure 1*). AP, LDH and γ-GT increased to 108 U/l, 915 U/ and 83 U/l, respectively. Bilirubin levels remained within normal limits. Serum levels of creatinine were normal. A mild hypoalbuminaemia developed nevertheless. Albumin decreased to a minimum value of 2.6 g/dl (3.2-5.0 g/dl). The tumour marker (CA 15.3) increased to 51.1 U/ml (nl <35).
An ultrasound examination of the abdomen only revealed a small cyst in liver segment 7, without other changes. There were no signs of liver metastases. This was confirmed by triphasic CT scanning.

Screening for acute viral hepatitis was negative; indications of hepatitis A, cytomegalovirus, Epstein-Barr virus, or human immunodeficiency virus (HIV) infections were not present. Hepatitis B surface antigen was negative; antibodies against hepatitis C were not present. There was no evidence of an infection with *Brucella abortus bovis, Treponema pallidum or Toxoplasma gondii*. Levels of copper and ceruloplasmin were normal. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-liver-kidney microsomal antibodies and antimitochondrial antibodies were within normal limits.
Since the cause of the liver enzyme disturbances was uncertain, a liver biopsy was performed. The biopsy

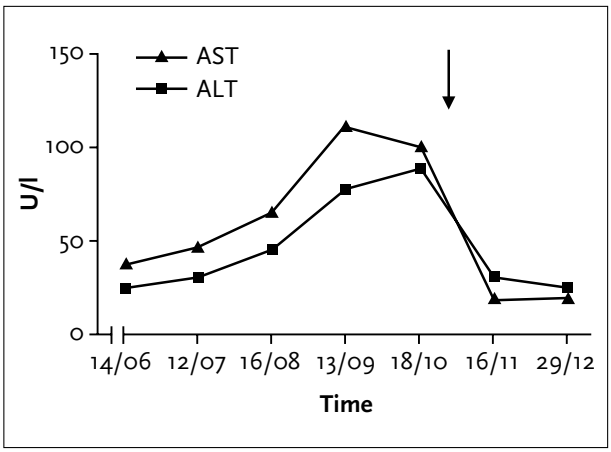

Figure 1
X-Y plot of the evolution of AST and ALT in our patient with breast cancer
AST = aspartate aminotransferase, ALT = alanine aminotransferase. The Y-axis indicates the value of AST and ALT in units per litre (U/l). The X-axis indicates the date on which these parameters were determined. On 14/06, treatment with CMF was started. The arrow indicates the cessation of treatment with methotrexate and the replacement by mitoxantrone. This replacement is followed by a normalisation of the liver function tests.

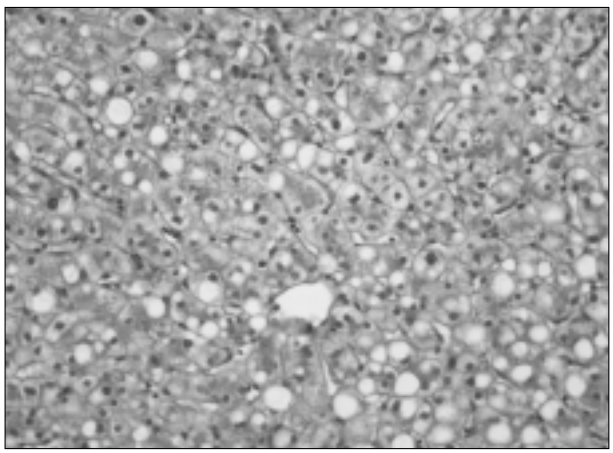

Figure 2
Liver biopsy demonstrating pericentral steatosis, moderate hepatocellular anisonucleosis, hepatocellular swelling (ballooning) and the presence of lipofuscinosis, pointing towards reversible, possibly toxic liver cell damage (Roenigk grade II) - final magnification x 200

specimen contained liver tissue with signs of pericentral liver steatosis and evanescence of hepatocytes in pericentral areas. The pathological findings were compatible with toxic liver damage (*figure 2*). There was no histological evidence of liver metastases.
Because a toxic hepatitis due to methotrexate was considered to be the aetiology of the liver enzyme disturbances, this drug was stopped and replaced by mitoxantrone (10 mg/m^2). The liver tests and CA 15.3 returned to normal values afterwards. Seventeen months after diagnosis, there is no evidence of metastatic disease and the liver function tests and tumour marker remain within normal limits.

DISCUSSION

Methotrexate (amethopterin) is the 4-amino, N^{10}-methyl analogue of folic acid. It is an inhibitor of the enzyme dihydrofolate reductase (DHFR), responsible for the maintenance of the intracellular folate pool in its fully reduced form as tetrahydrofolates. These folates are single carbon unit carriers and play a role in the synthesis of thymidylate, a precursor of DNA, and the purines adenosine and guanosine, precursors of both DNA and RNA. Therefore, it acts as a chemotherapeutic agent by DNA (and RNA) synthesis inhibition.

The folic acid analogues were introduced in 1948 by Farber *et al.* as antineoplastic agents for the treatment of children with acute lymphoblastic leukaemia (ALL).[1] A variety of dose schedules have been explored since then.[2] Nowadays, methotrexate is used in the treatment of breast cancer, osteosarcoma, head and neck cancer, choriocarcinoma, urothelial cancer, lung cancer, ALL and non-Hodgkin's lymphoma (NHL). It is also used to treat a variety of non-malignant diseases, including psoriasis, rheumatoid arthritis (RA), juvenile rheumatoid arthritis, dermatomyositis, Wegener's granulomatosis, sarcoidosis or bacterial and parasitic infections associated with HIV.
Furthermore, reports on the use of this agent in the treatment of inflammatory bowel disease have been published.[3] The drug has even been used in the treatment of patients with autoimmune hepatitis[4] or idiopathic granulomatous hepatitis.[5]

ADVERSE REACTIONS

Toxicity of methotrexate mainly consists of myelosuppression and mucositis. The elimination of the drug primarily occurs through renal excretion and toxicity is therefore more pronounced in patients with reduced renal function.[6] In rats with decreased renal function treated with high-dose schedules, methotrexate may cause renal impairment by tubular necrosis due to crystallisation of 7-OH-methotrexate in the kidney tubules.[7] The renal toxicity in humans treated with methotrexate is thought to result from the same intratubular precipitation of MTX and its metabolites.[8]
Acute systemic hypersensitivity reactions during initial administration (pruritus, urticaria and angio-oedema) have been reported[9] as well as late anaphylaxis after high-dose methotrexate.[10]
Other adverse reactions include methotrexate-induced pneumonitis[11] and neurological side effects[12] while numerous teratogenic effects of the drug have been demonstrated.[13] Life-threatening and even fatal toxicities have been described, in particular with high-dose regimens.[14]

HEPATOTOXICITY

Methotrexate is also associated with acute and chronic liver damage. Acute elevations of hepatic enzyme levels and/or hyperbilirubinaemia are seen in more than 50% of the patients treated with a high-dose regimen, but a normalisation of the liver function tests is expected within one or two weeks after treatment.[14] Chronic administration of methotrexate (e.g. patients with psoriasis) can be complicated by liver fibrosis. An evolution to cirrhosis is possible.[15] Intermittent administration is associated with a lower incidence of liver function disorders.[16,17] Severe hepatotoxicity rarely occurs.

MECHANISM OF TOXICITY

After intravenous administration, the half-life of methotrexate in plasma amounts up to 4.2 hours.[18] Methotrexate is possibly transported in hepatocytes by an active, sodium-dependent process.[19] After saturation of the active transport mechanisms, intracellular diffusion of methotrexate depends on the concentration gradient.[20] Methotrexate is then metabolised to polyglutamyl derivatives.[21] These conjugates may persist in liver cells and lead to prolonged inhibition of dihydrofolate reductase, resulting in a reduction of the folate coenzyme pool.[21,22] Schalinske *et al.* demonstrated a 70% reduction of the folate coenzyme pool after methotrexate treatment in rats.[23] This reduction has been shown to alter carbon flow through the hepatic folate dependent one-carbon pool. However, it is unclear whether this might play an important role in methotrexate-related hepatotoxicity. More likely, the formation of 7-OH-methotrexate after metabolisation of MTX plays a role in this species.[7] Translation to the human situation is, however, unclear as the elimination pathways of MTX and 7-OH-MTX in rats are different from those in humans, i.e. mainly biliary in rats and mainly renal in humans.
The effect of methotrexate therapy on Ito cells (fat-storing,

vitamin A-containing stellate cells) has been studied by Hopwood and Nyfors in psoriatics treated with methotrexate.[24] They found a statistically significant increase in the number of these cells after MTX therapy. Ito cells can be transformed into myofibroblasts, capable of secreting collagen. This collagenisation consequently leads to liver fibrosis.[25] Whether this mechanism plays a role in the occurrence of methotrexate-related hepatotoxicity in cancer patients treated with intermittent methotrexate regimens, is unknown.
In conclusion, the exact mechanism of MTX-induced hepatotoxicity is as yet unclear.

DETECTION OF MTX HEPATOTOXICITY

Although standard biochemical tests of liver function (AST, ALT, bilirubin, AP, prothrombin time or albumin) are not regarded as a reliable screening method in general,[26,27] some studies in psoriatic patients treated with methotrexate did find significant correlations between biochemical tests and histological findings.[28-30] O'Connor and colleagues were able to predict abnormal liver biopsy findings after methotrexate therapy, based on the following variables: age, gender, AST, AP, history of cholecystitis and cumulative dose of methotrexate (in grams).[30] The probability of concordance between the predicted probability and the observed response was 0.92. The joint sensitivity of AST, AP and total bilirubin to detect abnormal results from a post-treatment liver biopsy specimen in psoriatic patients was 0.86. The predictive value of three negative tests (AST, AP and total bilirubin) was 0.93.
Serial elevations in transaminases are thought to be a better predictor of liver damage.[31-33] In our patient, a progressive increase in AST, ALT, AP and γ-GT levels was observed, suggesting a progressive liver injury.
The antipyrine clearance,[29] galactose elimination capacity,[28,34] aminopyrine breath test[34] and bromosulphophthalein excretion test[28] are unreliable methods of detecting early stages of MTX-induced liver disease in patients treated with low-dose regimens. These tests can, however, be significantly impaired in high-dose regimens.[35] The aminoterminal peptide of type III procollagen (P3NP), detected in serum by radioimmunoassay, may be an indication of liver fibrosis, as has been observed in psoriatic patients on prolonged MTX treatment.[28]

Some imaging techniques of the liver (radionuclide scan, ultrasound examination, computed tomography and magnetic resonance imaging) are not accurate in the prediction of early liver disease.[36-38] Therefore, these imaging techniques remain complementary in the diagnostic work-up of patients with elevated liver tests.
The gold standard for the detection of MTX-induced liver damage is performing a liver biopsy. The Roenigk histological score is generally used for the staging of these biopsies.[26,32,39] The Roenigk scoring system consists of the following grades.[40]

Grade I	Normal; mild fatty infiltration, mild nuclear variability, mild portal inflammation
Grade II	Moderate to severe fatty infiltration; moderate to severe nuclear variability; portal tract expansion, moderate to severe portal tract inflammation and piecemeal necrosis
Grade IIIA	Mild fibrosis
Grade IIIB	Moderate to severe fibrosis
Grade IV	Cirrhosis

This scoring system is not sensitive enough to detect small changes in the degree of fibrosis. Therefore, new scoring systems have been developed which may be of particular interest for patients on prolonged low-dose methotrexate treatment for a non-malignant disease.[33,41] The semi-quantitative histological scoring system (SSS), developed by Chevallier and colleagues,[41] analyses the following four sites of fibrosis:

- Perisinusoidal space (PS, grade 0-2)
- Centrolobular vein (CLV, grade 0-2)
- Portal tract (PT, grade 0-3)
- Number and width of septa (number {NS}: graded 0-3; width {WS}: graded 1-5)

The total score is given by CLV+PS+PT+2x(WSxNS) and ranges from 0-35. SSS is normal from 0 to 1, reflects mild fibrosis between 2 and 4, moderate fibrosis between 5 and 10, and pre-cirrhosis ranges from 11 to 15. The diagnosis of cirrhosis is made when the score is higher than 15.
Guidelines for monitoring liver toxicity in MTX-treated patients with psoriasis were published in 1972,[42] 1973,[43] 1982[44] and 1988.[40] Guidelines for monitoring hepatotoxicity in patients with RA were published in 1994.[33] It is evident that these guidelines are not applicable to patients with breast cancer because of the different dose regimens and many other confounding factors.
Guidelines concerning the surveillance of patients with breast cancer after primary therapy were reviewed by the American Society of Clinical Oncology in 1998.[45]
However, as far as we know, no guidelines concerning the follow-up during treatment with chemotherapy have yet been published. Nevertheless, many chemotherapeutic agents alone or in combination may cause hypersensitivity reactions or direct hepatotoxicity, and altered liver function may alter drug metabolism and cause an increased risk of non-hepatic toxicity. Therefore, liver function tests should be performed regularly during treatment. If liver function disturbances persist, additional non-invasive imaging may reveal the underlying cause. A liver biopsy should in our

opinion be performed if imaging provides insufficient information and if the findings on biopsy have therapeutic implications. If a toxic hepatitis with apparent repercussion on the general performance status of the patient can be demonstrated, the treatment with methotrexate should be stopped. The liver biopsy in our patient only demonstrated a moderate fatty infiltration (Roenigk score II), but the repercussion on the general performance was more severe. After cessation of methotrexate, the asthenia in our patient disappeared; her performance status and liver function tests returned to baseline values. In contrast with psoriatics and patients with RA, where methotrexate is only stopped when a Roenigk IIIB or IV severity score is present on liver biopsy (Newman[26] and Kremer[33]), an earlier cessation of treatment with methotrexate (Roenigk II) may be necessary in patients with breast cancer. Higher-dose regimens are indeed used in these patients and a greater repercussion on their wellbeing can therefore be expected.
If risk factors for liver disease are present (abnormal baseline AST values, severe alcohol consumption, diabetes, hepatitis B and/or hepatitis C infection) before starting treatment with chemotherapeutic agents, the use of the least hepatotoxic agents should be considered.
Reactivation of hepatitis B during treatment with chemotherapy (methotrexate, etoposide, doxorubicin and other agents) has been reported.[46] Wong *et al.* described nine hepatitis B carriers with haematological malignancies (NHL, ALL) who developed an exacerbation of hepatitis during (one patient) or after completion (eight patients) of chemotherapy (among which methotrexate), which was fatal in six.[47]

RISK FACTORS FOR INCREASED METHOTREXATE TOXICITY

Methotrexate is bound to albumin for 50 to 60%.[32] Hypoalbuminaemia can therefore result in increased levels of free methotrexate and as a consequence, toxicity might increase.[14,48] Similarly, toxicity will increase in case of renal dysfunction as a result of a decreased methotrexate excretion. Low serum folic acid levels are known to increase the risk of methotrexate toxicity.[48] Methotrexate accumulates in third-space fluid collections, such as ascites and pleural effusions. Slow release of MTX from these third spaces also leads to increased toxicity.[8,49] Transfusions with red blood cells immediately after MTX administration could increase the risk for side effects from MTX.[49] In addition, apart from the dose of MTX used,[26,50,51] obesity,[26] amount of alcohol intake[50] and age[48,52] may also contribute to the development of liver damage.

INCIDENCE OF METHOTREXATE HEPATOTOXICITY IN PATIENTS WITH BREAST CANCER

In the study by Vaughan *et al.*, 17 out of 21 patients with breast cancer and normal baseline AST levels developed an AST elevation at some time in the course of their treatment with CMF. Cyclophosphamide 100 mg/m²/d was given orally on days 1 to 14, methotrexate 40 mg/m² i.v. on days 1 and 8, and 5-fluorouracil i.v. on days 1 and 8; the treatment cycle was repeated at 28-day intervals. The range of highest AST values was 22-49 IU/l (upper limit of normal = 19 IU/l). Ten of the 16 patients with a normal baseline value of AP before chemotherapy developed an elevation during chemotherapeutic treatment (62.5%). Four patients developed defects on liver scan accompanied by elevated AP and AST levels. Liver biopsies only revealed focal congestion, non-specific inflammation, fat deposition and no liver metastases. After cessation of chemotherapy, the hepatic lesions on liver scan improved or resolved completely. Nearly 50% (11/24) of the patients received 24 cycles of CMF.[36] The number of patients included was limited and the elevation of the liver function tests was only mild in most of these patients. Liver biopsies were not always performed.

Bajetta *et al.* studied the incidence of liver damage in 802 women with breast cancer. The patient population was randomised to receive either 6 or 12 cycles of adjuvant CMF (n=632). The dose of methotrexate was 40 mg/m² on days 1 and 8 of each monthly cycle. The control group consisted of women with breast cancer, only treated with a radical mastectomy (n=170). No increased incidence of abnormal liver tests with 6 or 12 cycles CMF was found compared with patients not receiving CMF (3.2% *versus* 4.1%). Liver biopsies (n=22) only revealed aspecific histological changes. Treatment with chemotherapy was never discontinued.[53] Statistical analysis was, however, not performed in this study, a historical control group was used. The definition of liver toxicity was insufficient and the time intervals at which liver function tests were performed during chemotherapy were not specified. Moreover, a liver biopsy was only performed in 22 patients, which makes the conclusions derived from these biopsies unreliable because of selection bias. Therefore, the incidence of liver function disturbances after MTX treatment is in all probability much higher than suggested by the latter article.
These studies nevertheless suggest that, although elevated liver function tests can occur during methotrexate treatment in patients with breast cancer, the treatment regimen can be continued without increasing the risk for serious hepatic side effects. Further studies are needed to assess these issues.

DRUG INTERACTIONS AND HEPATOTOXICITY OF OTHER COMPONENTS OF THE CMF REGIMEN

Dexamethasone has been reported to increase hepatotoxicity of MTX in children with brain tumours. The reason for this finding is unclear. Steroids are known to cause an enzyme induction in hepatocytes. Hence, an altered metabolism of MTX could be responsible for the increased hepatotoxicity.[54]

Cyclophosphamide administration rarely results in hepatic injury. However, Honjo *et al*. reported a transient elevation of aminotransferase serum levels in 43% of the patients treated with cyclophosphamide.[55] Whether the transient elevation of transaminases was due to the administration of cyclophosphamide is, however, difficult to prove. All the patients received a combination of antineoplastic agents, several of which are known to be hepatotoxic. At that time, screening for hepatitis C was not possible. Concomitant use of other drugs was not mentioned. The possible confounding factor of alcohol intake was not evaluated.

Hepatic toxicity is only rarely associated with a treatment with 5-fluorouracil. Mild and reversible hepatotoxicity is, however, more frequently observed in treatment regimens with 5-FU plus levamisole, but this seldom results in symptoms.[56]

The observed liver toxicity in our patient is therefore more likely to be caused by methotrexate. Liver function tests indeed returned to normal values after cessation of this drug and its replacement by mitoxantrone. The general performance status returned to baseline values.

MITOXANTRONE

Mitoxantrone is an anthracenedione that has shown therapeutic efficacy in NHL, acute non-lymphoblastic leukaemia and advanced breast cancer.[57,58] Mitoxantrone is mainly myelotoxic. It can safely be used in patients with breast cancer and moderate hepatic dysfunction.[59] Because repetitive blood samples showed a progressive increase in transaminases in our patient, and a liver biopsy revealed a toxic hepatitis, methotrexate was stopped and mitoxantrone was given instead. In our protocol methotrexate was considered to be the most hepatotoxic drug. A recovery of clinical symptoms and a normalisation of the liver tests were seen after cessation of MTX, which indeed proves that the hepatotoxicity was due to the treatment with this drug. We believe that in case of MTX-associated hepatotoxicity, a replacement of this agent by mitoxantrone can be a valuable alternative in the adjuvant treatment of patients with breast cancer.

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CASE REPORT

Magnetic resonance imaging in acute myocarditis: a case report and a review of literature

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ABSTRACT

We report a case of acute myocarditis in a 20-year-old male, suggested by the clinical picture, elevated cardiac enzymes, electrocardiography and serology. Diagnosis was confirmed by gadolinium-enhanced MRI showing part of the myocardium affected by an infiltrate. Impaired LV function and wall motion abnormalities were documented by echocardiography and FFE MRI. The patient recovered well within two weeks, but will be followed intensively since dilated cardiomyopathy may ensue.

INTRODUCTION

Myocarditis causes substantial mortality and therefore needs professional hospitalised care.[1-3] The present gold standard for diagnosis of myocarditis is endomyocardial biopsy. However, this technique has limitations due to the associated risks and low sensitivity. A new non-invasive technique is magnetic resonance imaging (MRI), which may be helpful to diagnose myocarditis by defining the site and extent of myocardial inflammation.[4-9] Since progression into dilated cardiomyopathy may develop, these imaging techniques are also helpful in the further evaluation of disease. We report a case of *M. pneumoniae* myocarditis and focus on current non-invasive diagnostic tools.

CASE

Two weeks after a pharyngitis, a 20-year-old man presented with chest pain radiating into the left arm for two days. The patient was admitted to the hospital. The next day he collapsed showing a polymorphous ventricular tachycardia followed by ventricular fibrillation. After electrical defibrillation sinus rhythm was regained. Physical examination showed a blood pressure of 110/60 mmHg, a pulse of 110 beats/min, a temperature of 38.4 °C and a third heart sound, but without any murmurs. The patient was not haemodynamically compromised, the jugular venous pressure was normal and the patient was not dyspnoeic. The white blood cell (WBC) count was 30,900/mm^3; sedimentation rate 55 mm/h; C-reactive protein 284 mg/l; aspartate-amino transferase 232 U/l; alanine-amino transferase 87 U/l; lactate dehydrogenase 1765 U/L; creatine kinase (CK) 1119 U/l; CK-MB 133 µg/l; troponin I 25.79 µg/l (maximum level 101.0 µg/l) (reference <0.2 µg/l). The electrocardiogram revealed sinus rhythm, right-axis deviation and ST-segment elevations in the anterior, inferior and lateral leads with preservation of the intrinsicoid deflection and ST-segment depression in aVR and V1, suggesting diffuse epicardial injury (*figure 1*). The chest radiograph showed a normal cardiothoracic ratio. Echocardiography on day 1 demonstrated an impaired left ventricular (LV) systolic function, with severe akinesia of the inferior and posterior wall and some pericardial effusion. The LVIDd (left ventricular internal dimension in diastole) evolved from 5.7 cm on day 1 to 6.8 cm on day 9, but the LVIDs remained 4.6 cm. The RVIDd (right ventricular internal dimension in diastole) did not actually differ between the measurements, being 2.2 cm and 1.9 cm respectively. The fractional shortening improved from

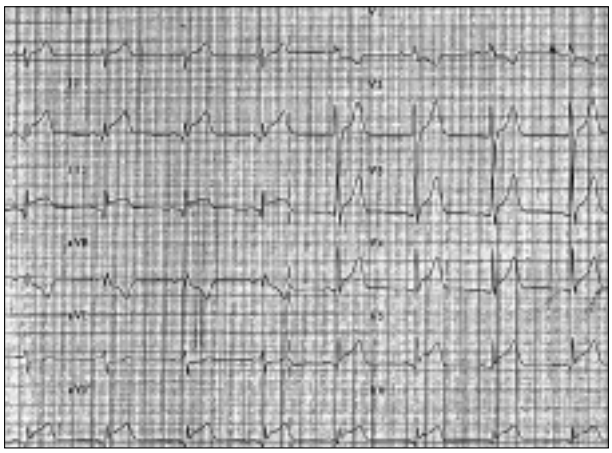

Figure 1
Admission 12-lead ECG demonstrating ST-segment elevation in the anterior, inferior and lateral leads and high R waves in V1

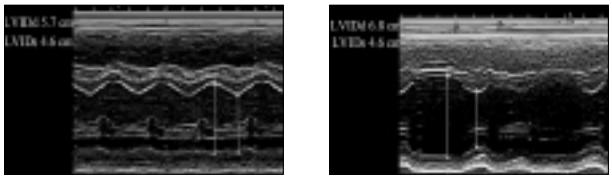

Figure 2a
M-mode registration from a parasternal window at presentation (left) and on day 9 (right)
Note the akinetic posterior wall at the initial stage, the left ventricle is slightly dilated with LVIDd of 5.7 cm (left). On day 9 (right) posterior wall contractions are seen but left ventricular dilatation has increased to LVIDd of 6.8 cm.

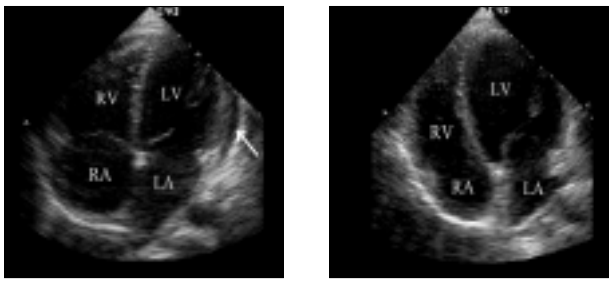

Figure 2b
The echocardiographic appearance of the RV and LV and of the RA and LA at initial presentation (left) and on day 9 (right)
RV = right ventricle, LV = left ventricle, RA = right atrium, LA = left atrium. The RV has normal dimensions on both days, but the LV has become more dilated on day 9. The pericardial fluid suggests pericardial involvement in the initial stage of disease (arrow).

19% on day 1 to 32% on day 9 (*figure 2*).
The MRI study on day 6 was performed on a 1.5 Tesla machine (Philips Medical Systems, Best, the Netherlands). ECG-triggered T1 turbo spin echo (T1-TSE) short-axis images, obtained before and after intravenous injection of 0.1 mmol/kg gadolinium-DTPA contrast medium, demonstrated myocardial enhancement of the posterior, lateral and inferior left ventricle wall and the anterolateral papillary muscle (*figures 3a* and *3b*). Short-axis and long-axis four-chamber cine balanced FFE images showed myocardial thinning of the posterior, lateral and inferior left ventricle wall and lack of wall thickening during the heart cycle (*figures 3c* and *3d*). This akinesia was also clearly demonstrated on the tagged images using a grid (*figures 3e* and *3f*).

Throat cultures for *Streptococcal* bacteria were negative. Blood serology showed elevated titres of *M. pneumoniae* antibodies on day 6, while no other seroconversions were noted. Besides bed rest and limitation of fluid intake (two litres/day), the treatment prescribed was heparin, ACE inhibitors and analgesics (but no NSAIDs or aspirin). When seroconversion of *M. pneumoniae* was confirmed, azitromycin therapy was started. Since *M. pneumoniae* occurs in epidemics, we asked whether there was any illness in the patient's environment, which was not the case.[10] Within two weeks the patient's condition improved clinically. Laboratory testing reported a decline in inflammation parameters and enzymes. Electrocardiography showed persistence of the ST-segment abnormalities. Echocardiography showed improvement of LV function due to improved regional motion of the inferoposterior wall and less pericardial effusion, despite the dilation of the left ventricle.

DISCUSSION

This case history shows that a flu-like syndrome is not always a self-limiting disease, but may conceal myocarditis with serious consequences such as ventricular arrhythmia, heart failure and even death.[11] The clinical and electrocardiographic data suggested the diagnosis of (peri)myocarditis. Echocardiography revealed a regionally affected left ventricle (LV) and impaired LV function, both characteristics of myocarditis. Myocarditis may mimic acute myocardial infarction, as reported by Said *et al.*[12] However, since our patient was 20 years of age and had none of the known cardiovascular risk factors, unrecognised ischaemic heart disease as underlying disease would be very unusual, and therefore coronary angiography was not performed. Additionally, elevated *M. pneumoniae* antibody titres and contrast-enhanced MRI of the myocardium supported the diagnosis of myocarditis.

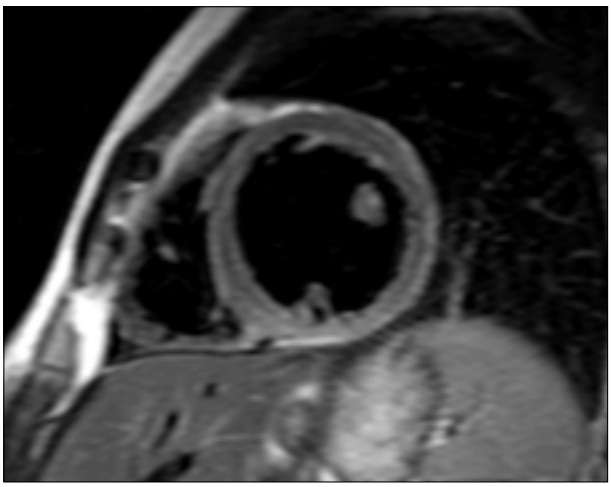

Figure 3a

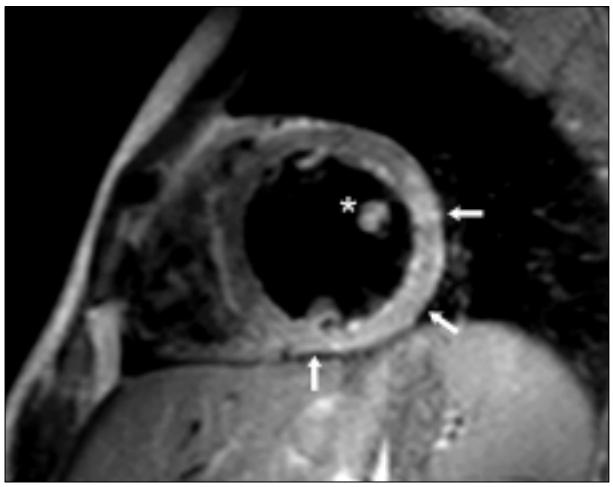

Figure 3b

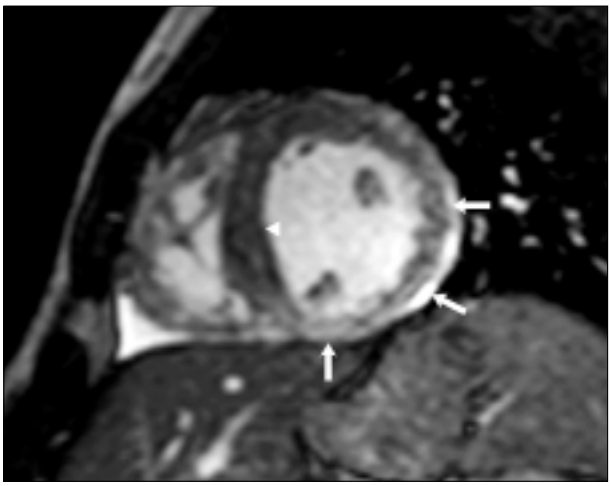

Figure 3c

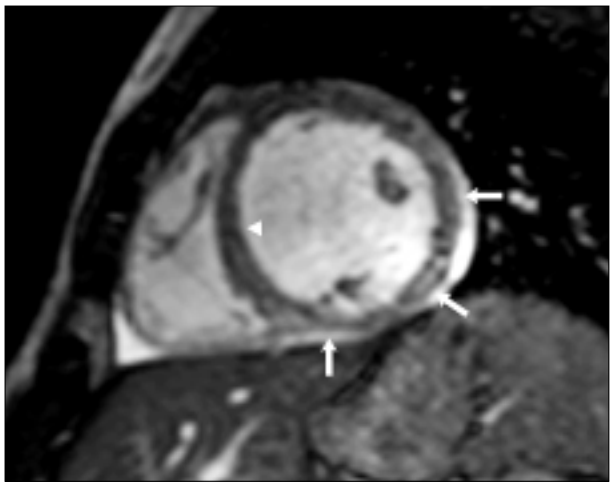

Figure 3d

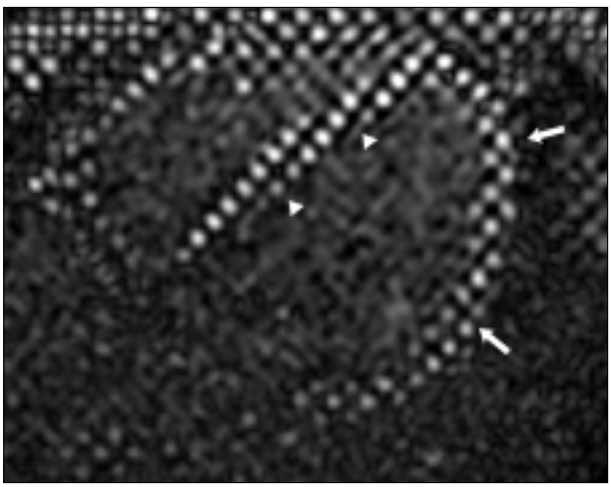

Figure 3e

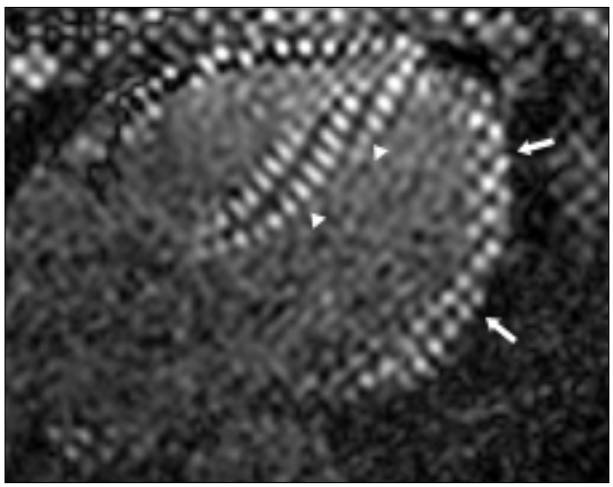

Figure 3f

MRI images on day 6

Short-axis T1 TSE pre-(3a) and post-(3b) contrast-enhanced images show myocardial enhancement of the posterior, lateral and inferior left ventricle (LV) wall (arrows) as well as the anterior papillary muscle (asterix). Short-axis balanced FFE cine images at end-diastole (3c) and end-systole (3d) demonstrate thinning, and lack of wall thickening during systole, of the posterior-lateral and inferior LV wall (white arrows). The akinesia is also shown on the tagged diastolic (3e) and systolic (3f) long-axis four-chamber views. The lateral LV wall grid does not change (arrows), demonstrating akinesia, in contrast to the warping of the septum grid showing normal septum thickening (arrowheads).

The infectious aetiology associated with myocarditis is mostly of viral origin.[13] Said *et al*. presented a case of an acute myopericarditis associated with a group A haemolytic streptococcal tonsillitis, which responded well to appropriate antibiotic treatment.[12] A more common causal agent is *Mycoplasma pneumoniae*. *M*. *pneumoniae* organisms are extracellular pathogens without a cell wall and belong to the group of smallest free-living bacteria. *M*. *pneumoniae* is a very common form of community-acquired pneumonia and occurs in epidemics.[14] Its incidence is highest during the first two decades of life.[10] Infection typically produces mild upper respiratory tract disease with only a minor fraction of these evolving to pneumonia.[14] However, *M*. *pneumoniae* is still responsible for 15 to 20% of all cases of pneumoniae and for 9% of all myocarditis cases.[10,13] *Mycoplasma* myocarditis occurs either through production of an organ-specific toxin, an autoantibody directed against the involved organ, or by direct invasion of the organisms.[15] Treatment of *M*. *pneumoniae* infections consists of erythromycin or quinolones, and a vaccine is currently being developed.[16]

The present gold standard for diagnosis of myocarditis has traditionally been endomyocardial biopsy, evaluated according to the 'Dallas criteria'.[17-19] During the acute phase, interstitial oedema, lymphocyte infiltration of the myocardium and myocyte necrosis is shown, but isolation of infectious aetiology is rare.[20] Endomyocardial biopsy has low sensitivity due to the focal and heterogeneous involvement of the myocardial disease and gives rise to major complications, particularly in the paediatric age group. In children suspected of myocarditis, the incidence of complications was 9%, with perforation in 5% and 0.6% mortality in a recent American review article.[21,22]

Tissue Doppler echocardiography (TDE) has recently been introduced into clinical practice to provide information on the LV systolic and diastolic function and on regional abnormalities.[23,24] As such, it may be of value in diagnosing the (regional) abnormalities of LV function. However, to our knowledge no specific studies using TDE in myocarditis have been described yet. Myocardial contrast echocardiography, on the other hand, may be of more value, according to preliminary data of Lindner *et al*.[25] This is also still in the experimental phase and has not yet been used in the clinical setting of myocarditis.[26]

Scintigraphic techniques with gallium-67 or indium-111 antimyosin antibodies can visualise leucocytic infiltrates or myocardial necrosis, respectively.[27,28] However, the usefulness of scintigraphy is limited by low specificity, radiation exposure and high costs.

An alternative non-invasive tool in the diagnosis and follow-up of patients with acute myocarditis has proved to be MRI in conjunction with gadolinium-DTPA contrast medium.[4-9] The major advantage of MRI is that it provides detailed anatomic information, in combination with left and right ventricular function (multiphase cine and tagging). Myocardial tagging is a method to evaluate the complex pattern of deformation of the heart during the cardiac cycle. A grid of taglines (*figures 3e* and *3f*) is applied on the image, typically on the short-axis or four-chamber view. By studying the slices during the heart cycle, segmental motion can be evaluated. Quantification of the myocardial strain is still in an experimental phase and not yet applicable in clinical practice.[29,30]

The contrast gadolinium accumulates in inflammatory lesions; it penetrates into extracellular fluid space but not into living cells. The accumulations provide an estimate of the sum of increased blood flow, acute cell damage and extravasation of fluid in areas of inflammation.[4] Therefore, contrast media-enhanced MRI can be used for the visualisation of myocarditis, i.e. the localisation, activity and extent of the inflammation. The inflammation process evolves from a focal to a disseminated process during the first two weeks of inflammation, which was first described by Friedrich.[4] The evolution of the inflammatory process is characteristic of myocarditis, but not of myocardial infarction. Therefore, MRI is a very useful diagnostic tool in diagnosing myocarditis. However, the contrast is not completely specific and therefore more efforts will be needed to optimise the results of contrast MRI. Myocardial enhancement can be quantified by measuring the global myocardial enhancement relative to the myocardial signal intensity prior to contrast injection and also relative to skeletal muscle.[4,8] The relative myocardial enhancement remains elevated in patients with persisting symptoms after three months.[4] Heavily T2-weighted breath-held MRI sequences, including short T1 inversion recovery (STIR), can also be used to demonstrate myocardial oedema but this requires further evaluation.[4,8,9]

Concerning the medical treatment, ACE inhibitors were given to improve symptoms and survival, because of the diminished ejection fraction.[31] Diuretics and spironolactone were considered but not used since the patient did not have signs of congestive heart failure when he was admitted.[32] Beta blockers were not prescribed in the acute phase because of the associated negative inotropic action, which has been described as being detrimental in myocarditis.[33]

As well as being useful for diagnostic purposes, imaging techniques are also of value in the further evaluation of the course of acute myocarditis. Progression into cardiomyopathy may occur and may lead to death in almost half of the patients within five years.[1,3,34] Long-term outcome is better in those patients who initially present with severe haemodynamic compromise and ventricular dysfunction (fulminant myocarditis), compared with patients with a less distinct onset of illness (acute myocarditis).[3] Echocardiography reveals that initially both patient groups have LV systolic dysfunction. However, only the patients with the fulminant presentation show a dramatic improve-

ment in fractional shortening at six months, which results in a better long-term prognosis in patients with fulminant versus acute myocarditis (reported transplantation-free survival at 11 years is 93% versus 45%).[3,19,34,35] One should thus be aware of possible progression into dilated cardiomyopathy and future need of cardiac transplantation.[20,22,36] Our patient's course of acute myocarditis will therefore be followed intensively, with the help of echocardiography and MRI.

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