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*A scrotal and inguinal mass: what is your diagnosis?*

CLOSTRIDIUM PERFRINGENS SEPTICAEMIA

•  
CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

•  
GOUT: A CLINICAL SYNDROME WITH CARDIOVASCULAR COMPLICATIONS

•  
ENDOSCOPIC ULTRASONOGRAPHY IN PANCREATIC MALIGNANCY

•  
ABDOMINAL PAIN AND MELENA IN A DELIRIOUS PATIENT

•  
FEVER AND A PAINFUL SWOLLEN LEG

•  
LAPATINIB IN HER2-POSITIVE ADVANCED BREAST CANCER

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# Netherlands The Journal of Medicine

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# Endoscopic ultrasonography and pancreatic cancer – close companions

P. Fockens

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The first description of endoscopic ultrasonography (EUS) in the Lancet dates back almost 25 years ago. In an editorial in 1987 the conclusion was that there was probably not much future for EUS. The authors stated in their last sentence: *'echoendoscopy will remain a somewhat uneasy marriage of two techniques, best restricted to research centres.'*<sup>1</sup> The future turned out to be different as it almost always does. EUS is currently an important technique for the detection, diagnosis and therapy of a variety of gastrointestinal and also pulmonary diseases. In the Netherlands around 30 to 40 hospitals are using EUS on a daily or weekly basis for indications such as staging of oesophageal cancer, diagnosing submucosal lesions in the gastrointestinal (GI) tract, detecting common bile duct stones, detecting early chronic pancreatitis, detecting and staging pancreatic tumours, treating pancreatic pseudocysts, staging rectal tumours and last but not least for biopsying mediastinal lymph nodes in patients with lung cancer, sarcoidosis and other diseases. The biggest advance in the technique of EUS has been the EUS-guided fine needle aspiration (FNA) biopsy. With the help of EUS-guided FNA biopsy it is now relatively easy to image but also to puncture lesions just outside the GI tract (such as mediastinal lymph nodes). The procedure can be performed under mild sedation and has a very low complication risk.

In this issue of the *Netherlands Journal of Medicine*, Meijer and colleagues provide an excellent illustration of one of the important applications of EUS.<sup>2</sup> They report on a group of patients that had a clinical suspicion of pancreatic cancer and a negative computed tomography (CT) scan. CT scanning has become the first-line imaging technique for these patients and it has markedly improved in the past decades. Twenty years ago we were looking at lightboxes with films containing 24 pictures per film, made with 1-cm slices through the body. Nowadays we scroll through the same body on a large computer screen with 2-mm slices and a resolution of around 1 mm. Advances in computer technique have made it possible to quickly scroll up and

down and also allow reconstructions in multiple planes. CT scan is clearly the current gold standard for imaging of the pancreas. The pancreas, however, is a difficult organ to image. Tumours are quite often only slightly hypodense or even isodense compared with the normal parenchyma. And therefore many tumours are detected because of secondary changes to the organ such as distortion of the normal contours of the pancreas, obstruction of the pancreatic duct or invasion into surrounding tissues.

The resolution of EUS is about ten times higher than that of CT. Ultrasonography additionally has a different tissue interaction compared with X-ray and thus provides a completely different way of imaging of the pancreas making EUS complementary to CT. When looking for relatively small (<2.5 cm) tumours the sensitivity of CT drops dramatically to around 50% whereas the sensitivity of EUS remains high at around 90%.<sup>3</sup> EUS is therefore an important second-line imaging technique since a negative CT scan clearly does not rule out the presence of a tumour. In the article from the University Medical Center in Groningen, a tertiary referral centre, 34 patients are described over an 18-month period who underwent EUS because of a negative or inconclusive CT. The authors have carefully followed these 34 patients and conclude that EUS assisted in a correct final diagnosis in 30 of these 34 patients. Exactly in line with the size limitation of CT discussed above, the average size of the lesions the authors found with EUS was 22 mm. It would be interesting to know how many patients with a suspicion of pancreatic cancer overall were seen in the study period as this would help further define the place of EUS in this patient group. It is our impression that around 20% of all patients referred for evaluation of a possible pancreatic mass undergo an EUS.

EUS is rather difficult to learn and requires a substantial annual volume to warrant quality. It is therefore logical that EUS is centralised in referral centres. Calculations have been made in the past that at least one EUS centre should be available for every one million inhabitants in

the Netherlands. With the growth of pulmonary EUS indications, this figure should probably be somewhat higher but in general one could state that we probably do not need more than around 30 active EUS centres. Dilution of EUS to more hospitals could endanger the good results as achieved in the current article. EUS is almost never an emergency procedure and this is another argument to call for concentration in larger hospitals.

In the current study, EUS was combined with EUS-guided FNA biopsy in almost 60% of patients. One could question why this was not done in all patients and this is a matter of continuous debate around the world. Let's look at sensitivity and specificity before drawing conclusions. EUS-guided FNA biopsy of pancreatic tumours has a sensitivity of maximally 90% and a very high specificity, approaching 100%.<sup>4</sup> In our opinion a sensitivity of 90% is not good enough to demand a positive biopsy for every patient before considering surgery. Therefore, at the current time a positive imaging study (CT or EUS) in a patient with a clinical suspicion of pancreatic cancer is considered an indication for surgery in the absence of signs of irresectability or metastases. This algorithm implicates that in our current practice about 5% of patients that are operated on because of suspected pancreatic cancer, end up with a postoperative diagnosis of focal pancreatitis. This 5% of patients being overtreated seems acceptable in view of the fact that 10% patients would be undertreated in case of limiting surgery to patients with a positive biopsy. Biopsies are therefore currently reserved for patients with inconclusive imaging studies, patients in whom a biopsy is considered a prerequisite because of high operative risk, and irresectable patients who will receive radiotherapy

and/or chemotherapy. With neoadjuvant therapy on the horizon for pancreatic cancer, we seem to be only years away from a preoperative biopsy in almost every patient since neoadjuvant chemotherapy and/or radiotherapy can only be administered in patients with a positive cytological or histological diagnosis.

Thirty years after its introduction, EUS has achieved a strong position in the workup of patients with pancreatic cancer and this position is likely to grow in the future. Pancreatic EUS nevertheless remains difficult because of the necessary expertise and expensive because of the manpower involved. An endoscopy room is blocked for 45 to 60 minutes with involvement of two nurses, one endoscopist and an available cytopathologist or cyto-technician in case of a biopsy. CT and EUS are therefore never in competition but in close cooperation. The marriage of inconvenience from the Lancet in 1987 has changed into a close companionship in 2010.

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## ERRATUM

In the article *Ascertainment and verification of diabetes in the EPIC-NL study* by I. Sluijs, D.L. van der A, J.W.J. Beulens, A.M.W. Spijkerman, M.M. Ros, D.E. Grobbee, Y.T. van der Schouw, which was published in Neth J Med. 2010 Jul/Aug(7/8):333-9, an error was made.

In the abstract, under Results, the sentence 'After verification of ascertained diabetes cases, 532 (66.9%) were defined as having diabetes' should read 'After verification of ascertained diabetes cases, 1532 (66.9%) were defined as having diabetes'.

And under Acknowledgements 'E. Wilson' should be 'E.C. Wilson'.

# *Clostridium perfringens* septicaemia with massive intravascular haemolysis: a case report and review of the literature

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## ABSTRACT

We describe the case of a 74-year-old man with cholangitis, complicated by *Clostridium perfringens* septicaemia and massive intravascular haemolysis. *Clostridium perfringens* septicaemia is a rare but well-known cause of massive intravascular haemolysis. Here we review 40 similar cases published since 1990. Most cases involve immunocompromised patients with underlying haematological disorder (22.5%), pancreatic or gastric cancer (12.5%) and/or diabetes (30.0%). Focus of infection is mostly hepatobiliary (45.0%), intestinal or gynaecological after invasive procedure. Eighty percent of reviewed cases did not survive; the median time between admission and death was only eight hours. If an attempt was made to remove the focus of infection (i.e. by drainage of liver abscess, cholecystectomy, hysterectomy or ERCP), this proved to be a strong prognostic indicator of survival. However, in many of the cases the patient had already gone into shock or died before a diagnosis could be made. In severely ill patients with fever and haemolysis on the emergency department *Clostridium perfringens* septicaemia should always be considered, since early antibiotic treatment and if possible removal of the focus of infection can rescue patients from an otherwise fatal outcome.

## KEYWORDS

Cholangitis, *Clostridium perfringens*, massive intravascular haemolysis

## INTRODUCTION

‘This is a disease that begins where other diseases end, with death.’<sup>1</sup>

*Clostridium perfringens* is capable of inducing a wide variety of clinical manifestations, ranging from asymptomatic patients with an incidental positive blood culture to full-blown infection and death.<sup>2</sup> *C. perfringens* septicaemia is a rare but life-threatening cause of massive intravascular haemolysis. Early recognition and antibiotic therapy is essential to avert an otherwise fatal outcome. We present the case of a patient with massive haemolysis as a result of *C. perfringens* infection and review similar cases published since 1990.

## CASE

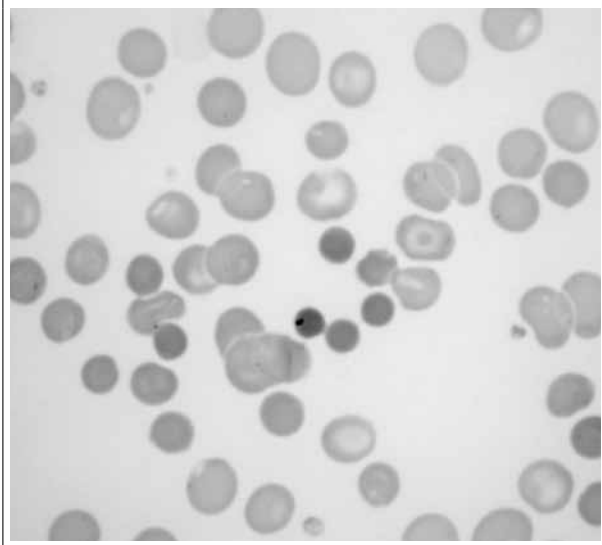
A previously healthy 74-year-old male was admitted to our hospital because of a six-day history of fever, nausea and vomiting. On arrival at the hospital he appeared ill. His temperature was 40.2 °C, his blood pressure was 171/88 mmHg and he was jaundiced with a tenderness of the upper abdomen. The haemoglobin (Hb) level was 9.8 g/dl (normal range (NR): 13.7 to 17.7 g/dl), haematocrit (Ht) 28% (NR: 40 to 50%), mean cell volume (MCV) 90 fl (NR: 80 to 100 fl), reticulocytes 1.4% (NR: 0.5 to 1.5%), white blood cell (WBC) count 29.8 × 10.9/l (NR: 4 to 10 × 10.9/l) (8% band cells) and platelets 140 × 10.9/l (NR: 150 to 400 × 10.9/l). Other laboratory results included the following: creatinine 3.1 mg/dl (NR: 0.5 to 1.3 mg/dl), serum aspartate transaminase (ASAT) 419 U/l (NR: <35 U/l), serum alanine transaminase (ALAT) 261 U/l (NR: <40 U/l), lactate dehydrogenase (LDH) 2300 U/l (NR: <250 U/l), alkaline phosphatase (ALP) 271 U/l (NR: <120 U/l), total bilirubin 23.7 mg/dl (NR: 0.2 to 1 mg/dl),

direct bilirubin 14.6 mg/dl,  $\gamma$ -glutamyltransferase ( $\gamma$ GT) 348 U/l (NR: <55 U/l), and creatinine phosphokinase (CK) 107 U/l (NR: <170 U/l).

An ultrasound of the upper abdomen showed sludge and gallstones in the gallbladder without dilatation of the hepatobiliary tree. Computed tomography (CT) of the abdomen revealed no abnormalities. Since no other focus of infection was found, cholangitis was thought to be the origin of sepsis in this severely ill patient. Broad spectrum antibiotics were administered (amoxicillin 6 g/24 h, gentamicin 5 mg/kg) and endoscopic retrograde cholangiopancreatography (ERCP) was performed. A dilated choledochus duct appeared without stones. After papillotomy impacted bile was seen, but no stones could be removed. In the hours following admission haemoglobin levels decreased to 7.9 g/dl with low haptoglobin (0.1 g/l) (NR: 0.3 to 2.0 g/l) and a negative direct antiglobulin test. Furthermore, haemoglobinuria occurred suggesting intravascular haemolysis. A peripheral blood smear showed spherocytes (figure 1). The following day, gas formation was observed in both blood culture bottles. Gram stain revealed large gram-positive rods that were subsequently identified as *C. perfringens*. Since biliary sepsis is usually polymicrobial, we chose to add metronidazole to the antibiotic regimen rather than to narrow therapy to penicillin only.

In conclusion our patient suffered from cholangitis, complicated by *C. perfringens* septicaemia and intravascular haemolysis. In the days following admission his renal function deteriorated, temporarily requiring haemodialysis, yet his condition stabilised and haemolysis ended. Three weeks later he had recovered sufficiently to be discharged with a remaining glomerular filtration rate (GFR) of 33 ml/min.

Figure 1. Peripheral blood film showing spherocytes



## RESULTS AND DISCUSSION

*C. perfringens*, an anaerobic, gram-positive rod, is a normal inhabitant of the human bowel and genital tract. *C. perfringens* septicaemia is an uncommon but almost invariably fatal condition following clostridial infection mostly from the uterus, colon or biliary tract. In general this occurs in patients with underlying malignancy or diabetes mellitus, or in otherwise healthy individuals with recent abdominal surgery or following abortion.

Massive intravascular haemolysis is a rare but well-known complication of *C. perfringens* septicaemia occurring in 7 to 15% of *C. perfringens* bacteraemias.<sup>3,5</sup> Recently, the current insights into the pathogenesis of bacterial sepsis were reviewed in this journal.<sup>6</sup> Alpha-toxin induced haemolysis is an additional prominent factor in the pathogenesis of *C. perfringens* sepsis. Alpha-toxin can damage the structural integrity of the red cell membrane by means of phospholipase activity.<sup>2</sup> This leads to spherocytosis and subsequent haemolysis. Besides spherocytes a blood smear can show ghost cells, which appear empty because they have a leaky membrane and no longer contain haemoglobin. Alpha-toxin is also the key virulence factor by inducing gas gangrene (or clostridial myonecrosis) in *C. perfringens* infection.<sup>2,7</sup>

The treatment of choice for *C. perfringens* bacteraemia is intravenously administered high-dose penicillin and surgical debridement of all involved gangrenous tissue, which is thought to be crucial in minimising production of toxins. In this case ERCP might have had a comparable effect to surgical debridement, by evacuating and therefore limiting the focus of infection.

We reviewed all 40 cases of *C. perfringens* septicaemia complicated by massive haemolysis published in the English literature since 1990 (table 1). Reported cases had a median age of 65 years (range 29 to 84) and 55% were male. No underlying condition was found in 15 of the 40 cases (37.5%); nine (22.5%) had a haematological disorder; five (12.5%) had either pancreatic or gastric cancer; there were two dialysis patients (5.0%) and two liver transplant recipients (5.0%). Diabetes was the only underlying disease in six patients (15.0%), overall 12 of the 40 cases (30.0%) were diabetic. The mean haemoglobin and haematocrit at presentation were 8.9 g/dl (standard deviation (SD) 3.3) and 21.3% (SD 12.1) respectively. Numerous cases mention a second measurement of haemoglobin or haematocrit within 24 hours of admission: in >80% this is less than half of the first blood sample.

Only eight of the 40 patients survived (mortality rate 80%); median time between admission and death was eight hours (range 0 to 96). Focus of infection was unknown in 11 cases (27.5%), hepatobiliary in 18 (45%), intestinal/abdominal in seven (17.5%) or uterine after invasive procedure in four (10%) cases. In eight cases an

**Table 1.** Cases of *C. perfringens* septicaemia and haemolysis published since 1990

	Author	Year	Age	Sex	Underlying disease	Origin infection	Focus removed	Hb (g/dl)	Ht (%)	WBCs (x10.9/l)	LDH (U/l)	Bili. (mg/dl)	Survival	Hours admission-death
1	Batge	1992	61	M	Pancreatic cancer	Liver abscess	Yes	11.6	32	38.2	7600	44	Yes	
2	Ifthikaruddin	1992	54	F	AML	Unknown	No	10.6		0.8			No	11
3	Hubl	1993	84	F	None	Intestinal	No	10.8	32	16.5	1344	21	No	3
4	Rogstad	1993	61	M	None	Micro abscesses liver	No						No	3
5	Clarke	1994	53	F	None	Necrotising enteritis	Yes	14.5		14		7	Yes	
6	Meyerhoff	1995	66	F	None	Unknown	No		10	28		36.7	No	9
7	Gutierrez	1995	74	M	None	Micro abscesses liver	No	13.1	41	19.8	1250	4.1	No	6
8	Jones	1996	66	F	Liver transplant	Liver abscess	No	11.3		11.2		2.5	No	10
9	Pun	1996	74	M	None	Cholecystitis	No		5	43.6			No	22
10	Bush	1996	58	F	DM	Biliary	No		26.6			9.9	Yes	
11	Singh	1996	73	F	CLL	Unknown	No		0				No	0
12	Singer	1997	55	F	Hodgkin's lymphoma	Unknown	No	3.4	0	0.2	4503	7.9	No	4
13	Alvarez	1999	77	F	None	Abdominal	No	4.8	7	25.6	14255	43.1	No	4
14	Thomas	1999	73	M	DM	Cholecystitis	Yes		33	39	3430	13.8	Yes	
15	Barrett	2002	NR	F	None	Septic abortion	Yes	8.7	23.6	29.7		12	No	NR
16	Halpin	2002	29	F	None	Postcaes. endometritis	Yes		22	28.9		17	Yes	
17	Jimenez	2002	79	M	Pancreatic cancer	Unknown	No	9	25	40	19000	10	No	96
18	Hamoda	2002	39	F	None	Postamn. endometritis	Yes	12.7		23.5		4.1	Yes	
19	Kreidl	2002	80	M	Dialysis	Liver abscess	No		32.1	29		12.6	No	11
20	Vaiopoulos	2004	74	M	AML	Intestinal and biliary	No		21.6				No	20
21	Au	2005	65	M	Dialysis	Liver abscess	No	6.2		25			No	72
22	Pirrota	2005	50	M	ALL	Unknown	No	3.5					No	4
23	Rodriguez	2005	57	M	Gastric cancer	Biliary	No	5.3	17.1			9.4	No	9.4
24	Kwon	2006	71	F	Pancytopenia	Unknown	No	2.2	1.4	6.2		9.7	No	2
25	Ohtani	2006	78	M	DM	Liver abscess	No	10	21.6	18.6	51382	1.4	No	3
26	McArthur	2006	49	M	Pancreatic cancer	Abdominal	No		6	1			No	1.5
27	Loran	2006	69	F	None	Liver abscess	No	8.7		26			No	6
28	Leeda	2006	59	M	Pancreatic cancer	Postop. intestinal leak	No	6		23.2			No	40
29	Eigenberger	2006	60	M	Liver transplant	Liver abscess	No	8.5		42.5		31.6	No	8
30	Daly	2006	80	M	DM	Liver abscess	No	8.7					No	3
31	Poulou	2007	74	M	DM	Unknown	No	12.6	36.4	17.2	7150	10.1	No	3
32	Poon	2007	64	F	None	Hepatobiliary	No	12.4		39.3			No	9
33	Kapoor	2007	58	M	AML	Unknown	No		25.7			8.4	No	16
34	Egyed	2008	39	F	Haemolytic anaemia	Unknown	No	3.7		10.5	1859		Yes	
35	Nadisauskiene	2008	31	F	Intermittent neutropenia	Postcaes. endometritis	No	9.3	25.5	1		19.7	No	60
36	Hess	2008	81	M	DM	Diverticulitis	No	10	19.7				No	8
37	Merino	2009	83	F	None	Liver abscess	No	12.2	36	26.5	2288	19.6	No	72
38	Boyd	2009	46	M	None	Cholecystitis	Yes	7.5	22	36			No	NR
39	Uppal	2009	61	M	Hepatitis C and cirrhosis	Unknown	No	11.7	32	38		28	No	8
40	Bunderen	2010	74	M	None	Cholangitis	Yes	9.8		29.8	2300	23.7	Yes	

Hb = haemoglobin at time of presentation; Ht = haematocrit at time of presentation; WBCs = white blood cells; LDH = lactate dehydrogenase; Bili. = total bilirubin; M = male; F = female; AML = acute myeloid leukaemia; DM = diabetes mellitus; CLL = chronic lymphoid leukaemia; NR = not reported; Postcaes. = post caesarean; Postamn.= postamnionocentesis; ALL = acute lymphoid leukaemia; Postop. = postoperative. References mentioned in this table are available on request.



attempt was made to remove the focus of infection (i.e. by drainage of liver abscess, cholecystectomy, hysterectomy or ERCP), which proved to be a strong prognostic indicator of survival. Only two out of these eight cases that underwent intervention died, compared with 30 out of 32 cases in which an invasive procedure was not attempted (relative risk (RR) of mortality associated with attempted intervention: 0.27 (95% confidence interval (CI) 0.08 to 0.89)). The presence of severe anaemia at presentation (defined as Hb <8 g/dl or Ht <24%) was not significantly associated with mortality (RR 1.24 (CI 0.91 to 1.71)), nor was age >65 years (RR 1.22 (CI 0.90 to 1.66)). Obviously the decision to operate on a severely ill patient will depend on the type and extensiveness of the infection, comorbidity and clinical condition. In many of the reviewed cases the patient had already gone into shock or died before a diagnosis could be made. However, if there is an apparent focus that can be removed, our case and this review illustrate that an attempt to do so will likely improve outcome.

In summary, *C. perfringens* septicaemia is a rare but well-known cause of massive intravascular haemolysis. In severely ill patients with fever and haemolysis on the

emergency department it should always be considered, since early antibiotic treatment and if possible removal of the focus of infection can rescue patients from an otherwise fatal outcome.

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# Epidemiology and management of chronic thromboembolic pulmonary hypertension

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## ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of acute pulmonary embolism (PE) with an estimated incidence of 0.5 to 1.5% in the Netherlands, depending on the aetiology of the PE. The underlying pathophysiological mechanism is largely unknown and may be caused by (recurrent) emboli or primarily by a characteristic arteriopathy of the pulmonary arteries. Patients with CTEPH present with nonspecific symptoms predominantly caused by right heart failure and up to 40% have no prior history of venous thromboembolism (VTE). The diagnostic approach of CTEPH aims at assessing the location and extent of the embolic obstruction to establish the operability and prognosis of the patients. A heart catheterisation for invasive pressure measurements is obligatory for the final diagnosis. CTEPH is associated with a poor prognosis if left untreated. The preferred treatment is pulmonary endarterectomy. In certain patients with inoperable disease or with persistent or recurrent pulmonary hypertension after surgery, pharmacotherapy might be beneficial.

## KEYWORDS

Pulmonary embolism, chronic thromboembolic pulmonary hypertension, epidemiology, diagnosis, therapy, prognosis

## INTRODUCTION

Pulmonary embolism (PE) is a common disorder with an estimated yearly incidence of 0.7 to 1 per 1000 inhabitants in the Western world. In addition to short-term adverse clinical outcomes, such as death,

bleeding or recurrent emboli, the long-term prognosis of patients with acute PE is complicated by high rates of other PE-related serious clinical events including increased mortality risk, arterial cardiovascular disease, i.e. previous studies have demonstrated an increased risk for myocardial infarction and cerebral vascular accidents after PE compared with control patients, and pulmonary hypertension caused by incompletely resolved pulmonary emboli.<sup>1,2</sup> This last-mentioned condition, known as chronic thromboembolic pulmonary hypertension (CTEPH), is a very serious disease associated with progressive physical disability and a high mortality risk.<sup>3-6</sup> Pulmonary hypertension is defined by an invasively measured mean pulmonary artery pressure exceeding 25 mmHg at rest and a normal pulmonary capillary wedge or left ventricular end-diastolic pressure of less than 15 mmHg.<sup>3,5</sup> In addition to intraluminal thrombus organisation resulting in fibrous stenosis or complete obliteration of the pulmonary arteries, CTEPH is characterised by intense remodelling of the small pulmonary arteries in those areas that are affected but also that are spared from thromboembolic occlusion, both processes leading to a chronic increase in pulmonary vascular resistance and progressive right heart failure.<sup>3,5</sup> Epidemiological and clinical aspects of this disease as well as the latest evidence on the management of patients with CTEPH will be the main focus of this summary.

## PATHOPHYSIOLOGY

In recent years, several plausible pathophysiological mechanisms for CTEPH have been postulated: 1) asymptomatic recurrent emboli after an initially effectively treated PE, 2) failure of resolving an acute embolus despite effective treatment or because of ineffective treatment and

3) in situ thrombus formation as a reaction to vascular remodelling from a nonthromboembolic origin, e.g. in pulmonary arterial hypertension (PAH).<sup>6</sup> However, numerous valid pro and contra arguments for these three mechanisms prevent the proposal of a straightforward pathophysiological concept.

The first important evidence against the first two proposed 'embolic' mechanisms is the lack of a prior history of symptomatic VTE in up to 40% of the patients with established CTEPH.<sup>7,8</sup> Second, a recent meta-analysis of imaging studies evaluating the thromboembolic resolution rate after acute PE found that possibly over 50% of the patients have evidence of residual emboli six months after the acute event. Only a very small proportion of these patients is at risk for developing CTEPH.<sup>9</sup> Third, there is a lack of correlation between elevated pulmonary artery pressure and the degree of angiographic vascular bed obstruction.<sup>10</sup> Furthermore, the pulmonary artery pressure can progress in the absence of recurrent PE or increased vascular obstruction rate.<sup>10</sup> Fourth, decreased fibrinolytic potential has not been identified in patients with CTEPH.<sup>3,11</sup> Finally, the remarkable resemblance between the histopathology of patients with CTEPH and those with PAH has been used as evidence against the existence of two distinct pathogenetic mechanisms.<sup>3,11</sup> On the other hand, there is clear evidence for a causal relation between VTE and CTEPH.<sup>8</sup> Further, CTEPH can be cured after a successful pulmonary endarterectomy, which opposes an underlying pulmonary artery endothelial condition.<sup>7,12</sup> Lastly, basic research has revealed a possible link between pulmonary emboli and the development of endothelial damage: thrombi cause a local increase in pulmonary artery endothelial permeability, resulting in an access of growth factors, cytokines and vasoreactive factors to both endothelial and pulmonary artery smooth muscle cells. These processes cause a local procoagulant and proinflammatory state and consequently initiate the remodelling process characteristic for CTEPH.<sup>7,13</sup>

Future studies should further investigate the pathogenesis behind the above-described observed associations. It is generally appreciated that CTEPH may not be explained simply by either unresolved or recurrent emboli, or by in-situ thrombosis only, and that all three processes are likely to contribute to the disease mechanism of CTEPH.

## EPIDEMIOLOGY

### Incidence of CTEPH

The true incidence and prevalence of CTEPH in the general population are unknown.<sup>3</sup> The incidence of CTEPH after acute PE, however, has been reported to vary between 0.1 and 8.8%.<sup>3,14-17</sup> This wide range can be explained by important differences in the inclusion and

diagnostic criteria between relevant studies: selection of patients was often based on the aetiology of the acute PE excluding patients with permanent or temporary risk factors for VTE, patients with further comorbid conditions associated with pulmonary hypertension were frequently excluded and the diagnosis of CTEPH was not always confirmed by right heart catheterisation.<sup>3,14-17</sup>

In the widely quoted study by Pengo *et al.*, 223 patients diagnosed with acute PE were followed for a mean period of 94.3 months.<sup>14</sup> Patients who had otherwise unexplained dyspnoea on exertion or at rest were considered to have CTEPH and underwent echocardiography. In the presence of supportive findings on echocardiography, further diagnostic tests including right heart catheterisation were performed. The cumulative incidence of CTEPH was 1.0% after six months, 3.1% after 12 months and 3.8% after 24 months.<sup>14</sup> Notably, because of strict exclusion criteria including the presence of pre-existing exertional dyspnoea or diseases that could have caused nonthromboembolic pulmonary hypertension, an unknown but relevant proportion of the patients were not included in the final analysis.

The incidence of CTEPH after acute PE was evaluated in a recent study by our department.<sup>18</sup> In order to construct a representative study population, all consecutive patients diagnosed with an episode of acute PE in the period between 1 January 2001 and 1 July 2007 in the Leiden University Medical Center (Leiden, the Netherlands) and affiliated teaching hospital Medical Center Haaglanden (The Hague, the Netherlands) were eligible for study inclusion, irrespective of age, medical history or comorbid conditions. The clinical and outpatient charts of these patients were searched for an established diagnosis of pulmonary hypertension. When present, all relevant data regarding the diagnosis, treatment and follow-up of these patients were collected. Further, the cause of death from all patients who had died before the start of the study (1 July 2007) was verified with the treating physician or general practitioner. Finally, all surviving patients who were not yet diagnosed with pulmonary hypertension were contacted and interviewed regarding their medical history and current clinical condition. All these patients were invited for a transthoracic echocardiography that was followed by right heart catheterisation and conventional pulmonary angiography when one of the predefined echocardiographic criteria for suspected pulmonary hypertension was met.<sup>18</sup> CTEPH was diagnosed according to the most recent international guidelines.<sup>5</sup> Of the 877 identified patients with acute PE, 11 (1.3%) were excluded due to geographical reasons, 259 (30%) had died and four (cumulative incidence 0.57%, 95% confidence interval (CI) 0.02 to 1.2%) were diagnosed with CTEPH.<sup>18</sup> The risk for CTEPH after unprovoked PE, i.e. PE according in the absence of thrombotic risk factors, was three times higher (cumulative incidence 1.5%, 95% CI 0.08 to 3.1%).<sup>18</sup> The

main limitation of this study was the lack of objective tests to rule out CTEPH in the patients who had died and those who refused or were not able to participate. In those patients, CTEPH was considered not present if an alternative cause of death was reported or in the absence of unexplained exertional dyspnoea. Of note, these diagnostic criteria were also applied by Pengo *et al.*<sup>14</sup>

### Risk factors for CTEPH

In a recently published controlled retrospective cohort study, prevalent CTEPH cases were collected in three European CTEPH referral centres and compared with nonthromboembolic precapillary PAH cohorts at the same institutions. The study population consisted of 687 patients diagnosed between 1996 and 2007. Blood groups other than o (odds ratio (OR) 2.1, 95% CI 1.1 to 3.9), a history of malignancy (OR 3.8, 95% CI 1.5 to 10), lupus anticoagulant/antiphospholipid antibodies (OR 4.2, 95% CI 1.6 to 12), previous VTE (OR 4.5, 95% CI 2.4 to 9.1), recurrent VTE (OR 15, 95% CI 5.4 to 43), thyroid replacement therapy (OR 6.1, 95% CI 2.7 to 15), splenectomy (OR 18, 95% CI 1.6 to 2.4), ventriculo-atrial shunts and infected pacemakers (OR 76, 95% CI 7.7 to 10) were more often associated with CTEPH.<sup>8</sup> Importantly, these odds ratios can not be applied to daily clinical presence in patients with acute PE since a history of venous thromboembolic disease was lacking in 40% of the CTEPH patients. Pengo, who used acute PE as the main inclusion criteria of his study, found younger age (OR 1.8 per 10 years age difference, 95% CI 1.2 to 1.9), larger perfusion defects at diagnosis (OR 2.2 per decile decrement in perfusion, 95% CI 1.5 to 3.3), unprovoked PE (OR 5.7, 95% CI 1.4 to 23) and recurrent PE (OR 19, 95% CI 4.5 to 80) to be independent predictors of CTEPH after acute PE.<sup>14</sup>

## DIAGNOSTIC MANAGEMENT

### Clinical signs and symptoms

Patients with CTEPH typically present with nonspecific symptoms of right heart failure: progressive dyspnoea on exertion, fatigue, palpitations, syncope, haemoptysis or chest pain.<sup>3,4</sup> Physical examination may reveal findings consistent with pulmonary hypertension and/or right-sided heart failure: a prominent component of S<sub>2</sub>, a systolic murmur of tricuspid regurgitation or a diastolic murmur of pulmonary valve regurgitation, jugular venous distension, lower-extremity oedema, hepatomegaly, ascites and cyanosis. The nonspecific symptoms and the often unremarkable physical examination in the early course of the disease contribute to diagnostic delay. However, exertional dyspnoea or a progressive decline in exercise capacity out of proportion to that expected, considering coexisting medical conditions, should raise the suspicion

of CTEPH. A possible diagnostic algorithm in the above-mentioned cases is demonstrated in *figure 1*.

### Diagnostic tests

Studies defining the optimal diagnostic management in case of suspected CTEPH are lacking. Nonetheless, experts agree that the primary evaluation of these patients should be focused on determining the degree of pulmonary hypertension and cardiac compromise present, to confirm the diagnosis CTEPH by ruling out alternative conditions and to establish surgical accessibility and the potential operability of the patient. This diagnostic algorithm should at least consist of transthoracic echocardiography, pulmonary function tests, high resolution computed tomography (CT) of the chest, VQ lung scan and right heart catheterisation for invasive pressure measurements and conventional pulmonary artery angiography.<sup>3,5,19,20</sup> The use of CT or MRI for pulmonary angiography or cardiac functional measurements in the diagnostic management of patients with suspected CTEPH is yet to be determined. However at present, these imaging modalities cannot replace right heart catheterisation.<sup>5,19</sup>

In the presence of a completely normal echocardiography or ventilation perfusion scintigraphy, the diagnosis of CTEPH is highly unlikely.<sup>5</sup> In addition, recent yet unpublished data from our department suggest that a combination of an ECG without signs of right ventricular overload in combination with a normal NT-pro-BNP level also virtually excludes CTEPH (*figure 1*): even with high assumed disease prevalences of up to 10%, the negative predictive value of this model proved to be over 99%.

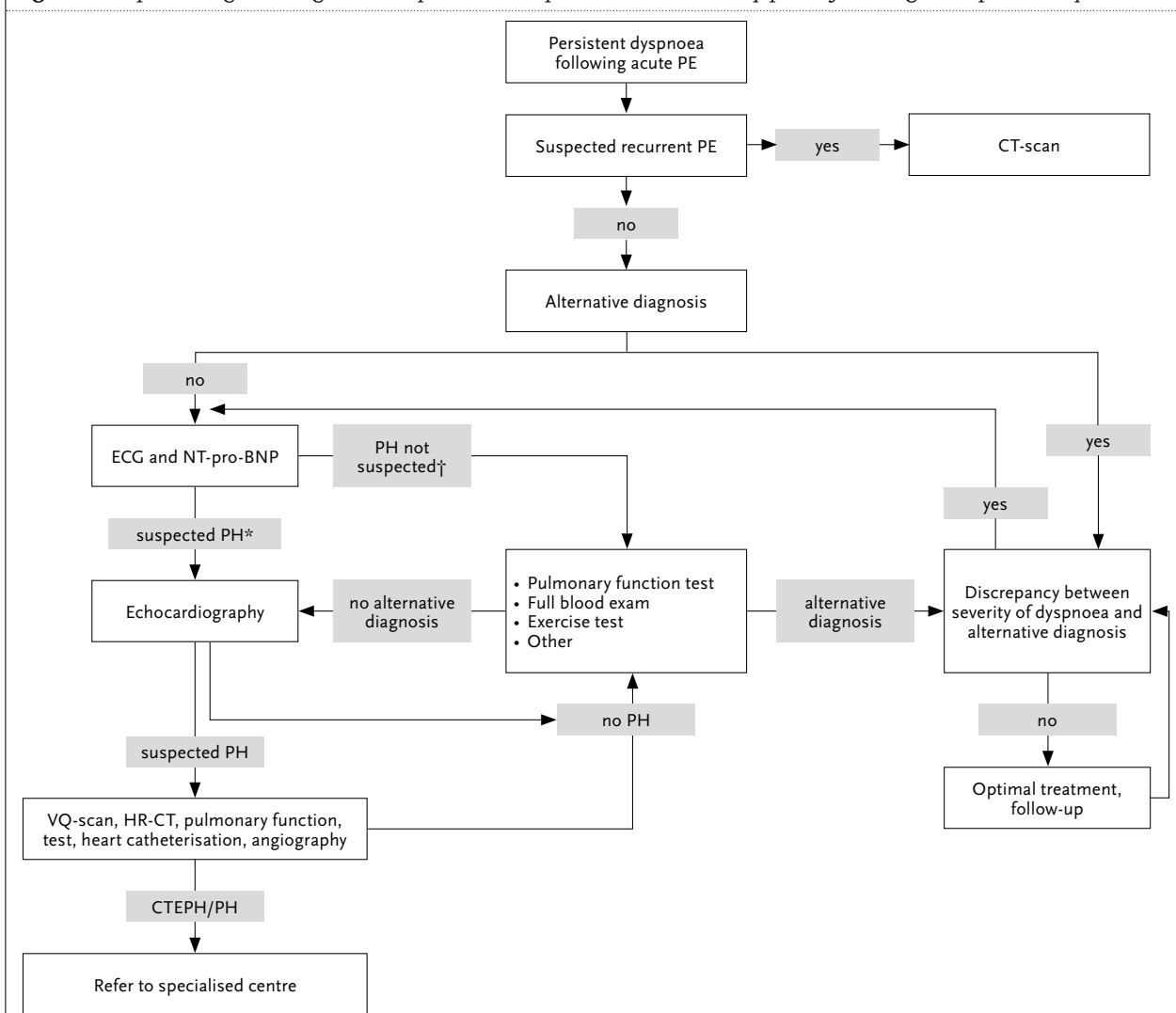
### Screening for CTEPH

Potential screening programs for CTEPH after PE should employ tools that are noninvasive, widely available and applicable, and importantly, that can distinguish patients who are in early stages of CTEPH from those who are not at risk of developing this condition. Because of the lack of understanding of the natural history of CTEPH, the absence of preventive treatment measures in very early stages of the disease as well as the very low risk of developing CTEPH following acute PE, screening for CTEPH does not seem warranted. In addition, one study showed a very low yield of an echocardiography based screening program on top of routine clinical care, underlining the former recommendation.<sup>18</sup>

## TREATMENT AND PROGNOSIS

Historical data indicate that if left untreated, CTEPH is associated with a poor five-year survival, ranging from 10 to 40% dependent on degree of elevation of the pulmonary artery pressure.<sup>6</sup> Although patients with CTEPH should receive lifelong anticoagulation treatment for the prevention

**Figure 1.** Proposed diagnostic algorithm in patients with persistent exertional dyspnoea following acute pulmonary embolism



†Normal age- and sex-corrected NT-pro-BNP levels and no evidence of right ventricular overload on ECG. \*Elevated age- and sex-corrected NT-pro-BNP levels or evidence of right ventricular overload on ECG (right axis deviation, right bundle branch block or right ventricular hypertrophy); PE = pulmonary embolism; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension; CT = computed tomography; ECG = electrocardiogram; VQ = ventilation perfusion.

of recurrent venous thromboembolism, this cannot prevent disease progression.<sup>5</sup> Surgical intervention with pulmonary endarterectomy (PEA) is the preferred treatment of CTEPH.<sup>3,12</sup> The success of PEA is based on the concept that a true endarterectomy, establishing a dissection plane to free the thrombotic residua from the native vessel wall, and not an embolectomy is necessary. The pulmonary artery is optimally exposed during periods of circulatory arrest and deep hypothermia to achieve a bloodless operative field.<sup>12</sup> The goal of PEA is to improve pulmonary haemodynamics, exercise capacity, symptoms and survival. The procedure may be curative in appropriately selected patients and is associated with an improved six-year survival rate of 75%.<sup>21-23</sup> There is general consensus that current surgical techniques allow removal of organised thrombi whose proximal extent

is in the main or lobar pulmonary arteries.<sup>12</sup> Consequently, PEA is contraindicated in patients with predominantly distal CTEPH, with severe comorbid conditions associated with increased perioperative mortality (in particular obstructive or parenchymal lung disease) or those with a preoperative haemodynamic profile with limited anticipated postoperative improvement. These patients as well as patients with persistent or recurrent pulmonary hypertension after PEA might be appropriate candidates for pharmacotherapy. Several open-label studies with prostaglandin derivatives, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors in patients with CTEPH have been reported, and most suggest haemodynamic or clinical improvement.<sup>23-26</sup> Up to now, only one randomised clinical trial has been performed in patients with inoperable CTEPH.<sup>27</sup> In this study, a 16-week

treatment with the oral dual endothelin receptor antagonist bosentan resulted in a significant reduction in pulmonary vascular resistance and NT-pro-BNP levels as compared with placebo. However, the treatment did not show any effect on the six-minute walking distance nor an improvement in the time to clinical worsening.<sup>27</sup> There is no evidence that pharmacotherapy in patients with CTEPH is associated with either increased survival or, when used as preoperative bridging therapy, with improved postoperative outcome. In general, patients with CTEPH should be referred to an expert centre for either PEA or inclusion in clinical trials.

## CONCLUSION

CTEPH is a very serious but infrequent complication of acute PE. The underlying pathophysiological mechanism is largely unknown and may be due to (recurrent) emboli or pulmonary artery endothelial dysfunction. Patients with CTEPH present with nonspecific symptoms predominantly caused by right heart failure and up to 40% have no prior history of venous thromboembolism. The diagnostic approach of CTEPH aims at assessing the location and extent of the embolic obstruction to establish the operability and prognosis of the patients. Invasive pressure measurements should be performed in all suspected cases based on abnormal echocardiography. The preferred treatment is PEA although in certain patients with inoperable disease or with persistent or recurrent pulmonary hypertension after surgery, pharmacotherapy might be beneficial.

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# Gout: a clinical syndrome illustrated and discussed

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## ABSTRACT

Gout is an acute inflammatory arthritis with the potency to fully destroy the integrity of the joint leading to severe disability. Besides joint destruction, gout is often associated with an accelerated atherosclerosis culminating in an increased risk of cardiovascular disease. The current existing therapy modalities allow an efficient treatment that not only controls local inflammation but might also have an effect on the generalised features that surround this condition. Here we discuss the modes of clinical appearance, how we are nowadays supposed to treat gout and the current knowledge about the pathogenesis of this clinical syndrome.

## KEYWORDS

Gout, cardiovascular risk, immunology

## INTRODUCTION

Gout is an acute inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals intra-articularly. Patients experience acute severe pain that often forces them to seek medical care. Besides the acute presentation patients can present with tophi, which can even precede joint involvement.<sup>1,3</sup> With an estimated prevalence of 1 to 2% in adults in developed countries, this therefore accounts for a substantial burden of work-related and medical costs. In the elderly (age >65 years) the incidence even increases to 8% for men and 3% for women.<sup>4</sup> The male:female ratio ranges from 7:1 to 9:1.<sup>5</sup> Most patients with gout (±90%) are diagnosed and treated by general practitioners in primary care.<sup>6</sup> Besides the involvement of joints, gout is often accompanied by other symptoms of hyperuricaemia such as the

formation of tophi in numerous tissues. The prevalence of hyperuricaemia is 10 to 20% in the Western population and a substantial number of these patients stay asymptomatic during life.<sup>7</sup> Only a minority of individuals with elevated serum urate levels develop gout (incidence rate less than 50/1000/year for ≥0.54 mmol/l; 5/1000/year for 0.42 to 0.54 mmol/l; 1/1000/year <0.42mmol/l).<sup>8</sup> Compared with other mammals humans have high uric acid levels due to two deletions in the promotor site of uricase.<sup>9</sup> This causes the uric acid plasma levels to be around 300 μM, a level at which a small increment could cause supersaturation and crystal formation. There is a strong association between hyperuricaemia and the metabolic syndrome (the constellation of insulin resistance, hypertension, obesity and dyslipidaemia), potentially explained by dietary and lifestyle changes.<sup>10</sup> This is profoundly demonstrated by the prototypic gouty patient being an obese, middle-aged man with a Burgundian lifestyle and a medical history of hypertension, kidney disease, diabetes mellitus and signs of vascular problems such as coronary artery disease, heart failure and stroke. But as previously reported gout can also present in elderly patients without known risk factors, even presenting only with tophi.<sup>11</sup> In gouty arthritis the formation of MSU crystals into the joint promotes acute inflammation. These crystals have the capacity to induce the release of various inflammatory mediators in inflammatory cells.<sup>12-16</sup> In the past ten years research on the role of the innate immune system in the pathogenesis of gout has extended rapidly. As our knowledge on the inflammatory processes accompanying atherosclerosis also increases it is tempting to discuss the development of cardiovascular diseases in gout patients via immunological perturbations.

In daily clinical practice the diagnosis of gout can be made easily and with a high certainty using the gold standard. The gold standard is the presence of MSU crystals in the

synovial fluid or a tophus, and therefore a puncture of a joint or tophus should always be performed. Recently it was shown that the American College of Rheumatology (ACR) criteria from 1977 have a limited validity, at least in primary care.<sup>17</sup> We describe two patients who visited the emergency department because of severe gouty arthritis. The aim of this study is to review the literature concerning cardiovascular risks and pathogenic aspects of gout. In addition, we provide an overview on the clinical assessment and therapeutic armamentarium.

## CASES

### PATIENT A

A 75-year-old male presented at the emergency unit with a five-day history of severe pain and swelling of digit IV of the left foot. The general practitioner had already started colchicine 0.5 mg ten times daily. This led to complaints of vomiting and diarrhoea and eventually to a visit to the emergency department. His medical history was characterised by major cardiovascular complications consisting of a myocardial infarction in 1986 followed by a large aneurysm of the left ventricle and mild mitral valve insufficiency (diagnosed in 1993). A second myocardial infarction followed in 1994. In 2002 an acute coronary syndrome led to dilation and placement of a stent in the right coronary artery. In 2008 diagnostic procedures were undertaken because of progressive dyspnoea and cardiac ultrasound revealed a markedly diminished function of the left ventricle (ejection fraction 25 to 30%), insufficiency of the mitral and aortic valves and suspicion of pulmonary arterial hypertension. Based on these observations, an intracardiac defibrillator was inserted. Besides his cardiac history, hypothyroidism, peptic ulcers and gout had been present for eight years. Physical examination revealed a swelling of digit IV of his left foot with a tophus that showed signs of infection and distinct tophi in the olecranal bursa bilaterally (*figures 1A and B*). Apart from the common signs of dehydration, no other signs of illness were present. Laboratory analysis was normal (no acute phase response present) except for the increased serum uric acid of 0.92 mmol/l (reference 0.20 to 0.40 mmol/l) and creatinine 306 µmol/l (reference 60 to 110 µmol/l) levels. Radiographic evaluation of the left foot revealed a complete resorption of the distal phalanx digit IV (*figure 1C*); no other abnormalities were present. Since the patient was dehydrated because of diarrhoea due to the high dose of colchicine, 120 mg, the arthritis was treated with triamcinolone acetonide intramuscularly and not with an NSAID, and the dosage of colchicine was lowered to 0.5 mg once daily. One week later the patient attended

our outpatient clinic. He was fully recovered and showed no signs of dehydration and pain in the toe. Although exceptional, since the gouty disease in this patient was very local and led to a high risk for an infectious complication, we discussed an amputation of digit IV with the patient. Not surprisingly, the toe had given many complaints over the past three years and the patient agreed to this approach. Two weeks after presentation at the emergency ward the toe was amputated. As expected, the histological analysis of the amputated digit showed clear MSU crystals and no evidence for infection. Two weeks after surgery the patient visited our outpatient clinic with complete healing of the site of amputation (*figure 1D*). Since the medical history of the patient included more than three gout attacks per year we started allopurinol 200 mg once daily under the cover of corticosteroids. This led to the normalisation of





the serum urate below the level of 0.36 mmol/l, which is the current target value of the European League against Rheumatism (EULAR), and absence of gout attacks after two years of follow-up.

## PATIENT B

A 93-year-old female came to the rheumatology clinic with pain and swelling in both hands and a probable 12-year history of gout. She had not received any treatment for her gout so far. Her only relevant medical history was primary hypertension. Physical examination showed multiple swollen proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints in both hands with an extensive amount of tophi (figures 2A and B). Inspection of digit IV of the right hand revealed a fistulating tophus (figure 2C). Laboratory analysis showed a serum uric acid of 0.46 mmol/l (reference 0.20 to 0.40 mmol/l) and creatinine 69  $\mu$ mol/l (reference 60 to 110  $\mu$ mol/l) and an acute phase reaction: ESR 34 mm/h and CRP 45 mg/l. To analyse the extent of joint damage conventional radiological examination was performed which revealed extensive destruction of multiple PIP and DIP joints (known as 'punched out' lesions). As treatment, clindamycin 200 mg was given three times daily (for two weeks) and methylprednisolone (120 mg) was administered

once intramuscularly. Two weeks later all the signs of inflammation had completely resolved. At that moment allopurinol 200 mg once daily was added, which led to the normalisation of the serum urate level (<0.36 mmol/l). After two years of follow-up, the patient had twice suffered from a gout attack which quickly recovered (within two days) by the addition of colchicine three times daily 0.5 mg for one week.

## GOUT AND CARDIOVASCULAR MORBIDITY AND MORTALITY: MORE THAN A LOCAL DISEASE?

While an association between gout and hypertension, other cardiovascular diseases and kidney diseases has been observed since the late 19th century, renewed interest started from the late 20th century through defining of new top priorities in medicine, such as reduction of cardiovascular morbidity and mortality.<sup>1</sup> To date, several studies underscore that gout is an independent risk factor for cardiovascular disease (table 1).<sup>10,18</sup>

In the prospective Framingham study 'clinical' gout was associated with an increased risk of coronary heart disease. Abbott *et al.* found an excess risk of 60% for coronary heart disease (CHD) among subjects with gout compared with those who did not have clinical gout.<sup>19</sup> The Meharry-Hopkins study showed contradictory results, the pooled risk-adjusted relative risk (RR) for cardiovascular disease was 0.59 (95% CI 0.24 to 1.46). However, this study was underpowered with just three events in the 31 subjects of the Meharry cohort and four events in 62 subjects of Johns Hopkins Precursors cohort.<sup>20</sup> A Dutch study based on data from general practitioners demonstrated that 270 patients with a first episode of gout had a statistically higher prevalence of one or more signs of cardiovascular disease (35 vs 26%) compared with 522 healthy counterparts. In follow-up of this study, 170 gout patients without cardiovascular disease were compared with 340 control patients from the general practitioners' database. Data revealed a statistically higher prevalence of hypertension (39 vs 14%), hypercholesterolaemia (8 vs 4%), diabetes mellitus (5 vs 1%) and obesity (52 vs 27%) among the 170 gout patients.<sup>21</sup>

The prospective Multiple Risk Factor Intervention Trial (MRFIT) was a randomised clinical trial designed to examine the efficacy of coronary risk reduction of adverse coronary events. During the six-year intervention phase gout was associated with an increased risk of nonfatal acute myocardial infarction, odds ratio 1.26 (95% CI 1.14 to 1.4).<sup>21,22</sup> In 2008, Krishnan *et al.* reported a 17-year follow-up study of the men in the MRFIT cohort who did not have CHD during the six-year intervention phase. The hazard ratio (HR) for CHD mortality for gout vs non-gout was 1.35 (95% CI 1.06 to 1.72).<sup>23</sup>

Figure 2. Patient B



A to C) Diffuse swelling of distal and proximal interphalangeal joints with multiple subcutaneous tophi and ulceration lateral side digit IV left, D) bone resorption and bone cysts due to chronic gouty inflammation. The patient provided consent to publish the photos.

**Table 1. Gout and cardiovascular morbidity and mortality**

Study	Population	Design	Follow-up (years)	Outcomes	Patients (total gout n)	Adjusted effect size (95% CI)
Abbott <sup>19</sup>	Framingham cohort	Cohort	32	CHD	37 (94)	1.60 (1.10-2.50)
Gelber <sup>20</sup>	Meharry-Hopkins cohort	Cohort	30	CHD	7 (93)	0.59 (0.24-1.46)
Janssens <sup>21</sup>	Continuous Morbidity Registration cohort	Case-control	11	CVD	44 (170)	(0.65-1.47)
Krishnan <sup>22</sup>	Multiple risk factor Intervention trial Cohort	Cohort	6.5	Fatal MIs All MIs	22 (1123) 118 (1123)	0.96 (0.66-1.44) 1.26 (1.14-1.40)
Krishnan <sup>23</sup>	Multiple risk factor Intervention trial Cohort	Cohort	17	Fatal MIs CHD mortality CVD mortality	36 (655) 78 (655) 110 (655)	1.35(0.94-1.93) 1.35(1.06-1.72) 1.21 (0.99-1.49)
Chen <sup>25</sup>	Ho-Ping Gout Cohort	Cross-sectional	NA	Q-wave MIs	393 (22,572)	1.18 (1.01-1.38)
Choi <sup>26</sup>	Health Professionals Follow-up cohort	Cohort	12	All-cause mortality CHD mortality CVD mortality	645 (2773) 238 (2773) 304 (2773)	1.28 (1.15-1.41) 1.55 (1.24-1.93) 1.38 (1.15-1.66)
Cohen <sup>27</sup>	US Renal Data System dialysis patients	Cohort	5	All-cause mortality CVD mortality	*(24,415) *(24,415)	1.49 (1.43-1.55) 1.47 (1.26-1.59)
Kuo <sup>28</sup>	Health Screening Program Chang Gung Memorial Hospital	Cohort	6	All-cause mortality CVD mortality	*(1311) *(1311)	1.46 (1.12-1.91) 1.97 (1.08-3.59)

\*Numbers of outcome not reported.  
CHD = coronary heart disease; CVD = cardiovascular disease; MIs = myocardial infarctions.

Recently, a large Taiwanese study reported about the relationship between clinical gout and electrocardiographic evidence Q-wave myocardial infarction using the Ho-Ping Gout database of 22,572 established gout patients according to the Wallace criteria.<sup>24</sup> In addition to this, Chen *et al.* demonstrated that gout was associated with Q-wave myocardial infarction.<sup>25</sup> The prospective Health Professional Follow-up Study investigated the relation between history of gout and the risk of death and myocardial infarction among 51,297 men. During the 12-year follow-up period, Choi *et al.* found RRs of 1.38 (95% CI 1.15 to 1.66) for cardiovascular-related death and 1.55 (95% CI 1.24 to 1.93) for cardiovascular-related death in males with gout.<sup>26</sup> Cohen *et al.* examined the association of gout and mortality among patients receiving dialysis therapy in the United States Renal Data System. In this study, gout was independently associated with CVD mortality with an HR of 1.47 (95% CI 1.26 to 1.59).<sup>27</sup> However, this national registry did not contain information on other potential risk factors for mortality such as malnutrition, infection and social circumstances. The most recent study to date by Kuo *et al.* further substantiates the relationship between cardiovascular disease and gout using a cohort of 61,527 individuals and a follow-up period of seven years.<sup>28</sup>

Together, these prospective reports strongly suggest that men with gout, adjusted for various cardiovascular risk factors, are associated with increased cardiovascular disease risk, especially coronary heart disease mortality.

Therefore aggressive management of cardiovascular risk factors in men with gout is warranted.

#### GOUT AND PERTURBATIONS IN THE IMMUNE SYSTEM

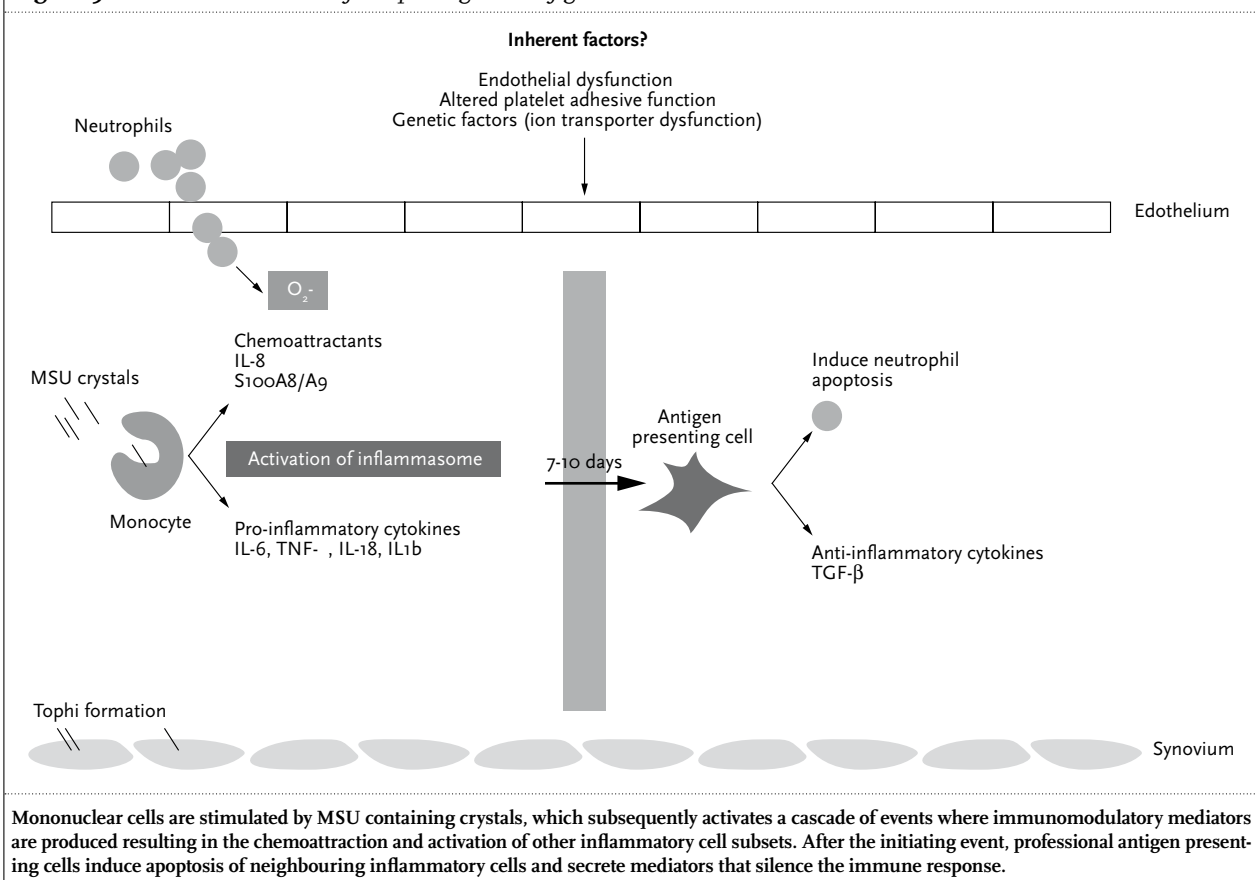
Whenever the level of uric acid in the synovial fluid fluctuates and the synovial fluid gets supersaturated with uric acid the risk for crystal formation increases. The solubility of urate in synovial fluid is influenced by more factors than solely the concentration, including temperature, level of dehydration and the presence of nucleating agents.<sup>29</sup> These factors in part explain the predilection of gout in the first metatarsal phalangeal joint (podagra, low temperature), in osteoarthritic joints (nucleating debris) and the nocturnal onset (dehydration).<sup>29</sup> An acute gouty attack causes a neutrophilic influx. The influx of neutrophils into the joint is caused by chemotactic factors.<sup>30</sup> Recent studies have shown that the most important phagocytic cells causing this gradient are the monocytes. Interaction between MSU and the lipid membrane and proteins in the cell membrane of a phagocyte cause activation of several signal transduction pathways resulting in IL-8 production, accounting for 90% of the neutrophilic chemotactic activity.<sup>30</sup> Other neutrophilic chemoattractant factors include S100A8 and S100A9.<sup>31</sup> MSU released by injured cells act as a danger signal activating the innate immune system.<sup>32</sup>

MSU crystals are potentially recognised by immune cells through Toll-like receptor 2 (and probably TLR4)<sup>33,34</sup> and FcγRIIIB/CD16<sup>35</sup> subsequently leading to NF-kappaB activation and downstream signalling culminating in the production of proinflammatory cytokines such as interleukin-6, tumour necrosis factor α, interleukin-1β and interleukin-8 (IL-8). Actually, the stimulating capacity of MSU crystals to activate monocytes/macrophages to produce interleukin-1β (IL-1β) was already recognised 20 years ago but to date controversy remains about the precise mechanisms through which urate crystals drive inflammation.<sup>12</sup> Recent studies have led to significant advances in the understanding of the basic biology of crystal-mediated inflammation. Uric acid has been identified as a danger signal that triggers a cytosolic sensor, the inflammasome, a signalling platform that is required for the activation of interleukin-1, a cytokine that is critical to the initiation of acute inflammation in gout (reviewed in Martinon, 2010).<sup>36</sup> Interestingly, several studies have now suggested an effective treatment with IL1b inhibitors; however, these observations need confirmation in RCTs.<sup>37,38</sup> Currently a study with canakinumab, an IL1b inhibitor, is underway. Another interesting finding recently published is the capacity of monocytes and/or the inflammatory environment in a

gout-prone individual to prime neutrophils to produce increased levels of superoxide in response to MSU stimulation.<sup>39</sup>

Intriguingly, the natural course of a gout attack is to spontaneously resolve in seven to ten days. Clearance of MSU by differentiated macrophages results in a decrease of leucocyte and endothelial activation with the end result that the inflammatory response fades away.<sup>40</sup> Further *in vitro* research showed that *in vitro* generated macrophages failed to secrete cytokines in response to MSU.<sup>40</sup> It is therefore interesting to hypothesise that the time to resolve a gout attack is directly correlated with the time a monocyte needs to become a fully differentiated macrophage *in vitro*. Further research is needed though to confirm this hypothesis. On the other hand in chronic gout low-grade synovitis persists even during remissions of acute flares. The ongoing inflammation causes joint damage through chondrocyte activation and the following matrix metalloproteinase production.<sup>41</sup> Furthermore, MSU is able to reduce the anabolic effects of osteoblasts, also contributing to irreversible joint damage. These series of events could possibly explain the inflammatory circuitry that leads to joint destruction when inflammation is not controlled (*figure 3*). Next to irreversible joint damage the increased cardiovascular risk in patients with gout is

**Figure 3.** Schematic overview of the pathogenesis of gout



still a medical conundrum. Two interesting hypotheses try to explain the pathophysiological mechanisms that lead to the accelerated atherosclerosis that underlies this phenomenon. First, activation of Toll-like receptors (TLRs) can block the induction of liver X receptor (LXR) target genes of the lipid metabolism.<sup>42</sup> As activation of LXR and PPAR gamma can potentially prevent the development of atherosclerosis, an interaction between LXR and MSU induced TLR activation could explain the association with the uncontrolled rate of atherosclerosis in patients with gout. Second, two studies in rats, using dietary adjustments to induce hyperuricaemia, have shown that increased uric acid caused nephropathy resulting in increased renin levels and hypertension.<sup>43,44</sup> Whether this mechanism can be translated to humans is a matter of debate and warrants further investigation. In addition, the contribution of chronic inflammation, oxidative stress and endothelial dysfunction to the development of cardiovascular disease in gout patients needs further attention as these processes intriguingly play a role in both diseases.

#### CURRENT INSIGHTS INTO THE MANAGEMENT OF GOUT

Following the clear evidence of the destructive effects of gout on the joints and the cardiovascular system a clinician facing a patient with gout should be triggered to start treatment for these aspects of this disease. The EULAR evidence-based recommendations for gout is a European combined effort to develop key recommendations concerning diagnosis and management of gout.<sup>4,45</sup> A total of 22 key recommendations were generated through six Delphi rounds. *Table 2* presents a selection of the most important key recommendations for management of gout. In the short term, the treatment goal is to relieve symptoms as quickly as possible. For this purpose oral colchicine (dose needs to be corrected for renal function), NSAIDs or a low dose of oral prednisone can be used. The importance of using the correct dosage of colchicine is clearly illustrated in patient A who was nearly intoxicated. The efficacy of colchicine and its side effect is further discussed in Terkeltaub *et al.*<sup>46</sup> In a double-blinded randomised clinical trial oral prednisone and naproxen were found to be equally effective in the initial treatment of gout arthritis over four days.<sup>47</sup> In the longer term, urate-lowering therapy is indicated in patients with recurrent acute gout attacks, arthropathy, tophi or radiographic changes of gout. The first choice for urate-lowering therapy is a xanthine oxidase inhibitor (allopurinol). Allopurinol has a proven efficacy in all cases of gout. The most common dosage of allopurinol is 300 mg once-daily with which 56 to 65% of patients reach the recommended urate level of <0.36 mmol/l.<sup>48,49</sup> If necessary, this dose can be increased to 600 mg daily. In 20% of the cases the use of allopurinol causes

**Table 2.** Modified recommendations for management of gout<sup>45</sup>

1. Optimal treatment of gout requires both nonpharmacological and pharmacological modalities and should be tailored according to:
  - (a) Specific risk factors for gout such as elevated serum uric acid, previous attacks and radiographic signs
  - (b) Clinical phase (acute/recurrent, chronic tophaceous gout)
  - (c) General risk factors (age, sex, obesity, alcohol consumption, urate raising drugs, drug interactions and comorbidity)
2. NSAID and/or prednisolone are first-line agents for systemic treatment of acute attacks. Low-dose colchicine is an alternative.
3. Intra-articular aspiration and injection of a long-acting steroid is an effective and safe treatment for an acute attack.
4. Urate-lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi or radiographic changes of gout. The therapeutic goal of urate-lowering therapy is achieved by maintaining the serum uric below the saturation point of monosodium urate (< 360 μmol).
5. Allopurinol is an appropriate long-term urate-lowering drug; it should be started at a low dose (for example, 100 mg daily) and increased by 100 mg every 2-4 weeks if required; the dose must be adjusted in patients with renal impairment; if allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, an uricosuric agent (benzbromarone) or allopurinol desensitisation (the latter only in cases of mild rash).
6. Prophylaxis against acute attacks during the first months of urate-lowering therapy can be achieved by colchicine (0.5-1 mg daily) and/or an NSAID.
7. When gout is associated with diuretic therapy, stop the diuretic if possible: for hypertension and hyperlipidaemia consider use of losartan and fenofibrate, respectively (both have modest uricosuric effects).
8. Associated comorbidity and cardiovascular risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity and smoking should be addressed as an important part of the management of gout.

side effects which are severe enough to stop treatment in 5% of the cases.<sup>50</sup> If there is intolerance against allopurinol an alternative approach is the use of an uricosuric drug; in the Netherlands benzbromarone as the only drug regularly available. In a recent randomised controlled trial the efficacy of benzbromarone 100 to 200 mg daily was equal to 300 to 600 mg allopurinol.<sup>51</sup> Recently, a novel drug for the treatment of gout was introduced: febuxostat (Adenuric®). Febuxostat is a novel non-purine xanthine oxidase inhibitor. Urate levels of lower than 0.36 mmol/l were reached in 48 to 53% with daily use of 80 mg febuxostat and in 62 to 65% in the case of 120 mg febuxostat daily vs 56 to 62% and 85 to 93% with the use of 300 mg and 600 mg of allopurinol daily.<sup>32-54</sup> However, the current position of febuxostat in the Netherlands is as a second choice after failure of allopurinol and/or benzbromarone (See Dutch Guidelines febuxostat [www.nvr.nl](http://www.nvr.nl)) following the international recommendations.<sup>55</sup> Currently, there is a large debate about the effects that these treatments could have on cardiovascular risk. Aside from this urate-lowering therapy traditional cardiovascular risk factors such as hyperlipidaemia, hypertension, obesity and smoking should be addressed according to national cardiovascular risk management guidelines. Although clear trends are present

that suggest that gout/hyperuricaemia is associated with an increased risk for premature death due to cardiovascular diseases, the final answer needs to come from clinical intervention studies that still need to be performed.

## CONCLUSION

The cases discussed in this report clearly illustrate the severity of gout and demonstrate that even today, gout is not always recognised and treated as it should be. Nowadays, gout can be treated very effectively with the currently available therapeutic armamentarium. So far, prospective studies supported by evidence from basal immunology studies clearly show that gout is an independent risk factor for CVD. In the coming years the precise interplay of inflammatory mediators mediating the arthritic symptoms and the potential connection with an increased cardiovascular disease profile is to be expected. For now, correct and proactive management of gout taking into account the present risk factors for the development of cardiovascular disease should have a place in the treatment of every patient with this clinical syndrome.

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# Endoscopic ultrasonography in suspected pancreatic malignancy and indecisive CT

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## ABSTRACT

**Background:** In the assessment of patients with a clinical suspicion of malignant pancreatic disease, computed tomography (CT) findings are sometimes negative or inconclusive.

**Aims:** To determine whether endoscopic ultrasonography (EUS) with or without fine needle aspiration (EUS/FNA) was conclusive in patients with a clinical suspicion of pancreatic malignancy, in whom CT scan was negative or inconclusive.

**Methods:** Retrospective case series in a tertiary referral centre. From February 2006 to December 2007, EUS/FNA was performed in all patients suspected of having malignant pancreatic disease with negative or inconclusive CT findings. Main outcome measurement was the diagnostic yield of EUS in these patients.

**Results:** 34 patients had a negative (n=11) or inconclusive (n=23) CT scan. EUS/FNA established a correct diagnosis in 30/34 cases (88%). Malignancy was diagnosed in 19/34 patients and nonmalignant disease in 8/34 cases. In 3/34 patients no lesions were found and no malignant disease developed during follow-up (mean=728 days). EUS/FNA was inconclusive in 4/34 patients.

**Conclusion:** In patients with a clinical suspicion of pancreatic malignancy with negative or inconclusive CT findings, EUS/FNA was able to establish a diagnosis in 88% of cases. EUS should therefore be considered a diagnostic modality in this complex group of patients.

## KEYWORDS

Endoscopic ultrasonography, computed tomography, pancreatic disease, malignancy

## INTRODUCTION

Pancreatic malignancy is notorious for its long asymptomatic onset and poor prognosis. In 2006 the incidence of malignant pancreatic disease in the Netherlands was 8.3/100,000.<sup>1</sup> Curative treatment options are limited in most cases because of unfavourable tumour characteristics at the time of diagnosis. Therefore long-term survival after surgery is still limited with an overall five-year survival of less than 10%. Early detection of pancreatic cancer is of utmost importance for optimal treatment.

Computed tomography (CT) and endoscopic ultrasound (EUS) have both shown to be sensitive diagnostic modalities in patients suspected of having malignant pancreatic disease. CT is a widely available diagnostic modality and has obtained the first place in the work-up of these patients. Multiple studies have investigated the value of EUS and CT for the detection and assessment of pancreatic masses. A pooled analysis comparing the diagnostic accuracy of helical CT and EUS showed that EUS is a sensitive imaging modality for detecting pancreatic lesions.<sup>2</sup> For the detection of pancreatic malignancy, and the assessment of resectability and vascular invasion, EUS is equivalent<sup>3,4</sup> or even superior to helical CT scan.<sup>5,6</sup> Compared with helical CT, EUS has a remarkably higher detection rate for small tumours (<20 mm).<sup>2,3,7</sup>

As a result of current developments in CT imaging techniques, multidetector computed tomography (MDCT) is slowly taking over the position of helical CT. In MDCT both spatial and temporal resolution are improved. Dual-phase, contrast-enhanced MDCT imaging optimises pancreatic vascular enhancement, therefore improving tumour detection and staging.<sup>8</sup> Reconstruction of curved multiplanar reformatted MDCT images allows a better evaluation of the main pancreatic duct, which may lead to a higher detection rate of small tumours.<sup>9</sup> Despite these advances in CT imaging, EUS showed to be superior for

tumour detection (sensitivity 98 vs 86%) and staging in patients with known or suspected loco regional pancreatic cancer.<sup>10</sup> In addition EUS yields the practical advantage that tissue diagnosis can be obtained during the same procedure by performing fine needle aspiration (FNA).

In clinical practice there are a substantial number of patients with a high suspicion of a pancreatic lesion, based on characteristic clinical criteria or findings at endoscopic retrograde cholangiopancreatography (ERCP) or abdominal ultrasonography (US), in whom no lesions can be identified on CT imaging.

Although CT and EUS have both independently demonstrated their diagnostic value, the role of EUS in cases where CT fails to establish a diagnosis is still undefined. Therefore our aim was to determine whether EUS with or without FNA (EUS/FNA) was able to establish a correct diagnosis in patients with a clinical suspicion of pancreatic malignancy, in whom CT scan was negative or inconclusive.

## METHODS

Patients were retrospectively identified through a database of all patients who underwent EUS/FNA at the endoscopy facility of the Department of Gastroenterology and Hepatology at University Medical Centre Groningen (UMCG), the Netherlands, which is a tertiary referral centre. From February 2006 until December 2007, 34 consecutive patients were identified who were suspected of having malignant pancreatic disease and referred for an EUS/FNA because of negative or inconclusive CT findings. Clinical suspicion of malignant pancreatic disease was defined by the referring clinician and included abdominal pain and/or painless jaundice and/or weight loss and/or double-duct sign established at previous ERCP or abdominal US. CT findings were classified as 'negative' if CT images appeared completely normal, and 'inconclusive' if a mass was seen on CT. This mass could be solid, cystic or both cystic and solid. Patients with a documented history of acute pancreatitis within 12 months were excluded. All patients initially underwent an abdominal CT scan followed by EUS/FNA. CT scans were performed using a Siemens Sensation 64-slice multidetector CT scan (Erlangen, Germany) using a standardised pancreas protocol with rapid administration of contrast and 2-mm slices. CT images were evaluated by a specialised experienced radiologist (EWvdJ). CT scans from patients referred from other hospitals were re-evaluated by the same specialised experienced radiologist (EWvdJ).

EUS was performed on an outpatient basis using conscious sedation (midazolam and pethidine) by two experienced endosonographers (HvD and RKW). The endoscopists were not blinded for the findings at CT scan. For EUS imaging a Pentax linear array EG-3870UTK echo-endoscope was

used in combination with a Hitachi EUB-8500 processor. FNA was performed with a Medi-globe 22-gauge SonoTip® II FNA needle system, using standard techniques.<sup>11</sup> A cytological analyst judged the amount and quality of the aspirate on-site. If the quality or quantity was insufficient a second or third FNA pass was performed.

An EUS procedure was defined as 'conclusive' if 1) EUS identified suspected malignant lesions with cytological FNA confirmation of malignancy or 2) EUS identified suspected malignant lesions without cytological FNA confirmation but confirmation of malignancy in resected surgical specimens was established or 3) in the case of nonmalignant disease, when the diagnosis of chronic pancreatitis, autoimmune pancreatitis or pancreatic pseudocysts was established during EUS and no malignancy developed in the follow-up period. An EUS procedure was defined as 'inconclusive' when no diagnosis could be established during EUS with or without FNA. EUS findings of a lesion were described as 'suspected for malignant lesion' when the lesion was hypo-echogenic, sharply delineated and located within the parenchyma of the pancreas.

## RESULTS

Thirty-four patients were included. Eleven patients had a negative CT scan (group I) and 23 patients had inconclusive CT findings (group II).

Patient characteristics are shown in *table 1*. The study cohort consisted of 21 men and 13 women. Mean age of patients included in group I was 66.4 years (range 37 to 75) and 56.2

**Table 1.** Characteristics of patients suspected of having malignant pancreatic disease with completely normal (group I: negative CT) or inconclusive CT findings (group II: inconclusive CT)

	Group I: negative CT (n=11)	Group II: inconclusive CT (n=23)
Age (years)	66.4 (37-75)	56.2 (17-83)
<b>Gender</b>		
• Male	6	15
• Female	5	8
<b>Time between CT and EUS (days)</b>	25.7 (range 7-61)	49.8 (range 4-184)
<b>EUS</b>		
• Number of patients with identified lesions	8	19
• Mean lesion diameter (mm)	20.9 (median 21.8 / range 14-32.5)	22.3 (median 20.75 / range 5-39.5)
• FNA performed	7	13
- Mean number of punctures	2.3 (range 1-5)	1.9 (range 1-4)
CT = computed tomography; EUS = endoscopic ultrasonography; FNA = fine needle aspiration.		



years (range 17 to 83 years) in group II. The mean interval between initial CT scan and EUS was 43 days (range 4 to 184 days). In 27 patients a lesion was identified with EUS. Lesions seen with EUS had a mean diameter of 20.9 mm in group I (median 21.8 mm/range 14 to 32.5 mm) and 22.3 mm in group II (median 20.75 mm/range 5 to 39.5 mm). In 20 patients EUS was accompanied by FNA.

**Table 2.** Distribution of malignant, nonmalignant and no disease found, in case of conclusive and inconclusive EUS/FNA findings in group I (negative CT) and group II (inconclusive CT) patients (total n=34)

		CT	
		Group I: negative	Group II: inconclusive
EUS/FNA	<b>Conclusive</b>		
	Malignant	8	11
	Nonmalignant	-	8
	No disease	2	1
		10	20 30/34
	<b>Inconclusive</b>		
	Malignant	1	-
	Nonmalignant	-	2
	No disease	-	1
		1	3 4/34

An EUS procedure was defined as 'conclusive' if 1) EUS identified suspected malignant lesions with FNA confirmation of malignancy or 2) EUS identified suspected malignant lesions without FNA confirmation but confirmation of malignancy in resected surgical specimens was established or 3) in the case of nonmalignant disease, when the diagnosis of chronic pancreatitis, autoimmune pancreatitis or pancreatic pseudocysts was established during EUS and no malignancy developed in the follow-up period. An EUS procedure was defined as 'inconclusive' when no diagnosis could be established during EUS with or without FNA. CT = computed tomography; EUS/FNA = endoscopic ultrasound-guided fine needle aspiration.

**Figure 1A.** Abdominal multidetector computed tomography scan (2-mm slices) of a patient with a clinical suspicion of pancreatic malignancy using a Siemens Sensation 64-slice multidetector CT scan (Erlangen, Germany). No lesion can be identified in the pancreatic head

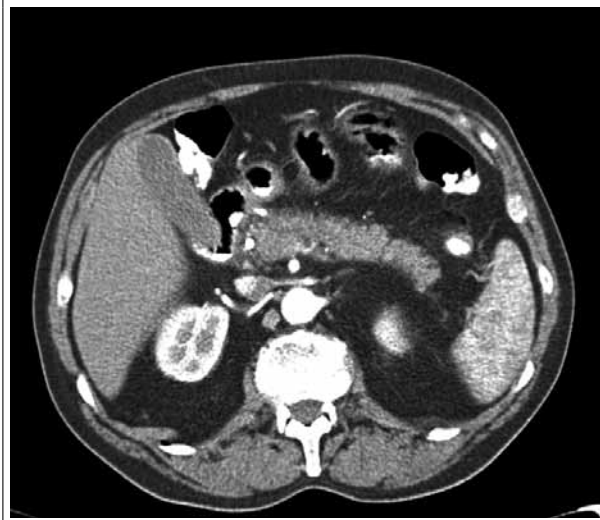


Table 2 shows whether EUS/FNA was conclusive or inconclusive in these patients and the distribution of malignant, nonmalignant disease and no lesions seen on EUS. Overall EUS/FNA was able to establish a diagnosis in 30/34 cases (88.2%). In eight out of 11 patients with normal CT findings, lesions with a diameter of up to 32.5 mm could be identified (figure 1A and 1B). Final diagnostic results of the EUS/FNA procedures are summarised in table 3.

In 19/34 (55.9%) patients a malignancy was diagnosed. Pancreatic adenocarcinoma was proven in 12 patients of

**Table 3.** Diagnosis established with EUS/FNA in patients with negative or inconclusive CT findings and clinical suspicion of pancreatic malignancy

Diagnosis	N
Malignant disease	19
• Pancreatic adenocarcinoma	12
• Neuroendocrine tumour	2
• Cholangiocarcinoma	1
• Metastatic lung carcinoma	1
• Metastatic melanoma	1
• Intraductal papillary mucinous neoplasma	1
• Mucinous cystic tumour	1
Nonmalignant disease	8
• Chronic pancreatitis	5
• Pseudocysts	2
• Autoimmune pancreatitis	1
No lesion	3
• No diagnosis	4
• No disease in follow-up	1
• Pancreatic adenocarcinoma (at surgery)	1
• Chronic pancreatitis (at surgery)	2
<b>Total N</b>	<b>34</b>

**Figure 1B.** Endosonography of the pancreatic head of the same patient using a Pentax linear array EG-3870UTK echo-endoscope and Hitachi EUB-8500 processor. An apparent hypoechogenic irregular-shaped lesion can be identified with a maximum diameter of 21.4 mm. Fine needle aspiration revealed adenocarcinoma



whom seven underwent surgical resection. In two cases the tumour was irresectable. Of those who underwent pylorus-saving pancreaticoduodenectomy, one patient was still alive at the end of follow-up (974 days). Palliation was the only therapeutic option for the single patient diagnosed with cholangiocarcinoma, as was the case for five patients with pancreatic adenocarcinoma who were not eligible for surgery. One out of two neuroendocrine tumours was due to Von Lippel-Hindau disease and this was managed without surgery. The second neuroendocrine tumour turned out to be irresectable at surgery. Successful resection was possible in case of intraductal papillary mucinous neoplasma. EUS/FNA revealed one cystic mucinous tumour which was managed expectantly. In two patients metastases were found from either lung carcinoma or melanoma. Palliative therapy was instituted in both cases. EUS/FNA revealed nonmalignant disease in 8/34 cases (23.5%). In one of these patients EUS was suspect for malignancy, but FNA revealed an autoimmune pancreatitis. In 3/34 patients no lesions were found (8.8%). Mean follow-up in these patients was 728 days (range 683 to 767 days) and revealed no pancreatic disease. In 4/34 patients (11.8%) EUS/ FNA was not able to establish a definite diagnosis. Out of these four patients, one had a pancreatic adenocarcinoma at surgery and two patients had chronic pancreatitis confirmed by surgery. In case of the last patient in whom no definite diagnosis could be made, the lesion seen on CT and EUS was most likely a pseudocyst. Therefore surgery was not indicated and watchful waiting could be justified. Follow-up of 1054 days did not reveal benign nor malignant disease.

## DISCUSSION

EUS/FNA established a correct diagnosis in 30 out of 34 patients (88%) suspected of having malignant pancreatic disease with completely normal or inconclusive CT findings. In 19 out of 34 patients EUS/FNA confirmed the clinical suspicion of pancreatic malignancy. Pancreatic malignant disease could be excluded using EUS/FNA in 11 out of 34 patients. These findings show the strength of EUS/FNA in this complicated group of patients. Pancreatic cancer is known for its insidious course. Pancreatic cancer proves to be one of the most difficult diagnoses to establish just on clinical grounds. Hence, there are abundant data that show the effectiveness of both EUS/FNA and CT in the detection and staging of pancreatic malignancy. However, in everyday clinical practice, CT may fail to establish a diagnosis. Relatively little is known about the value of EUS/ FNA in these cases with a negative or inconclusive CT scan. One study showed that both EUS and EUS/FNA had an accuracy of 92% in patients suspected of having malignant pancreatic disease although no definite mass was seen on

MDCT.<sup>12</sup> In our study, EUS has proven to be a highly valuable diagnostic modality in these cases of unconvincing CT findings and sustained clinical suspicion. These results are supported by an earlier publication presenting ten patients with obstructive jaundice and inconclusive US and CT, in whom EUS established a correct diagnosis.<sup>13</sup> Performing FNA enables a cytological diagnosis and therefore increases the diagnostic capability of EUS. EUS/FNA is known for its high sensitivity, specificity and diagnostic accuracy in the assessment of pancreatic masses in patients suspected of having malignant pancreatic disease.<sup>14,15</sup> With a complication rate <1%, EUS/FNA may be considered a safe procedure.<sup>7,16</sup> Based on symptoms we suspected 34 patients of having malignant disease, which was confirmed by EUS/FNA in 19 cases and by surgery in one patient. In addition EUS has proven to be extremely helpful for excluding pancreatic disease. In this study none of the patients (3/34) in whom no lesion was found by EUS developed pancreatic malignancy during follow-up. These findings are consistent with two studies showing a negative predictive value of 100% in case of clinical suspicion of pancreatic cancer, indeterminate CT scan and normal pancreatic EUS.<sup>17,18</sup> Yet, standardised helical CT imaging techniques were not standard of care in all patients included in these studies.

One of the limitations of our study is the variability in time between CT and EUS procedures. The mean number of days between CT and EUS was 26 for group I and 50 days for group II. This might be explained by different reasons. First of all it reflects the diagnostic difficulty and delay in this complex group of patients. Second it reflects the relative unfamiliarity of clinicians with the capacities of EUS/FNA and thirdly, it reflects the relatively low availability of EUS in the Netherlands. In one case it took 184 days before EUS was performed. This patient turned out to have chronic pancreatitis at the final diagnosis. Based on our findings CT scan should immediately be considered by an EUS/FNA when there is a clinical suspicion of malignant pancreatic disease.

In conclusion, we show that in patients with a clinical suspicion of pancreatic malignancy with negative or inconclusive CT findings, EUS with or without FNA was able to establish a diagnosis in the majority of cases. Complementary to CT, the use of EUS/FNA should therefore be considered as an accurate diagnostic modality in the work-up of this complex group of patients.

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# Abdominal pain and melena in a delirious older patient: think out of the box

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## CASE REPORT

A man, 81-years-old, was admitted to a geriatric ward with a pneumonia accompanied with a severe hypermotoric delirium. Halfway through his admission the nurses reported melena. The patient complained of abdominal pain, but because of his delirium and underlying dementia he was unable to provide details about the duration, severity and accompanying symptoms. The nurses had observed a poor appetite, but no vomiting or swallowing problems. The abdominal examination was normal. His medical history did not reveal dyspepsia or a bleeding diathesis. He was taking acetylsalicylic acid and mirtazepine together with omeprazole to counterbalance the slightly increased risk of bleeding of this combination of drugs. He had already been on this combination for years without problems. His blood counts beforehand were normal, with a 1.2 mmol/l drop in haemoglobin during the melena.

## WHAT IS YOUR DIAGNOSIS?

See page 368 for the answer to this photo quiz.

**Figure 1.** Radiograph including an arrow pointing to the drawing pin



# A 56-year-old female with fever and a painful, red, swollen leg

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## CASE

A 56-year-old woman, with a medical history of breast cancer, for which a lumpectomy was performed in 2003 with additional radiotherapy, presented with a blister-like lesion on her lower left leg. The leg was swollen from the ankle towards the knee and red with a tender and shiny aspect (*figure 1*). This was accompanied by general discomfort and fever (38.3 °C). The skin lesion had developed in a few hours. There were no risk factors for deep venous thrombosis. Approximately two hours before development of the skin lesion our patient was stung by a mosquito. At physical examination we could not detect any abnormalities apart from the demonstrated skin lesion. There were no wounds on her feet or legs.

Figure 1.



## WHAT IS YOUR DIAGNOSIS?

See page 369 for the answer to this quiz.

# Scrotal and inguinal mass

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## CASE REPORT

A 47-year-old man presented with painless scrotal enlargement and bilateral inguinal masses. The lesions had progressed slowly over the last ten months. No weight loss, fatigue, fever or night sweats were reported, neither a history of visits to tropical countries. Physical examination revealed a large testicular mass with scrotal skin infiltration and bilateral massive ulcerative inguinal lymph nodes (*figure 1*). On laboratory investigation lactic dehydrogenase was elevated (11,355 U/l).

## WHAT IS YOUR DIAGNOSIS?

See page 370 for the answer to this photo quiz.

**Figure 1.** Patient presented with a large testicular mass with scrotal skin infiltration and bilateral massive ulcerative inguinal lymph nodes



## DIAGNOSIS

Ultimately a nurse reported that she had seen the patient investigating a cup of drawing pins on the drawing board. A plain abdominal radiograph showed a drawing pin in his intestines with no signs of perforation. It is likely that the pin had scratched the mucosa of the oesophagus and stomach. We had no other explanation for the melena. Furthermore, after omeprazole in a high dose of 40 mg twice daily for a few days and extra laxatives, the melena and abdominal pain resolved. The drawing pin was no longer present on a subsequent radiograph two weeks later. Because of the severe delirium, a gastroscopic evaluation had not been feasible to check for mucosal damage or other pathology. Although the pin is the likely cause of the melena, given the patient's impaired memory and the unknown ingestion time of the pin, the exact cause will remain a mystery.

How can you ingest a sharp drawing pin? Probably the delirium had changed the perception of the pin into something appetising, or the patient had ingested it accidentally. Despite this plausible explanation and the many patients with a delirium at risk of ingesting foreign bodies, this problem has not been described in this subgroup before. Presumably it is often unnoticed by staff and unreported by the patient.

Ingestion of small objects is commonly reported in children as is the involuntary ingestion of (fish)bones in healthy adults. In psychiatric patients and prison inmates deliberate ingestion of foreign bodies is common.<sup>1</sup> Most

ingested foreign bodies pass spontaneously, usually over seven to ten days. Endoscopic or surgical intervention is indicated only when significant symptoms develop, necessary in 1 to 14% of cases.<sup>2</sup> Serious complications encompass bowel perforation, gastrointestinal bleeding, inflammation and obstruction.<sup>3</sup> Risk factors are impaction at the level of the cricopharyngeus or oesophagus and a delayed presentation of more than two days after swallowing.<sup>4</sup> Thin, sharp objects carry the highest risk of perforation.

In conclusion, just as people in a delirium can do unusual things, caregivers should consider unusual causes of symptoms and be aware of potential dangerous items in the rooms of delirious patients.

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## SKEETER SYNDROME

Mosquito bites typically give rise to local cutaneous reactions consisting of immediate wheals and flares with delayed pruritic indurated papules peaking at 24 to 36 hours and diminishing over days or weeks.<sup>1</sup> Allergic reactions to mosquito bites are characterised by development of large or atypical local reactions, such as red, itchy, warm swellings appearing within minutes of the bites and itchy papules, ecchymotic, vesiculated, blistering bullous reactions appearing two to six hours after the bites and persisting for days or weeks.<sup>2</sup> Mosquito bites can also result in anaphylaxis.

Skeeter syndrome is defined as a mosquito saliva-induced large local inflammatory reaction that may be accompanied by low-grade fever.<sup>1</sup> Due to its comparable clinical picture it is often misdiagnosed as cellulitis.

Allergic mosquito bite reactions are due to specific sensitisation to mosquito salivary proteins, as exposure to mosquito species to which an individual has not previously been exposed causes no reaction. Mosquito saliva contains many proteins, most of which are allergenic in humans.<sup>3</sup> Mosquito bite reactions involve mosquito saliva-specific immunoglobulin (Ig)E and IgG antibodies as well as lymphocyte proliferation.<sup>1</sup> In local allergic reactions IgE and IgG levels and lymphocyte proliferation index are elevated, whereas in systemic reactions only IgE seems to be involved. Non-IgE-mediated mast cell degranulation is also involved in allergic responses leading to fluid extravasation and neutrophil recruitment.<sup>1</sup>

Diagnosing mosquito allergy is mainly based on the medical history of an allergic reaction following a witnessed bite. Immunoassays, detecting mosquito salivary specific IgE antibodies, have been developed recently, but they showed low sensitivity and specificity.<sup>2</sup>

People with mosquito allergy should avoid mosquito-infested areas, wear protective clothes and apply mosquito repellents (N,N-diethyl-m-toluamide (DEET)) to exposed skin. Administration of H<sub>1</sub>-antihistamines reduces itching in early-phase responses. Mild late-phase reactions can be treated with local application of glucocorticoid cream and severe large local reactions should be treated with systemic administration of prednisone (1 mg/kg for five to

seven days). There is no place for antibiotic treatment in these reactions.<sup>1</sup> Immunotherapy is neither well studied nor widely used because currently commercially available mosquito whole body extracts contain little mosquito saliva proteins and many nonsalivary proteins, which are ineffective in downregulating the specific immune responses to mosquito salivary allergens.<sup>4</sup> In our patient treatment with 50 mg prednisone for seven days led to complete remission of the skin lesion (*figure 2*) three days after start prednisone).

Figure 2. Three days after start prednisone



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## DIAGNOSIS

Further laboratory examination revealed elevated beta-human chorionic gonadotropin ( $\beta$ HCG, 42 U/l, normal <1 U/l), while alpha-fetoprotein was normal ( $\alpha$ FP, 4.5 U/l, normal <10 U/l). Histopathological examination of an inguinal lymph node showed seminoma. Staging of the patient with CT scanning of brain, thorax and abdomen demonstrated para-aortal lymphadenopathy and impressive inguinal lymphadenopathy (*figure 2*). Treatment with bleomycine, etoposide and cisplatinium was started. After four cycles a complete pathological remission of both the lymph nodes and primary tumour was demonstrated by orchidectomy.

**Figure 2.** CT scanning of brain, thorax and abdomen demonstrated para-aortal and inguinal lymphadenopathy



Testicular cancer is the most common malignancy in men under the age of 50 years and its incidence is increasing.<sup>1</sup> Patients often present with a painless scrotal mass without systemic signs or symptoms. Typically, metastatic spread occurs via efferent lymphatic vessels following the spermatic cord towards iliac and retroperitoneal lymph nodes. Inguinal lymph nodes drain the scrotal skin, perineum and penis. Involvement of inguinal lymph nodes in testicular cancer is rare<sup>2</sup> and is generally related to either a history of locoregional surgery, local invasion of the tumour into the tunica vaginalis or scrotal skin, or bulky retroperitoneal lymph node metastases.<sup>2-4</sup> Since surgical correction of cryptorchidism early in childhood has become common practice, the incidence of inguinal lymph node involvement in testicular cancer will probably increase. The occurrence of inguinal lymphadenopathy is not related to a specific histological subtype of testicular cancer. Our patient underwent surgery for a hydrocele 13 years ago but, given the bilaterality of the inguinal lymphadenopathy, the infiltration of the scrotal skin has probably contributed to this rare presentation.

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# Lapatinib: clinical benefit in patients with HER2-positive advanced breast cancer

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## ABSTRACT

**Background:** Lapatinib, a tyrosine kinase inhibitor of human epidermal growth factor receptor 2 (HER2), has shown activity in combination with capecitabine in patients with HER2-positive advanced breast cancer progressive on standard treatment regimens. We present results on preapproval drug access for this combination in such patients occurring in the general oncology practice in the Netherlands.

**Methods:** Patients with HER2-positive advanced breast cancer progressive on schedules containing anthracyclines, taxanes, and trastuzumab were eligible. Brain metastases were allowed if stable. Lapatinib 1250 mg/day was given continuously in combination with capecitabine 1000 mg/m<sup>2</sup> twice daily for two weeks in a three-week cycle. Efficacy was assessed by use of response evaluation criteria in solid tumours version 1.0. Progression-free survival (PFS) and overall survival (OS) were calculated.

**Results:** Eighty-three patients were enrolled from January 2007 until July 2008. The combination was generally well tolerated and the most common drug-related serious adverse events were nausea and/or vomiting (5%) and diarrhoea (2%). Seventy-eight patients were evaluable for response. Clinical benefit (response or stable disease for at least 12 weeks) was observed in 50 patients (64%) of whom 15 had a partial response and 35 stable disease. The median PFS and OS were 17 weeks (95% CI: 13 to 21) and 39 weeks (95% CI: 24 to 54), respectively. For OS, higher Eastern Cooperative Oncology Group (ECOG) status ( $p=0.016$ ), brain metastases at study entry ( $p=0.010$ ) and higher number of metastatic sites ( $p=0.012$ ) were significantly negative predictive factors.

**Conclusion:** In a patient population with heavily pretreated HER2-positive advanced breast cancer lapatinib plus capecitabine was well tolerated and offered clinical benefit.

## KEYWORDS

Advanced breast cancer, capecitabine, HER2, lapatinib

## INTRODUCTION

Human epidermal growth factor receptor 2 (HER2; ErbB2) is overexpressed in 20% of patients with breast cancer. HER2 amplification is associated with a more aggressive phenotype.<sup>1,2</sup> Trastuzumab is a humanised monoclonal antibody against the extracellular domain of HER2. Combination with chemotherapy improves overall survival in patients with HER2-positive breast cancer, both in the metastatic and in the adjuvant setting.<sup>3</sup> Recently, lapatinib, an oral small molecule tyrosine kinase inhibitor targeting both HER2 and epidermal growth factor receptor (EGFR; HER1), has been approved for patients with advanced HER2-positive breast cancer previously treated with other anticancer drugs including trastuzumab. It is licensed for use in these patients in combination with capecitabine.<sup>4,5</sup> Several trials have demonstrated the safety and efficacy of lapatinib alone and in combination with capecitabine, paclitaxel or endocrine therapy in patients with advanced HER2-positive breast cancer.<sup>4,9</sup> Lapatinib is not active against EGFR-positive/HER2-negative disease.<sup>8,10</sup> Of

interest, lapatinib can cross the blood-brain barrier and has modest activity in breast cancer metastases in the central nervous system.<sup>4,7,8,10,11</sup> As monotherapy, lapatinib is well tolerated. Main toxicities are mild diarrhoea, nausea and skin rash.<sup>12</sup> Cardiac toxicity is rarely seen with lapatinib.<sup>13</sup> In the registration trial in which the lapatinib + capecitabine combination was investigated in HER2-positive breast cancer patients who had previously been treated with an anthracycline, a taxane, and trastuzumab, disease progression was significantly delayed.<sup>4,5</sup> Median time-to-progression with the combination was 6.2 months as compared with 4.3 months for treatment with capecitabine alone ( $p=0.00013$ ). This improvement was achieved without an increase in serious toxic effects or symptomatic cardiac events. A global Lapatinib Expanded Access Program was initiated in 2007 to offer preapproval drug access to lapatinib in combination with capecitabine in order to provide potential clinical benefit to patients with HER2-positive breast cancer, who had previously received anthracyclines, taxanes and trastuzumab. In contrast to the strict inclusion and exclusion criteria in the registration trial, the program allowed entry of a broader patient population: eligibility criteria allowed nonmeasurable disease, Eastern Cooperative Oncology Group (ECOG) performance status 2, previous capecitabine treatment, irradiated brain metastases if stable, and a maximum dose of dexamethasone 2 mg/day.

## METHODS

### Patients

Eligible patients had HER2-positive locally advanced or metastatic breast cancer that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab. Previous treatment with capecitabine was permitted. Patients had measurable or evaluable disease; an ECOG performance status of 0 to 2; a left ventricular ejection fraction (LVEF) within the institution's normal range; a life expectancy of at least 12 weeks; adequate renal, hepatic, and haematological function: haemoglobin  $\geq 9$  g/dl, neutrophils  $\geq 1.5 \times 10^9/l$ , platelets  $\geq 100 \times 10^9/l$ , serum bilirubin  $\leq 3 \times$  upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase  $\leq 5 \times$  ULN, calculated creatinine clearance according to the Cockcroft and Gault method  $\geq 30$  ml/min. Patients with central nervous system (CNS) metastases were eligible if they had been clinically stable for at least three months; a dexamethasone dose  $>2$  mg/day and anticonvulsant therapy were not allowed. Since lapatinib is predominantly metabolised by the cytochrome P450 isoenzyme 3A4 (CYP3A4), inhibitors or inducers of CYP3A4 were prohibited.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The institutional review board of each participating institution approved the study protocol. All patients gave written informed consent.

### Treatment

Treatment consisted of lapatinib 1250 mg/day continuously, one hour before or after breakfast and capecitabine 1000 mg/m<sup>2</sup> twice daily for two weeks in a three-week cycle. In case of side effects, standard recommendations for lapatinib and capecitabine dose modifications were advised according to the protocol. Briefly, lapatinib was withheld for up to 14 days for grade 2 haematological toxicity or any grade 3 or 4 toxicity. After recovery to grade 0 or 1, lapatinib was to be resumed at a dose of 1250 mg/day, although the site investigators could reduce the dose to 1000 mg/day if this was considered to be in the patient's interest. Resumption of lapatinib administration after grade 4 toxicity was optional, but required a dose reduction to 1000 mg/day. Lapatinib was permanently discontinued if improvement (a change to grade 0 or 1) did not occur within 14 days or if grade 3 or 4 interstitial pneumonitis or cardiac dysfunction occurred. Treatment continued until the investigator identified disease progression or unacceptable toxic effects.

### Measurements

Patients were clinically assessed every three weeks and at the end of treatment. Side effects were recorded as serious adverse events (SAEs), defined as any event that was fatal, life-threatening, disabling or incapacitating or resulted in hospitalisation, prolonged a hospital stay and any experience which the investigator regarded as serious or which would suggest any significant hazard, contraindication, side effect or precaution that might be associated with the use of the drug. Monitoring of the LVEF by means of echocardiography or multiple gated acquisition scanning was performed every 12 weeks with the use of the same technique for the duration of the study. A cardiac event was defined as a decline in the LVEF that was symptomatic or was asymptomatic, but with a relative decrease of 20% or more from baseline or to a level below the institution's normal range.

Efficacy was assessed every 12 weeks according to the response evaluation criteria in solid tumours (RECIST) version 1.0. Progression-free survival (PFS) was defined as the time from the start of treatment until disease progressed or death from any cause. Overall survival (OS) was defined as the time from the start of treatment until death from any cause. Clinical benefit was defined as a complete response, partial response or stable disease for at least 12 weeks.

### Statistics

Comparison of categorical data between groups was done using the  $\chi^2$  test or Fisher's exact test. PFS and OS

were assessed using Kaplan-Meier curves. Comparison of survival between groups was done with the log-rank test or the log-rank test for trend in case of ordered groups (ECOG status and number of metastatic sites). Multivariate analysis of prognostic factors (ECOG status, prior treatment, disease extent) was done using Cox regression. P values (two-sided)  $\leq 0.05$  were considered significant.

## RESULTS

### Patients and treatment duration

Eighty-three patients were enrolled in the expanded access study in the Netherlands from January 2007 until July 2008. Patient characteristics are shown in *table 1*. The median age was 50 years and the median ECOG performance score was 1. At the start of treatment, 98% of patients had metastatic disease and 53% had a median of three different sites. Thirty patients (36%) had central nervous system (CNS) metastases. Prior treatment consisted of a median of one hormonal (range: 0 to 5) and three cytotoxic schedules (range: 1 to 8) and 56 patients (67%) had received a prior fluoropyrimidine.

**Table 1.** Baseline patient characteristics

Characteristics	Numbers of patients or median (range)	%
Age (years)		
• Median	50	
• Range	26-70	
ECOG performance status		
• 0	18	22
• 1	50	60
• 2	15	18
Hormone receptor status		
• Positive for ER and/or PR	42	51
• Negative	40	48
• Unknown	1	1
Stage of disease		
• Locally advanced	2	2
• Metastatic	81	98
No. of metastatic sites		
• >3	44	53
• 2	28	34
• 1	11	13
Metastatic sites		
• Bone	52	63
• Lung	36	43
• Liver	53	64
• Brain	30	36
• Lymph node	38	46
• (Sub)cutaneous	17	20
• Other	12	14
Previous chemotherapy regimens (incl. adjuvant)		
• Median	3	
• Range	1-8	
Previous fluoropyrimidine	56	67

ER = oestrogen receptor; PR = progesterone receptor; No = number.

The median treatment duration of lapatinib plus capecitabine was 18 weeks (range 3.5 to 68 weeks). Seventy-eight patients discontinued treatment, most frequently because of progressive disease, and entered into the follow-up phase. Additional discontinuation reasons were toxicity (4%) and withdrawal of consent (1%).

### Safety

All patients were evaluable for safety analysis. SAEs were reported in 19 patients of whom seven were considered to be related to the study drug. These SAEs consisted of nausea and/or vomiting (4 reports), diarrhoea (2), dehydration (1), increase in hepatic enzymes (1), malaise (1) and venous thrombosis (1). In four patients fatal SAEs were reported: myocardial ischaemia, cardiogenic shock, central nervous system metastases and arterial haemorrhage, respectively. These four events were not considered to be related to treatment in the opinion of the reporting investigator. The safety profile of lapatinib plus capecitabine was consistent with other studies on this combination.<sup>4</sup> Toxicity resulted in withdrawal from study drug in 4% of patients.

### Efficacy and determinants for survival

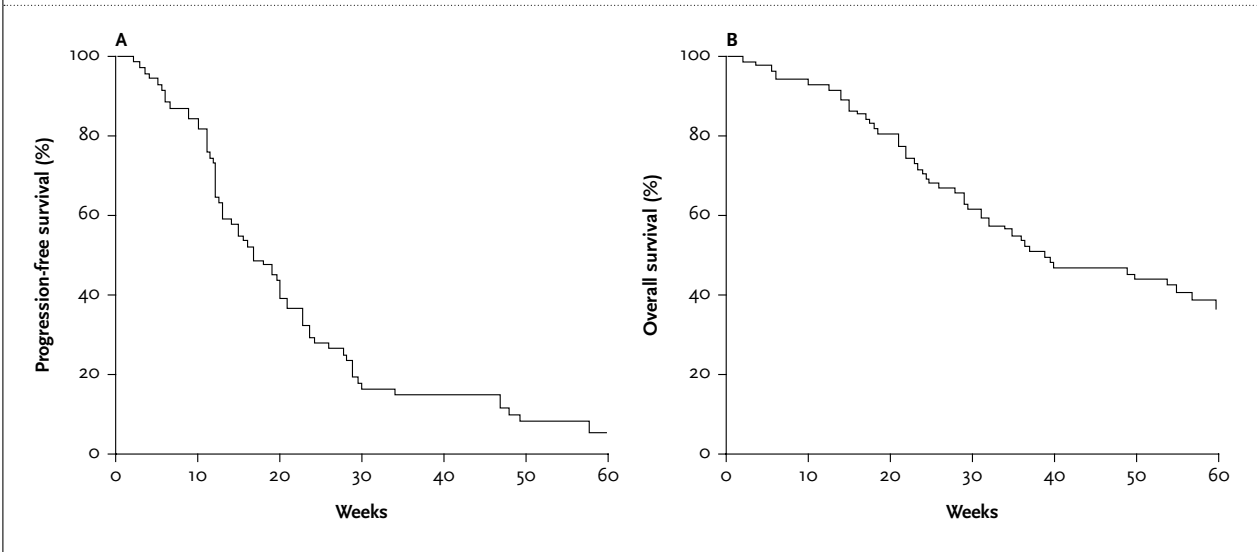
The efficacy endpoints are depicted in *table 2* and *figures 1A* and *B*. The median PFS in all evaluable patients was 17 weeks (95% CI: 13 to 21; *figure 1A*). OS for all patients at a median follow-up of 35 weeks was 39 weeks (95% CI: 24 to 54; *figure 1B*). Seventy-eight patients were evaluable for response. A partial response was observed in 15 patients (three not confirmed) resulting in an overall response rate of 19% (95% CI: 11 to 30). Stable disease for at least 12 weeks occurred in 35 patients (45%). Therefore, the clinical benefit rate was 64%. *Figure 2* illustrates a partial response in a single patient upon treatment with the lapatinib + capecitabine combination.

Several patient characteristics were tested for a possible relation with OS. OS decreased significantly with increasing ECOG status ( $p=0.016$ ; *figure 3A*). Additionally, survival decreased with a higher number of metastatic sites: median survival gradually shortened from 64 weeks if one site was reported to 29 weeks if five or more sites were present ( $p=0.012$ ). The number of prior hormonal

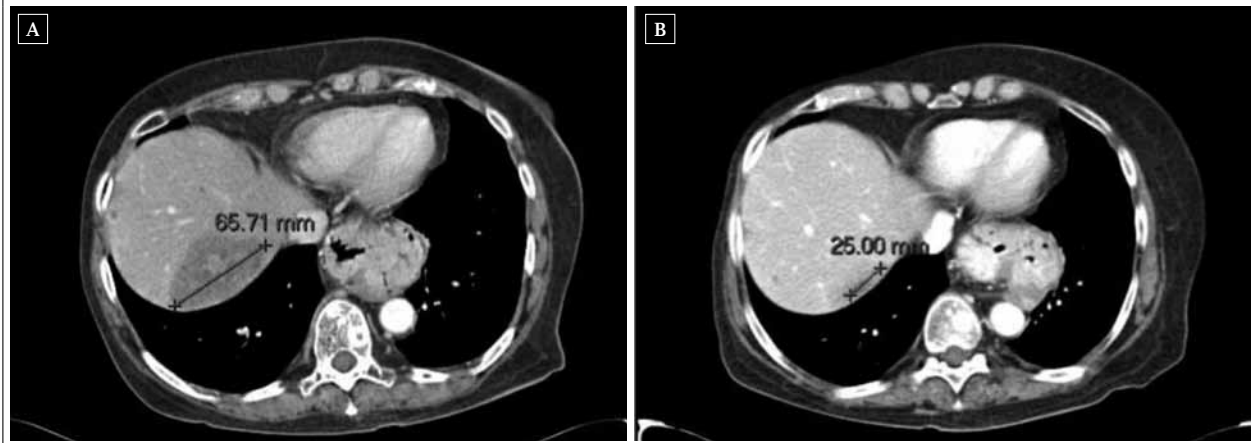
**Table 2.** Efficacy in evaluable patients ( $n=78$ )

Endpoint	Numbers of patients	%
Complete response (CR)	0	0
Partial response (PR)	15	19
Stable disease (SD)	35	45
Progressive disease (PD)	28	36
Clinical benefit (PR + SD $\geq 12$ weeks)	50	64

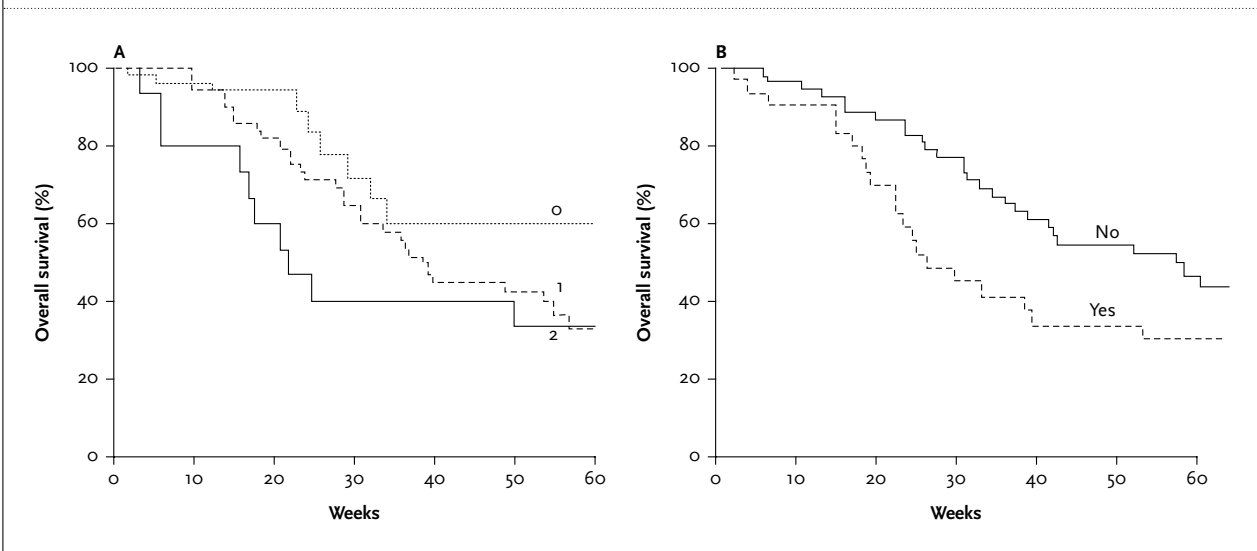
**Figure 1.** Kaplan-Meier curves of progression-free survival (A) and overall survival (B) of patients with HER2-positive advanced breast cancer treated with lapatinib and capecitabine



**Figure 2.** Liver metastasis before (A) and after (B) treatment with lapatinib and capecitabine



**Figure 3.** Overall survival in relation to Eastern Cooperative Oncology Group status ( $p=0.016$ ) (A) and the presence (yes) or absence (no) of brain metastases at study entry ( $p=0.010$ ) (B) of patients with HER2-positive advanced breast cancer treated with lapatinib and capecitabine



and chemotherapy schedules was not significantly related to outcome. The median OS of 35 weeks in patients with prior fluoropyrimidine exposure, either consisting of a 5-fluorouracil-containing regimen or capecitabine, tended to be shorter when compared with the 55 weeks ( $p=0.143$ ) in patients without previous fluoropyrimidine treatment. The presence of brain metastases at entry into the study was predictive of a worse survival ( $p=0.010$ ; *figure 3B*).

## DISCUSSION

The combination of lapatinib and capecitabine was well tolerated and provided clinical benefit in a population of patients with heavily pretreated HER2-positive advanced breast cancer. Inclusion criteria were less strict than in the registration trial. Therefore, our results represent the safety profile and efficacy that can be expected in a patient population known to occur in the general oncology practice.

Although slightly different study designs do not permit comparison of data, in our patients treated with lapatinib and capecitabine the median OS was nine months, whereas this was 15.6 months in the registration trial.<sup>5</sup> Differences in baseline inclusion criteria, such as performance status, might explain this finding as ECOG status was significantly related to OS. Brain metastases at study entry and a higher number of metastatic sites were also found to be related to a worse OS. Data of the recently published global Lapatinib Expanded Access Program showed a median PFS of 21.1 weeks and a median OS of nine months,<sup>14</sup> which are in line with the results of a similar program from the United Kingdom<sup>15</sup> and the current study. The majority of our patients responded or had stable disease for at least 12 weeks (maximal 68 weeks), which may be considered as clinical benefit. We, therefore, believe that the lapatinib + capecitabine schedule is a useful addition to the treatment armamentarium for patients with HER-2-positive advanced breast cancer. The current study showed a trend towards a better survival for patients who had not received previous fluoropyrimidine treatment, which reflected the results observed in the global lapatinib program.<sup>14</sup> It might be considered to reserve capecitabine for its combination with lapatinib in patients with HER2-positive disease. Further characterisation of the predictors for response is important to select patients who might particularly benefit from this combination.

The limitation of our study is that it concerns an expanded access program and data were partially analysed in a retrospective way. Besides SAEs, common adverse events were not required to be reported. For toxicities known to occur from the lapatinib + capecitabine combination, such as diarrhoea, nausea, vomiting, hand-foot syndrome, and skin rash,<sup>4</sup> the protocol was followed for dose delays or

reductions depending on the severity of adverse events. We observed that the drug-related SAEs were consistent with the global lapatinib program and they generally resolved upon treatment discontinuation. In this study no drug-related cardiac SAEs were reported, which is in agreement with the favourable cardiac toxicity profile of lapatinib.<sup>13</sup> These safety data also support the lapatinib + capecitabine combination as an appropriate new treatment option for heavily pretreated patients with HER2-positive disease.

Brain metastases develop in 25 to 40% of patients with advanced HER2-positive breast cancer,<sup>16</sup> which is in accordance with the 36% of the patients included in this study. Although the presence of brain metastases at entry into the study was predictive of a worse survival, the PFS of patients with evaluable brain metastases ( $n=22$ ) was not different from the overall PFS (data not shown). There are limited therapeutic options for these patients after cranial radiotherapy. In a phase II trial, CNS objective responses obtained with lapatinib monotherapy as well as with the lapatinib + capecitabine schedule were observed in 6 and 20% of patients, respectively.<sup>17</sup> An exploratory analysis revealed a  $\geq 20\%$  volumetric reduction of CNS lesions in 21 and 40% of patients, respectively. Prospective trials of lapatinib combinations are underway in patients with CNS metastases. The observed clinical benefit of the lapatinib + capecitabine treatment might be explained by different features of lapatinib to escape the mechanisms of resistance to earlier treatments. First, patients with advanced breast cancer expressing p95HER2, a constitutively active, truncated form of HER2 with kinase activity but lacking the extracellular domain, have a low chance of a response to trastuzumab.<sup>18</sup> Lapatinib, as an intracellular small molecule, has been shown to inhibit p95HER2 phosphorylation *in vitro*, leading to reduced downstream phosphorylation of Akt and MAPK, and inhibition of cell growth as well as experimental tumour growth. Second, HER2 epitope masking may also be a mechanism of resistance to trastuzumab. Mucin 4 is a large, highly O-glycosylated membrane-associated glycoprotein that hinders the binding of an antibody, but a tyrosine kinase inhibitor may reach its target.<sup>19</sup> Possible advantages of lapatinib over resistance to other HER2 inhibitors should be further unravelled. This also holds for the role of lapatinib in the adjuvant setting. In current clinical trials in early HER2-positive breast cancer lapatinib is being compared with trastuzumab, with trastuzumab followed by lapatinib, or with a combination of lapatinib and trastuzumab (ALTTO) or lapatinib is being compared with control in a delayed adjuvant therapy design (TEACH).

In conclusion, exploratory data from lapatinib in combination with capecitabine from eight Dutch hospitals confirmed that this schedule is well tolerated. The combination provides clinical benefit in the majority of heavily pretreated patients with HER2-positive metastatic breast cancer, including

patients who have been treated with a fluoropyrimidine before and patients with brain metastases.

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# CAPD peritonitis after colonoscopy: follow the guidelines

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## ABSTRACT

We present two cases of peritonitis shortly after endoscopic examination of the large bowel with polypectomy in patients on continuous ambulant peritoneal dialysis (CAPD) despite the standard preventive measure to drain the dialysate from the abdomen prior to the procedure. We have reviewed the current literature on this topic. These cases demonstrate that the administration of prophylactic broad-spectrum antibiotics next to the drainage of the abdomen prior to colonoscopy in CAPD patients should be considered as recommended in the International Society for Peritoneal Dialysis (ISPD) guidelines 2005.

## KEYWORDS

Peritonitis, CAPD, colonoscopy, prophylactic antibiotics

## INTRODUCTION

Peritonitis in CAPD patients after colonoscopy is a known complication. A retrospective study from Hong Kong revealed an average risk of peritonitis after colonoscopy of 6.3% in 77 CAPD patients after 97 endoscopic procedures.<sup>1</sup> Colonic biopsy or other interventions such as polypectomies apparently did not increase the risk of peritonitis.<sup>2</sup>

After colonoscopy in CAPD patients it is thought that bacteria may translocate to mesenteric lymph nodes, then to portal circulation resulting eventually in systemic bacteraemia with peritoneal seeding. In CAPD patients the glucose-containing fluid in the peritoneal cavity impairs the local immune response by diluting cytokines and reducing the macrophage level. The function of mesothelial surface and cells, another local host defence

system, may be altered due to presence of dialysis solution. Further, activated cytokines and macrophages are constantly removed by daily changes of the dialysate.<sup>3</sup> All these factors may facilitate bacterial growth in the peritoneal cavity even with a small inoculum of bacteria.

## CASE REPORTS

A colonoscopy was performed at our outpatient clinic in a 67-year-old female patient with chronic end-stage renal failure maintained on continuous ambulant peritoneal dialysis (CAPD) because of recurrent rectal bleeding, frequent loose stools and faecal incontinence since a few months. She has been undergoing CAPD since November 2006. She had one episode of a culture-negative CAPD peritonitis two years ago.

The patient drained her abdomen shortly before scheduled endoscopy. No prophylactic antibiotics were given. During endoscopy diverticula were seen in the sigmoid colon. A sessile polyp in the mid-transverse colon was removed with a snare after lifting the lesion with 6 cc adrenaline/saline. Histology revealed a serrated adenoma. The procedure was uneventful and the patient left hospital a few hours after the procedure.

Two days after colonoscopy the patient was readmitted because of abdominal discomfort and a cloudy dialysate, suggestive of CAPD peritonitis. On admission we saw an obese female, not in distress. There was no abdominal distension nor rebound tenderness. On X-ray there was no evidence of perforation. Laboratory analysis at admission showed an elevated C-reactive protein of 37 mg/l with a mild leucocytosis of  $10.7 \times 10^9/l$  with a leftward shift. The dialysate contained 5500 leucocytes/mm<sup>3</sup> with 80% neutrophils.



The diagnosis of CAPD peritonitis after colonoscopy with polypectomy was evident. After obtaining cultures therapy was started with a single-dose vancomycin 2 g and ceftazidime 1 g intraperitoneally. Treatment was continued with ceftazidime intraperitoneally once daily for a period of three weeks. The diagnosis was confirmed by a positive dialysate culture for *Escherichia coli*. The patient recovered completely.

The second patient from a district hospital, a 73-year-old man, on CAPD for years due to end-stage renal failure without any prior peritonitis, underwent a colonoscopy for the analysis of overt rectal bleeding. A large caecal polyp was removed with a snare. Two days later the patient was readmitted with abdominal pain and a cloudy dialysate. On admission the patient was not in distress and no evidence of perforation was seen on X-ray. Laboratory analysis revealed an elevation of C-reactive protein (58 mg/l) and a mild leucocytosis ( $10.5 \times 10^9/l$ ). The dialysate contained 11,467 leucocytes per mm<sup>3</sup>. This patient was treated immediately with vancomycin and gentamicin intraperitoneally according to the local protocol and left hospital after six days, fully recovered. This treatment was continued for two weeks. The pre-emptive diagnosis of CAPD peritonitis after colonoscopy was confirmed by a positive dialysate culture for *Escherichia coli*, *Klebsiella oxytoca* and *Enterococcaceae*.

## DISCUSSION

In the 2005 guidelines for CAPD peritonitis of the International Society for Peritoneal Dialysis (ISPD) drainage of the peritoneal cavity and antibiotic prophylaxis with ampicilline, an aminoglycoside with or without metronidazole intravenously prior to colonoscopy is recommended. However, due to the lack of prospective trials there is scarce evidence to support this recommendation. Therefore, this guideline is not widely accepted and implemented. In the current guidelines of the Dutch Federation of Nephrology (NfN) the use of prophylactic antibiotics additionally to drainage of the dialysate before colonoscopy is recommended.<sup>4</sup> However it is mentioned that this is currently not daily practice in the Netherlands. Furthermore, these nephrology guidelines are widely unknown among gastroenterologists who are responsible for the planning and performance of endoscopic procedures. In the current guidelines of the American Society for Gastrointestinal Endoscopy (ASGE),<sup>5</sup> the British Society of Gastroenterology (BSG)<sup>6</sup> and the European Society of Gastrointestinal Endoscopy (ESGE),<sup>7</sup> the risk of peritonitis in PD patients is not mentioned. No advice is given about antibiotic prophylaxis in these patients prior to colonoscopy.

In 2009, two colonoscopies in 32 CAPD patients were performed in our hospital with one episode of peritonitis. Although peritonitis after colonoscopy in CAPD patients might be a rare event, it may lead to serious complications in the short and long term and even to death.<sup>8</sup> Recurrent peritonitis remains the primary reason to switch from PD to haemodialysis.<sup>9</sup> In distinction, the prophylactic use of a single-dose antibiotic prior to colonoscopy has almost no risks.

The implementation of the ISPD guidelines should be considered in every endoscopy unit performing colonoscopies in CAPD patients. We strongly recommend the use of antibiotic prophylaxis next to drainage of the peritoneal cavity prior to colonoscopy in CAPD patients as advised in the ISPD guidelines. A clear, interdisciplinary communication over these patients between gastroenterologist and nephrologist is important to prevent this serious complication.

## CONCLUSION

CAPD peritonitis after colonoscopy is not a rare event. It may lead to serious morbidity. With our cases we have demonstrated that drainage of the peritoneal cavity prior to endoscopy is not sufficient to prevent infectious complications. We therefore recommend implementing the current ISPD guidelines to use additional antibiotics. The gastroenterologist should be familiar with this guideline.

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# Benign uterine uptake of FDG: a case report and review of literature

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Dear Editor,

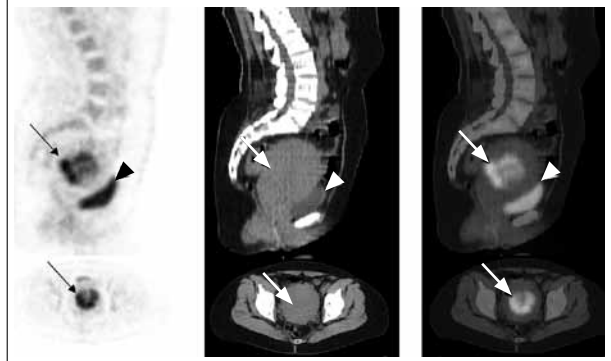
We observed very high uterine [<sup>18</sup>F]-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) in what proved to be a benign uterine leiomyoma. Although clinically apparent in 25% of women<sup>1</sup> and prevalent in up to 77%,<sup>2</sup> this phenomenon is only incidentally described. Here we present a case of a 49-year-old woman. Our patient underwent an FDG-PET/CT for follow-up of an infectious focus on the lower back. Apart from a metabolically active lymph node and bone marrow, it revealed a ~9.6 cm large, inhomogeneous but sharply demarcated FDG-avid lesion in the posterior uterine wall (figure 1). The lesion was ultrasonographically a typical large leiomyoma.

An abdominal hysterectomy was performed for lumbago and anaemia due to menometrorrhagia. Histopathological examination revealed an enlarged uterus with an intramural leiomyoma of 7.8 cm in diameter and multiple small subserosal leiomyomas, the size below the resolution of the PET/CT scanner. Microscopy showed the typical image of a leiomyoma, without signs of necrosis, haemorrhage, atypia or inflammation. There was no cervical atypia and the endometrium was thin (<1 mm) and showed some changes corresponding to progestagen suppletion.

In search of an explanation for the high FDG uptake, sections of the anterior – on PET normal – uterine myometrium were compared with sections of the leiomyoma. Immunohistochemical staining of markers for proliferation, inflammation, hypoxia, apoptosis, vascularity, glucose metabolism and glycogen content was quantified. This quantification demonstrated a slight increase in proliferation and glycogen content.

Incidentally found leiomyomas are occasionally reported to have elevated FDG uptake (standardised uptake value (SUV)

**Figure 1.** [<sup>18</sup>F]-fluorodeoxyglucose (FDG) positron emission tomography with nondiagnostic, low-dose x-ray computed tomography performed in a 49-year-old woman with a history of soft tissue infection of the lower back. Arrow: intense FDG uptake (max SUV: 12.7, mean SUV: 8.4) in the enlarged uterus, posterior wall. Arrowhead: urinary bladder. SUV = standardised uptake value, parameter representing the relative increase of the regional uptake of the tracer above expected from homogenous distribution over the body.



6.0 to 16).<sup>3,4</sup> Retrospective analysis of screening FDG-PET in 589 healthy women found increased FDG-uptake due to leiomyomas in 22 females of which only 14% showed FDG uptake higher than the liver.<sup>5</sup> A screening FDG-PET in 1357 healthy women found an SUV larger than 3.0 in 10% of the leiomyomas in premenopausal women and in only 1.2% in postmenopausal women.<sup>6</sup> A prospective study of 61 proven leiomyomas showed that 17% have an SUVmax higher than 2.5, but only one had an SUV larger than 5.0.<sup>7</sup> The differential diagnosis of increased uterine FDG-uptake should include the menstrual and ovulation phase of the

menstrual cycle, menorrhagia, postpartum changes, atypical polypoid adenomyomas and intrauterine devices. The SUV in leiomyosarcoma is significantly higher than in leiomyomas but the overlap limits its ability to distinguish these in individual patients.<sup>8</sup> The reason for enhanced FDG uptake in leiomyomas is suggested to be related to the high levels of cervical and endometrial tissue glycogen in a myomatous uterus, the increased blood fraction and the proliferation of the smooth muscle cells due to increased metabolic need. Finally, it has been established that leiomyomas may experience severe hypoxia, even though a stress reaction with HIF-1 $\alpha$ , CAIX or GLUT1 has never been quantified.<sup>9</sup>

To clinicians and nuclear medicine specialists it is important to be aware of the fact that benign leiomyomas of the uterus may rarely show high FDG uptake. Although leiomyosarcomas show higher FDG uptake than leiomyomas, it does not distinguish benign and malignant disease.

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