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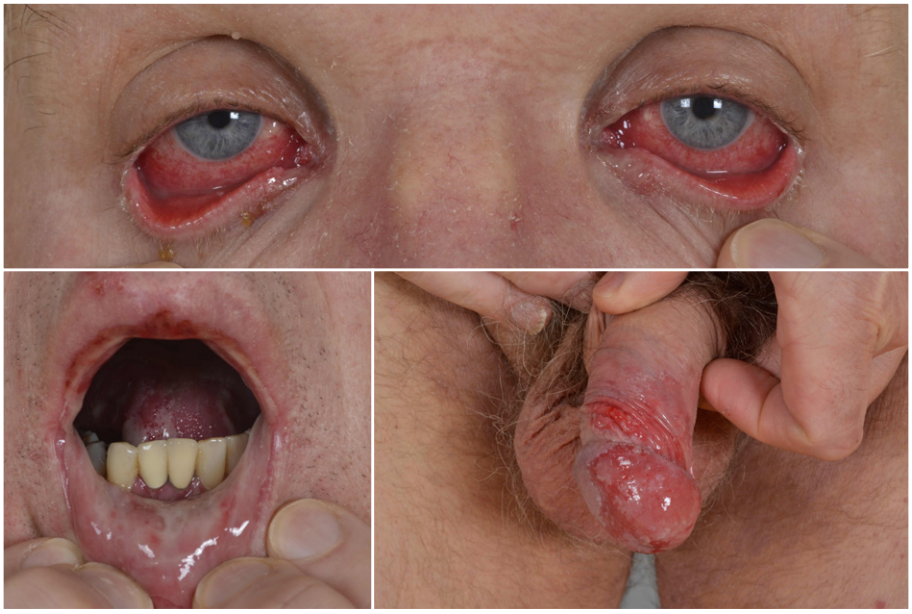

Red eyes and mucous ulcers; what is your diagnosis?

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EDITORIAL

How one plane crash changed the way we work

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In 1976 Dr James K. Styner, an orthopaedic surgeon and amateur pilot, was involved in a plane crash in a dark field in Nebraska. The crash resulted in the death of his wife, leaving him with his four children, of which three were heavily injured and unconsciousness. He eventually hitchhiked with his children to a small and already closed hospital in Hebron, Nebraska. When the trauma team eventually arrived Styner noticed that the medical team was unprepared for such an emergency and the standard of care was poor and inadequate. Back at work he and his colleague Paul Collicott founded the initial advanced traumatic life support (ATLS) course. In 1980, the ATLS course was adopted by the Committee on Trauma of the American College of Surgeons and it was recommended that all trauma patients should be approached using the ABCDE assessment.

If properly implemented, ATLS can lower mortality in traumatic patients by at least 15%.[1] The cornerstone of ATLS is the systematic ABCDE assessment for the early recognition and treatment of potentially life-threatening conditions. Although developed for traumatic patients, the ABCDE assessment has been increasingly implemented on emergency wards for medical emergencies in the recent years. The Dutch minister for healthcare even obliged all medical doctors in an emergency ward to attend an ABCDE course. However, evidence for the clinical benefits for the ABCDE assessment in medically ill patients is lacking. In the current issue of the journal, Olgers et al. assessed the frequency of the use of the ABCDE assessment in potentially unstable medically ill patients and determined factors influencing the choice whether or not to use the ABCDE approach.[2] A fast majority of potentially unstable patients (67%) where not assessed using the ABCDE approach. However, in (potentially) unstable patients with more urgent triage codes the ABCDE assessment was performed more often and in a highly efficient manner.

The study by Olgers et al. is the first to assess the use of the ABCDE assessment in medically ill patients. Although it is a single-centre observational study with multiple limitations, this study is a great step forward. Especially in current times with overcrowded emergency wards and an ageing population, geriatric patients are becoming more and more prominent in the emergency ward. They often present without a clear complaint or in an altered mental state and unable to clarify their symptoms. These alterations can impair the accuracy of the diagnosis of the main complaint and mask potentially serious diseases. In this group of patients, a systematic approach following the ABCDE assessment could probably increase the chance of a correct and fast diagnosis.

In my opinion, a systematic routine could maybe lower the amount of misdiagnosis and subsequently prevent further harm in patients presenting to the emergency wards. Since it is fast and easy to use also young and unexperienced physicians will be able to assess a critically ill patient. However, further studies are needed. These further studies should focus on the efficacy and efficiency of the ABCDE assessment in medically ill patients.

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REVIEW

Statins for prevention of cardiovascular disease in systemic lupus erythematosus

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ABSTRACT

Objective: In systemic lupus erythematosus (SLE), cardiovascular disease (CVD) is an important cause of long-term morbidity, which could be affected by statin use. Here we review the evidence for the use of statins for the prevention of CVD in patients with SLE.

Methods: The PubMed database was searched using a query combining SLE and statins.

Results: The search yielded nine relevant clinical studies. Seven studies reported on radiological findings that correlate with atherosclerosis and mainly revealed that statin treatment resulted in a slight decrease in progression of carotid intima-media thickness and an increase in flow-mediated vasodilatation. Two studies investigated CVD and mortality. In a group of SLE patients that had received a kidney transplantation, three of 23 statin-treated SLE patients experienced cardiac events compared with four of ten placebo-treated controls. Moreover, in a retrospectively studied cohort of SLE patients with dyslipidaemia, statin treatment in 777 patients was associated with a large decrease in coronary heart disease (hazard ratio [HR] = 0.20), cerebrovascular disease (HR = 0.14), end-stage renal disease (HR = 0.22) and mortality (HR = 0.44) compared with 1317 patients that had not been prescribed statins. However, the latter retrospective study was subject to bias and causality can only be proven in a randomised trial. Statins showed a good safety profile in SLE patients.

Conclusion: Whilst awaiting new prospective randomised studies, we recommend prescription of statins in SLE patients with increased cardiovascular risk according to the current recommendations for cardiovascular risk management in rheumatoid arthritis.

KEYWORDS

Cardiovascular disease, prevention, statins, systemic lupus erythematosus

INTRODUCTION

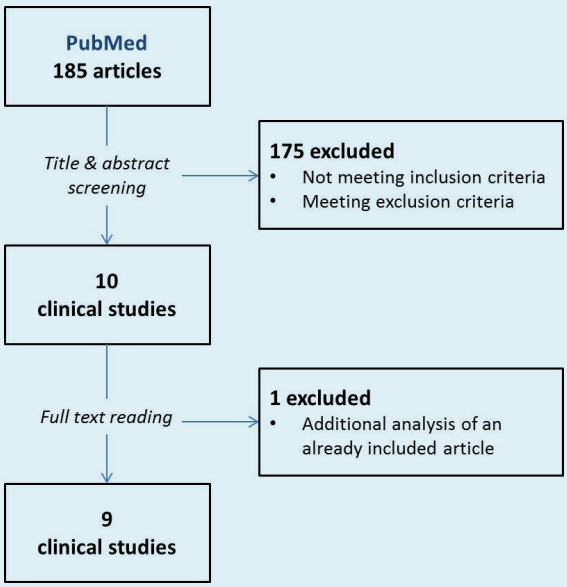
Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can involve many organs, including the skin, joints, kidneys, serosae and haematopoietic system. While inflammation of these tissues often defines acute flares, the most important causes of long-term mortality are renal failure, infections and cardiovascular disease (CVD), encompassing ischaemic heart disease, cerebrovascular disease and peripheral artery disease. The standardised mortality ratio for CVD in SLE patients was 2.7 in a recent meta-analysis.[1] Furthermore, in a large cohort of female SLE patients, the risk of myocardial infarction was increased 2- to 52-fold compared with controls. The relative risk was highest amongst young females with SLE, whereas the absolute risk was highest in older patients.[2] Other presentations of CVD are more prevalent as well, with a 1.3- to 2.3-fold increased risk for cerebrovascular events amongst SLE patients and a 9.4 times higher incidence of peripheral artery occlusive disease.[3,4] A major cause of CVD in SLE is premature atherosclerosis.[5,6] Several factors contribute to this phenomenon. First, inflammation stimulates atherogenesis. Secondly, therapies aimed at suppressing inflammation (e.g. corticosteroids and disease-modifying antirheumatic drugs) often have cardiovascular side effects. Third, the prevalence of classic cardiovascular risk factors amongst SLE patients is increased (e.g. smoking, hypertension and obesity).[7]

Several treatment strategies are available to reduce morbidity from CVD in SLE. The cornerstone is treatment of general inflammation using anti-inflammatory drugs, thereby suppressing inflammation-driven atherosclerosis. Another important intervention is reversal of dyslipidaemia using statins. Apart from reducing intracellular cholesterol synthesis, statins also exert pleiotropic effects including inhibition of thrombosis and endothelial dysfunction, plaque stabilisation and immunomodulation.[8,9] Examples of the latter are inhibition of LFA-1-mediated leukocyte adhesion, reduction of major histocompatibility complex-II

expression on endothelium and suppression of the production of pro-inflammatory cytokines such as type I interferons and interleukin-17.[9-11] These pleiotropic effects may provide additional benefits, especially in inflammatory diseases such as SLE.

Given the high burden of CVD-related morbidity and mortality in SLE, prevention of these complications could result in a robust health benefit. Amongst Dutch general practitioners, internists and European rheumatologists in general, clear guidelines are formed on cardiovascular risk management for the general population. Furthermore, specific recommendations are defined for patients with rheumatoid arthritis (RA), because of increased CVD risks.[12,13] Lupus patients are even more at risk for CVD than RA patients,[14,15] with a standardised mortality ratio for CVD of 2.7 compared with 1.5-1.8 in RA.[1,16] However, these guidelines do not specify the management of SLE patients. Therefore, our aim was to review the evidence on the use of statins for prevention of CVD in SLE patients and provide a recommendation for future management.

Figure 1. *Flowchart of the literature search*



SEARCH STRATEGY

The PubMed database was searched on 2 October 2016 using the following query: *((pravastatin [Title/Abstract]) OR (rosuvastatin [Title/Abstract]) OR (atorvastatin [Title/Abstract]) OR (simvastatin [Title/Abstract]) OR (fluvastatin [Title/Abstract]) OR (statin* [Title/Abstract]))* **AND** *((lupus [Title/Abstract]) OR (SLE [Title/Abstract]))*. Inclusion and exclusion criteria are stated in *table 1*. The outcomes of interest were CVD, measures (such as radiological findings) suggestive of CVD and mortality.

RESULTS

The search results are summarised in the flowchart in *figure 1*. The initial search yielded 185 entries. After screening of the title and abstract and subsequent reading of the full text of the remaining articles, nine clinical studies remained. The study characteristics and results are summarised in *table 2* and *table 3*.

Table 1. *Inclusion and exclusion criteria*

Inclusion criteria
Patients with systemic lupus erythematosus Interventions include statins Outcomes include CVD, measures suggestive of CVD or mortality
Exclusion criteria
Languages other than English or Dutch Only the abstract was available Review articles

CVD = cardiovascular disease.

Prevention of cardiovascular disease

Three randomised controlled trials (RCTs) reported the carotid intima-media thickness (CIMT) of SLE patients that were treated with statins or a placebo. In a recent study, it was shown that CIMT significantly correlates with cardiovascular events in SLE patients.[17] During a mean follow-up of 24-36 months on 212 SLE patients (113 with paediatric SLE), atorvastatin treatment did not significantly reduce CIMT progression compared with similar-sized groups of placebo-treated SLE patients, and neither did rosuvastatin (n = 36) in comparison with 36 controls.[18-20] Amongst two RCTs, the level of computed tomography scan-determined coronary calcifications and myocardial perfusion were also not significantly influenced by atorvastatin treatment.[19,21] However, only two months of atorvastatin treatment resulted in a 0.13 mm increase of brachial artery diameter in 64 SLE patients which was significantly different from the 0.02 mm decrease in 24 SLE patients that were not treated ($p < 0.001$). Furthermore, flow-mediated vasodilatation (FMD) increased 1.9% in the statin group versus a 0.3% decrease in the control group ($p = 0.009$).[22] FMD is a measure of endothelial dysfunction, a process that plays a role in the pathophysiology of atherosclerosis.[23] The FMD also improved from 7.58% to 18.22% in 12 months in 22 SLE

Table 2. *Study overview*

	Design	Country	Population (mean age)	Gender & ethnicity (if available)	Intervention Control	Outcome	Follow-up (m)	Results
[18]	RCT	North America	Paediatric SLE *(15.7y)*	83% ♀ 52% Caucasian 24% Hispanic	113 atorvastatin 108 placebo	CIMT (US)	36	Progression of mean common CIMT was 0.0010 mm/year vs. 0.0024 mm/year in controls *(p = 0.24)*
[20]	RCT	China	SLE + subclinical atherosclerosis *(50.8y)*	97% ♀	36 rosuvastatin 36 placebo	CIMT (US)	24	Mean CIMT (6 sites) changed -0.01 mm (-1.5%) vs. + 0.04 mm (+ 6.1%) in controls *(ns)*
[19]	RCT	USA	SLE without clinical CVD *(44.7y)*	92% ♀ 61% Caucasian 33% African-American 2% Hispanic 2% Asian	99 atorvastatin 101 placebo	CIMT (US) Coronary calcifications (CT)	24	No significant difference in the progression of all outcomes vs. controls CIMT increased > 10% in 44 (46%) vs. 61 (67%) of controls *(p = 0.014)*
[21]	RCT	Poland	SLE *(41.5y)*	90% ♀	28 atorvastatin 32 placebo	Coronary calcifications (CT) Perfusion defects (SPECT)	12	Controls: Increase in coronary calcifications and plaque volume *(p < 0.05)* Atorvastatin: Slight decrease in plaque volume, slight increase in calcifications *(ns)* Perfusion defects unchanged.
[22]	Cohort	Brazil	SLE *(31.8y)*	100% ♀ 65% Caucasian 35% non-Caucasian	64 atorvastatin 24 no medication	FMD (US)	2	Change in resting brachial artery diameter: + 0.13 mm vs. - 0.02 mm in controls *(p < 0.001)*. Change in FMD: + 1.9% vs. -0.3% in controls *(p = 0.009)*. No significant difference in change of flow between groups.
[24]	Cohort	Mexico	SLE *(40y)*	95% ♀	22 pravastatin + ezetimibe *No controls*	FMD (US)	12	FMD increased from 7.58% to 18.22% *(p < 0.001)*
[25]	Cohort	Spain	SLE *(47y)*	100% ♀	37 atorvastatin (for 2 months) *No controls*	Carotid-femoral PWV (US+ECG)	6	In the 12 patients with pathological PWV at baseline, a decrease of 1.01 m/s (12%) was seen after 2 months *(p = 0.002)* that sustained throughout the follow-up
[26]	RCT	Northern Europe, Canada	SLE + kidney transplant *(46.6y)*	Unknown	23 fluvastatin 10 placebo	Coronary heart disease Cardiac mortality	87	Cardiac events in 3 (13%) vs. 4 (40%) of controls *(p = 0.064)*
[27]	Cohort (retrospective)	Taiwan	SLE + dyslipidaemia	88% ♀	1673 low-dose statins 777 high-dose statins 328 non-statin lipid-lowering drugs 1317 no medication	Myocardial infarction Cerebrovascular disease ESRD Mortality	144	See *table 3*.

m = months; RCT = randomized controlled trial; SLE = systemic lupus erythematosus; CIMT = carotid intima-media thickness; US = ultrasound; CT = computed tomography scan; SPECT = Single Photon Emission Computed Tomography; FMD = flow-mediated vasodilatation; PWV = pulse wave velocity; ECG = electrocardiogram; ESRD = end-stage renal disease; ns = not significant (p-value not given).

Table 3. *Results of the study by Yu et al.*[27]

	Coronary disease‡	Cerebrovascular disease‡	End-stage renal failure‡	All-cause mortality‡
Low-dose statins	0.41 (0.32-0.53)	0.27 (0.19-0.39)	0.39 (0.32-0.47)	0.79 (0.63-0.99)
High-dose statins	0.20 (0.13-0.31)	0.14 (0.08-0.25)	0.22 (0.16-0.29)	0.44 (0.32-0.60)

The hazard ratios for SLE patients with dyslipidaemia that were treated with statins compared with SLE patients with dyslipidaemia that were not treated with lipid-lowering drugs as reported by Yu et al.[27]
‡ = hazard ratio (95% confidence interval).

patients who received the combination of pravastatin and the non-statin cholesterol lowering drug ezetimibe ($p < 0.001$).[24] Finally, one study measured carotid-femoral pulse wave velocity (PWV) in 37 SLE patients that were treated with atorvastatin. In patients with a pathological PWV, a 12% decrease was seen over two months ($p = 0.002$).[25]

Two studies measured CVD and mortality. One RCT measured these outcomes in 33 SLE patients who had received a kidney transplantation during a follow-up of 87 months. Coronary heart disease and cardiac mortality were reported in three of 23 patients treated with fluvastatin versus four of the ten patients that received a placebo ($p = 0.064$).[26] Although a large reduction in severe outcomes was seen here, this was not statistically significant, which could be the result of the small study population.

In 2015, a retrospective cohort study described the effects of lipid-lowering drugs on myocardial infarction, cerebrovascular disease, end-stage renal disease and all-cause mortality in a cohort of 4095 SLE patients that were all diagnosed with dyslipidaemia. Because of the sample size and the relevance of the findings, this study will be discussed in more detail. This study was conducted in Taiwan and used a national health-insurance registration system that included 98% of the country's complete population. ICD-9 codes were used to identify SLE patients, the presence of dyslipidaemia and the above-mentioned outcomes. Patients were stratified in groups that used low-dose statins (cumulative dose < 365 daily doses), high-dose statins (cumulative dose > 365 daily doses), other lipid-lowering drugs and controls that used no lipid-lowering medications. During the follow-up of up to 144 months, all-cause mortality was significantly reduced in the groups treated with high-dose statins: hazard ratio (HR) 0.44; 95% confidence interval (CI) 0.63-0.99. Furthermore, the high-dose statin group showed a significant reduction in coronary disease (HR 0.20; 95% CI 0.13-0.31), cerebrovascular disease (HR 0.14 [0.08-0.25]) and end-stage renal disease (HR 0.22 [0.16-0.29]). These effects were also seen in the low-dose statins group, but to a lesser extent *(table 3)*. These HRs were adjusted for many confounders, including sex, age, socioeconomic status, hypertension, diabetes mellitus, chronic renal disease, medication use and mean number of hospital admissions (as a measure for disease activity and severity). However, smoking, alcohol and body weight were not corrected for because there were no data on these factors.[27] An assessment of the study quality is given in *table 4*. The main shortcomings included the lack of correction for these remaining confounders, the fact that therapy compliance was unknown, the risk for selection bias and the non-randomised retrospective study design that complicates determination of causality.

Pleiotropic effects

A recent meta-analysis showed that statin use did not affect SLE disease activity index scores across five studies with a follow-up ranging from 3-24 months.[28] The concentrations of C-reactive protein (CRP) were also not influenced by three months of rosuvastatin treatment in 14 SLE patients with low baseline CRP concentrations (mean 5.2 mg/l).[29] However, a meta-analysis that combined seven larger controlled studies, including a study on 12 months of rosuvastatin treatment, found that high-sensitivity (hs)-CRP levels significantly decreased upon statin treatment, supporting a beneficial effect of statins on SLE disease activity.[28]

Statin safety

In order to make a well-judged decision on a therapy, potential adverse effects should also be considered. In general, statins are associated with relatively few side effects. The most important adverse effects are increased serum liver transaminases in < 1% at standard doses and myopathy in up to 0.5% of users.[30] Rhabdomyolysis was seen in only 0.023% of almost 40,000 statin users versus 0.015% in a similar number of controls.[31] Furthermore, statins are safe in patients with impaired renal function, a common comorbidity in SLE.[30] Very rare complications of statin use are the development of lupus-like disease, dermatomyositis, polymyositis and interstitial lung disease.[32,33]

Specifically in SLE patients, the rates of typical adverse effects of statins (such as muscle and liver toxicity) were not significantly increased in statin-treated SLE

Table 4. *Study quality assessment of the retrospective cohort study by Yu et al.*[27]

	Outcomes	+	Very relevant outcomes (severe morbidity and mortality)	
	Sample size	+	Large sample given the rarity of SLE	
	External validity	+ -	All SLE patients in the country were included, representing the population in clinical practice in Taiwan Because only Taiwanese SLE patients were included, the external validity for other countries was limited	
Internal validity	**Information bias**	+ - - -	Clear endpoints that are not easily misdiagnosed Use of an insurance database The study was not blinded Therapy compliance is unknown	
	Selection bias	+ + + - - -	All SLE patients in the country were included No loss-to-follow-up The exclusion criteria were not very restrictive Over 12% of patients were excluded because no blood lipid tests were performed. The reason for not performing these tests was unknown It is unclear what percentage of the clinicians actually registered a second diagnosis of dyslipidaemia for SLE patients if applicable It is unclear what percentage of the clinicians consequently prescribed statins for SLE patients with hyperlipidaemia and to what extent this decision was influenced by the presence of cardiovascular risk factors or events	
	Confounding	+ -	Adequate statistical correction for many important confounders Information on some major confounders was not available	
	Statistics	+	Appropriate statistics	

Green = high quality; orange = medium quality; red = low quality.

patients compared with the placebo-treated group in most studies,[18-21,26] although one study reported an increased prevalence of elevated liver transaminases in the statin group.[19]

DISCUSSION

Premature atherosclerosis with subsequent CVD is an important cause of long-term morbidity and mortality in SLE patients. In this article, we reviewed the available evidence on the use of statins for prevention of CVD in SLE patients. Although data from prospective, randomised studies are lacking, there is a reasonable basis to support strict statin use in SLE patients with increased CVD risk similar to rheumatoid arthritis guidelines.

Most studies investigated radiological findings consistent with atherosclerosis[18-20,22,24] rather than reductions in CVD and mortality, or concerned only a small subpopulation of SLE patients (after renal transplantation),[26] and therefore cannot be directly extrapolated to reductions in cardiovascular events in the main SLE population. Current recommendations on statin treatment in SLE are therefore mainly dependent on the effect of statin use on CVD and mortality in a large Taiwanese SLE cohort with dyslipidaemia.[27] However, a causal relationship cannot be established based on this study design. Furthermore, therapy compliance was unknown, selection bias could not be ruled out and correction or stratification for smoking, alcohol and obesity was not possible, which hampers the interpretation of the effects of statin use on the study outcomes. Therefore, prospective RCTs are required to substantiate these findings and to establish causality.

In a recent meta-analysis,[28] statins were found to reduce the concentration of hs-CRP in SLE patients. Although SLE disease activity index scores remained unaffected, chronic (low-grade) inflammation is a major factor that contributes to premature atherosclerosis in rheumatic diseases[7] and hs-CRP is associated with CVD in SLE.[34-36] Furthermore, reduction of hs-CRP by rosuvastatin has been associated with a reduction of CVD events in the general population.[37] Therefore, statins might be beneficial in patients with elevated hs-CRP.

Finally, from a safety perspective, statins can be safely prescribed for SLE patients.

CONCLUSION AND RECOMMENDATIONS

In conclusion, the use of statins was associated with a large decrease in CVD and mortality, although causality still has to be proven. Furthermore, statins show a good safety profile and are widely used in people at risk in the general

population and in patients with RA, where these drugs are safe and effective in reducing CVD.

These findings provide a reasonable basis to support strict guidelines for statin therapy for SLE patients with an increased risk of CVD. Since the risk of CVD in SLE patients surpasses that in RA patients, we highly recommend that SLE patients should be treated according to the current EULAR recommendations[13] for cardiovascular risk management in rheumatoid arthritis. This implicates that a 10-year risk for CVD should be calculated by the Systemic Coronary Risk Evaluation (SCORE)[38] or another prediction model and subsequently be multiplied by 1.5. Patients should then be treated accordingly using the national guidelines for cardiovascular risk management. Furthermore, statins may be considered for SLE patients without dyslipidaemia with elevated hs-CRP levels. Meanwhile, prospective RCTs that investigate the influence of statins on CVD and mortality in SLE patients are necessary to establish causality and further guide the treatment of SLE patients. Because of the expected high impact of statin use on morbidity and mortality, these studies should be conducted at short notice.

DISCLOSURES

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ORIGINAL ARTICLE

The ABCDE primary assessment in the emergency department in medically ill patients: an observational pilot study

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ABSTRACT

Background: Competency in the Airway Breathing Circulation Disability Exposure (ABCDE) approach is required for working in the emergency department. There is limited knowledge on how often and how completely the ABCDE approach is applied to medical patients. The objectives of this study were to assess the frequency with which the ABCDE approach was used in potentially unstable patients and to determine factors influencing the choice of whether or not to use the ABCDE approach.

Methods: This observational pilot study included 270 medical patients admitted to the emergency department and it was observed if and how completely the ABCDE approach was performed. We registered several factors possibly determining its use.

Results: Of the 270 patients included, 206 were identified as possibly unstable patients based on their triage code. The ABCDE approach was used in a minority of these patients (33%). When the ABCDE approach was used, it was done rapidly (generally within 10 minutes) and highly completely (> 80% of needed items). The choice not to use the ABCDE approach was frequently based on a first clinical impression and/or vital signs obtained during triage. The ABCDE approach was used more often with a higher triage code.

Conclusions: We show that the emergency department staff are capable of performing the ABCDE approach rather completely (83%), but it was only used in the minority of potentially unstable patients. Important factors determining this choice were the vital signs on triage and a quick first impression. Whether this adequately selects patients in need for an ABCDE approach is not clear yet.

KEYWORDS

ABCDE, primary assessment, medical emergencies, emergency department

INTRODUCTION

A structured approach is considered a hallmark of the initial care of specific medical emergencies. It facilitates optimal use of time and early recognition of deterioration, especially in the so-called 'golden hour' which is the first hour after onset of injury or illness when resuscitation could be most beneficial.[1,2] This golden hour has been recognised in various emergencies such as trauma, stroke, sepsis and shock.[3-5] The application of a structured approach has become standard in trauma. This approach for early recognition and treatment of life-threatening conditions in trauma has been trained in trauma courses for decades.[5,6] Training of a systematic approach using the Airway Breathing Circulation Disability Exposure (ABCDE) primary assessment in other medical emergencies has increased during recent years, although solid evidence of the clinical benefits for patients using the ABCDE approach is lacking. Despite this lack of hard evidence, the Dutch Inspection for Healthcare (IGZ) requires that physicians treating patients in the emergency department are ABCDE trained.[7] The scale of transfer to real practice and the extent of the application of a structured approach in the emergency department (do they actually apply what they have learned in training) is not exactly known. The basics of the ABCDE approach are shown in *table 1*.[8]

Table 1. *Basics of the ABCDE approach*

Letter	Life-threatening condition
A – Airway	Airway blockage, cervical spine injury
B – Breathing	Tension pneumothorax, pulmonary oedema, bronchospasm
C – Circulation	Shock (hypovolaemic, obstructive, distributive, cardiogenic)
D – Disability	Seizure, hypoglycaemia, meningitis, intracranial haemorrhage or infarction, intoxication
E – Exposure	Hypothermia or hyperthermia, critical skin conditions such as fasciitis or urticaria

We have completed an observational pilot study to register the use of the ABCDE approach in the emergency department (ED) in medically ill patients. We investigated whether triage code was associated with performing an ABCDE approach and why a doctor did not deem an ABCDE approach necessary.

MATERIALS AND METHODS

An observational pilot study was conducted in the ED of a tertiary care university hospital with over 34,000 ED visits annually. During a seven-week period from August 2014 until October 2014 a convenience sample was obtained by screening all medical patients older than 18 years admitted to the ED for the internist or emergency physician between 08.00 and 17.00 hours from Monday to Friday on 30 random days. All staff and residents/interns in our ED, except medical students, had to successfully complete a two-day ABCDE course before they could treat patients in the ED. In the Netherlands, there are several of these ABCDE courses provided, consisting of lectures and practical hands-on sessions using simulation. If the attending physician planned to use the ABCDE approach, informed consent was obtained from the patient and physician to observe the procedure. The observer was able to observe/include only one patient at a time. Before assessing the patients, the treating physician was asked which approach he was going to use and the reasons for this specific approach, including reasons for not performing the ABCDE approach. Baseline data were registered including elapsed time until the start of the ABCDE approach, duration of the ABCDE approach, basic patient characteristics (triage code, reason for ED visit) and physician characteristics (physicians and residents were asked about their specialty, duration of current education and years of experience since graduation from medical school). The triage code was allocated by a trained triage nurse based on the main complaint, basic vital parameters and expected amount of resources needed, according to the Emergency Severity Index. This results in five triage codes: red meaning immediate resuscitation needed; orange almost immediate resuscitation needed (within ten minutes); yellow denotes a potentially ill patient with resuscitation needed within one hour, or two or more resources (investigations/diagnostics) needed; green no resuscitation needed but treatment within two hours and only one resource needed and finally blue no resources needed and treatment within four hours. Patients were divided into two groups based on their triage code: red, orange and yellow were grouped together as urgent or (potentially) unstable patients, green and blue as non-urgent or stable patients. Potentially unstable patients can have various serious conditions, for example sepsis, overdose or acute abdominal pain. The ABCDE approach was observed and its completeness was registered using an observational list (*figure 1*). Completeness scores were calculated by dividing the number of performed checklist items by the total number of checklist items (26) multiplied by 100, resulting in a possible score between 0 and 100. Data collection was performed by one investigator. The study was approved by our local Medical Ethics Committee.

Data analysis

Data were analysed using IBM SPSS version 22.0. A p-value less than 0.05 was considered statistically significant. Descriptive statistics were used. The Jonckheere-Terpstra test was used for the relation between triage code and time until the ABCDE approach. A Cochran-Armitage trend test and gamma association were used to describe the relation between the frequency with which ABCDE was used and the triage code. Fisher's exact test compared the frequency of performed ABCDE approaches between the two different triage groups (potentially unstable or not potentially unstable). A Mann-Whitney U test was used to compare not normally distributed ABCDE scores between different groups.

RESULTS

We enrolled 270 patients and the ABCDE approach was used in 69 (26%) of them. All 270 patients were included in the data analysis. For data analysis concerning the scoring of the completeness of the ABCDE approaches, 19 of the 69 (29%) ABCDE approaches were excluded due to the following reasons: two patients waived informed consent and in 17 patients the observer had more than one patient at one time so was not able to observe both. No patients were missed due to decreased level of consciousness. Based on their triage code, 206 of 270

Figure 1. *Observation list for assessing the ABCDE approach*

	Tick box if performed
Airway	
Assess if patient is able to talk normally	□
Assess skin colour (cyanosis, pallor, etc.)	□
Aware of abnormal (wheeze, stridor, gurgling or snoring) or no breathing sounds	□
Inspect mouth	□
Assess possibility of cervical spine injury	□
Breathing	
Ask helper to apply pulse oximetry and assess saturation	□
Perform lung auscultation	□
Assess respiratory rate	□
Aware of laboured breathing (e.g. use of accessory respiratory muscles nasal flaring, etc.)	□
Inspect chest wall movements for symmetry	□
Circulation	
Ask helper to perform blood pressure measurement and assess blood pressure	□
Assess pulse rate	□
Assess capillary refill time	□
Perform auscultation of heart	□
Assess cardiac rhythm (regular or irregular)	□
Perform orienting abdominal examination (auscultation and palpation)	□
Assess skin temperature and moisture (e.g. warm/cool, dry/clammy)	□
Inspect if jugular venous pressure is elevated	□
Palpate central or peripheral pulse	□
Disability	
Assess level of consciousness using the Glasgow Coma Score or the AVPU method	□
Examine motor function of limbs for lateralising signs	□
Evaluate size of pupils and pupillary light reflexes	□
Assess meningeal irritation	□
Ask helper for blood sugar value	□
Exposure	
Ask helper to measure body temperature and assess temperature	□
Perform head-to-toes clinical examination for signs of trauma, skin reactions (rashes), signs of DVT	□

AVPU = Alert Verbal Pain Unresponsive; DVT = deep venous thrombosis

(76%) patients were classified as potentially unstable. In these 206 patients, the ABCDE approach was used in 67 (33%) of the cases in contrast to 2 of 64 (3%) in the stable patients ($p < 0.001$, *table 2*).

With increasing acuity of patients, defined as an increase in triage code, the ABCDE approach was applied more frequently (Gamma association $r = 0.779$, *table 3*). In patients with the highest triage code (red) the ABCDE approach was used in 100% of the cases ($n = 3$) while in the lowest groups (green and blue) in only 0-4 %. In patients with triage code yellow the ABCDE approach was used in only 24% of the cases.

Time delay before commencing the ABCDE approach significantly decreased by an increasing triage code (*table 4*). In unstable patients (triage code red and orange) the primary assessment was initiated within 10 minutes in more than 75% of patients. The duration of the ABCDE approach itself was less than 10 minutes in 75% of patients, with a median time of 7 minutes.

The ABCDE approach was not performed in 139 (67%) of the (potentially) unstable patients (those with triage code red, orange and yellow grouped together). The main reasons were: 1) the patient seemed stable after a short clinical assessment (30%), 2) the reason for the ED visit suggested a stable patient (20%), 3) the patient was first seen by a medical student who was not trained in the ABCDE approach (11%) and 4) the vital signs measured by the triage nurse suggested a stable patient (10%).

In total 50 ABCDE approaches were observed, performed by 21 different physicians including 7 consultants (grouped as specialists), 11 residents and 3 medical students (last two grouped as non-specialists) (*table 5*). Mean observed ABCDE approaches where 2.38 for every physician.

Despite the difference in years of experience between the two groups, the ABCDE completeness scores were similar (82.2 and 84.0; $p = 0.309$). Vital parameters were noted in every patient while investigation of cervical spine injury or palpation of central or peripheral arteries in less than 50% (*table 6*).

Table 2. *ABCDE in stable and (potentially) unstable patients*

Patients (n = 270)	Stable* (n = 64)	Potentially unstable** (n = 206)
ABCDE (n = 69)	2 (3.1%)	67 (33%)
No ABCDE (n = 201)	62 (97%)	139 (67%)
P-value	< 0.001†	

Baseline characteristics for using the ABCDE approach in absolute numbers and (percentages). *Patients with triage codes non-urgent (blue or green). **Patients with triage codes urgent (yellow, orange and red). †Fischer's exact test to compare frequency of use of ABCDE approach between stable and unstable patients.

Table 3. *Relation between triage code and ABCDE use*

Triage code	Red (n = 3)	Orange (n = 44)	Yellow (n = 159)	Green (n = 55)	Blue (n = 9)
ABCDE (n = 69)	3 (100%)	26 (59%)	38 (24%)	2 (4%)	0 (0%)
No ABCDE (n = 201)	0 (0)	18 (41%)	121 (76%)	53 (96%)	9 (100%)

n = total number of patients. Cochran-Armitage trend test for relation between triage code and frequency of ABCDE approach use, $p < 0.001$.

Table 4. *Time elapsed until ABCDE approach*

	Time elapsed until ABCDE approach			
Triage code	**Median**	**P25-75**	**Min-max**	**p-value***
Red (n = 3)	4	3-4	3-7	0.015
Orange (n = 19)	7	4-9	2-19	
Yellow (n = 27)	9	4-24	3-57	
Green (n = 1)	16	16-16	16-16	
Blue (n = 0)	-	-	-	

n = total number of patients with this triage code. Time in minutes. P25-75 reflects 25th and 75th percentile, min-max reflects minimum and maximum time elapsed until ABCDE. *Jonckheere-Terpstra for relation between time intervals to ABCDE and triage code.

Table 5. *ABCDE completeness score*

	Total group (n = 50)	Specialist (n = 13)	No specialist (n = 37)	P-value*
Completeness score (0-100)	83.5 (1.3)	82.2 (2.2)	84.0 (1.6)	0.309
Experience (years)	5.0 (0.9)	14.0 (1.3)	1.8 (0.3)	

Completeness score as mean (standard error). *Mann-Whitney U test.

DISCUSSION

This is the first study investigating the use of the ABCDE approach in medical patients in the ED. It shows that the ABCDE approach is performed more often and sooner after admission in (potentially) unstable patients with more urgent triage codes. It was performed in 100% of patients with the highest triage code although this group included only three patients. This supports the idea that *if* an acutely ill patient is recognised, the ABCDE approach is the preferred method for assessing these patients. However, we found that in the majority (67%) of potentially unstable patients (those with triage code red, orange and yellow grouped together) the ABCDE approach was not used to assess the patient. In the group with the second highest triage code (orange) the ABCDE approach was performed in only 59% of patients, which decreased to 24% in patients with triage code yellow. Therefore, although the use of the ABCDE approach is associated with triage code, it is only performed in the minority of all potentially unstable patients despite the medical staff being trained to perform this approach in such patients.

We also found that if the ABCDE approach is performed, it is done efficiently with high completeness scores. There was no significant association between completeness scores and triage code. All staff and residents in our ED, except medical students, had to complete an ABCDE course before they could treat patients in the ED, which might explain the high completeness scores. Interestingly, residents and experienced staff have similar but not maximum ABCDE completeness scores (83 instead of 100) which might reflect that doctors think they do not need all the parameters to exclude potentially life-threatening diseases or stabilise the patients. For example, immediate testing for hypoglycaemia may not be necessary when the patient has a maximum Glasgow Coma Scale without signs of neurological impairment.

We tried to identify other factors, apart from triage code, affecting the use of the ABCDE approach. The main reasons for omitting the ABCDE approach were that the

Table 6. *Percentage of items performed*

	Examination	Performed
Airway	Responsiveness patient	100%
	Skin colour	98%
	Breath sounds	94%
	Mouth inspection	58%
	Cervical spine injury	30%
Breathing	Pulse oximetry	100%
	Lung auscultation	98%
	Respiratory rate	92%
	Aware of laboured breathing	79%
	Chest wall movements	76%
Circulation	Blood pressure	100%
	Pulse rate	100%
	Capillary refill time	96%
	Heart auscultation	92%
	Cardiac rhythm	92%
	Global abdominal examination (auscultation and palpation)	92%
	Skin temperature and sweating	76%
	Jugular venous pressure	52%
	Palpation of central or peripheral artery	46%
Disability	Level of consciousness (Glasgow coma score or AVPU-scale)	98%
	Lateralisation	90%
	Pupillary light reflexes	88%
	Sign of meningeal irritation	70%
	Blood glucose	64%
Exposure	Temperature	98%
	Head-to-toe clinical examination	92%

Percentage of checklist items performed based on all observed ABCDE-approaches.

patient seemed stable at a first glance (clinical impression), the reason for visiting the ED or the vital signs done by the nurse did not indicate instability or the medical student had no training in the ABCDE approach. In a previous study, we showed that a higher clinical impression score given by the attending physicians and ED nurse correlated with the severity of sepsis and amount of resources needed.[9] It is not known if it is safe enough to use only a clinical impression score initially and then to decide if an ABCDE approach is needed. Our data indicate that a complete ABCDE can be performed within 10 minutes in the majority of patients, so the time benefit of performing only a clinical impressions score may not weigh up against the risk of not recognising an unstable patient. The fact that a few vital signs are normal or the medical student is not trained in treating acutely ill patients is in our opinion not a good argument to omit an ABCDE approach.

Limitations

An observational single-centre pilot study was conducted in a tertiary academic hospital. We performed a pilot study to gain insight into whether the ABCDE approach learned in a simulation-based training was applied in real practice. It is as yet unknown whether our results also apply to other EDs. We expect that in our region, the use and completeness of the ABCDE approach is lower in other EDs as we are a tertiary university hospital with multiple unstable patients presenting to our ED every day.

The physicians knew they were under observation and this may also lead to both more frequent use of the ABCDE approach and higher completeness scores in this study (the Hawthorne effect: research participants alter their behaviour when observed).[10] It is possible that these scores are lower when they are not under observation and this Hawthorne effect may also partially explain the high percentage of ABCDE use in patients with the highest triage codes. Video recording is not allowed in our ED so we were not able to correct for this bias. We asked the physicians if they planned to use the ABCDE approach which may have positively influenced this number.

We only scored whether an item was performed but we did not register the quality of the ABCDE parameters or the following interventions and treatments. Although we conclude that junior doctors and staff have similar completeness scores it is possible that the actions and diagnosis after the ABCDE approach are different. In this study, it is possible that associations are not significant because of the small sample size. The checklist was developed and used by a single researcher. The Emergency Severity Index score is the triage system used in our hospital. We have chosen to group triage codes of red, orange and yellow together as potentially unstable. This might overestimate the number of patients who are labelled as potentially unstable but we believe this is the most practical cut-off value to screen for those in whom an ABCDE approach might be beneficial (high sensitivity). This study was not designed to register the clinical course of the patients in whom an ABCDE approach was omitted, so no conclusion can be made if the lack of an ABCDE approach negatively influenced patient outcome. It is currently not known if using the ABCDE approach improves patient care compared with only clinical judgment and experience. In many EDs in the Netherlands though, the treating physicians are young and

inexperienced, especially during evenings and weekends. We hypothesise that the ABCDE approach might help them to improve recognition of life-threatening disease and early resuscitation. It is also not known if the potential benefits of the ABCDE approach are explained by more coordinated and intensified care or by the specific interventions itself. These are important issues to address in subsequent studies.

CONCLUSION

Our study shows that although the ABCDE primary assessment is performed more often and sooner in (potentially) unstable patients with more urgent triage codes, it was still not used in the majority (67%) of potentially unstable patients. When the ABCDE approach was used, it was performed efficiently (e.g. high completeness scores). The ABCDE approach is the preferred method, as stated by the government and several professional specialty organisations, for assessing an acutely ill patient but it seems not to be clear when to use it. Important factors determining not to use the ABCDE approach were: 1) using a short clinical impression of the patient instead, 2) stable vital signs recorded by the nurse, 3) the reason for visiting the ED suggests a stable patient and 4) the patient was first seen by a medical student who was not trained in the ABCDE approach. Currently it is not known if replacing the ABCDE approach by a short clinical impression (including only looking at a few vital signs recorded by the nurse) is a safe strategy to select patients in need for early resuscitation. Hospitals (and ABCDE courses) therefore should not only focus on teaching the content of the ABCDE itself, but also on the implementation of its use in every potentially unstable patient. More research is needed to determine whether performing the ABCDE approach indeed improves patient outcomes, since early treatment in various conditions begins with early recognition.

DISCLOSURES

The authors declare that they have no competing interests and that they have full control of all primary data. The authors agree to allow the journal to review their data if requested.

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CASE REPORT

Expanding the clinical spectrum of self-limiting, rare Kikuchi disease

A case with overwhelming multi-organ involvement

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ABSTRACT

Kikuchi disease is a rare disorder with an unknown pathogenesis and a typically self-limiting natural course in predominantly previously healthy young women. Here we present a 54-year-old woman suffering from an overwhelming presentation of Kikuchi disease, associated with haemophagocytic syndrome, liver cell necrosis and nephrotic syndrome. She recovered fully without immunosuppressive treatment. This case report adds to the already broad clinical spectrum of Kikuchi disease described in literature. Awareness among physicians of the full clinical spectrum of Kikuchi disease and the self-limiting nature of this syndrome leads to a good diagnostic approach and may prevent initiation of longstanding immunosuppressive therapy.

KEYWORDS

Kikuchi disease, haemophagocytic syndrome, nephrotic syndrome, liver cell necrosis

What was known on this topic?
Kikuchi disease is a rare and self-limiting disorder with unknown pathogenesis, especially characterised by fever and lymphadenopathy.

What does this add?
This case report enlarges the clinical spectrum of Kikuchi disease, with an overwhelming multi-organ presentation associated with haemophagocytic syndrome, liver cell necrosis and nephrotic syndrome. Awareness of the self-limiting nature of Kikuchi disease may prevent longstanding immunosuppressive therapy or even aggressive therapy with cytotoxic agents.

INTRODUCTION

Kikuchi disease, also known as Kikuchi-Fujimoto disease or histiocytic necrotising lymphadenitis, was first described in Japan in 1972. The pathogenesis of the disease is unknown, but an immune-mediated response of T-lymphocytes and histiocytes to an as yet unspecified infectious agent is suggested. Kikuchi disease is a rare, benign, self-limiting condition characterised by fever and especially cervical lymphadenopathy. Additionally there is a wide variety of other symptoms and manifestations of the disease that usually recover within one to four months without treatment.[1-8]

We present a well-documented unique case of a patient suffering from Kikuchi disease with serious multi-organ failure, including nephrotic syndrome, liver cell necrosis and haemophagocytic syndrome. With this case report we aim to enlarge the clinical picture of this rare disease, since nephrotic syndrome in Kikuchi disease has never been reported. Despite the disseminated presentation of the disease, this patient recovered fully without any corticosteroid, immunoglobulin or etoposide treatment.

CASE REPORT

A 54-year-old Caribbean woman, with an unremarkable medical history, was admitted to our hospital because of a six-day history of fever (up to 40°C), cold chills and night sweats. She also complained of generalised joint stiffness, without any signs of arthritis. She received antibiotic treatment (amoxicillin and clavulanic acid),

which was not effective. She reported diarrhoea, without any blood or mucus or abdominal pain. She did not report any unprotected sexual contacts or contact with domestic animals.

On admission, physical examination was unremarkable, except for a temperature of 39.7°C and a tachycardia of 116 beats/min. There was no palpable lymphadenopathy and there were no clues for an infectious focus. Laboratory results on admission are shown in *figure 1*. Chest radiography and abdominal ultrasound were normal except for hepatic steatosis.

During admission all urine cultures, repeated blood cultures and faecal analysis for *Salmonella, Shigella, Campylobacter, Yersinia,* Shiga toxin-producing *Escherichia coli* and *Clostridium difficile* toxin were negative. Serology for syphilis, hepatitis B, C and E, human immunodeficiency virus, Parvovirus B19, toxoplasma, *Brucella* and *Leishmania* was negative and showed primary infections with Cytomegalovirus, Epstein-Barr virus and hepatitis A in the past. Testing for systemic autoimmune disease, including antinuclear antibody (weakly positive, with low anti-extractable nuclear antigens), rheumatoid factor 11 kU/l (normal < 20 kU/l) and anti-CCP < 7U/ml (normal < 10 U/ml), was unremarkable.

A PET-CT scan, performed eight days after admission because of persistent fever, showed pathological cervical, supraclavicular, axillar, mediastinal and inguinal lymph nodes with sizes that varied from 7 x 15 mm to 7 x 22 mm and a maximum standardised uptake value of 8.9. Histological examination of a cervical lymph node showed reactive lymphadenitis most probably of viral origin without signs of malignant lymphoma (*figure 2*).

On day 18 after admission, the patient developed nephrotic syndrome with peripheral oedema and rapidly rising liver enzymes (*figure 1*). There was no hypotension or oliguria and diuresis at that time varied from 1650 ml

Figure 1. *Laboratory values and course of temperature during admission*

	Normal value	Days after admission			
		Day 1	Day 18	Day 79	Day 198
Haemoglobin	7.5-10 mmol/l	6.9	5.7	6.9	7.8
Erythrocyte sedimentation rate	< 8 mm	120			
White blood cell count	4-10x10^9/l	6,7x10^9	10.8	3.9	3.7
C-reactive protein	< 5 mg/l	249	146	10	8
Potassium	3.5-5 mmol/l	2.9	4.6	3.4	3.7
Lactate dehydrogenase	< 250 U/l	527	2420	196	187
Aspartate aminotransferase	< 40 U/l	58	609	23	19
Alanine aminotranferase	< 45 U/l	19	269	16	12
Alkaline phosphatase	< 120 U/l	88	152	110	117
Gamma-glutamyl transpeptidase	< 40 U/l	36	306	70	27
eGFR	> 60 ml/min	77	47	61	66
Ferritin	14-150 ug/l		47147	91	37
Triglycerides	< 150 mg/dl		259		
Albumin	35-50 g/l		17	34	37
Protein/creatine ratio (spot urine)	< 0.15		8.6	0.5	0.26

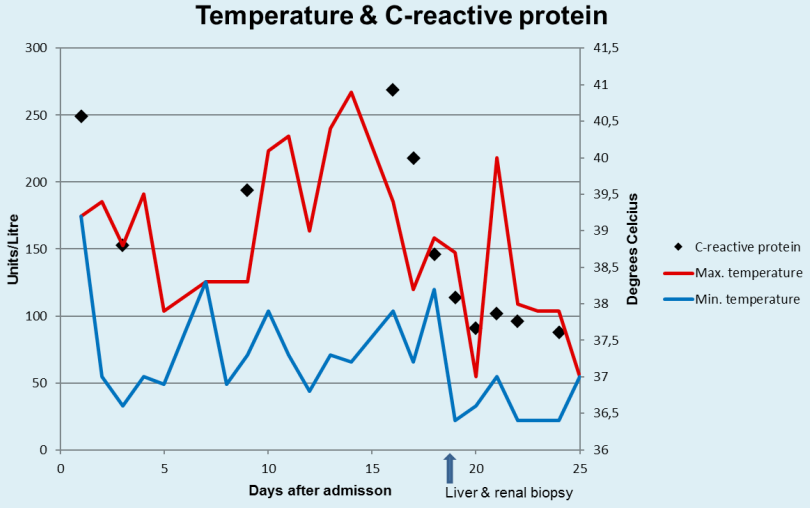
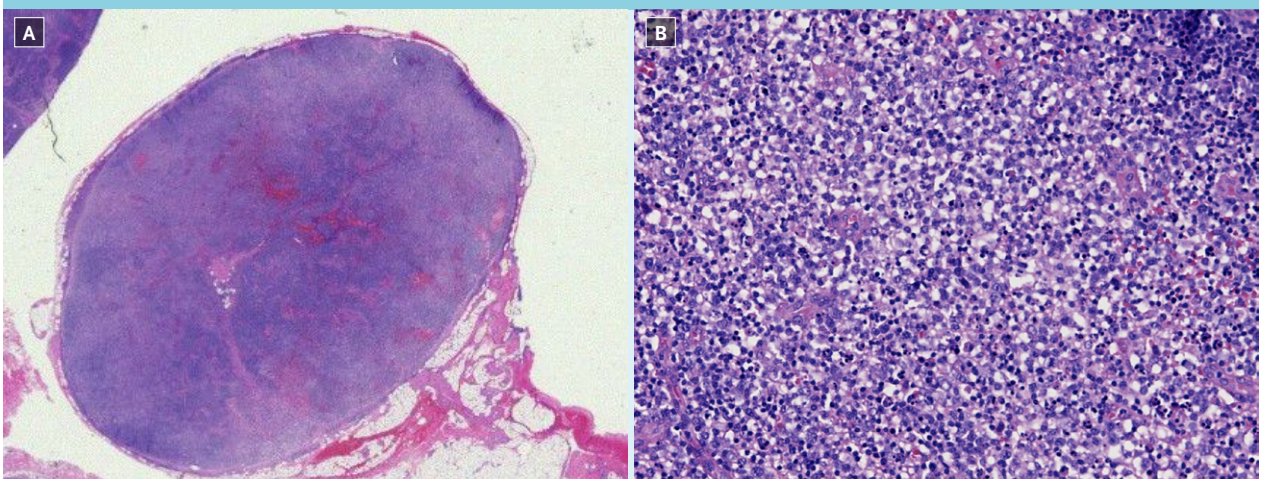


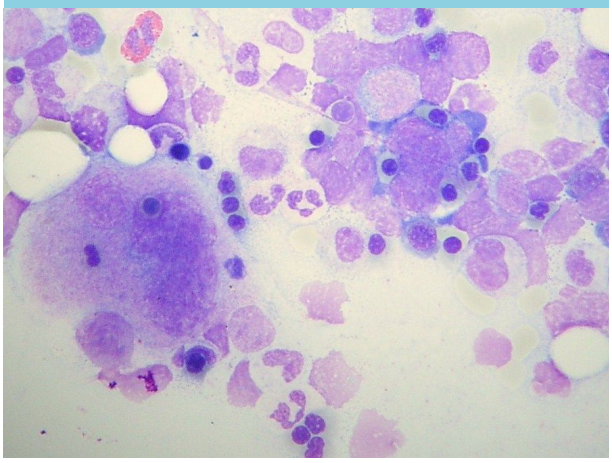
Figure 2. *A) Low-power overview of a lymph node with preserved architecture, the cortex shows a few follicular structures (subcapsular dark blue stained nodi) and the interfollicular regions are remarkably expanded with branching venules. Within these T-cell interfollicular regions pale staining zones can be observed. B) High-power view of a pale zone. This is composed of apoptotic cells intermingled with histiocytes, lymphocytes and blastoid cells. Characteristic massive necrosis with influx of neutrophils was not seen probably reflecting the histological spectrum of the Kikuchi reaction pattern. The differential diagnosis is a reactive lymphadenitis in the context of systemic lupus erythematosus*



to 2700 ml per day. Minimal change disease could not be confirmed because electron microscopy was not performed. Renal biopsy showed acute tubular necrosis and podocyte damage. Liver biopsy showed cellular necrosis. Additionally, haemophagocytic syndrome with hyperferritinaemia, hypertriglyceridaemia and extensive haemophagocytosis in the bone marrow was diagnosed (*figure 3*). At this point, treatment with steroids was postponed because of spontaneous improvement of the clinical and laboratory parameters.

Expert haematopathology panel consultation with additional staining of a cervical lymph node resulted in the diagnosis of Kikuchi disease four weeks after admission. Before immunosuppressive therapy such as corticosteroids, immunoglobulins or etoposide was initiated, the patient improved and recovered fully. During follow-up no residual organ damage was observed.

Figure 3. *Bone marrow showing histiocytes with haemophagocytosis*



DISCUSSION

In this case report we present a woman with an impressive presentation of Kikuchi disease with multi-organ failure, including renal insufficiency and nephrotic syndrome due to podocyte damage, liver cell necrosis and haemophagocytic syndrome. She recovered completely without any treatment. So far, the combination of renal failure with nephrotic syndrome in the context of Kikuchi disease and the combination of three serious organ manifestations in one patient has not been reported in the literature.

Kikuchi disease is predominantly observed in young females and is primarily characterised by fever and cervical lymphadenopathy. Other frequently observed clinical features are erythematous rashes, arthritis, fatigue, night sweats, diarrhoea, weight loss, anaemia, leukopenia, hepatosplenomegaly and a high erythrocyte sedimentation. Liver failure has been reported in the literature. In accordance with our case, liver biopsies in cases of Kikuchi disease associated with liver failure showed liver cell necrosis.[1,3,6,9]

As illustrated in our case, enhanced activation of histiocytes can even result in acute renal failure caused

by acute tubular necrosis with nephrotic syndrome due to podocyte damage. This renal complication in the course of Kikuchi disease, maybe due to the concomitant haemophagocytic syndrome, is extremely rare. Indeed the combination of nephrotic syndrome in the context of haemophagocytic syndrome has been reported in the past.[10] We only found one case of Kikuchi disease with renal failure, but in this case no classifying renal diagnosis was reported.[11] Several other rare manifestations of Kikuchi disease have been described, such as aseptic meningitis, cerebellar symptoms and haemophagocytic syndrome. Haemophagocytic syndrome in the context of Kikuchi disease has been documented in 20 case reports until now.[12-31]

Haemophagocytic syndrome is a rare syndrome of pathological immune activation characterised by clinical signs and symptoms of extreme inflammation. Proliferation of the haemophagocytic cells of the monocyte-macrophage-histiocyte lineage results in uncontrolled phagocytosis of normal haematopoetic cells. It is proposed that Kikuchi disease and haemophagocytic syndrome are part of a disease continuum rather than representing separate entities.[16,22] This hypothesis originates from the fact that both diseases are associated with marked activation of lymphocytes and histiocytes.[28] Most of the patients described with the combination of Kikuchi disease and haemophagocytic syndrome are diagnosed in Asian countries and were children or young adults, with a mean age of 16 years.[12,15-23,25,26,29-31]

The pathogenesis of Kikuchi disease is still unknown. An immune-mediated response of T-lymphocytes and histiocytes to an as yet unspecified infectious agent is suggested. Examples include Epstein-Barr virus, HIV, parvovirus B19 and human herpes virus 6 and 8.[1,3,4,6] There is also an association with systemic lupus erythematosus, since both diseases share histological features. In our case, no underlying provoking infectious agent or disease could be detected and during one year of follow-up, no systemic or rheumatic disease was observed. We can only speculate why our patient developed this serious multi-organ presentation of Kikuchi disease. Compared with other Kikuchi patients with haemophagocytic syndrome, our patient was relatively old. One might hypothesise that in our patient a more profound pro-inflammatory response occurred, mediated by cytotoxic T-lymphocytes and histiocytes resulting in apoptotic cell death in several organ systems due to decreased numbers of regulatory T-lymphocytes, which are essential for immune homeostasis.

The treatment of Kikuchi disease with a variety of clinical characteristics is challenging, especially if complicated by serious multi-organ problems as described in this case report. Because Kikuchi disease is self-limiting in the majority of patients, only supportive care seems to be required. Patients with severe or persisting symptoms can be treated with glucocorticoids or immunoglobulins.[32,33] In patients with haemophagocytic syndrome, etoposide-containing regimens can be considered.[34] In our case, we have elegantly shown that an accurate diagnostic approach, including collecting biopsies from the organs involved, can allow potentially toxic therapy to be withheld from the patient. In the literature only a few patients with haemophagocytic syndrome were not treated with corticosteroids, immunoglobulins or etoposide.[17,18,21,28]

In summary, we present a 54-year-old woman with a disseminated presentation of Kikuchi disease, complicated by nephrotic syndrome, liver cell necrosis and haemophagocytic syndrome, who fully recovered without any immunosuppressive treatment. Although this combination is extremely rare, awareness for early recognition is mandatory and with this case report we enlarge the clinical picture of Kikuchi disease. A thoroughly diagnostic approach can lead to the diagnosis of Kikuchi disease and thus may prevent longstanding immunosuppressive therapy or unnecessary aggressive therapy with cytotoxic agents.

DISCLOSURES

The authors declare no conflict of interest. No funding or financial support was received.

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CASE REPORT

Hepatitis E during lenalidomide treatment for multiple myeloma in complete remission

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ABSTRACT

Lenalidomide has a central role in the treatment of multiple myeloma and results in improved survival. As with other chemotherapeutics, it can cause several serious side effects. This is the first reported case of hepatitis E during lenalidomide treatment for multiple myeloma in complete remission. In case of liver chemistry abnormalities during lenalidomide treatment, the differential diagnosis should include hepatitis E infection.

KEYWORDS

Hepatitis E, lenalidomide, multiple myeloma

What was known on this topic?
During the last decade lenalidomide has taken a central role in the chemotherapeutic treatment of multiple myeloma. Its use has resulted in increased progression-free and overall survival. Adverse effects due to lenalidomide therapy primarily include cytopenia and in some cases hepatotoxicity. Thus far lenalidomide is not linked to an increased risk of viral hepatitis.

What does this add?
This is the first report of hepatitis E during lenalidomide treatment in a patient with multiple myeloma in complete remission. Temporary cessation of lenalidomide treatment resulted in spontaneous clearance of the virus, although ribavirin treatment to prevent chronic infection should be considered. We conclude that during lenalidomide treatment patients are at risk of acute hepatitis E.

INTRODUCTION

Multiple myeloma is a relatively frequent lymphoproliferative malignancy, representing 10% of diagnosed haematological malignancies.[1] It is recommended to treat multiple myeloma depending on risk stratification as well as eligibility for autologous stem cell transplantation, although age can also influence the treatment strategy. During the past decade, lenalidomide is taking a central role in this treatment, for both standard, intermediate and high-risk patients. Lenalidomide can result in serious complications, the most frequent of which is cytopenia,[2] but is also related to hepatic complications.[3] We present the case of a 69-year-old female who had liver chemistry abnormalities due to acute hepatitis E during lenalidomide therapy for multiple myeloma in complete remission.

CASE REPORT

A woman was diagnosed with a symptomatic multiple myeloma IgA lambda (International Staging System stage 2) at the age of 66 years. She suffered from mild hypercalcaemia and X-rays showed osteolytic lesions in the cranium, left humerus and right femur. Bone marrow biopsy displayed 80% plasma cells and FISH analysis showed 1q amplification, +5, +9, +11, +15, +15. The patient was included in the HOVON 95 study. After completion of a chemotherapeutic regimen consisting of four courses of bortezomib/cyclophosphamide/dexamethasone, there was a very good partial response. The patient was randomised for high-dosage melphalan followed by autologous stem cell transplantation, resulting in complete remission. Based on the second randomisation, the patient started on maintenance therapy with lenalidomide 10 mg once daily in three out of four weeks. Due to neutropenic fever after six months of maintenance therapy, the dosage was adjusted to 5 mg once daily.

After 2.5 years of lenalidomide therapy, routine blood tests showed abnormal liver chemistry, consisting of a normal bilirubin level with γ-glutamyltransferase of 54 U/l (< 38), alkaline phosphatase of 117 U/l (< 120), ASAT of 102 U/l (< 31), ALAT of 100 U/l (< 34) and lactate dehydrogenase of 269 U/l (< 248) (*table 1*). The complete blood count showed mild leukopenia (3.7 x 10^9/l) with normal differentiation, intermittently present throughout treatment, together with normal IgG and IgA levels and a mild IgM depletion (0.30 g/l; range 0.40-2.3 g/l), which was chronic in nature. The IgA lambda count was stable at < 1 g/l and renal function was unaffected. Lenalidomide treatment was discontinued. The patient was, however, admitted eight days later as the derangement of the liver enzymes was progressive and abdominal ultrasound suggested an iso-echogenic lesion of 2.7 x 2.3 cm diameter in the right liver lobe. CT scan of the liver did not show any abnormalities. Serology for hepatitis A/B/C and for autoimmune diseases (ANA, anti-smooth muscle cell and anti-mitochondria antibodies) was negative, and showed prior infection with Cytomegalovirus, Epstein-Barr virus, and toxoplasmosis (e.g. IgG-positive, IgM-negative). However, IgG and IgM antibodies against hepatitis E virus were present, indicating a recent or current hepatitis E infection. The viral load was 245,000 IU/ml and genotyping showed hepatitis E virus genotype 3c. The infection was treated conservatively and 35 days after cessation of lenalidomide treatment, with a slightly elevated γ-glutamyltransferase (45 U/l), lenalidomide was restarted at 5 mg once daily. One month after restarting lenalidomide treatment, the liver chemistry remained normal and the patient was free of symptoms. Repeated PCR analysis for hepatitis E virus was negative.

Table 1. *Liver chemistry*

	Day -29	Day -1	Day 7	Day 10	Day 35	Day 62
Bilirubin (2-20 µmol/l)	7	6	8	-	8	7
γGT (< 38 U/l)	10	54	170	133	45	21
AP (< 120 E/l)	66	117	241	202	90	64
ASAT (< 31 U/l)	12	102	284	190	13	11
ALAT (< 34 U/l)	9	100	338	282	16	11
LD (< 248 U/l)	198	269	407	276	231	91

Days are compared with the date of stopping lenalidomide (cessation date is considered day 0). Day -29 represents the last liver chemistry prior to derangement. Day 7 shows peak values. Day 35 is date of re-initiating lenalidomide therapy (5 mg once daily).
γGT = gamma-glutamyl transferase, AP = alkaline phosphatase, ASAT = aspartate aminotransferase, ALAT = alanine aminotransferase, LD = lactate dehydrogenase.

DISCUSSION

The addition of lenalidomide to multiple myeloma treatment has improved progression-free survival and overall survival, in subjects with[5] and without autologous stem cell transplantation,[6] as well as in subjects with newly diagnosed multiple myeloma[7] and multiple myeloma relapses.[8] The main adverse effect of lenalidomide is cytopenia, presenting in approximately 50% of patients on lenalidomide therapy.[2] Neutropenia is most common, occurring in 27%[2] to 33%[9] of patients and resulting in increased risk of infections, which can be lethal.[2] Thromboembolic complications are also observed relatively frequently.[2,9] Direct hepatotoxicity from lenalidomide has only been described in four patients with multiple myeloma.[3] This adverse effect presented within two weeks after starting treatment and cessation of lenalidomide resulted in normalisation of the liver chemistry within 30 days. Although the exact mechanism for the hepatotoxicity was unknown, renal insufficiency might have contributed to it. Two of these four patients had renal insufficiency prior to treatment and as lenalidomide is primarily excreted via the kidneys, dose adjustment in such patients is advised.[10] These patients, however, received a high dosage of lenalidomide, e.g. 25 mg/day, not adjusted to renal function. One additional case report described a clear cause of the liver chemistry abnormalities during lenalidomide treatment, namely an acute hepatitis B virus infection, although this patient was suffering from a myelodysplastic syndrome.[11]

We present a case of acute asymptomatic hepatitis E during lenalidomide treatment for multiple myeloma in complete remission. Hepatitis E is primarily diagnosed in developing countries, but its incidence in the Western world is rising.[12] Transmission of the hepatitis E virus varies between the different genotypes. Genotype 1 and 2 are transmitted via human contact, mainly via ingestion of faecally contaminated water, whereas genotypes 3 and 4 are zoonotic viruses, often transmitted via undercooked pork, deer, bore or swine. Genotype 3 is the most prevalent in the developed world and can also be transmitted via blood transfusions and solid organ transplantations. Our patient was not exposed to these risk factors and blood analyses did not show quantitative changes in leukocytes or immunoglobulins. Other than ingestion of contaminated food, we do not have a clear cause of hepatitis E infection. The influence of lenalidomide on the immune system, as has been shown for T-cells, natural killer cells and cytokine production, might have made our subject prone to hepatitis E infection,[13] but being the first case of hepatitis E during lenalidomide treatment, this is not supported by scientific evidence.

Hepatitis E infection is often asymptomatic and self-limiting but in immunocompromised patients can result in a chronic disease (e.g. HEV RNA present in serum/stool > 3 months). A chronic infection can ultimately cause liver failure or liver graft rejection and these complications are primarily related to hepatitis E virus infection with genotype 3. Risk groups include patients with haematological malignancies, HIV infection or after organ transplantation.[12,14] Incidence rates in solid organ transplant patients vary between 4 and 8%, with 60% conversion to chronic infection.[14] Treatment options for acute hepatitis E in patients with haematological malignancies, with the aim of preventing chronic infection, are either conservative or ribavirin treatment.[15] Conservative treatment results in clearance of the virus in 64% of cases, although it is uncertain whether maintenance treatment for the haematological malignancy should be temporarily discontinued. Ribavirin treatment for at least three months can result in a 100% clearance of the virus, during which 75% of patients can continue maintenance treatment as planned. Based on the current data, all retrospective in nature, we would therefore consider a three-month ribavirin treatment regimen while continuing cytotoxic therapy, but prospective studies are warranted. The risk of haemolytic anaemia due to ribavirin, especially in combination with cytotoxic maintenance therapy, is a matter of concern.

Thus far, in immunocompromised patients the focus was mainly pointed towards the risk of hepatitis B reactivation, especially during rituximab treatment.[16] Based on the case presented here, the differential diagnosis for liver chemistry abnormalities during lenalidomide treatment should include acute hepatitis E (*table 2*). When hepatitis E is suspected, PCR analysis is warranted, as the immunocompromised state due to lenalidomide can result in negative serological testing.[12,15] This can aid in timely diagnosis and treatment of hepatitis E and as such prevention of chronic hepatitis E and possible liver failure.

CONCLUSION

This is the first reported case of hepatitis E infection in a patient with complete remission of multiple myeloma, while being treated with lenalidomide. Cessation of lenalidomide resulted in normalisation of liver chemistry and clearance of the virus within one month. Physicians should be aware of the risk of hepatitis E during lenalidomide treatment. In case of acute hepatitis E, treatment with ribavirin has to be considered to prevent chronic infection and hepatic complications.

Table 2. *Causes of liver chemistry abnormalities in multiple myeloma patients*

Cause: groups	Examples
MM-related	Amyloid infiltration Extramedullary haematopoiesis Extramedullary plasmocytoma Vascular free chain depositions Vascular tumour growth
Treatment-related	Direct hepatotoxicity (drug-induced hepatitis, cholestasis) Infectious (liver abscess, viral hepatitis (B, C and E))

Table 2 shows causes of liver chemistry abnormalities that have been reported in subjects with multiple myeloma. In addition, general causes should always be taken into account.

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DISCLOSURES

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CASE REPORT

Spontaneous fracture of the femur due to osteomyelitis caused by the *Streptococcus anginosus* group

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ABSTRACT

A 57-year-old man was admitted because of pain in the right upper leg due to an osteolytic lesion of the femoral bone which was complicated by a spontaneous fracture. At first a malignancy was suspected. However, blood and bone cultures revealed the *Streptococcus anginosus* group. A diagnosis of acute osteomyelitis was made. In spite of extensive antibiotic and surgical treatment the patient developed severe septic shock with multiple organ failure and died. In the case of a pathological fracture, one should consider the broad differential diagnosis, including osteomyelitis, which should lead to a laboratory work-up and imaging studies. When bone biopsy for histological analysis is necessary, a microbiological culture to look for osteomyelitis should always be performed.

KEYWORDS

Osteomyelitis, streptococcus anginosus group, spontaneous fracture

CASE REPORT

A 57-year-old man was admitted because of progressive pain in his right upper leg. His medical history was unremarkable except for hypertension and excessive alcohol use of six units per day. He did not report any recent infection, fever, drug abuse, trauma, surgery or dental procedure. On physical examination he had normal vital signs and no endocarditis stigmata were found. His right upper leg showed a diffuse painful swelling on the medial side.

An X-ray of the femur showed a lytic lesion of the diaphyseal femoral cortical bone (*figure 1*). Magnetic resonance image (MRI) revealed fluid collection next to the osteolytic lesion in the adjacent soft tissue (*figure 2*). Bone scintigraphy showed an increased uptake in the femoral lesion. The differential diagnosis consisted of a metastatic lesion, plasmacytoma, intracortical abscess/osteomyelitis, malignant fibrous histiocytoma, lymphoma

Figure 1. *X-ray of the femur which shows a lytic lesion*

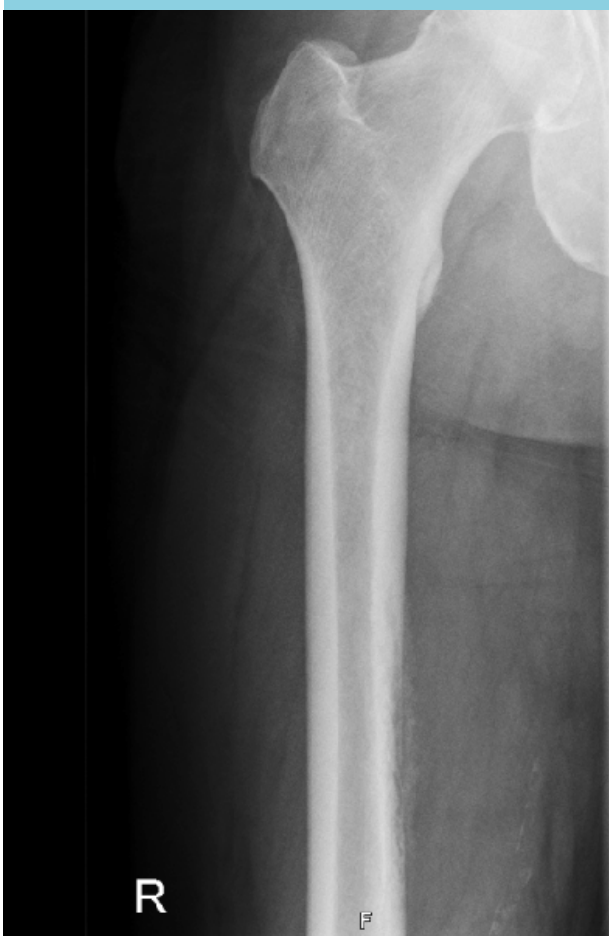
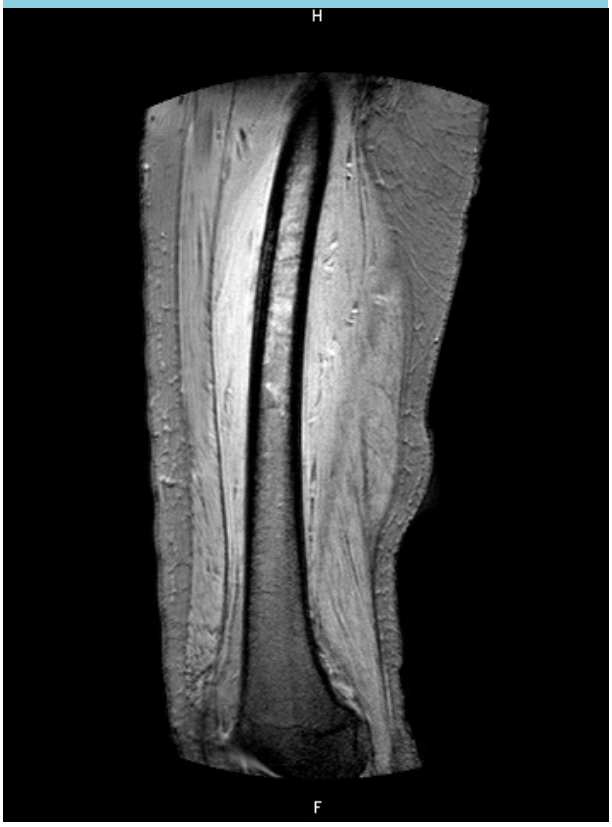


Figure 2. *MRI image of the femur showing a fluid collection next to the osteolytic lesion in the adjacent soft tissue*



or, although less likely, primary osteosarcoma or Ewing sarcoma. Computed tomography of the chest and abdomen was unremarkable. Laboratory results revealed a C-reactive protein (CRP) of 110 mg/l (normal value < 10) and leucocytes of 9.9 x 10^9/l (normal value: < 10). A monoclonal protein (M-protein) was not present. The liver synthesis function, measured by serum bilirubin, PT-INR, APTT and albumin, was normal, as were renal function and the electrolytes including calcium.

On the fifth day of admission the patient developed a spontaneous femur fracture. From that moment on he developed fever and deteriorated. Blood cultures were taken and antibiotic treatment, consisting of amoxicillin-clavulanate and tobramycin, was started. In consultation with the National Committee of Bone Tumours a surgical bone biopsy was performed. The original plan was to apply external fixation after the biopsy; however, it had to be postponed due to haemodynamic instability during surgery. Despite the clinical suspicion of a bone malignancy, the biopsy solely showed signs of inflammation. Cultures of the bone biopsy as well as blood cultures yielded the *Streptococcus anginosus* group (specified as *Streptococcus intermedius*). The antibiotic treatment was changed to penicillin G and clindamycin. Transthoracic as well as transoesophageal echocardiography did not show any signs of endocarditis. The dental surgeon did not find a focus of infection in the oral cavity. The patient developed severe septic shock with multiple organ failure consisting of acute respiratory distress syndrome, acute renal failure and disseminated intravascular coagulation. A second surgical bone biopsy was taken and the external fixator was now placed. Histological analysis was inconclusive, but showed necrosis, bone renewal and cells suspected for epithelial tumour cells with nuclear atypia, highly suspicious for carcinoma. Unfortunately, in spite of the treatment given, the patient died a few days later. Post-mortem examination of the patient confirmed the diagnosis of osteomyelitis in the right femur. Malignancy was not found in the femur or anywhere else. The liver showed signs of cirrhosis.

DISCUSSION

In this case, as in many other cases with osteolytic lesions or pathological fractures, the suspicion of a metastatic bone disease was initially high. Differential diagnosis at that point also consisted of osteomyelitis and, although less likely, a primary bone tumour. Even though computed tomography did not show a primary tumour, we still considered metastatic bone disease to be the most likely diagnosis, since it is not uncommon that computed tomography does not reveal the primary tumour. However, during the first operation, a smelly substance was found and these cultures yielded *S. intermedius*. Of course, our differential diagnosis changed considering osteomyelitis in the first place followed by a malignant lesion with a secondary infection.

The differential diagnosis concerning pathological fractures is actually very broad and includes osteoporosis, neoplastic metastatic disease, primary bone tumours, multiple myeloma, hyperparathyroidism, Paget's disease, renal osteodystrophy and osteomyelitis. The initial work-up should at least consist of radiological imaging and laboratory studies on complete blood count, CRP, creatinine, calcium, albumin, alkaline phosphatase and M-protein. MRI is considered the golden standard for diagnosis, which should be followed by bone biopsy for culture to guide optimal antibiotic treatment as well as for histological analysis to rule out other diseases.

Tubular pathological fractures due to acute osteomyelitis in adults are rare.[1-4] Osteomyelitis is an infection which leads to progressive bone destruction and can be due to contiguous spread from adjacent soft tissue or joints, haematogenous spread or direct inoculation of microorganisms after trauma or surgery. Osteomyelitis is often accompanied by local pain and swelling, but

general symptoms such as fever can be absent. Unlike acute osteomyelitis in children, were there is a predilection for tubular bones of the arms and legs, osteomyelitis in adults mainly occurs in the mandible or maxilla due to contiguous spread in the oral cavity and in the vertebrae, sternoclavicular joint, sacroiliac joint and symphysis pubis due to haematogenous spread. In case of haematogenous spread, the infection is usually monobacterial, whereas in contiguous spread or direct inoculation of microorganisms the infection is often polymicrobial. *Staphylococcus aureus*, coagulase negative staphylococci and Gram-negative bacilli are the most commonly encountered pathogens. In children most cases are due to *S. aureus*, group B beta-haemolytic *Streptococcus, Streptococcus pyogenes* and *Streptococcus pneumoniae*.[5,6]

The *S. anginosus* group is a group of organisms which includes *S. intermedius, S. anginosus* and *S. constellatus*.[7] *S. anginosus* group was formerly known as *Streptococcus milleri*, a name still widely used. These organisms are part of the normal flora of the human oral cavity and upper part of the respiratory tract, the gastrointestinal tract and the vagina. They have the ability to cause systemic infections such as endocarditis, gastrointestinal and genitourinary tract infections, and have the propensity to form abscesses in different organs, for example cerebral and intra-abdominal abscesses.[8-10] The *S. anginosus* group rarely causes infections in otherwise healthy individuals in the absence of trauma.[11] Bacteraemia is often associated with an identifiable source of infection, profound neutropenia, abdominal or dental surgery.[8,11]

The *S. anginosus* group is an uncommon causal agent of osteomyelitis.[9] It has only been reported in a few case reports.[8-10] Spontaneous fracture due to osteomyelitis caused by the *S. anginosus* group has been reported once, also concerning the femur.[12]

The initial treatment for osteomyelitis with unknown causative pathogen should consist of broad-spectrum antibiotics with good tissue penetration combined, especially in chronic osteomyelitis, with surgical interventions such as adequate drainage and debridement of all infected tissue, and bone stabilisation. Osteomyelitis can be complicated by sequestration, sinus formation or sepsis.

Specific treatment for the *S. anginosus* group should consist of antibiotics such as penicillin or third-generation cephalosporins occasionally followed by surgical debridement. The use of fluoroquinolones and macrolides should be avoided as empirical therapy because of increasing resistance for these antibiotics.[13-15] As with many other infectious diseases, due to a lack of prospective randomised controlled studies and the heterogeneity of the disease, the optimal duration of antibiotic treatment is unknown. Although guidelines concerning osteomyelitis in adults are currently not available, antibiotic treatment for at least 4-6 weeks is generally recommended.

CONCLUSION

The above-described case is extraordinary, as the patient did not have any known risk factors for osteomyelitis, such as recent trauma, medical interventions, diabetes mellitus, intravenous drug abuse or endocarditis. Although the post-mortem examination revealed cirrhosis of the liver, the synthesis function of the liver was still intact on admission. Moreover, liver cirrhosis is not recognised as a risk factor for the development of *S. anginosus* group infections. Osteomyelitis caused by the *S. anginosus* group is rare and occurs particularly in the mandible, maxilla or the vertebrae.[8] A spontaneous fracture of the femur due to acute osteomyelitis caused by the *S. anginosus* group has only been reported once. In the case of a pathological fracture, one should consider the broad differential diagnosis, including osteomyelitis which should lead to a laboratory work-up and imaging studies. When considering biopsy for histological analysis, do not forget to perform a microbiological culture to look for osteomyelitis.

DISCLOSURES

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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PHOTO QUIZ

Facial rash and alopecia in a patient with systemic lupus erythematosus

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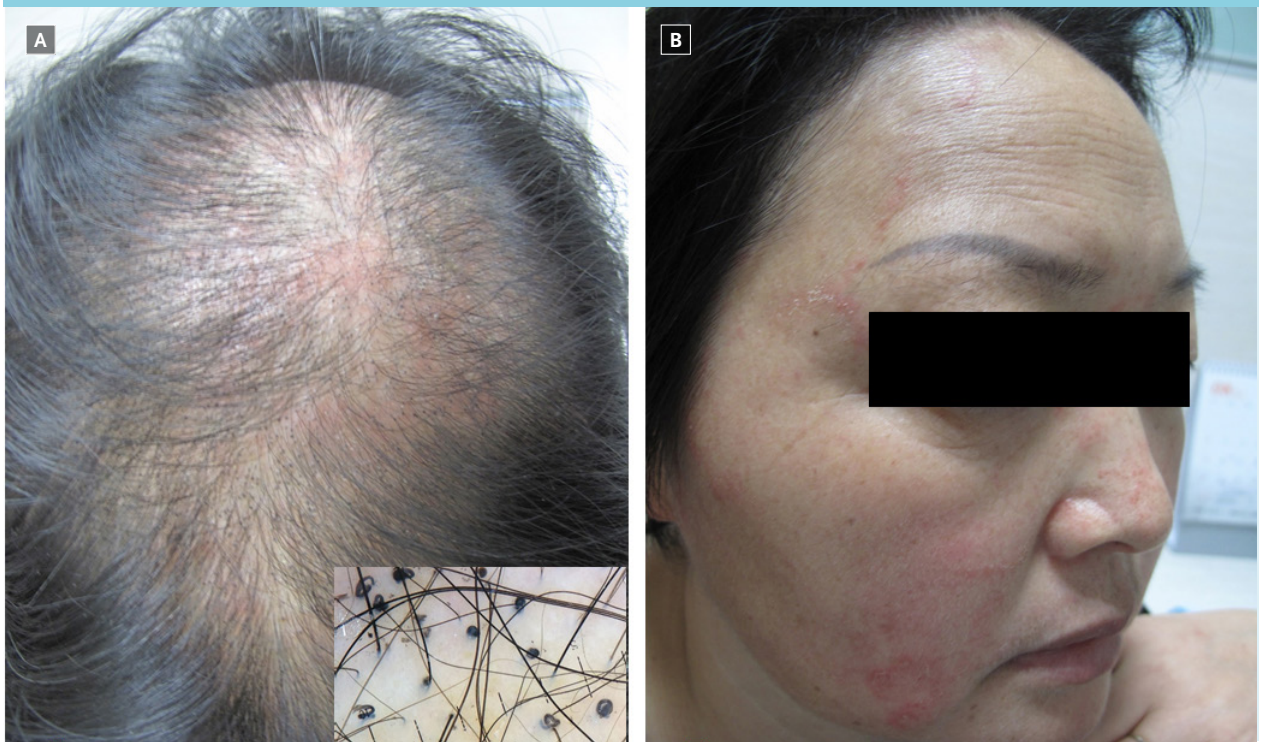
CASE REPORT

A 58-year-old woman presented with a one-month history of hair loss and lesions on her scalp and face. Two years ago, she was diagnosed as systemic lupus erythematosus because of a facial butterfly rash, recurrent oral ulceration, and positive serum tests of ANA and dsDNA. The systemic lupus erythematosus was well controlled by oral prednisone 15 mg/day and hydroxychloroquine 400 mg/day. Hair loss of the scalp with black dots and scaly erythematous plaques and papules were found on the scalp and face (*figure 1A and B*). Dermoscopy examination of the scalp revealed corkscrew hairs and comma hairs (*figure 1A inset*).

WHAT IS YOUR DIAGNOSIS?

See page 126 for the answer to this photo quiz.

Figure 1. *A) Hair loss of the scalp with black dots on the scalp. Dermoscopy examination of the scalp revealed corkscrew hairs and comma hairs (inset). B) Scaly erythematous plaques and papules on the face.*
The photos were placed with the permission of the patient involved.



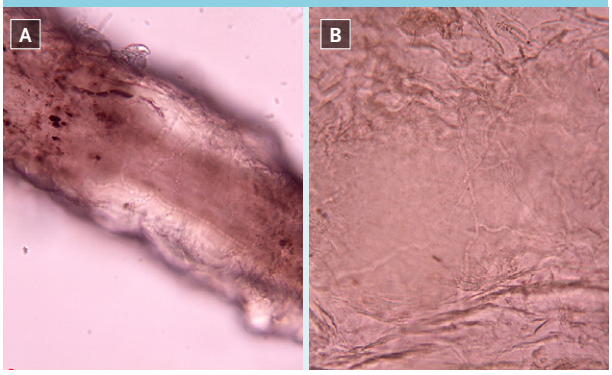
ANSWER TO PHOTO QUIZ (PAGE 125)

FACIAL RASH AND ALOPECIA IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS

DIAGNOSIS

Endothrix and hyphae were found on microscopic examination of the hair (*figure 2A*) and skin scrapings (*figure 2B*). Cultures of the hair and the scrapings of skin grew *Trichophyton tonsurans*. A diagnosis of tinea capitis and tinea faciei was made. She achieved clinical and mycological clearance after being treated with oral terbinafine 250 mg/day for six weeks.

Figure 2. *Microscopic examination of the hair (A) and facial rash (B) showed endothrix and hyphae*



Tinea capitis is one of the common causes of hair loss in children; it is rare in adults.[1] However, tinea capitis is far from unusual in immunocompromised adults.[2,3] Hair loss is a common cutaneous adnexal manifestation in systemic lupus erythematosus patients (20-60%).[4] It may be correlated with the disease activity index in systemic lupus erythematosus,[5] therefore tinea capitis should be carefully differentiated from primary hair loss in patients with systemic lupus erythematosus using immunosuppressive drugs. Tinea faciei may be atypical in immunocompromised individuals.[4] The lesions of tinea faciei should be differentiated from the cutaneous lesions of lupus.

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PHOTO QUIZ

Red eyes and mucous ulcers

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CASE REPORT

A 58-year-old male presented with malaise, ocular discharge and ulceration of his oral mucosa and glans penis. His medical history lists atrial fibrillation and idiopathic pancreatitis. Approximately one week prior to presentation he experienced fatigue, diffuse myalgia and fever. Four days later, he developed redness of his sclerae, a sticky discharge in his eyes and a sore throat. His general practitioner started chloramphenicol eye drops. Since then, he developed swelling, ulceration and painful aphthous lesions of his oral mucosa and his glans penis. Two days later, an allergic reaction to chloramphenicol was suspected and his general practitioner discontinued the eye drops. Our patient was started on oral prednisolone and clemastine tablets, one day thereafter he was admitted to our hospital. There was no fever upon presentation. The patient stated that he did not have sexual relations outside his marriage. Laboratory analysis showed a mild leukocytosis of 11.6 x 10^9/l (reference range 4-10 x 10^9/l), and an elevated C-reactive protein of 65 mg/l (reference range < 5 mg/l). The chest X-ray showed no signs of infiltration. Urinalysis showed leukocyturia, mild erythrocyturia and absence of nitrite.

WHAT IS YOUR DIAGNOSIS?

See page 128 for the answer to this photo quiz.

Figure 1. *Conjunctivitis*

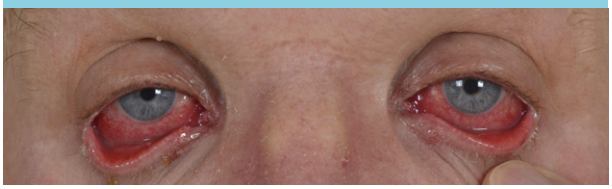

Figure 2. *Ulcerations and aphthous lesions of the oral mucosa*

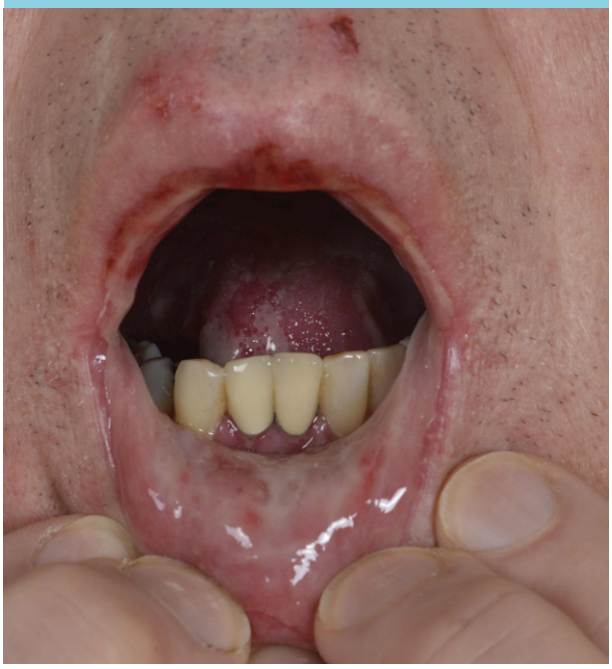

Figure 3. *Ulcerations and aphthous lesions of the glans penis*

ANSWER TO PHOTO QUIZ (PAGE 127)

RED EYES AND MUCOUS ULCERS

DIAGNOSIS

The complex of symptoms of conjunctivitis, stomatitis and urethritis, as can be seen in the clinical images, was mistakenly thought to be an allergic reaction. Taking into consideration the general malaise and the sore throat the patient had had previously, our preliminary diagnosis was *Mycoplasma pneumoniae* infection. The differential diagnosis included viral infection, systemic disease (Behçet's syndrome, Crohn disease or IgG4-related disease) and Stevens-Johnson syndrome.

The patient's serology was positive for *M. pneumoniae* IgG and IgM. Furthermore, laboratory analysis showed no eosinophilia (which could indicate an allergic reaction), autoimmune screening with ANA/ANCA was negative and there were no signs of arthritis. Absence of arthritis and aphthae makes Reiter syndrome and Behçet's syndrome less likely. In the blood cultures, no growth was seen. PCR assay on sputum was positive for both *M. pneumoniae* and herpes simplex virus (HSV) type 1. Primary infection or recurrence of HSV type 1 was less likely the cause of conjunctivitis or stomatitis because the lesions were neither vesicular nor painful and the conjunctivitis was bilateral. It is possible that there was a mild recurrence of HSV type 1 upon presentation.

Our diagnosis was *M. pneumoniae* associated mucositis (MPAM), also called *M. pneumoniae*-induced rash and mucositis (MIRM; and in this case MIRM sine rash). The patient was treated with azithromycin for three days. After one month his symptoms resolved completely. There was a decrease in *M. pneumoniae* serology titres (56.5 and 33.0 at diagnosis and 52.2 and 26.6 after one month for IgG and IgM, respectively).

M. pneumoniae is known for its extrapulmonary manifestations, which can include cardiovascular symptoms, symptoms of the digestive tract, neurological symptoms, symptoms of the haematopoietic system, urogenital symptoms and dermatological manifestations.[1] In fact, approximately 25% of the patients experience extrapulmonary symptoms.[2] *M. pneumoniae* can cause clinical images similar to toxic epidermal necrolysis, Stevens-Johnson syndrome (SJS) and bullous erythema multiforme. In the past years, however, MPAM or MIRM is more and more recognised as a separate entity instead of 'atypical SJS'.[1-3] Respiratory symptoms usually precede mucositis by a week; however, in patients with extrapulmonary manifestations of *M. pneumoniae* infection, overt pneumonia and even respiratory symptoms may be absent.[1,3]

In patients with MPAM/MIRM painful oral lesions are present in 94% of the cases,[3] ocular involvement is seen in 82% of the cases and urogenital lesions are present in at least 63% of the cases. Urogenital lesions are probably underreported. Anal lesions are rarely seen.[4,5] The exact aetiology of these extrapulmonary manifestations is unknown. The involvement of autoimmunity and formation of immune complexes is suspected, which explains the delay between respiratory symptoms and the onset of mucositis.[1] The optimal treatment strategy remains unclear, but supportive care is usually sufficient. There is evidence that suggests that antibiotic treatment and/or steroids reduce antigenic stimuli and bacterial load, which could lead to a decrease in immune responses. Treatment is seldom necessary, but should be considered in severe cases. The majority of patients recover completely.

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PHOTO QUIZ

Multiple PET-avid osteolytic lesions and hyperparathyroidism: tissue is the issue

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CASE REPORT

A 66-year-old woman was admitted to our hospital with a long-term history of bone pain, fatigue and myalgia. Some years earlier, she received radioactive iodine for toxic nodular struma followed by L-thyroxin substitution. At physical examination her thyroid gland was still enlarged. Laboratory data showed an elevated serum calcium level (4.16 mmol/l), alkaline phosphatase (767 U/l), parathyroid hormone (148 pmol/l) and low serum phosphate (0.83 mmol/l). CT scan showed left-sided multinodular enlargement of the thyroid gland and a bone lesion at the third rib but no enlargement of one or more parathyroid glands (*figure 1A* and *B*). Whilst the parathyroid hormone value was still unknown, the bone lesion seen on CT in combination with hypercalcaemia gave rise to the suspicion of malignancy. These findings prompted whole body positron emission tomography/ computed tomography (PET/ CT) to be able to image the whole skeleton and to differentiate avid from non-avid lesions. This study showed multiple FDG-avid osteolytic lesions in multiple ribs, the pelvis, scapulae, claviculae and femur, and humerus on both sides (*figure 2A* and *B*). In addition, to study the activity of the parathyroid glands a Tc-99m-sestamibi scan was performed. Intense uptake was found in the caudal region of the left thyroid lobe, with no retention in the skeletal lesions.

Figure 1. *A) CT scan (transversal slice) disclosing an abnormal contour of the third left rib with complete destruction of bone tissue. B) CT scan (transversal slice) showing the above-mentioned lesion in more detail*

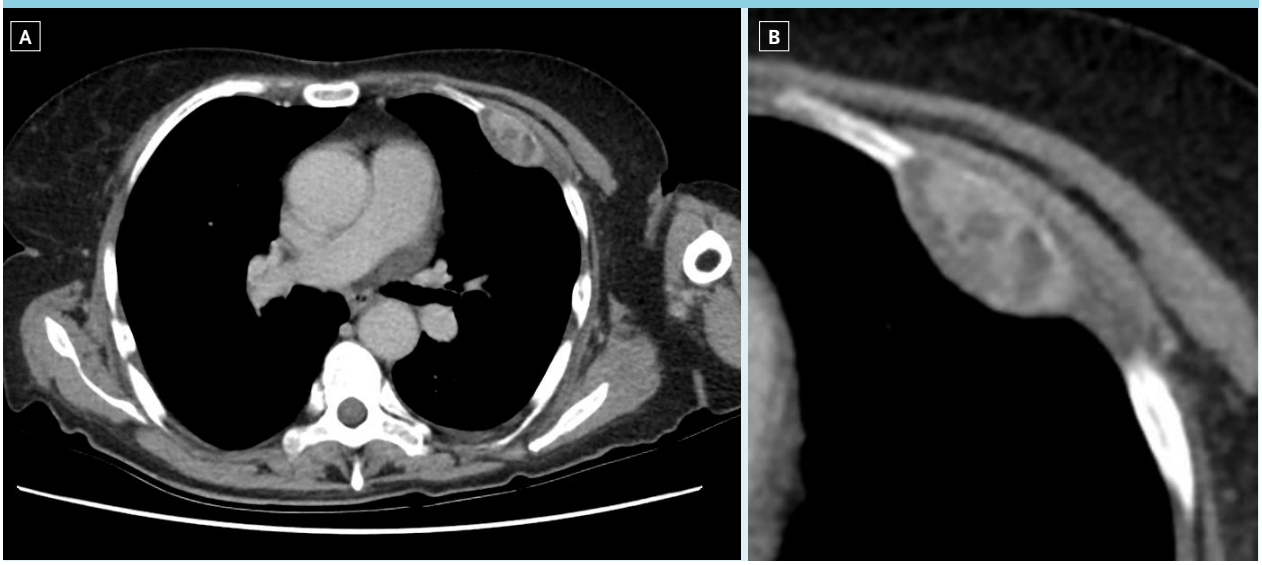
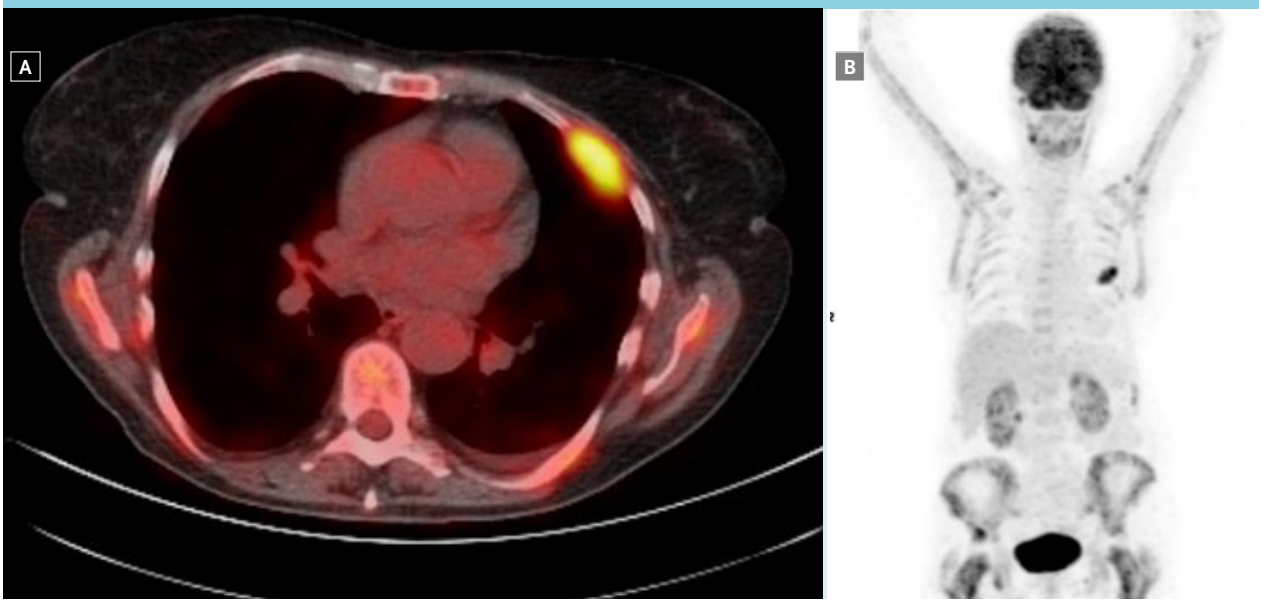


Figure 2. *A) PET/CT scan (transversal slice) disclosing a FDG-avid lesion of the third left rib agreeing with CT scan images. B) PET/CT showing patchy uptake of FDG in the mandible, shoulders, femoral heads and long bones*



WHAT IS YOUR DIAGNOSIS?

See page 131 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGES 129-130)

MULTIPLE PET-AVID OSTEOLYTIC LESIONS AND HYPERPARATHYROIDISM: TISSUE IS THE ISSUE

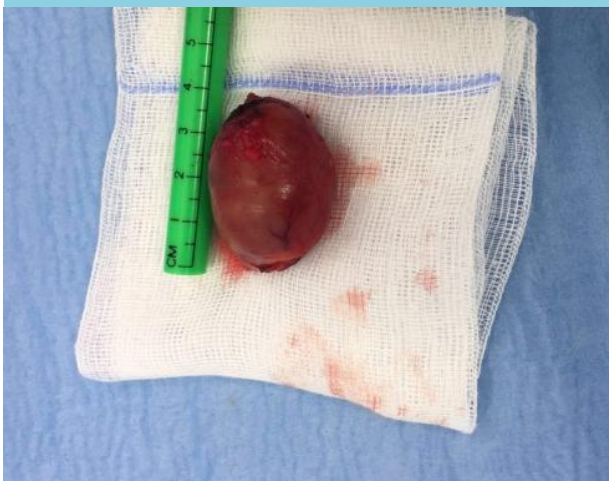
DIAGNOSIS

The multifocality of the bone lesions raised the suspicion of malignancy. Therefore, the patient was referred for biopsy of the lesion of the left third rib. Microscopy revealed numerous multinucleated giant cells compatible with a brown tumour of the bone. No signs of malignancy were revealed. Minimal invasive parathyroidectomy was performed disclosing a large parathyroid gland of 14 g (4.0 x 2.5 x 2.0 cm) (*figure 3*). The gland was perfectly encapsulated. Histology revealed a follicular and trabecular architecture of chief cells. Between these cells, multiple vascular structures and fibroblasts were present. Postoperatively, the calcium and parathyroid hormone (PTH) levels rapidly normalised.

This is one of the first demonstrations of multiple FDG-avid lesions of brown tumours due to hyperparathyroidism.[1] The histological features of brown tumours consist of mononuclear stromal cells as well as multinucleated giant cells. The brown colour originates from haemorrhagic infiltrates and haemosiderin deposits by macrophages in response to bone destruction. The bone defect fills with fibroblastic tissue that can deform the bone structure and may resemble a neoplastic process.[2] The elevated FDG uptake in this process can be explained by the high bone turnover, immunogenic activity and inflammatory response by haematopoietic cells, fused osteoclasts (multinuclear giant cells) and macrophages.

Skeletal changes due to high PTH exposure result in bone pain and arthralgia along with high hypercalcaemia as in our case.[3] PET/CT imaging is a novel technique for the discrimination of FDG-avid from non-avid lesions but histology remains the cornerstone for the final diagnosis of either brown tumour lesions or bone metastases.

Figure 3. *Encapsulated parathyroid adenoma (4 x 2.5 x 2 cm) of 14 g*



CONCLUSION

FDG-avid lesions of brown tumours can mimic skeletal metastases in patients with hyperparathyroidism. The diagnosis of brown tumours should always be considered in patients with primary hyperparathyroidism and multiple bone lesions.

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PHOTO QUIZ

An unusual cause of breast enlargement

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CASE REPORT

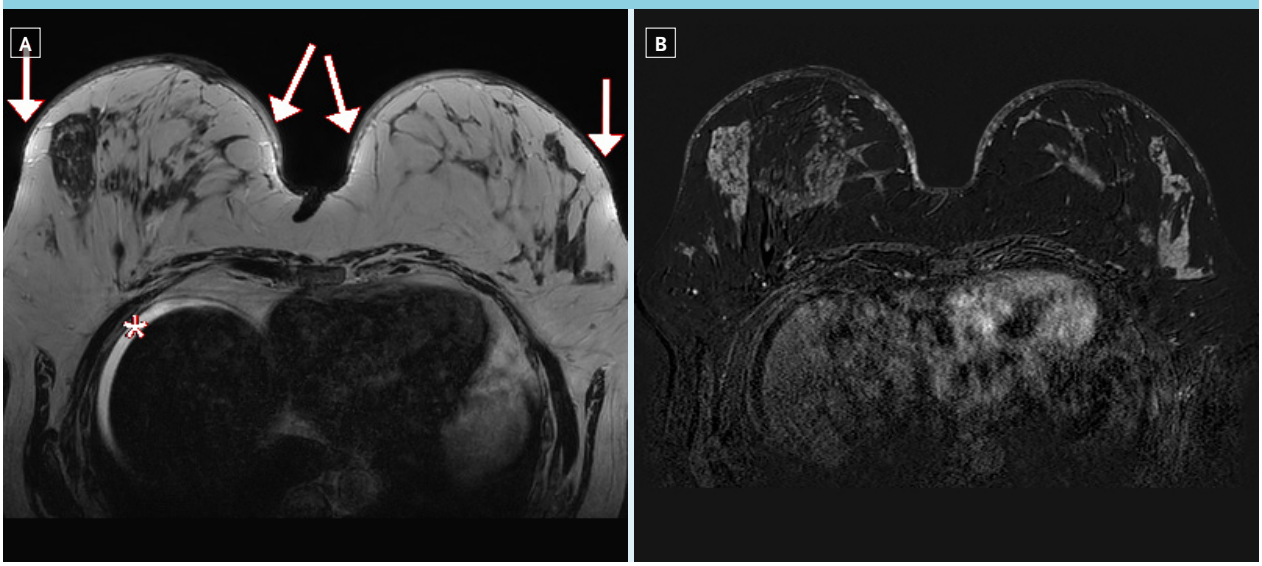
A 66-year-old woman presented to the outpatient clinic with bilateral breast enlargement in the last three months. Her medical history reported bilateral breast reduction surgery 20 years prior to presentation, and a hysterectomy 40 years ago due to myoma. She complained of bilateral breast tenderness and a tight feeling in the scars of the previous breast surgery. On physical examination both breasts appeared oedematous and a regular, firm mass measuring 50 mm was palpated on both sides. She had always participated in the Dutch population-based screening program and no abnormalities were seen on mammography two years earlier. A new mammography and ultrasound showed diffuse architectural disturbances with an increase of glandular tissue. No suspicious lymph nodes were seen in the axillae.

We decided to perform breast magnetic resonance imaging (MRI) for inconclusive findings (*figure 1*).

Bilateral core needle biopsy was performed, revealing adenosis and benign ductal hyperplasia, but no signs of malignancy. The diffuse contrast enhancement of the glandular tissue suggested hormonal stimulation, such as the overuse of hormone preparations, but our patient did not report the use of such medication.

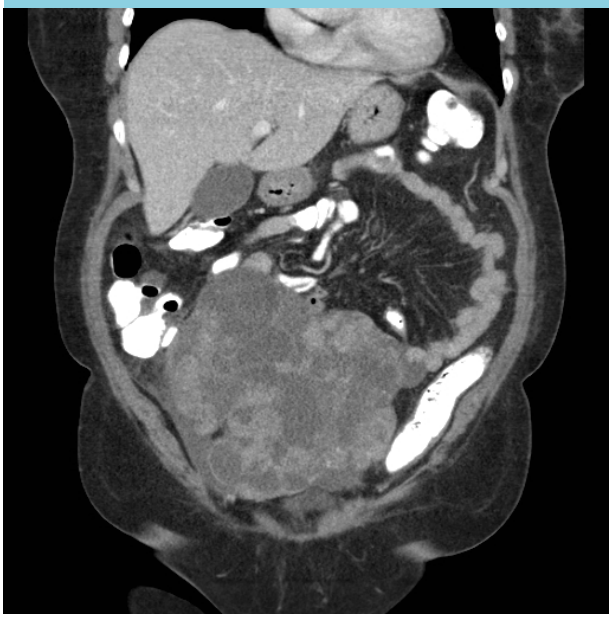
The MRI did not only show abnormalities in the breasts, but ascites was detected as an extramammary finding (*figure 1*). Additional physical examination revealed

Figure 1. *Bilateral breast MRI, consisting of a transverse T2w (A) and subtracted contrast-enhanced T1w (B) sequence. A) Shows bilateral skin thickening and subcutaneous oedema (arrows), but also ascites surrounding the liver parenchyma (*). B) Shows bilateral, diffuse enhancement of the fibroglandular tissue, without any circumscribed masses or areas of pronounced non mass enhancement. No axillary lymphadenopathy was observed (not shown)*



a large mass in the abdomen, which, on abdominal ultrasound, seemed to be originating from the ovarium. The gynaecological ultrasound showed an irregular, multilocular solid mass of the right ovary, which was thought to be of malignant origin. Additional computed tomography scan (CT scan) is shown in *figure 2*.

Figure 2. *CT scan of the abdomen, coronal view. A large, heterogeneous mass was observed in the lower abdomen, supposedly of ovarian origin*



WHAT IS YOUR DIAGNOSIS?

See page 134 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGES 132-133)

AN UNUSUAL CAUSE OF BREAST ENLARGEMENT

DIAGNOSIS

We had a working diagnosis of ovarian cancer and therefore decided to perform a staging laparotomy. Both adnexa were removed and omentectomy was carried out. Histopathological examination of the material showed a malignant granulosa cell tumour of the right ovary (*figure 3*). The inhibin-B and CA 125 were preoperatively measured and proved to be 88,470 ng/l (reference post-menopausal women: < 10 ng/l) and 115 kU/l (reference: < 35 kU/l), respectively. Our final diagnosis was a malignant granulosa cell tumour (stage Ia) of the right ovary.

Granulosa cell tumours (GCTs) are rare, malignant, ovarian tumours, comprising approximately 2 to 4% of all ovarian malignancies.[1] Presenting symptoms are often related to the tumour itself (abdominal pain, swelling, bloating) but the majority of GCTs also produce oestrogen, making vaginal bleeding a common presenting complaint.[2] The mainstay of treatment for GCTs remains cytoreductive surgery. Complete surgical staging consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy and exploration of the peritoneal cavity. There is little or no evidence for adjuvant chemotherapy.[1] GCTs have a more favourable prognosis than epithelial tumours of the ovary, because they are generally discovered at an early stage when the tumour is confined to the ovary.[1,2]

Our patient also presented with symptoms indicative of overproduction of female sex hormones, but instead of the more common vaginal bleeding, her presenting symptom was bilateral mammary gland enlargement. After removal of the tumour, the swelling of the breasts disappeared and her inhibin B levels dropped to < 10 ng/l. She has been in follow-up for almost a year now and there are no signs of residual or recurrent disease.

This case illustrates the importance of ruling out sex hormone-producing malignant ovarian tumours in case of unexplained breast enlargement.

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Figure 3. *A) Haematoxylin and eosin stain: the tumour shows densely cellular sheets with focally trabecular pattern. It consists of bland uniform cells with oval, partly grooved nuclei and little cytoplasm. B) Inhibin: diffuse staining with inhibin, consistent with sex cord-stromal tumours*