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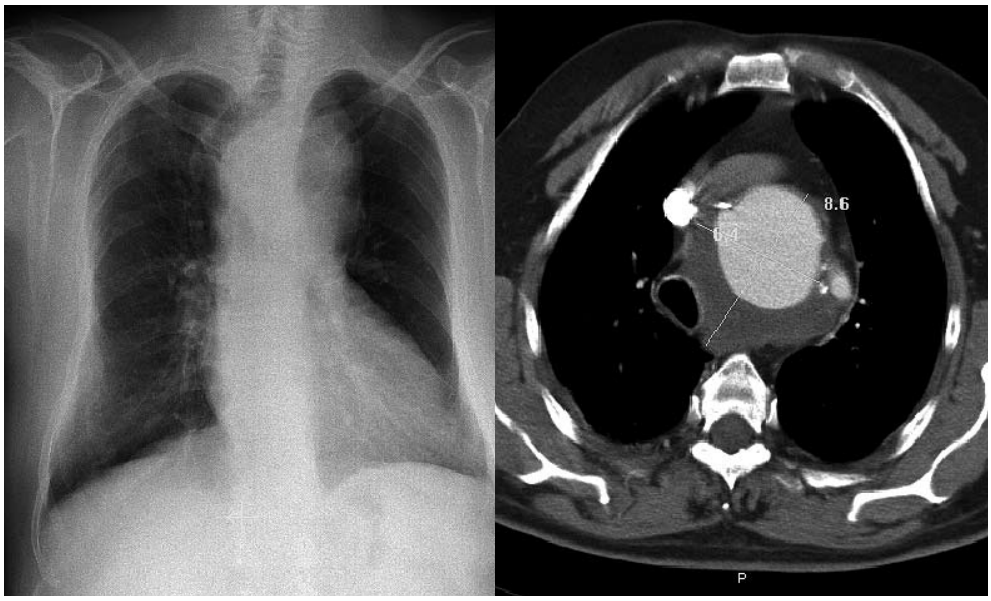

PHOTO QUIZ: Patient with hoarseness of voice, see page 307

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EDITORIAL

Thorotrast toxicity: the safety of gadolinium compounds

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In this issue of the Netherlands Journal of Medicine, Kampen *et al.* describe a patient with a hepatic angiosarcoma resulting from exposure to Thorotrast.[1] Thorotrast was developed in 1928 and used as a radiocontrast agent in the period 1930 to 1960.[2] Thorotrast is a colloidal solution containing the naturally occurring radionuclide Thorium. Thorotrast particles are deposited in the reticulo-endothelial cells of the liver, spleen, bone marrow and lymph nodes, retained lifelong, and lead to continuous exposure of surrounding tissue to radiation. It was not until the late 1940s that the first cases of Thorotrast-related malignancies were described, consistent with the long latency interval. In fact, malignancies may occur more than 45 years after drug exposure. Most practising physicians will not be familiar with Thorotrast or only have a vague recollection of this agent from their old study books. As such, the description by Kampen *et al.* may be considered outdated and a case for the historical archives. Still, patients who were exposed to Thorotrast in the 1950s are at increased risk for malignancies, with an estimated cumulative incidence of 35 to 86%!

More importantly, the Thorotrast story points to an important weakness in the procedures that are used for the registration of new drugs, i.e. the detection of unexpected, late occurring, infrequent but severe side effects. Postmarketing surveillance has become more important and is being heavily discussed in the light of recent withdrawals of drugs because of side effects.[3-6] Examples of drugs that have been removed from the market are listed in *table 1*. It is not very surprising that side effects are not recognised in the randomised controlled trials that are used for registration of the drugs. Many studies include no more than 1000 to 4000 patients. In fact, health authorities are satisfied with safety issues if 1500 patients are exposed overall, with 300 treated for at least one year.[3] Side effects that occur in less than one in every 500 patients will not be detected. Furthermore, in the randomised controlled trials patients with comorbidities, such as renal failure, and patients who use other drugs are often excluded. Side effects may thus occur more frequently in a real-life population but may stay unnoticed for a long time.

In the past year, a new example of an unexpected severe side effect related to a contrast agent has become apparent: gadolinium-induced fibrosing dermatopathy in patients with severe renal failure. International drug authorities such as the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) have recently issued warnings for patients and healthcare professionals.[7,8]

In 2000, Cowper *et al.* described a new skin disorder involving dialysis patients, characterised by thickening of the skin, predominantly involving the limbs.[9] Histologically the skin lesions consisted of irregular bundles of collagen, and an increase in spindled fibroblast-like cells. Shortly thereafter the term nephrogenic fibrosing dermopathy (NFD) was coined. Several years later it became apparent that in some patients the disorder may progress to a systemic disease (nephrogenic systemic fibrosis, NSF) with involvement of muscle, diaphragm and organs, ultimately leading to death.[10] In 2006, a relationship between NFD/NSF and the use of gadolinium was suggested.[11,12]

Table 1. *Overview of drugs withdrawn because of safety concerns*[6]

Drug	Indication	Side effect
Astemizole	Antihistamine	Cardiac arrhythmias
Cerivastatin	Cholesterol lowering	Rhabdomyolysis
Cisapride	Gastrointestinal motility	Cardiac arrhythmias
Fenfluramine	Obesity	Cardiac valve disease
Nefazodone	Antidepressant	Hepatotoxicity
Terfenadine	Antihistamine	Cardiac arrhythmias
Mibefradil	Hypertension	Drug interactions
Rofecoxib	Antirheumatic	Cardiovascular disease

Grobner described five patients with end-stage renal disease, treated with haemodialysis, who developed NFD within two to four weeks after administration of gadolinium DTPA. Subsequently, 13 cases of NFD were described by Marckman *et al*. All patients had severe renal failure; however, five patients were not yet receiving renal replacement therapy. The first sign of NFD was noted two to 75 days after exposure to gadodiamide. NSF deteriorated and caused severe disability in seven patients, contributing to death in one. Grobner suggested a role for acidosis in the development in NFD; however, this was not confirmed in Marckman's study. A recent case-control study confirmed the association of NFD/NSF with gadolinium exposure.[13] The study contained 19 cases. In a multivariate analysis, exposure to gadolinium was the most independent predictor of the development of NSF. In this study, 18 out of 19 cases had been treated with a gadolinium-containing contrast agent, in four of them the interval between exposure and onset of the disease was more than 12 months. Thus far, more than 200 patients with NFD/NSF have been reported.[14] More than 95% of the evaluated patients were exposed to gadolinium within three months prior to the onset of disease.[14] The incidence of NSF in patients with end-stage renal disease exposed to gadolinium is estimated at 3 to 5%.[14]

Gadolinium is a heavy metal, used as a contrast agent for magnetic resonance imaging.[7] Gadolinium is very toxic, and free gadolinium causes severe hepatic necrosis. Therefore, the currently used gadolinium-containing contrast agents are all chelates, which must ensure that no free gadolinium is present in the circulation. Several chelates are available, and they differ in structure and ionic strength (*table 2*). Still, some free gadolinium will be present and the amount is dependent on the physicochemical properties of the chelate. It has been suggested that the risk of free gadolinium is highest with a linear chelate, and lowest with an ionic, cyclic chelate. Indeed, most reported cases of NFD/NSF have been associated with the use of gadodiamide, and few cases have been described after the use of other linear compounds (*table 2*). The exact mechanism of gadolinium-induced skin fibrosis is unknown, although it is suggested that gadolinium may cause changes in fibroblast characteristics. It is not surprising that patients with kidney failure are at increased risk, since the half-life of the gadolinium-containing chelate is increased in patients with renal failure. Although limited data are available, it is likely that also the dose of the contrast agent is an important issue.

The health authorities have issued warnings on the use of gadolinium-containing compounds. Kuo *et al*. have recently provided guidelines in a recent review. These authors do not use gadodiamide in patients with a glomerular filtration rate below 30 ml/min. They advise considering alternative imaging techniques in these patients and if magnetic resonance imaging is performed to use the lowest possible dose of another gadolinium chelate. In patients with end-stage renal disease they perform haemodialysis within three hours after gadolinium administration and repeat this after 24 hours. Since haemodialysis results in a better clearance of gadolinium than CAPD, a course of haemodialysis should also be considered in patients undergoing continuous ambulant peritoneal dialysis. If patients are not receiving renal replacement therapy, the benefit of haemodialysis must be balanced against the risk involved with catheter placement, etc. Admittedly, these recommendations are based on expert opinion and not on evidence.

What important lessons can be learned from the Thorotrast and the gadolinium stories? Individual physicians must remain vigilant when using new drugs, and always consider late side effects. It is also important to report suspected side effects. Health authorities must pursue better postmarketing surveillance strategies. With respect to gadolinium, physicians must be aware that severe toxicity can occur, especially in patients with renal failure. Although some compounds may be more toxic than others, we will have to await further studies before we can really consider the cyclic compounds safe. Although NFD/NSF has predominantly been reported in patients with end-stage renal disease, we must keep in mind that toxic effects may occur less frequently, later, and only

Table 2. *Gadolinium-containing contrast agents*[7]

Name	Acronym	Structure	Charge	Cases with NFD
Gadodiamide	Gd-DTPA-BMA	Linear	Non-ionic	Yes
Gadopentetate dimeglumine	Gd-DTPA	Linear	Ionic	Yes
Gadobenate dimeglumine	Gd-BOPTA	Linear	Ionic	No
Gadoxetic acid	Gd-EOB-DTPA	Linear	Ionic	No
Gadofosveset	Gd-DTPA	Linear	Ionic	No
Gadoteridol	Gd-HP-DO3A	Cyclic	Non-ionic	No
Gadobutrol	Gd-BT-DO3A	Cyclic	Non-ionic	No
Gadoterate meglumine	Gd-DOTA	Cyclic	Ionic	No

after repeated exposure in patients with less severe renal dysfunction. These considerations must be taken into account when considering the best diagnostic strategy in the individual patient.

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REVIEW

Thorium dioxide-related haemangiosarcoma of the liver

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ABSTRACT

Rare tumours of the liver are occasionally seen; thorium dioxide-related haemangiosarcoma of the liver, with an estimated frequency of 0.14 to 0.25 per million in the normal population, is one of these. Causes, epidemiology and pathobiology are described related to a clinical case of angiosarcoma. A differentiation of hepatic tumours with imaging techniques is presented. Last, a short review on up-to-date treatment of haemangiosarcoma is discussed. Lessons can always be learned from history: will the contrast agent gadolinium be the Th^{232} of this era?

KEYWORDS

Hepatic haemangiosarcoma, postradiation cancer, thorium dioxide

INTRODUCTION

Liver carcinoma, especially primary hepatocellular carcinoma, is quite a common tumour in the world, accounting for 1 to 2% of malignant tumours at autopsy in Western Europe and the United States.[1] Beside these more common liver carcinomas, rare tumours of the liver are occasionally seen in daily clinical practice. Angiosarcoma of the liver, with an estimated frequency of 0.14 to 0.25 per million,[2] is one of these rare tumours. Aetiological factors in angiosarcoma are exposure to thorium dioxide (Th^{232}), polyvinyl chloride, arsenic, inorganic copper and anabolic steroids. Th^{232} is the most known iatrogenic cause of angiosarcoma of the liver. Pathobiology, radiological signs and epidemiology will be presented related to a recent illustrative case in our hospital.

CASE REPORT

Patient A, a 67-year-old man with a history of osteomyelitis of the right femoral bone, left parietal cerebral infarction and a Whartonian tumour of the parotid gland, was sent to our emergency room for severe malaise of several weeks' duration. A weight gain of 6 kilos within a week was accompanied by progressive dyspnoea and oedema of the lower extremities. The patient smoked five to six cigarettes a day; he was not taking any medication at presentation. Physical examination showed a slightly icteric man with normal blood pressure, pulse and temperature. No pathological lymph nodes were found. Heart and lungs revealed no abnormalities, the abdomen was spherical and tense with minimal peristalsis. Signs of shifting dullness were present; the liver and spleen could not be evaluated because of the ascites. The lower extremities showed pitting oedema. Laboratory tests revealed a haemoglobin level of 6.5 mmol/l, with normal leucocytes and platelets. Creatinine measured 74 μmol/l, and there were abnormalities in the liver function tests: bilirubin 38.3 μmol/l, alkaline phosphatase 365 U/l, aspartate aminotransferase and alanine transaminase 73 and 93 U/l, respectively. The lactate dehydrogenase (LDH) was 494 U/l and albumin 32 g/l. Alpha-fetoprotein level was 2.6 IU/ml. Paracentesis produced 5.5 litres and was a transudate (total protein <20 g/l, LDH 188 U/l). Cytology showed reactive mesothelial cells. No abnormalities were seen on the chest X-ray; abdominal X-ray showed calcifications in the upper left abdominal quadrant (*figure 1*). An ultrasound revealed multiple echo-dense lesions in the liver, which was followed by abdominal computed tomography (CT) scanning. An enlarged liver with capsular and subcapsular densities and a very small spleen, filled with contrast-like agent, were noticed (*figure 2*). The native CT scan also spotted contrast-like agent in the large visceral vasculature.

Figure 1. *Calcifications in the upper abdomen with a spotty appearance of the skeleton, indicating Thorotrast deposition in lymph nodes and skeleton in patient A*

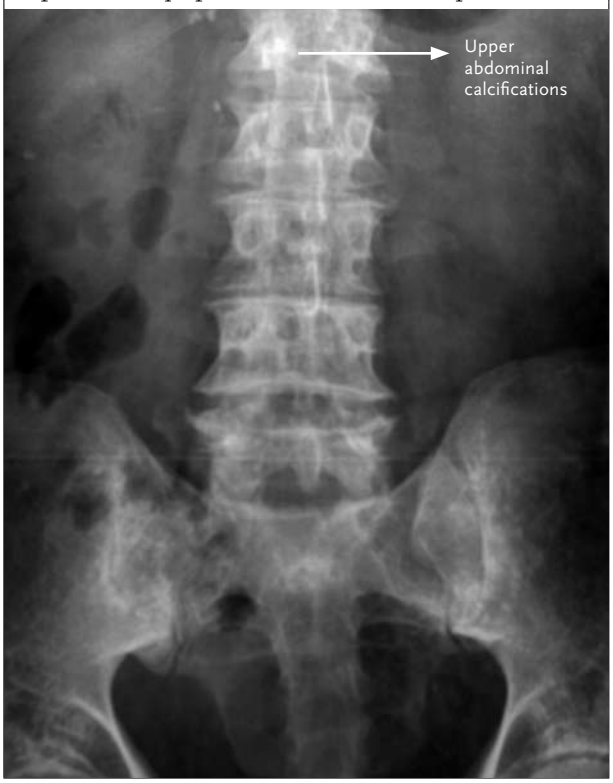
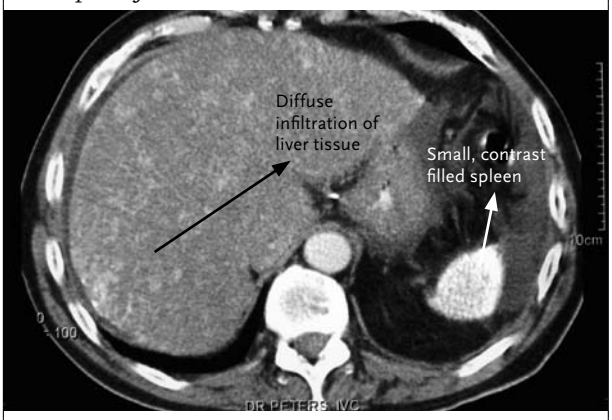


Figure 2. *Abdominal CT scan of patient A showing multiple defects*



Small, high-density spleen. Multiple lucent defects in the liver resembling thorium deposition and defects resembling metastases. Again lucent deposition was noticed in the spine.

Repeated anamnesis resolved the phenomenon: a cerebral angiography was performed when the patient was 17 years (1954) because of an unexplained coma, pointing in the direction of exposure to Th^{232}. The patient denied exposure to polyvinyl chloride.

In the diagnostic procedure a liver biopsy was performed, which revealed a hepatic haemangiosarcoma. Three weeks after diagnosis our patient died due to progressive hepatic failure. Post-mortem section revealed a very small, contrast-filled spleen and a large liver diffusely infiltrated with tumour. Microscopically, the diagnosis of hepatic haemangiosarcoma was confirmed and large quantities of Th^{232} agent were seen in the liver, spleen and bone tissue.

Thorium dioxide and its effects

Thorotrast was a 25% thorium dioxide (Th^{232}) colloidal solution, used worldwide between 1928 and 1955 as a contrast medium for various roentgenographic examinations. Th^{232} was developed for specific imaging of liver and spleen but it was mostly used in cerebral angiographies. Approximately ten years after its introduction, reports of possible carcinogenic effects, especially tumour formation in the liver, were published in the international literature. Despite these publications, the use of Th^{232} increased, because of the lack of acute toxicity and excellent radiological results compared with other contrast media. With time, the carcinogenic effects of Th^{232} became increasingly clear and numerous cases of Th^{232}-related malignancies were reported, especially malignant hepatic tumours, such as hepatocellular carcinoma, cholangiocarcinoma and haemangiosarcoma.[3,4] Other Th^{232}-related neoplasms such as granuloma, bone sarcoma, plasmacytoma and malignant peritoneal or pleural mesothelioma were also reported. Coexistent Th^{232}-related neoplasms were seen in one patient.[5]

Th^{232} is a radioactive isotope that naturally emits α-, and β-particles and γ rays. Ninety percent are α-particles and Th^{232} has a half-life of 14 billion years.[6] After intravascular injection Th^{232} is stored for life in the reticulo-endothelial system, particularly the liver, spleen and bone marrow. Chronic irradiation with an estimated radiation dose of approximately 0.250 grays a year results.[7] Higher amounts of injected Th^{232} seem to account for a higher incidence of liver tumours.[6] Although cholangiocarcinoma is most frequently seen, thorium-related angiosarcoma is characteristic for chronic α-radiation.[8] Characterisation of genetic changes in Th^{232}-induced liver tumours revealed that large deletions were not frequently seen. Typically most mutations were transitions, as is also seen in neoplasms in the general population. This suggests that the changes in thorium-induced carcinomas are not the direct effect of radiation, but mainly of delayed mutations.[9] The effects of these delayed mutations lie around 40 years after exposure, but cases up till 60 years after exposure have been published.

Epidemiology

The effects of chronic low-dose α-particle radiation have been investigated in cohorts of patients previously injected with Th^{232} in several countries. In a Swedish

cohort of 432 patients injected with Th^{232} with a follow-up period of 40 years, 170 cases of cancer were diagnosed. According to the standardised incidence ratio, 57 cases were expected.[10] In a Portuguese cohort study (1931 exposed patients, 2258 non-exposed patients) overall mortality was increased in the Th^{232} group, peaking 30 years after administration. This rise in overall mortality was essentially due to liver cancer (RR 70.8; 95% CI 19.9-251.3) and nonmalignant liver disorders (RR 5.67; 95% CI 3.13-10.3) such as liver cirrhosis. As mentioned before, a strong and consistent gradient with cumulative α-particle radiation dose was seen.[11,12] In a large international study, a cohort of 3143 patients were followed for up to 40 years. A significantly increased mortality among patients exposed to Th^{232} was detected (RR 1.7; 95% CI 1.5-1.8).[7,13]

Radiographic and pathological signs

CT findings of Th^{232} deposition are pathognomonic. Typically, high-density deposits within the liver, spleen and lymph nodes are seen (*figures 1* and *2*). Atrophy of the spleen because of fibrosis is also a typical sign of previous Th^{232} exposure. Deposition of Th^{232} in bone marrow is also described, which can cause anaemia, thrombocytopenia and leucopenia in patients. CT and magnetic resonance imaging (MRI) of the liver provide a useful means of early detection of Th^{232}-related tumours, but can be notoriously nonspecific.[14] The CT appearance of hepatic haemangiosarcoma is consistent with a vascular tumour, in which two growth patterns can be seen: multifocal and an, often large, solitary mass. Shapes can vary from ring-shaped to irregular shapes. Most of the time nodules are hypoattenuating, but isoattanuation or hyperattanuation are also seen. This seems to be a reflection of the varied pathological features of hepatic haemangiosarcoma.

Addition of angiography and/or MRI might improve differentiation between haemangiosarcoma and several other hepatic tumours. Presence of Bud-Chiari syndrome or veno-occlusive disease and the absence of cirrhosis make the presence of primary hepatic haemangiosarcoma more plausible.[15]

Shortly after exposure to Th^{232}, depositions are present in Kupffer cells located within sinusoids and uniformly distributed throughout the liver parenchyma from portal tract to central veins. At that time extracellular deposits are not usually seen. With time, mononuclear cells containing Th^{232} may form and extracellular deposits may be seen. Collagen deposition and areas of fibrosis are seen.

Haemangiosarcoma is characterised by spindle-shaped cells, demonstrating vascular formation in different patterns. Substantial areas of necrosis and haemorrhage are present most of the time (>80%). Immunochemically factor VIII stains are positive.

Treatment

The prognosis of hepatic haemangiosarcoma is very poor, almost every patient dying within one year of diagnosis. Several sarcoma studies with angiosarcoma included as a subgroup show rather disappointing results. Schedules containing doxorubicin and cyclophosphamide, which are considered the first-line therapy, reveal response rates of 20% in the entire group of advanced sarcomas. In approximately 5% of the entire group an improvement in overall survival is seen. A number of phase II and III trials with several agents, e.g. docetaxel, gemcitabine and the combination of ifosfamide and liposomal daunorubicin in first- and second-line therapy, result in almost the same response rates. Some small nonrandomised trials with high-dose chemotherapy and autologous stem cell rescue showed a five-year survival rate of up to 50% in a diverse sarcoma patient group. Whether this only reflects selection of patients needs to be tested in a prospective randomised trial.[16]

Attempted radical resection in case of localised disease, even in R0 resections, seems very disappointing with fast relapses of the haemangiosarcoma. In case of liver transplantation where a haemangiosarcoma was unexpectedly found in the resected liver, relapse-free and overall survival did not last longer than one year. Liver transplantation does not seem feasible in this disease.[17]

CONCLUSIONS

Angiosarcoma of the liver is a neoplasm very rarely seen in the general population, certainly in the case of prior Th^{232} exposure. This is partially due to the relatively small number of patients living today who were exposed to Th^{232}. But nowadays exposure to polyvinyl chloride, a major component in the production of PVC, remains a major cause of angiosarcoma. This is mainly in non-Western countries with inappropriate facilities to prevent exposure in factory workers.

We also think that the story of Th^{232}-related malignancy should remind us of the possible dramatic effects of (formerly) prescribed medications in patients. For example, in the last decades, the accrual of gadolinium as a contrast agent in MRI studies has been welcomed as an almost ideal and nontoxic agent, compared with the known toxicities of conventional iodine-containing contrast agents. But several recent reports have associated intravenous gadolinium with a rare, relatively new, and as yet idiopathic disorder called nephrogenic systemic fibrosis.[18]

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REVIEW

Ascites in cirrhosis: a review of management and complications

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ABSTRACT

Ascites is the most common manifestation in cirrhotic patients, and is associated with a reduced survival rate. Management of ascites is primarily focused on sodium restriction and diuretic treatment to which most patients respond appropriately. For the small group of patients who do not respond sufficiently, interventions such as large volume paracentesis and transjugular intrahepatic portosystemic shunt placement should be considered.

Most important in the management of cirrhotic patients with ascites is prevention of complications. Spontaneous bacterial peritonitis and hepatorenal syndrome are severe complications with a poor prognosis when not detected and treated in an early stage. In all hospitalised patients with ascites, an infection of the ascitic fluid should be ruled out. For those patients at risk of developing spontaneous bacterial peritonitis, in particular patients after a first episode and patients with gastrointestinal bleeding, antibiotic prophylaxis should be given. To prevent the hepatorenal syndrome, substitution with albumin is essential, both in patients who experience an episode of spontaneous bacterial peritonitis and in patients treated with large volume paracentesis. For those patients unresponsive to standard treatment regimens, liver transplantation may be the only suitable treatment option.

KEYWORDS

Ascites, cirrhosis, diagnosis, treatment

INTRODUCTION

Ascites is the most common complication in patients with cirrhosis of the liver, developing in more than 50% of the patients within ten years of the initial diagnosis.[1] Cirrhosis of the liver is the most common aetiology for ascites, responsible for 80% of all cases of ascites.[2] The onset of ascites marks a turning point in the prognosis of cirrhotic patients with a mortality rate of 50% within two to five years after its first appearance.[3-6]

In this article, we review the pathophysiology and management of ascites and the most common complications, including spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS).

PATHOPHYSIOLOGY

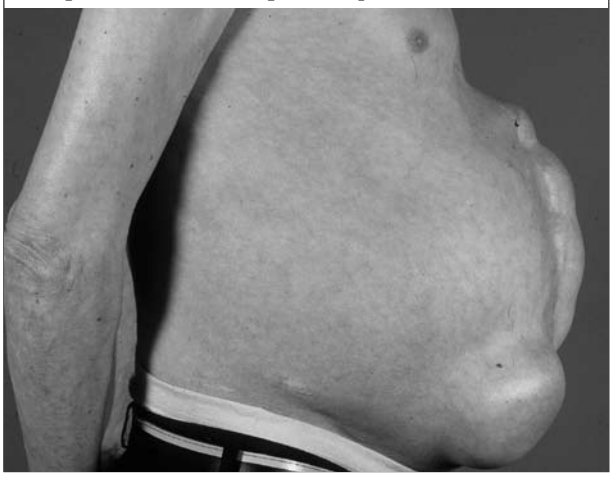
The precise mechanism leading to the formation of ascites is not completely understood. The prevailing theory now is that portal hypertension, and specifically sinusoidal hypertension, is the central pathophysiological abnormality. Increased portal pressure causes splanchnic vasodilatation, mainly due to increased local production of nitric oxide, thereby creating a hyperdynamic circulation. This results in increased capillary pressure and permeability and a decreased effective arterial blood volume. An increase in plasma volume and cardiac output are accommodating mechanisms for this reduction in arterial blood volume.[7,8] Activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) lead to a compensatory sodium and water retention, thereby facilitating the formation of ascites.[4,5,9]

EVALUATION

Abdominal ultrasound is the gold standard for the evaluation of ascites and portal hypertension. Ultrasound examination can reliably detect amounts of peritoneal fluid as low as 100 ml that are not usually detected on

physical examination. According to the quantity of ascites, physical examination may suggest the presence of ascites by shifting dullness or by demonstration of a fluid thrill or wave. Patients with ascites usually have additional stigmata of chronic liver disease such as cutaneous collaterals of the abdomen, vascular spiders, and splenomegaly. In patients with large amounts of ascites the nutritional status is often poor. Umbilical, inguinal, and incisional hernias are particularly frequent (*figure 1*). The hyperdynamic circulation and raised cardiac output are evidenced by a normal/low blood pressure and tachycardia; an ejection systolic murmur may be present. Leg oedema is variably found.

Figure 1. *Incisional hernia in patient with ascites and previous midline laparotomy*



Pleural effusions (hepatic hydrothorax), due to migration of ascites through micropores in the diaphragm, may also be present. In about 80% of cases the effusions are right-sided. It should be stressed that ascites may well be absent in patients with hepatic hydrothorax.[10]

When in doubt about the aetiology of ascites, diagnostic paracentesis is indicated. In recent years the transsudate-exudate concept has been replaced by a classification based on the serum ascites albumin gradient (SAAG).[4] A SAAG of ≥11 g/l is indicative for a hepatic cause of ascites (*table 1*). In addition to the albumin concentration in ascites, other useful laboratory investigations may be the determination of the number of (polymorphonuclear) leucocytes, amylase, triglyceride concentration, chylomicrons and in selected cases cytological and immunological examination.

In all patients with ascites who clinically show deterioration (e.g. renal dysfunction, encephalopathy, admission to hospital) or have signs of infection (e.g. fever, abdominal discomfort, increased C-reactive protein level), diagnostic paracentesis should be performed to rule out infection.

Table 1. *Aetiology according to the serum ascites albumin gradient*

<11 g/l	Infection
	Nephrotic syndrome
	Malignancy
	Pancreatitis
≥11 g/l	Cirrhosis
	Budd-Chiari syndrome
	Veno-occlusive disease
	Alcoholic hepatitis
	Congestive heart failure

TREATMENT

The management of ascites should be dictated by the severity of symptoms. The mere presence of ascites does not merit active treatment and cosmetic reasons are only relative. Overtreatment, especially with diuretics, may easily lead to serious complications including hyponatraemia, renal failure, and encephalopathy. Therefore, the key management rule is that it is better to have a patient 'wet and wise' than 'dry and demented'. Primary focus for treatment should be the underlying liver disease. For instance, abstinence of alcohol in alcoholic liver disease and immunosuppressive treatment in autoimmune hepatitis may result in disappearance of ascites that had been difficult to manage.

Besides treating the underlying liver disease, the aim of the treatment should be aimed at achieving a negative sodium balance in order to diminish the ascites. In symptomatic patients the first therapeutic step is dietary sodium restriction to 60 to 90 mmol/day. Trials comparing low *vs* marked sodium restriction have shown comparable efficacy but better compliance with the more liberal diet.[5,11] To verify compliance to sodium restriction or in difficult-to-treat patients quantification of urinary sodium excretion can be used as a diagnostic tool.

Diuretic treatment

Most patients with symptomatic ascites do not respond sufficiently to sodium restriction alone and require additional diuretic treatment. In general, the preferred regimen is to start with spironolactone, an aldosterone antagonist, and to add a loop diuretic if necessary. The usual initial dose of spironolactone for moderate ascites is 50 to 100 mg/day; the maximal daily dose is 400 mg. Commonly experienced side effects are (painful) gynaecomastia and hyperkalaemia. Most patients show a significant decrease in ascitic fluid when spironolactone is given alone, usually in doses of up to 200 to 300 mg/day.[12] When the response is insufficient, combination therapy with furosemide, starting with doses of 20 to 40 mg/day, is recommended.[13,14] The American Association for the

Study of Liver Diseases (AASLD) guidelines have advised starting this combination therapy immediately so that side effects due to the spironolactone, i.e. hyperkalaemia, can be prevented.[12]

Especially during the phase of ascites mobilisation, regular monitoring of body weight, renal function and electrolytes is mandatory. As a rule of thumb, the daily weight loss should not exceed 1 kg for those patients with ascites and peripheral oedema, and 0.5 kg for those patients without oedema.[11]

New alternatives in the treatment of ascites are the aquaretics, selective V2 receptor antagonists. These agents improve urinary output and free water clearance by blocking the action of the antidiuretic hormone in the collecting tubuli and may be particularly helpful in the management of hyponatraemia.[15,16] Thus far aquaretics have only been used in the context of clinical studies. Before implementing aquaretics in clinical practice, further research on dosage and side effects is necessary.[17]

Paracentesis

In about 90% of the patients, ascites diminishes adequately with sodium restriction and diuretic treatment.[18] In patients where ascites does not diminish sufficiently in response to maximal diuretic treatment, or when severe side effects occur due to diuretic treatment, such as renal impairment, ascites is considered to be refractory. For patients with refractory ascites several therapeutic options remain available. The least invasive procedure is (repeated) large volume paracentesis (LVP) with removal of >5 litres of ascitic fluid. This can be done as an outpatient procedure and it is safe to remove all the ascites within one to three hours. Obviously, LVP is a symptom-relieving treatment and does not influence the mechanisms leading to the formation of ascites. LVP can be complicated by paracentesis-induced circulatory dysfunction (PICD). This is defined as an increase in plasma renin concentration >50% of the baseline value on day 6.[19] PICD is triggered by a decrease in systemic vascular resistance (SVR). The decrease in SVR is predominantly caused by an accentuation of the arterial vasodilatation already present. The mechanism as to how paracentesis induces an additional arterial vasodilatation is not yet understood. PICD induces compensatory activation of the RAAS, facilitating the development of notorious complications, such as HRS.[19-21] Studies have shown that PICD can be prevented by intravascular plasma expansion during or directly after paracentesis when ≥5 litres of ascites are removed. The preferred substitution is albumin, given intravenously in a dosage of 8 g per litre of ascites removed. Other plasma volume expanders, such as saline, dextran, and polygeline, have been compared with albumin, but none have shown to be superior or safer in the prevention of PICD.[22-25] Recent studies have explored the use of vasoconstrictors to prevent PICD.[26-29] Terlipressin, a vasopressin prodrug, administered as two to three bolus injections of 1 to 2 mg during and after paracentesis, appears to be as effective as albumin.[26,29] Larger studies are ongoing to see whether terlipressin can be considered a definite alternative for intravenous albumin administration.

Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is another treatment modality for refractory ascites, especially when patients frequently require, or poorly tolerate, LVP.[14] TIPS reduces portal pressure; when this pressure is <12 mmHg, ascites is less likely to develop in cirrhotic patients.[30] Placement of TIPS leads to an increase in urinary sodium excretion 7 to 30 days after stent placement.[31-33] This is correlated with reduced activity of the RAAS and improvement of effective arterial blood volume.

In approximately 70% of patients TIPS is effective, although in most patients (low-dose) diuretic treatment must be continued.[33]

A main disadvantage of TIPS placement is the risk of new onset or worsening of pre-existent encephalopathy, a complication that occurs in about one-third of patients.[34] Risk factors are the presence of pre-TIPS hepatic encephalopathy, age >65 years, a low post-TIPS portosystemic pressure gradient and serum creatinine level.[35] The vast majority of patients developing encephalopathy respond well to standard treatment with lactulose; only 3 to 10% require narrowing or obliteration of the shunt.[33,36]

TIPS has shown to be better in preventing recurrence of ascites than paracentesis (48 *vs* 84%), but is associated with a higher incidence of hepatic encephalopathy (42 *vs* 23%) while mortality rates of the two treatment modalities are comparable.[33]

In most studies performed thus far uncovered stents were used. These stents are prone to occlude and in >50% of cases treated with TIPS, revision of the stent is required within one year. A newer stent, coated with polytetrafluoroethylene, is less prone to occlude. TIPS is probably more effective in controlling ascites when these covered stents are used.[37,38]

Eligibility for TIPS placement depends on several factors. Generally, established contraindications for TIPS placement are age >70 years, pulmonary hypertension, pre-existing cardiac dysfunction, renal failure due to organic kidney disease, hepatic malignancy and a Child Pugh score >11.[33,37]

Peritoneovenous (LeVeen; Denver) shunts have not been shown to be more efficacious than repeated paracenteses and complications, including occlusion, infection, and disseminated intravascular coagulation, are frequent.[39] These devices are nowadays rarely used in the treatment of refractory ascites.

Liver transplantation

The onset of ascites in patients with cirrhosis is associated with a markedly decreased survival. In patients with ascites, evaluation for liver transplantation should therefore always be considered, preferably before complications as SBP and HRS occur.

COMPLICATIONS

Spontaneous bacterial peritonitis

SBP, with a lifetime incidence of 10 to 30%, is the most common infection in patients with cirrhosis, primarily seen in hospitalised patients.[11,40] SBP is defined as an infection of ascitic fluid with an ascitic polymorphonuclear leucocyte count (PMN count) of ≥0.25 x 10^9/l, in the absence of an identifiable focal source of infection.[40]

Factors currently implicated in the pathogenesis of SBP are intestinal bacterial overgrowth, combined with a delayed intestinal transit time and increased permeability of the intestinal wall. Local intestinal immunodeficiency, such as decreased levels of mucosal IgA, may also play a role. These factors facilitate translocation of bacteria through the mucosal barrier. Intestinal bacteria may then migrate via the mesenteric lymph nodes and the systemic circulation and subsequently may lead to infection of the ascitic fluid. Low ascitic protein and complement levels are probable contributory factors.[41,42]

Diagnostic paracentesis should be performed in all patients with ascites who require hospitalisation to rule out SBP. A large proportion of patients with SBP are asymptomatic, while others show signs of fever, abdominal pain, nausea, encephalopathy or a deterioration in renal function. In approximately half of the cases encephalopathy develops or progresses at the time of SBP.

In the diagnostic work-up for SBP the ascitic PMN count should be determined. At least 10 ml ascitic fluid per bottle should also be inoculated into aerobic/anaerobic blood culture bottles. This should be done immediately, at the bedside, to increase the sensitivity of this method. Even with this method cultures of ascitic fluid at the time of SBP remain negative in up to 60%.[43]

SBP is typically monobacterial and caused predominantly by gram-negative bacteria, especially *E. coli* and *Klebsiella* species. With the increased use of prophylactic antibiotics in cirrhotic patients, gram-positive bacteria are becoming increasingly common.[43,44] More than one bacterial species suggests the possibility of secondary bacterial peritonitis and possible causes, including appendicitis, diverticulitis and cholecystitis, should be evaluated.

After the diagnosis of SBP has been established by means of the PMN count, treatment should be started immediately. At present, third-generation cephalosporins are generally considered the gold standard in the treatment of SBP.[45] Especially cefotaxim 2 g/12 hours intravenously during at least five days has been extensively studied and found to be an effective regimen.[46,47] Reports on the use of amoxicillin/clavulanic acid, 1.2 g intravenously, four times daily, have shown comparable results with considerably lower costs, making them a safe alternative treatment regimen.[48]

Two randomised controlled trials have demonstrated that the intravenous administration of albumin may reduce the incidence of renal impairment and improve short-term survival in patients with SBP. The beneficial effect was obtained by the additional administration of albumin at a dose of 1.5 g/ kg body weight at the day of diagnosis of SBP followed by a dosage of 1 g/kg body weight at day 3.[49,50] The remaining question is whether albumin treatment should be limited to, for example, Child's stage C patients, while there is also room for more studies with respect to the optimal dosage regimen.

The long-term prognosis of cirrhotic patients with SBP is extremely poor, with reported mortality rates of 50 to 70% and 70 to 75% after one and two years, respectively.[40,51] This is largely attributable to the advanced stage of liver cirrhosis that is nearly always present in patients who acquire SBP. Septic shock, progressive renal and multiorgan failure, and variceal bleeding are frequent complications of SBP and account for significant in-hospital mortality.[11] Considering the poor prognosis, patients who overcome an episode of SBP should be evaluated for liver transplantation.

Given the high risk of recurrence of SBP of up to 70% within one year, there is consensus that patients who have recovered from an episode of SBP should receive secondary antibiotic prophylaxis. Certain groups at risk for SBP should also be considered for primary antibiotic prophylaxis, in particular cirrhotic patients with gastrointestinal bleeding. *Table 2* summarises the current recommendations for antibiotic prophylaxis.

Table 2. *Cirrhotic patients eligible for spontaneous bacterial peritonitis (SBP) prophylaxis*

Short-term prophylaxis	Long-term prophylaxis
Norfloxacin 400 mg twice daily for 7 days	Norfloxacin 400 mg daily
Patients with gastrointestinal bleeding	Patients recovered from episode of SBP
	Patients with ascites and low ascitic fluid protein count (<10g/l) (no consensus)

HEPATORENAL SYNDROME

HRS is a severe complication, occurring in ~10% of the patients with cirrhosis and ascites.[11] It is characterised by renal vasoconstriction leading to renal failure. The renal vasoconstriction is a compensatory effect of the

renin-angiotensin-aldosterone system and antidiuretic hormone, triggered by an extreme underfilling in the arterial circulation.[52]

The diagnosis of HRS is based on several criteria, of which the major criteria are necessary to establish the diagnosis of HRS (*table 3*).[18] Minor criteria for the diagnosis of HRS can be used as an additional tool to strengthen the diagnosis, but have recently been abandoned by the International Ascites Club as official minor criteria for establishing the diagnosis.[53] The urinary sodium excretion may help differentiate between HRS and acute tubular necrosis (ATN). A sodium excretion of <10 mmol/l strengthens the diagnosis of HRS whereas a sodium excretion of >10 mmol/l is more likely to fit the diagnosis of ATN.

There are two subtypes of HRS. HRS type 1 is rapidly progressive, often precipitated by a triggering event such as SBP, and has a median survival of approximately two weeks when treatment is not started rapidly. HRS type 2 develops gradually, as a consequence of aggravation of end-stage liver disease and requires no additional treatment.

Table 3. *Major criteria for diagnosing the hepatorenal syndrome*

Serum creatinine >130 μmol/l
No shock, ongoing bacterial infection, volume depletion, or treatment with nephrotoxic drugs
No improvement after cessation of diuretics or fluid challenge (1.5 litre saline infusion or albumin infusion 1 g/kg body weight, max 100 g albumin)
No proteinuria (<500 mg/day) or evidence of parenchymal renal disease or obstructive uropathy by ultrasound

General management of patients with HRS type 1 consists of close monitoring of vital signs, electrolytes, and fluid balance. A fluid restriction of 1 litre a day is only advised in patients with a dilutional hyponatraemia (<125 mmol/l). To retain renal function and prevent electrolyte dysbalance cessation of diuretic treatment is necessary. Since 30% of the episodes of HRS are precipitated by SBP a diagnostic puncture of ascitic fluid should always be performed to rule out infection. Until now no consensus has been reached as to whether it is safe to perform LVP in patients with HRS type 1. LVP with adequate suppletion of albumin may provide comfort to the patient, but it may also attenuate the arterial underfilling already present, thereby worsening renal dysfunction.

Most important in patients with HRS type 1 is pharmacological treatment. Treatment consists of a combination of a plasma expander and a vasoconstrictor. The preferred plasma expander is albumin intravenously in a dosage of 1 g/kg body weight on the first day followed by 20 to 40 g/day for the remainder of treatment. The first choice for vasoconstrictor therapy is vasopressin analogues, for which the best results have been obtained with terlipressin.[18,27] Terlipressin has its primary action in the splanchnic area. The drug is administered in a stepwise schedule with a starting dosage of 0.5 mg/4 hours. The dosage can be increased stepwise every two to three days to 1 to 2 mg/4 hours, according to the effect of treatment. The effect of therapy is measured by a decrease in serum creatinine level; the goal is to obtain a serum creatinine of <130 μmol/l.

There are alternative vasoconstrictor treatments, such as combinations of noradrenaline or midodrine and octreotide, but their effect has been less thoroughly studied.[27]

Patients with HRS type 2 can be monitored in an outpatient setting. Caution should be applied in dosing diuretics to preserve renal function. Special attention should be given to prevention of triggers that lead to a deterioration into HRS type 1; in specific SBP, variceal bleeding, or no adequate substitution during LVP.

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ORIGINAL ARTICLE

Cardiac and noncardiac, particularly neuromuscular, disease with troponin-T positivity

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ABSTRACT

Objectives: Although elevated cardiac troponin T is caused by myocardial damage in the vast majority of the cases (primary cardiac causes), noncardiac disease with secondary damage to the myocardium (secondary cardiac causes) is being increasingly recognised. The present study aimed to retrospectively evaluate the frequency of primary cardiac and secondary cardiac causes of troponin-T positivity, in particular how often troponin-T positivity is associated with neuromuscular disorders.

Results: Of 16,944 troponin-T determinations in a secondary centre between April 2004 and April 2005, troponin T was positive in 1408 of them (8.3%). Of these, 622 were included for evaluation. Troponin-T positivity was associated with elevated creatine kinase in 54.5% and with creatinine >2 mg/dl (177 μmol/l) in 16.6% of the tests. The most frequent primary cardiac causes of troponin-T positivity were myocardial ischaemia (59%), atrial fibrillation (23%), and heart failure (22%). The most frequent secondary cardiac causes of troponin-T positivity were renal insufficiency (22%), chronic obstructive lung disease (10%), and acute stroke (4%). There was one cause for troponin-T positivity in 249 cases and more than one in 373 cases. A neurologist saw patients with troponin-T positivity in 9.5% of the cases. Troponin-T positivity was associated with a neuromuscular disorder in 6.3% of the cases. Causes of troponin-I positivity were also frequently causes of troponin-T positivity.

Conclusions: Ischaemic heart disease is the most frequent cause of troponin-T positivity, followed by heart failure and renal insufficiency. Many causes previously described to be only responsible for troponin-I positivity also cause troponin-T elevation. Troponin-T positivity is frequently associated with neuromuscular disorders, most likely due to cardiac involvement of these conditions.

KEYWORDS

Cardiac involvement, cardiomyopathy, myocardial infarction, myocardial ischaemia, skeletal muscle, troponin

INTRODUCTION

Cardiac troponin T was introduced in the routine laboratory diagnostic work-up in 1989[1] and was conceptualised to sensitively indicate acute myocardial ischaemia, even in the absence of angina pectoris, creatine kinase (CK), or CK-MB elevation.[2] Meanwhile, it turned out that, in addition to primary cardiac causes of troponin-T positivity, various extracardiac disorders are associated with troponin-T positivity due to secondary damage to the myocardium (secondary cardiac causes).

The aim of the present study was 1. To retrospectively evaluate how often troponin T is positive in a secondary centre; 2. How often troponin-T positivity is associated with elevated CK or elevated creatinine; 3. Which are the primary cardiac or secondary cardiac causes of troponin-T positivity in these patients; 4. How often patients with troponin-T positivity are seen by a neurologist; and 5. How often troponin-T positivity is attributable to a neuromuscular disorder (NMD).

METHODS

From all patients who attended an inpatient unit of the general hospital Krankenanstalt Rudolfstiftung in Vienna, Austria between April 2004 and April 2005 (13 months) with the initials A to P and in whom troponin T was determined as positive during this period, the electronic

records were reviewed for 19 previously reported causes of troponin-T positivity and 27 previously reported causes of troponin-I-positivity (*table 1*). Patients with the initials Q to Z were excluded because frequency distribution of troponin-T positivity no longer varied with progression of the data acquisition. We did not look for the diagnoses cardiac tamponade, rhabdomyolysis, hypovolaemia or cirrhosis because they were not recognised to be associated with troponin elevation before completion of the data acquisition. Also registered were the CK and creatinine values in case the patient was seen by a neurologist, as well as the number of causes of troponin-T positivity found per admission. If the patient was seen by a neurologist, the neurological diagnosis was registered, in particular in case an NMD was responsible for the troponin-T positivity. Causes of troponin-T positivity were classified as primary cardiac or secondary cardiac (*table 1*). If a patient was admitted several times during the study period and had a positive troponin T at some or all of these admissions, each admission was regarded as a distinct entity. If troponin T was determined several times during a single hospitalisation, only one positive determination was used for statistical analysis. If there was more than one single cause to explain troponin-T positivity, all possible causes were registered. If there was disagreement on the cause of troponin-T positivity, the investigators discussed the case until agreement was reached.

Troponin T was measured with the qualitative analytical troponin-T test TROP sensitive Rapid Assay (Roche Diagnostics). All assays were performed according to the manufacturer's instructions. Venous whole blood from patients anticoagulated with EDTA was used in all assays. The cut-off for troponin-T positivity in this assay is 0.08 ng/ml. The results are expressed as troponin-T negative or positive. The sensitivity of the assay is >95% for acute myocardial infarction and subacute infarction with an analytical specificity of >92%. All determinations with a positive or slightly positive result were initially considered. Heterophilic antibodies, which may cause a minor release of troponin, were not determined. Creatinine was measured with the Creatinine Jaffe Gen.2 test (Roche Diagnostics) on a COBAS INTEGRA 700/800 system. The test relies on the buffered kinetic Jaffé reaction without deproteination. Zero point of the creatinine reaction to picrate acid was measured at 512 nm, which is directly proportional to the serum creatinine concentration.

RESULTS

Between April 2004 and April 2005, 16,944 determinations of troponin T were carried out in the hospital's laboratory. Among them, 1408 determinations were troponin-T positive (8.3%). Of these 190 were only slightly positive (*table 2*). After exclusion of patients with

Table 1. *Causes of troponin-T and troponin-I positivity*

	Troponin T	Troponin I
Primary cardiac causes		
Myocardial ischaemia, unstable coronary heart disease	[27]	[28]
Myocarditis	[29]	[30]
Pericarditis	NR	[31,32]
Dilated cardiomyopathy	[33]	NR
Hypertrophic cardiomyopathy	[29]	[32]
Uraemic cardiomyopathy	[8]	NR
Atrial fibrillation	NR	[34]
Tachycardia	NR	[31,32]
Congestive heart failure	[35]	[9,31,32,36]
Increased left ventricular mass	NR	[13]
Severe aortic valve disease	NR	[32]
Coronary vasospasm	NR	[32]
Takotsubo phenomenon	[37]	[12]
Cardiac contusion	NR	[32]
Cardiac tamponade	NR	[38]
Hypertensive crisis	NR	[32]
Hypotonia, hypovolaemia	[3]	NR
Implantable cardioverter defibrillator shocks	NR	[39]
Electrical cardioversion	NR	[10]
Percutaneous coronary intervention, ASD closure	[40]	[41]
Radiofrequency ablation	NR	[42]
Cardiac transplantation	NR	[43]
Pacemaker implantation	NR	[44]
Secondary cardiac causes*		
Pulmonary		
• Pulmonary embolism	[45]	[32,46]
• Chronic pulmonary hypertension	[47]	NR
• Chronic obstructive pulmonary disease	NR	[48]
Neuromuscular		
• Duchenne muscular dystrophy	[7,49]	NR
• Dermatomyositis	[2,7,18-20,49]	NR
• Polymyositis	[2,49]	NR
• Inclusion body myositis	[17]	NR
• Rhabdomyolysis	NR	[50]
• Physical exertion	NR	[31]
Other		
• Sepsis, systemic inflammatory respons	NR	[51]
• Acute stroke	[52]	[49]
• Subarachnoid haemorrhage	NR	[26]
• Amyloidosis	NR	[53]
• Chemotherapy	NR	[54]
• Lymphoma	[17,55]	NR
• Chronic renal insufficiency	[7,8,56,57]	[7]
• Scorpion or jellyfish envenoming	NR	[58,59]
• Eclampsia, pre-eclampsia	NR	[60]
• Rheumatoid arthritis	NR	[61]
• Epileptic seizures	NR	[62]
• Diabetic ketoacidosis	[63]	[16]
• Noncardiac surgery	[64]	NR
• Gastrointestinal bleeding	NR	[32]
• Electrical trauma	NR	[32]
• Cirrhosis	NR	[65]

NR = not reported so far. *Disorders with secondary cardiac damage as an explanation for troponin-T or troponin-I positivity.

Table 2. *Stratification of troponin-T tests carried out between April 2004 and April 2005 (13 months)*

Stratification	Absolute number (n)
Total number of troponin-T tests	16,944
Total number of positive troponin-T tests	1408
Number of slightly positive troponin-T tests	190
Total number of positive troponin-T tests after exclusion of the patients with initials Q to Z	1008
Number of positive troponin-T tests after exclusion of repeated determinations per admission	729
Number of positive troponin-T tests with insufficient data on the electronic records (excluded)	107
Number of admissions (cases) with at least one positive test	622
• Cases with 1 cause	249
• Cases with >1 cause	373
• Cases with 2 causes	211
• Cases with 3 causes	103
• Cases with 4 causes	44
• Cases with 5 causes	14
• Cases with 6 causes	1
Number of patients with at least one positive test	595

the initials Q to Z, 1008 positive troponin-T determinations remained for further analysis (*table 2*). Of these, all multiple determinations per admission were excluded. Additionally, 107 admissions were discarded because the electronic files no longer contained the information required. Thus, altogether 622 admissions (cases) were finally used for statistical analysis (*table 2*). The 622 cases were attributable to 595 patients since 23 were admitted twice, 3 three times, and 1 five times during the observational period. CK was elevated, >144 U/l in women and >170 U/l in men, in 337 of 618 determinations (54.5%). Creatinine was elevated >1.1 mg/dl (97.4 µmol/l) in 303 of 604 determinations (50.2%) but a creatinine value (177 µmol/l) was only found in 100 of 604 determinations (16.6%).

The frequencies of the various other causes of troponin-T positivity are listed in *table 3*. The most frequent causes of troponin-T positivity were myocardial ischaemia, followed by heart failure, renal insufficiency, and atrial fibrillation (*table 3*). A single cause of troponin-T positivity was found in 249 cases, two causes in 211 cases, three causes in 103 cases, four causes in 44 cases, five causes in 14 cases, and six causes in a single case (*table 2*). If only patients with a single cause were considered, the most frequent causes of troponin-T positivity were myocardial ischaemia, renal insufficiency, and atrial fibrillation (*table 3*). In 24 cases no plausible cause, as listed in *table 1*, could be detected (*table 3*). Causes of troponin-T positivity previously attributable only to troponin-I-positivity were found in 34 cases (*table 3*). The most frequent single causes of troponin-T positivity, previously only observed together with troponin-I positivity, were atrial fibrillation, chronic obstructive lung disease, tachycardia, and electrical cardioversion (*table 3*). Causes of troponin-T positivity previously described but not found in the present cohort were Duchenne muscular dystrophy, polymyositis, and

Table 3. *Frequency of causes for troponin-T positivity*

Cause	Multiple causes	Single causes
Myocardial ischaemia	369	134
Atrial fibrillation*	140	11
Congestive heart failure	137	9
Chronic renal insufficiency	135	19
Percutaneous cardiac interventions	70	1
Chronic obstructive pulmonary disease*	60	6
Tachycardia*	57	5
Acute stroke	26	2
Electric cardioversion*	24	0
Dilated cardiomyopathy	20	2
Increased left ventricular mass*	19	3
Sepsis*	16	2
Epileptic seizures*	16	1
Pulmonary embolism	13	8
Aortic valve disease*	13	1
Hypertensive crisis*	12	1
Gastrointestinal bleeding*	12	0
Noncardiac surgery	8	4
Pacemaker implantation*	7	1
Chronic pulmonary hypertension	6	0
Myocarditis	5	1
Subarachnoid haemorrhage*	4	2
Chemotherapy*	4	0
Hypertrophic cardiomyopathy	3	0
Pericarditis*	3	1
Septic shock*	3	0
Systemic inflammatory response*	3	0
Lymphoma	2	0
Implantable cardioverter defibrillator shocks*	2	0
Uraemic cardiomyopathy	1	0
Takotsubo phenomenon	1	1
Inclusion body myositis	1	1
Dermatomyositis	1	0
Coronary vasospasm*	1	0
Radiofrequency ablation*	1	0
Physical exertion*	1	0
Amyloidosis*	1	0
Polymyositis	0	0
Diabetic ketoacidosis	0	0
Duchenne muscular dystrophy	0	0
Cardiac contusion*	0	0
Cardiac transplantation*	0	0
Scorpion or jellyfish envenoming*	0	0
(Pre)eclampsia, gestational hypertension*	0	0
Rheumatoid arthritis*	0	0
Electrical trauma*	0	0
No cause	0	24

*Diagnosis so far only associated with troponin-I positivity.

ketoazidosis (*table 3*). Causes of troponin-I positivity previously described, but absent in the present cohort, were cardiac contusion, heart transplantation, scorpion envenoming, eclampsia, rheumatoid arthritis, and electrical trauma (*table 3*). Among the 33 patients who were repeatedly admitted during the observational period the cause or causes of troponin-T positivity changed in nine, remained unchanged in three, and partially changed in 15 patients. The departments with the highest prevalence of troponin-T positivity were the cardiology, endocrinology/oncology, and the nephrology departments (*table 4*).

Table 4. *Frequency of troponin-T positivity in the different hospital departments*

Department	Frequency (n)
Cardiology	388
Oncology, endocrinology	89
Nephrology	41
Gastroenterology	15
Neurology	14
Neurosurgery	13
1. Surgery	10
Oto-rhino-laryngological	7
2. Surgery	4
Urology	3
Dermatology	3
Ophthalmology	2
Gynaecology	0
Paediatrics	0

Table 5. *Definite neurological diagnoses among 39 patients and suspected neurological diagnoses among all patients with troponin-T positivity*

Neurological diagnoses	Definite (n)	Suspected (n)
Neuromuscular disorder	14	25
Metabolic myopathy	4	22
Polyneuropathy	4	0
Myopathy of unknown aetiology	3	3
Limb girdle muscular dystrophy	1	0
Dermatomyositis	1	0
Rhabdomyolysis	1	0
Ischaemic stroke	10	0
Epilepsy	5	0
Subrachnoidal bleeding	4	0
Encephalitis/meningitis	3	0
Unknown	3	0
Dementia	2	0
Parkinson's syndrome	2	0
Neurologically normal	2	0
Apallic syndrome	1	0
Gait disturbance	1	0
Depression	1	0
Syncope	1	0
Carotid artery stenosis	1	0
Intracerebral bleeding	1	1
Subdural haematoma	1	0
Confusional state	1	0
Multiple sclerosis	1	1
Cerebral metastasis	1	0
Tremor	0	1
Lumbago, disc herniation	0	1
Acute deafness	0	1

Altogether, a neurologist saw 59 of the 622 cases (9.5%). The most frequent neurological diagnoses in these cases were NMD, stroke, or epilepsy (*table 5*). An NMD was detected in 14 of the 595 patients (*table 5*). The most frequent NMDs were metabolic myopathies, polyneuropathy, and myopathy of unknown aetiology. An NMD was responsible for troponin-T positivity as the single cause in four cases. From the retrospective study of the records additional neurological diagnoses were found or suspected (*table 5*). Among these, the most frequent were metabolic myopathies and myopathies of unknown aetiology. Altogether, an NMD was found in 39 of 622 cases (6.3%).

DISCUSSION

This study shows that troponin T is positive in 8.3% of the troponin-T determinations in a secondary centre, that troponin-T positivity is associated with elevated CK in 54.5% and with elevated creatinine in 50.2% of the determinations, that the most frequent primary cardiac causes of troponin-T positivity are myocardial ischaemia, heart failure, and atrial fibrillation, that the most frequent secondary cardiac causes of troponin-T positivity are renal insufficiency, chronic obstructive lung disease and stroke, that patients with troponin-T positivity are seen by a neurologist in 9.5% of the cases, and that troponin-T positivity is associated with an NMD in 6.3% of the cases.

Troponins are regulatory proteins which control the interaction of actin and myosin.[3] Troponins consist of three subunits, troponin T, I, and C. Troponin T binds to tropomyosin and facilitates contraction, troponin I binds to actin and inhibits actin/myosin interaction, and troponin C binds to calcium ions, which mediate the interaction of actin and myosin.[4] Troponins are not only expressed in myocardiocytes, but also in skeletal striated muscle and smooth muscle cells. In the three muscle cell types they occur as three different isoforms. Since the amino-acid sequence of the skeletal and cardiac isoforms of troponin T and I are dissimilar, they are differentiable by monoclonal antibody-based assays.[3] Since the number of false-positive results may be different between the various tests, it is generally recommended to interpret troponin-T test results only in the clinical context and not as

a test result alone.[5] The high number of causes of troponin-T positivity in the present investigation previously reported only for troponin-I positivity can be explained by the fact that troponin-T determination was not performed in most of these studies or that the applied test also recognises troponin I. That troponin T is more frequently elevated than troponin I in patients with chronic renal disease is attributable to the fact that elimination of troponin T is more dependent on renal function than is the elimination of troponin I.[6]

In accordance with the present investigation, troponin T is derived from the myocardium in almost all cases. Cardiac troponins are released from cardiomyocytes in case of irreversible cell damage or reversible membrane permeability dysfunction.[3] In the latter case myocardial damage is transient and not associated with necrosis of cardiomyocytes. Nonspecific troponin-T elevation is a common finding among hospitalised patients and associated with a worse prognosis. High troponin-T levels are significant predictors of death or rehospitalisation in patients with heart failure. Troponin-T positivity is also associated with a poor outcome in patients with ST-segment elevation acute myocardial infarction. Troponin-T levels are also independent predictors of long-term mortality, cardiovascular events, or death, and of noncardiovascular death in patients with chronic peritoneal dialysis. The most frequent cardiac condition resulting in troponin-T positivity is acute myocardial infarction, where troponin T is elevated in up to 97% of the cases.[7] In stable angina pectoris cardiac troponin remains normal but in unstable angina pectoris cardiac troponin T is elevated in 33 to 41% of the cases.[7] Troponin T may also be increased in 43% of the patients with heart failure.[8,9] In these patients troponin T is a predictor of decreased survival.[8] Contrary to the present findings, electrical cardioversion has so far only been reported to increase troponin I.[10] Troponin-T positivity in patients undergoing percutaneous coronary interventions is most likely due to irreversible myocardial injury as assessed by periprocedural delayed-enhancement MRI.[11] Also the Takotsubo phenomenon, which is triggered by emotional or physical stress, gastrointestinal infection, or surgical intervention,[12] may be associated with troponin-T positivity (*table 1*).[12] There is no evidence to support an association between cardiac troponin T and increasing left ventricular mass,[8] but troponin I has been found positive in this condition.[13] Primary cardiac causes of troponin-T positivity previously only found in association with troponin-I positivity are pericarditis, atrial fibrillation, tachycardia, increased left ventricular mass, severe aortic valve disease, coronary vasospasm, cardiac contusion, cardiac tamponade, hypertensive crisis, ICD shocks, pacemaker implantation, radiofrequency ablation, or cardiac transplantation (*table 1*). Other primary cardiac causes of troponin-T positivity are listed in *table 1*. That a neurologist saw 9.5% of the troponin-T positive patients is most likely due to the polymorbidity of these patients.

Secondary cardiac causes of troponin-T positivity are variable and include a number of disorders (*table 1*). As confirmed by the present investigation, the most frequent secondary cardiac cause of troponin-T positivity is chronic renal failure, where troponin T is elevated in up to 39% of the cases.[7,14] The mechanism by which renal failure causes troponin-T positivity is unknown, but there are indications that it is due to secondary myocardial thickening or myocardial ischaemia.[15] In patients with chronic kidney disease troponin T is a marker of poor survival[8] and predicts an increased mortality.[7] In these cases the blood pH correlates negatively with serum troponin T.[16] Secondary cardiac causes of troponin-T positivity previously only found in association with troponin-I positivity are chronic obstructive pulmonary disease, rhabdomyolysis, physical exertion, sepsis, subarachnoid haemorrhage, amyloidosis, chemotherapy, scorpion envenoming, eclampsia, rheumatoid arthritis, epileptic seizures, gastrointestinal bleeding, electrical trauma, or cirrhosis (*table 1*). Other secondary cardiac causes of troponin-T positivity are listed in *table 1*. In all these conditions myocardial involvement in the underlying disease is held responsible for the troponin positivity. Because of the high frequency of multicausality of troponin-T positivity in most of the presently investigated cases, it was difficult to identify a single or major cause of troponin-T positivity in the majority of the cases.

Only single studies attribute elevated troponin T to skeletal muscle disorders. So far, troponin-T positivity has been found in association with dermatomyositis, polymyositis, inclusion body myositis, and Duchenne muscular dystrophy (DMD) (*table 1*).[2,17-20] Troponin-T positivity was also reported in DMD carriers.[21] Troponin T may be also elevated in 75% of the patients with Becker's muscular dystrophy.[7] Additionally, cardiac troponin-T mRNA has been found in patients with sarcoglycanopathies.[22] Other studies, however, did not find elevated levels of troponin T or troponin I in DMD patients.[23] The present study additionally suggests that also patients with metabolic myopathy may present with troponin-T positivity. In NMD patients, troponin-T positivity is most likely due to cardiac involvement in myopathy, a frequently observed finding in the majority of the NMDs. Expression of the cTnT gene in skeletal muscle cells, however, cannot be definitively excluded as an additional explanation for troponin-T positivity in these patients, although there is currently no evidence that upregulation of cTNT genes is related to troponin-T or troponin-I levels.

Generally, troponin-T positivity without evident myocardial damage is attributable to a number of different causes. First, it may be explained by a low specificity of the applied tests, due to the presence of heterophilic antibodies, which may not only recognise cardiac troponin T but, to a variable degree, also troponin T derived from the skeletal muscle or even the smooth muscle. An argument

against this assumption, however, is that second to fourth generation cTnT tests show hardly any cross-reactivity with the skeletal muscle and are highly cardiospecific. Another reason for secondary cardiac troponin-T positivity in extracardiac disease may be the fact that various disorders are associated with secondary cardiac disorders. This may be the case with sepsis/SIRS, which is accompanied by myocardial depression and a supply/demand mismatch, intake of sympathomimetic agents, which have a direct adrenergic effect, chemotherapy, which is cardiotoxic in the majority of the cases, pulmonary embolism or pulmonary hypertension, or strenuous exercise, which all cause right ventricular strain.[3] A third reason could be the production of cardiac troponin T by tissues other than the myocardium. However, there is currently no evidence that upregulation or re-expression of the appropriate cTnT genes or post-transcriptional modifications of mRNAs result in the production of cardiac troponin T by noncardiac cells.[22,24,25] A fourth mechanism by which noncardiac disease might cause troponin-T positivity could be the release of norepinephrine from sympathetic nerves, resulting in damage to both myocytes and nerve terminals in the autonomic nervous system.[26] This mechanism may explain why intracranial haemorrhage is sometimes associated with troponin-T positivity. Which of these hypotheses is the most plausible remains speculative.

Limitations of the study were that it was retrospective, that patients with the initials Q to Z were excluded, that the electronic records were not available in a number of cases, the occurrence of multiple causes of troponin-T positivity in a number of patients, and the difficulty to identify a single cause of troponin-T positivity in the majority of the cases.

CONCLUSION

This study shows that troponin-T positivity is most frequently associated with ischaemic heart disease, followed by atrial fibrillation and heart failure. Many previously described causes of troponin-I positivity are also responsible for troponin-T elevation. NMDs are frequently associated with troponin-T positivity, most likely due to cardiac involvement of NMDs. Neurologists should be more frequently involved in the diagnostic work-up of troponin-T positive patients and clinicians should be aware of the large variety of causes and multicausality of troponin-T positivity.

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ORIGINAL ARTICLE

Diuretics, plasma brain natriuretic peptide and chronic obstructive pulmonary disease

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ABSTRACT

Background: Brain natriuretic peptide (BNP) is associated with increased myocardial stretching. This study aims to assess the effect of mild diuretics on plasma BNP levels in patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) who have high plasma concentrations of BNP.

Methods: Thirty consecutive patients with an acute exacerbation of COPD without any clinical evidence of cor pulmonale who had elevated plasma BNP concentrations (group 1) and 15 patients with stable COPD as controls (group 2) participated in this study. A mild diuretic treatment in addition to the standard treatment for an acute attack of COPD was randomised to 15 patients in group 1 (group 1A). The remaining patients in group 1 only took standard treatment for acute COPD exacerbation (group 1B). Plasma BNP concentrations were measured on admission and repeated on the 5th and 10th days.

Results: There was a significant decrease in plasma BNP concentrations, more striking in group 1A than 1B. Both in group 1A and 1B, the fall in plasma BNP concentrations was independent of either presence or absence of right ventricular dysfunction on echo evaluation.

Conclusion: Adding mild diuretics to the standard treatment for an acute attack of COPD may rapidly reduce plasma BNP levels in COPD patients with acute exacerbations who have high plasma BNP levels without any clinical evidence of cor pulmonale.

KEYWORDS

Brain natriuretic peptide, chronic obstructive pulmonary disease, cor pulmonale, diuretics

INTRODUCTION

Brain natriuretic peptide (BNP) originates from the ventricular myocardium and is secreted as a response to increased ventricular pressures and/or volume overload. It plays a role in the control of sodium excretion and blood pressure, and has a compensatory role in cardiorenal homeostasis.[1-4] A high plasma level of BNP is an important criterion for cardiac failure.[5-7] BNP has also been shown to increase in hypoxaemic patients with chronic obstructive pulmonary disease (COPD) and it is significantly increased, particularly in patients with cor pulmonale when compared with patients with COPD alone. It is especially increased in proportion to the degree of right ventricular (RV) dysfunction.[3,8-11] Elevated plasma BNP concentrations in COPD patients could be a useful early indicator of RV systolic dysfunction and monitoring changes in plasma BNP may provide a quantitative method for assessing RV function during follow-up.[12]

Since high plasma concentration of BNP is associated with increased strain on the ventricles, patients with COPD who have elevated plasma BNP levels should have some degree of RV strain, contributing to raised BNP levels even in the absence of clinical findings of RV dysfunction. Therefore, patients suffering an acute attack of COPD with high plasma levels of BNP might benefit from mild diuretics to decrease the volumetric strain on the right ventricle. Based on this hypothesis we planned a study that aims to evaluate the effect of mild diuretic treatment on the plasma BNP level in patients with an acute exacerbation of COPD who have high concentrations of BNP.

MATERIALS AND METHODS

Subjects

Thirty-seven consecutive patients with acute exacerbation of COPD, according to the criteria of the Global Initiative

for Obstructive Lung Diseases (GOLD),[13] without any clinical findings of cor pulmonale and any other diseases such as pneumonia, diabetes mellitus, renal failure, lung cancer, atherosclerotic or congenital cardiac disease and left ventricular failure and 15 patients with stable COPD admitted to the chest diseases department for continuous medical treatment prescription as a control group were enrolled in this study. Clinical and radiological examinations were performed in all subjects and all underwent pulmonary function tests, arterial blood gases and electrocardiographic evaluation, and Doppler echocardiography (echo) examination. The study was approved by the local ethics committee and each subject gave written informed consent.

BNP measurement

Plasma BNP levels were measured in all patients included in the study. Blood samples for BNP were obtained from peripheral blood into ethylenediamine tetra-acetic acid-containing tubes. Measurements were performed within two hours using the Roche commercial kit for BNP and the electrochemiluminescent method via the Elecsys 1010 Automated Analyser (Roche Diagnostics, Mannheim, Germany). The reference interval was 0 to 125 pg/ml.

Study design

Plasma BNP levels were elevated in 30 of 37 patients who presented with acute COPD exacerbation on admission. Seven patients were excluded from the study since they had normal plasma BNP levels. The remaining 30 patients were categorised as group 1 (29 males, 1 female). Measurements of plasma BNP levels were repeated on the 5th and 10th days in all group 1 patients. All patients in group 1 received the standard treatment for acute COPD exacerbation as defined below.

- All patients received oxygen through nasal cannulae to maintain a target oxygen saturation of 88 to 92%.
- Nebulised salbutamol (5 mg/4 hours) or terbutaline and nebulised ipratropium bromide (500 μg/6 hours) were preferred as bronchodilators initially. Later the treatment was maintained by formaterol fumarate dehydrate (9 μg/twice daily) and tiotropium bromide (18 μg/day) dry powder inhalations according to the patient's condition.
- Methylxanthenes (theophylline, 5-6 mg/kg as loading dose; 0.5 mg/kg/hour infusion as maintenance), corticosteroids (methyl-prednisolone 1 mg/kg/day intravenously; then decreasing doses of oral methyl-prednisolone for 15 days) and antibiotics (when signs of bacterial infection were present) were given to all patients.

A mild diuretic treatment (a combined preparation of triamterene 50 mg and hydrochlorothiazide 25 mg/day) in addition to the standard acute attack treatment was randomised to 15 patients who were categorised as group 1A. The remaining 15 patients in group 1, who were not on mild diuretic treatment, were categorised as group 1B. Group 2 served as a control group and consisted of 15 patients who presented with stable COPD. Patients in group 2 received only formaterol fumarate dehydrate (9 μg/twice daily), budesonide (200 μg/twice daily) and tiotropium (18 μg/day) dry powder inhalations. All patients on mild diuretic treatment were also followed for any electrolyte disturbance.

The echocardiographer was blinded to both the medications and the BNP levels of the patients. The echocardiographic evidence of RV hypokinesia with or without dilatation was used to define RV dysfunction. RV dysfunction and pulmonary arterial pressures on echo examination and evidence of RV strain on the electrocardiograms of all patients were noted.

Statistical analysis

Data were expressed as mean ± SD and median (with 25th and 75th percentages) where appropriate, and analysed using SPSS 13.0 for Windows. The independent samples t-test for continuous variables and χ^2 test for categorical variables were used to analyse differences between groups. For the comparison of 1st day measurements of BNP, the Kruskal-Wallis variance analysis test was used among groups and Mann-Whitney U test was used for binary comparisons if a significant difference was observed among groups. The latter was also used to compare the 5th and 10th day measurements of BNP between groups 1A and 1B. Friedman's variance analysis test was applied to compare three consecutive measurements of BNP in each group. Wilcoxon's test was used for binary comparisons if a significant difference was observed among measurements. Spearman's correlation test was used where applicable. A value of $p<0.05$ was considered significant.

RESULTS

The study included a total of 45 COPD patients, 30 with acute exacerbation and 15 with stable COPD. Patients' characteristics are summarised in *table 1*. No significant correlation was found between plasma BNP levels and the parameters of arterial blood gases ($p>0.05$).

Plasma BNP levels on the 1st day measurements were statistically different among the three groups ($p=0.0001$); however, no significant difference was noted among patients with acute exacerbations of COPD in groups 1A and 1B ($p>0.05$). First day plasma BNP levels differed significantly in patients who presented with stable COPD and acute exacerbations.

There was a gradual decrease in plasma BNP concentrations measured on the 1st, 5th and 10th days, more striking in group 1A than in group 1B (*table 2*).

Table 1. *Patients' characteristics*

Groups	Group 1A (n:15)	Group 1B (n:15)	Group 2 (n:15)
Age (years)	62.2±6.8	64.8±6.6	65.2±6.7
Smoking (pack-years)	45.3±13.5	47.0±17.9	33.3±8.9
FEV_1 (% predicted)	61.7±21.2	67.0±19.0	61.3±18.3
FVC (% predicted)	78.0±15.3	78.2±13.0	73.1±23.7
FEV_1/FVC	60.4±12.3	68.3±13.4	66.4±11.8
FEF_{25-75} (% predicted)	41.1±20.9	44.5±22.4	37.5±15.0
PEF (% predicted)	63.6±37.8	58.6±21.3	69.1±25.8
pH	7.40	7.39	7.41
PaO_2 kPa	7.8±0.7	8.6±0.7	9.4±1.1
$PaCO_2$ kPa	5.8±0.7	5.5±1.0	5.4±0.5
SaO_2 (%)	89.7 ±3.1	91.7 ±1.6	93.1± 1.9
HCO_3 (mol/l)	23.5± 2.2	23.3± 3.4	24.3± 2.4
Echo			
• Positive for right ventricular dysfunction	6 (40.0%)	4 (26.7%)	4 (26.7%)
• Negative for right ventricular dysfunction	9 (60.0%)	11 (73.3%)	11 (73.3%)
• Pulmonary arterial pressure (mmHg) (in patients with right ventricular dysfunction)	39.5±5.5	36.2±4.7	36.2±4.7

FEV = forced expired volume; FVC = forced vital capacity; PEF = peak expiratory flow; PaO_2 = partial pressure of oxygen; $PaCO_2$ = partial pressure of carbon dioxide; SaO_2 = arterial oxygen saturation.

Table 2. *Plasma brain natriuretic peptide levels ((pg/ml) median, IQR) of the groups*

BNP	Group 1A	Group 1B	Group 2	P value
1st day	742.0 (283.0-3228.0)	405.1 (184.4-2108.0)	100.9 (63.0-342.0)	0.0001
5th day	186.0 (127.0-2369.0)	230.6 (168.7-842.0)	-	0.983
10th day	168.5 (85.9-602.8)	205.7 (160.0-749.0)	-	0.513
P value	0.0001	0.038		

Although the fall in plasma BNP levels in group 1A was statistically significant among all three measurements, no significant drop was observed between the 5th and 10th day measurements in group 1B (*table 3*).

Among all patients included in the study, 14 subjects (31.1%) had echo findings of RV dysfunction without any clinical evidence of right heart failure (6 patients in group 1A, 4 in group 1B and 4 in group 2). The groups did not differ for the presence of RV dysfunction on echo evaluation. Plasma BNP levels of the patients with acute exacerbation who had echo evidence of RV dysfunction were significantly different to those without evidence of RV dysfunction: 1459.5 pg/ml (IQR: 857.3-3017.5) *vs* 312.8 pg/ml (IQR: 222.6-737.5); p=0.01. There was a positive correlation between 1st day BNP levels and the presence of echo evidence of RV dysfunction in patients with acute COPD exacerbations (p=0.008, r=0.474). However, both in group 1A and 1B, the fall in plasma BNP concentrations was independent of either presence or absence of RV dysfunction in echo evaluation.

Table 3. *P values for plasma brain natriuretic peptide levels among three measurements*

	P value	
Plasma BNP levels	**Group 1A**	**Group 1B**
1-5 days	0.003	0.038
5-10 days	0.004	0.609
1-10 days	0.001	0.015

DISCUSSION

We planned this study based on the fact that a likely RV strain in COPD patients may be responsible for high levels of plasma BNP concentrations and patients presenting with acute exacerbation of COPD who have high plasma BNP levels might benefit from a mild diuretic treatment to reduce plasma BNP concentrations. For this purpose we added a diuretic (a combined preparation of triamterene 50 mg and hydrochlorothiazide 25 mg/day) to the standard management of an acute attack of COPD in the studied population. We demonstrated that the fall in plasma BNP concentration was markedly higher in patients receiving additional diuretics than in patients receiving only standard acute attack treatment although significant decreases in plasma BNP levels were observed both in group 1A and 1B (p=0.0001 *vs* p=0.038). This finding indicates that adding diuretic treatment in patients with an acute exacerbation of COPD

may have a role in reducing increased plasma BNP levels and thus the RV strain. It may be considered that plasma BNP concentrations may decrease more rapidly in those patients who have received diuretic treatment. Intravascular volume increases following RV insufficiency, polycythaemia, and sodium and water retention due to hypervolaemia. An increased RV afterload enhances RV contractility. Later RV failure develops and water leaks into the extravascular space. If the intravascular volume is decreased, pulmonary haemodynamics, RV performance and gas exchange may improve.[14] Diuretics may act to reduce volume overload by enhancing salt and water excretion. Therefore, they may decrease the pulmonary arterial pressure and the workload of the right ventricle and thus the shift of interventricular septum into the left ventricle, which is caused by an increased volume load of the right ventricle.[15]

Subjects in group 1B showed gradual decreases in plasma BNP levels, as well; however, a statistically significant decrease was not observed between the second and third measurements in contrast to that in group 1A (*table 3*). Theophylline, a drug that has a mild diuretic effect, which was used as part of the acute attack treatment in these patients, might contribute to the early fall of plasma BNP level in group 1B. The continuing statistical fall in plasma BNP levels between the second and third measurements in group 1A may justify the role of mild diuretics in patients with acute COPD exacerbations.

Both the natriuretic peptides, atrial natriuretic peptide (ANP) and BNP, have a counter-regulatory role in cor pulmonale.[16] They are released in response to atrial and ventricular stretching and attenuate increases in RV afterload in response to hypoxaemia and may therefore be important as a regulator.[17,18] These peptides can produce significant pulmonary vasodilatation in cor pulmonale, as well. Both natriuretic peptides have beneficial effects on plasma aldosterone levels and these properties may be important in attenuating the overactivitity of the renin-angiotensin-aldosterone system observed in cor pulmonale.[16,19] By suppressing renin release and decreasing angiotensin II and aldosterone production, ANP and BNP may act to prevent excessive salt and water retention which may well be important in acute exacerbations of cor pulmonale.[20] In the present study we did not include patients with a clinical picture of cor pulmonale. Our aim was to indicate increased RV afterload in patients with acute exacerbations of COPD without clinical evidence of cor pulmonale. BNP may also be a valuable marker of increased RV strain in patients with an acute COPD attack and diuretic treatment may help to reduce acute increases in RV strain. Thus BNP may be useful in the follow-up of such patients. Yap has also noted that assessment of the plasma BNP concentration may be a noninvasive means of diagnosing RV dysfunction and pulmonary hypertension and may be used in follow-up of these patients.[21]

In the literature, studies enrolling patients with congestive heart failure have demonstrated that a low dose of spironolactone reduced plasma BNP levels, left ventricular diastolic volumes, and improved echocardiographic left ventricular ejection fraction.[22,23] The BNP level also correlated well with the degree of ventricular overload.[1,24] It has been demonstrated that long-term spironolactone treatment decreased plasma BNP levels in patients with congestive heart failure.[22,23,25] Johnson, too, reported that neurohormonal activation in patients with class IV heart failure rapidly decreased after a short-term therapy with intravenous diuretics and vasodilators by decreasing elevated filling pressures.[26] In our study we also found a correlation between plasma BNP levels and the echo evidence of RV dysfunction among patients with acute COPD exacerbations. However, the total number of patients with RV dysfunction in all groups was not statistically sufficient for any inference.

Plasma BNP concentrations may be found to be elevated in most patients with an acute exacerbation of COPD even if the patient has no clinical or echo evidence of cor pulmonale. Increased plasma BNP levels in these patients may be due to pulmonary hypertension during acute exacerbation. In the literature it has been reported that high BNP concentrations predicted moderate-severe pulmonary hypertension with 100% sensitivity and 73 to 89% specificity.[10,27] Compared with the 69% sensitivity and 94% specificity of the echo, as established in the WHO Multicentre Study,[28] the plasma BNP concentration appears to be a more sensitive but less specific means of predicting pulmonary hypertension and cor pulmonale. Leuchte especially emphasised that BNP could be regarded as a potentially helpful diagnostic tool to detect pulmonary hypertension in patients with pulmonary fibrosis.[27] Ishii also showed that plasma BNP concentration closely correlated with the mean pulmonary arterial pressure and pulmonary vascular resistance in patients with chronic respiratory diseases.[29]

Our study has some limitations, as it is the first in this respect. We did not use invasive cardiac imaging procedures, especially right heart catheterisation. Pulmonary arterial pressures of the subjects might have been measured via right heart catheterisation before and after treatment in this study. Instead, we only included subjects who were evaluated by echo. Doppler echo allows an estimation of the pulmonary arterial pressure and provides information about right and left ventricular function. However, it has limited accuracy. In this study we also used a small stable dose of a combination of triamterene and hydrochlorothiazide, which has a mild diuretic effect, so the dose-response effect of this combined preparation on the plasma BNP concentration must also be evaluated. BNP may act to prevent excessive salt and water retention by decreasing plasma aldosterone levels.

We did not quantitatively evaluate the plasma aldosterone level. Therefore, we were not able to show in what way the diuretics might have a lowering effect on plasma BNP levels in COPD patients.

We suggest evaluating plasma BNP levels in all patients who have an acute COPD exacerbation without any clinical evidence of cor pulmonale, as a high plasma BNP level may be a noninvasive means of showing increased RV afterload as previous studies have documented. A more rapid decrease in plasma BNP levels in the group treated with diuretics compared with the non-treated group may aid in early clinical improvement in the COPD patients with high plasma BNP concentrations; however, this hypothesis should be tested by using a daily symptom scoring questionnaire, which could be the subject of another study.

As a conclusion, in patients with a high level of plasma BNP concentration, adding a mild diuretic to the standard treatment for an acute COPD attack may aid in rapidly reducing plasma BNP levels and may prevent the clinical findings of cor pulmonale from developing. However, before considering a mild diuretic therapy as a possible therapeutic strategy in COPD patients with acute exacerbation who have high plasma BNP levels, there is a need for additional data obtained from studies enrolling large numbers of COPD patients.

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CASE REPORT

Severe *Yersinia enterocolitica* sepsis after blood transfusion

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ABSTRACT

A 23-year-old male received multiple blood transfusions following complicated thoracic surgery. He developed progressive haemorrhagic shock and multiple organ dysfunction syndrome. Blood cultures grew *Yersinia enterocolitica*. The patient was proven negative for *Yersinia enterocolitica*; however, one of the donors was found to be positive. Although strict selection of blood transfusion donors is warranted in the Netherlands, contamination of blood components may still occur and therefore should be considered whenever adverse events occur during or after blood transfusion.

KEYWORDS

Adverse events, blood transfusion, contamination, sepsis, *Yersinia enterocolitica*

INTRODUCTION

In the treatment of patients with severe haemorrhagic shock, control of the bleeding focus, restoration of the intravascular volume and haemoglobin levels are essential initial treatment goals. Therefore, massive blood transfusions are often needed for resuscitation in uncontrolled bleeding. However, blood transfusions are not without side effects and complications.[1]

Although blood transfusions in the Netherlands are relatively safe, side effects may occur.[1] In the Netherlands a rigorous screening programme aims to reduce blood transfusion reactions and side effects and has reduced the incidence to 0.14%. This screening programme comprises questionnaires to obtain information on the current state of health of the donor at the time of donation, testing for infection markers and quality control of blood components.[2]

We present a surgical patient who developed progressive circulatory shock and progressive organ dysfunction after haemorrhagic shock, even after adequate bleeding control and resuscitation. A rare complication of blood transfusion was found to be the underlying cause.

CASE REPORT

A 23-year-old male was admitted to the pulmonary ward with symptoms of a recurrent spontaneous right-sided pneumothorax. Video-assisted thoracoscopy (VATS) and pleurectomy were performed. A chest tube was inserted perioperatively. Postoperatively the patient developed hypotension and haemoglobin (Hb) levels dropped to 3.4 mmol/l (8.5-11.0 mmol/l). Although the chest tube was not productive, chest X-ray showed a massive right-sided pleural effusion suggestive of a haemothorax. Re-exploration revealed an intercostal arterial bleeding focus that was surgically repaired. The patient received six units of packed erythrocyte concentrates and two units of fresh frozen plasma and was admitted to the intensive care unit.

Postoperatively, the patient became febrile with a temperature of up to 39.3°C. Blood, sputum and urine cultures were taken and subsequently intravenous cefotaxime was started. At that stage no relation with the blood transfusions was considered. For progressive circulatory shock even after adequate volume resuscitation, noradrenaline and dopamine were commenced. Corticosteroids were administered. The platelet count dropped to 12 x 10^9/l (150-400 x 10^9/l) due to diffuse intravascular coagulation and consumption coagulopathy. Renal function deteriorated indicated by a rise in serum creatinine to 149 μmol/l (60-110 μmol/l) and mechanical ventilation had to be continued for acute lung injury

(P/F-ratio: 62). Severe sepsis with multiple organ dysfunction syndrome was diagnosed. Surprisingly, the blood cultures grew *Yersinia enterocolitica* type III. Cefotaxime was switched to ciprofloxacin.

Initially, bacterial translocation due to severe shock and mesenteric hypoperfusion was considered, but cultures from the patient's stools and early post-sepsis serological tests for *Yersinia* antibodies were negative. His partner's blood and stool cultures were also negative for *Yersinia*. All blood cultures grew gram-negative rods. *Yersinia* typing was performed by identification using API 20NE (bioMérieux, Boxtel, the Netherlands) technology. Anti-*Yersinia enterocolitica* test serum (SIFIN, Berlin, Germany) was used in our present case.

Therefore, the possible source of the *Yersinia* infection was suggested to be contaminated blood transfusions. The patient was weaned successfully and could be discharged from our hospital with no persistent sequelae after 21 days.

All donors were serologically screened using homemade Western Blot technology able to identify *Yersinia* IgG and in case of positive testing, an additional IgA antibody test for *Yersinia* outer protein (YOP) was performed (UMCN, Nijmegen, the Netherlands). In one donor only *Yersinia* IgG antibodies were found indicating a *Yersinia* infection before donation. A second donor presented with both IgG and IgA *Yersinia* antibodies, and stool cultures positive for *Yersinia enterocolitica*. At the time of donation this donor did not have any symptoms such as diarrhoea or abdominal pain. Thus, the most likely source of contamination was this specific *Yersinia*-positive donor. However, DNA testing revealed that these two *Yersinia* strains were not identical. Therefore, the other donor could also have been the source. Both donors were removed from the blood donor programme.

DISCUSSION

We present a rare case of a *Yersinia enterocolitica* sepsis likely related to contaminated blood of a *Yersinia*-infected blood donor. Initially, clinical signs were related to haemorrhage and it was only later that the clinical symptoms indicating sepsis became more pronounced.

Fever and emerging multiple organ dysfunction led us to review other causes than an inflammatory response after severe haemorrhagic shock, such as sepsis. A transfusion-related cause was not initially considered.

Sepsis is defined as the presence of at least two criteria of the systemic inflammatory response syndrome (SIRS) related to an infection.[3] SIRS criteria are: 1. Body temperature <36°C or >38°C; 2. Heart rate >90 beats/min; 3. Hyperventilation, evidenced by respiratory rate >20/min or $PaCO_2$ <32 mmHg; 4. White blood cell count >12.0 x 10^9/l or 4.0 x 10^9/l. SIRS criteria can also be found in allergic and anaphylactic reactions, after ischaemia/reperfusion and after multiple blood transfusions.[4]

Donation of blood in the Netherlands is only allowed if rigorous restrictions are respected to prevent contamination of the donated blood. Furthermore, there are no financial or other incentives for blood donation in the Netherlands, and extensive questionnaires are used and physical examination is performed. The health status, lifestyle and background of the donors are extensively addressed. In addition, donated blood is tested for HIV, hepatitis B and C, syphilis and human T cell lymphotrophic virus in every case.[5] Bacterial transmission through blood transfusion is extremely rare. The overall incidence rate is estimated at 0.2% of all blood products. Mild infections may go unnoticed.[6]

Bacterial contamination of blood may occur during donation or processing and usually involves commensal bacteria. In addition, contamination may also be caused by bacteraemia in the donor during donation.[6] This latter mechanism may have played a role in our patient.

Of all blood products, platelets are most at risk for bacterial contamination because these are stored at 20 to 24°C. To prevent bacterial contamination all platelet transfusions are cultured. Fresh frozen plasma is frozen for six months. If all serological and other tests are negative at the next donation, the plasma is released.[5]

In contrast to these rigorous measures for platelets and plasma, packed red-blood cells are only cultured in quality control samples and indirectly in case of thrombocyte transfusion processing from the same donor. With thrombocyte donation (20-30% of cases), cultures are always performed. If these thrombocyte transfusions are bacterially contaminated, all blood components including red packed cells from this specific donor are removed.

Thus, bacterial contamination of packed red blood cells may go unseen in the majority of cases. However, bacterial contamination of red blood cells is extremely rare and estimated at only 1 in 500,000. This low rate may be partly due to the low storage temperatures of 4°C preventing bacterial outgrowth.

Severe transfusion-related infections are mainly caused by gram-negative bacteria and in particular by *Yersinia enterocolitica* as these bacteria are able to grow at low temperatures. Furthermore, they show enhanced growth in environments rich in iron. Thus, packed red cells can be considered to be an ideal culture medium for *Yersinia enterocolitica*.[7-10]

It is not compulsory to notify health authorities of *Yersinia* infections. Therefore it is hard to predict the prevalence precisely. However, it is estimated at a few 100 cases of gastroenteritis per year in the Netherlands. *Yersinia* sepsis is extremely rare and is most frequently related to blood transfusions. Often the clinical course is severe. Mortality of *Yersinia* sepsis is around 50%.[11] Quinolones are first-line antibiotics for treatment.

Our case has some limitations: the molecular typing of the *Yersinia enterocolitica* from our patient could not be genetically related to the *Yersinia enterocolitica* from the culture-positive donor. Another possible explanation could be that the culture-positive donor was infected with multiple *Yersinia* species and a different strain contaminated the blood than we isolated from the stools. However, multiple species infections have not been reported in the literature. Still, it seems very unlikely that our patient could have had a source of *Yersinia* sepsis other than blood transfusions. Therefore, the *Yersinia* probably originated from the other donor who presented only serological positivity for *Yersinia*. Due to the fact that we were unable to culture *Yersinia* in this donor we were unable to prove genetic identity.

It is well known that *Yersinia*-infected patients may have antibodies against this bacterium while stool cultures remain negative. The fact that our patient tested negative, and that only a limited number of people per year in the Netherlands have proven *Yersinia enterocolitica* infections, serological positivity for *Yersinia* still could suggest a causal relation.[12]

The question to be answered remains whether we should put more efforts into preventive measures by applying more specific tests for bacterial contamination. Specific PCR assays for *Yersinia enterocolitica* are available, but other bacteria would not test positive so the clinical relevance in using this strategy may be very limited.[13]

To markedly increase the sensitivity, all samples could be cultured, but this will result in more cultures and incur higher costs. However, in general, patients who receive blood transfusions are not in good health and thus at risk of developing severe consequences from bacterial contamination. Therefore, selective sampling of packed erythrocyte concentrates for quality control and indirectly through thrombocyte component culturing could be reconsidered. Other techniques are under evaluation such as the Mirasol pathogen reduction process based on riboflavin photochemistry. Recently, costs and benefits of bacterial culturing and pathogen reduction (PRT) for platelet transfusions were evaluated and the authors concluded that blood cultures are without doubt more cost-effective than PRT in the Netherlands.[14] This debate will not solve the actual problem of many red blood cell transfusions that are not cultured.

In conclusion, we present a case of *Yersinia enterocolitica* bacteraemia very likely due to contaminated blood transfusion of red packed cells, leading to severe sepsis and multiple organ dysfunction syndrome.

We strongly advocate to further reduce risks and complications of our treatments, and suggest more effort is put into the reduction of bacterial contamination of blood transfusions, even if this incurs higher costs. The time has come not to selectively culture, but to culture all blood transfusions to further reduce this risk.

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CASE REPORT

Cough and alterations in semen after a tropical swim

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ABSTRACT

This case report describes a patient with cough and haematospermia shortly after visiting a *Schistosoma* endemic area. Numerous *S. haematobium* eggs were found in the ejaculate, while no eggs were seen in the urine.

KEYWORDS

Cough, genital, male, schistosomiasis, *Schistosoma haematobium*, semen

INTRODUCTION

Schistosomiasis is a parasitic disease caused by the blood dwelling trematode of the genus *Schistosoma*. People get infected in tropical areas through contact with fresh water containing the skin-penetrating infectious larvae.[1] In the area of Lake Malawi, where several popular tourist resorts are situated, *Schistosoma haematobium* is the predominant *Schistosoma* species.[2] In humans, the adult worm of this species is normally hosted in the perivesical venous plexus and eggs are excreted via urine. Haematuria is one of the main clinical signs of an established *S. haematobium* infection. However, a majority of affected individuals are initially free of symptoms,[1] with substantial risk of developing serious complications many years after infection. Due to relatively low worm burden, infections are easily missed in travellers, in particular if examination is limited to the detection of eggs in urine only. Determination of specific antibodies significantly increases the sensitivity of diagnosis.[3] Here, we describe an uncommon presentation of a *S. haematobium* infection in a traveller shortly after visiting Lake Malawi.

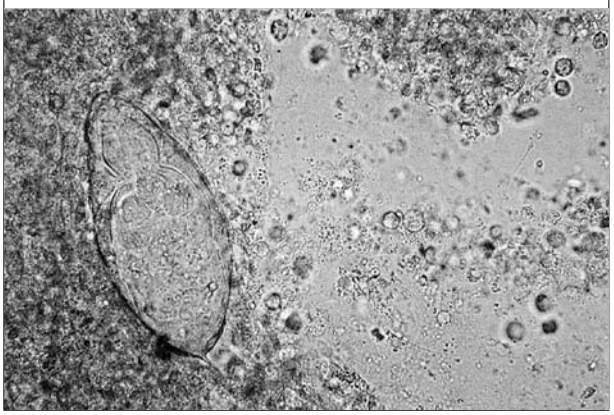
CASE REPORT

A 26-year-old Dutch medical student consulted his general practitioner with a five to six weeks' history of persistent dry cough accompanied by general malaise and periods of slight fever. Two months before the patient had travelled through Southern Africa where he visited several hospitals in Zambia and was in contact with fresh water at Cape Maclear, Malawi. Besides mild hay fever there was no medical history of relevance. On physical examination wheezing was heard over the lungs. Chest radiography showed enlarged hili, but no nodular lesions. Laboratory examination revealed eosinophilia (1.73 x 10^9/l). Allergic asthma was hypothesised and cetirizine was prescribed to suppress the cough with moderate effect.

Three weeks later, the patient noticed watery, rust-coloured semen and scrotal tenderness. Micturition was normal and no perineal trauma had occurred. His testes were of normal size and consistency. Rectal examination did not show signs of prostatitis. Because of the contact with fresh water in a *Schistosoma* endemic area, a parasitologist from Leiden University was consulted. Microscopic examination of ejaculate, collected after refraining from sexual activities for 36 hours, revealed about 1000 *S. haematobium* eggs in total (*figure 1*). Number and motility of spermatozoa were normal, but many leucocytes were seen, 60% were eosinophils. Low numbers of *S. haematobium* eggs were found in the stool, and none in urine. *Schistosoma*-specific antibody levels against adult worm and soluble egg antigen[3] were highly positive. Both serum and semen samples were negative for the schistosome circulating antigen CAA.[3]

The patient was treated with praziquantel 40 mg/kg bodyweight given in one dose. During intensive follow-up the macroscopic aspect of the semen returned to normal within 11 days and no more viable eggs were demonstrated from four weeks after treatment. Specific antibody levels

Figure 1. *Schistosoma haematobium egg in the semen of the patient described*



hardly changed in four months; eosinophilia decreased to 0.48 x 10^9/l. The initial cough persisted and was ascribed to bronchial hyperreactivity. Successful treatment with inhalation glucocorticosteroids was installed.

DISCUSSION

This is the first report describing an extremely high number of *Schistosoma* eggs (1000) in the ejaculate of a traveller with a Katayama syndrome and haematospermia. On average, an adult worm pair produces a few hundred eggs per day. More than half of these eggs do to not reach the environment, but get trapped in the host tissues.[1] Our finding therefore suggests that this ectopic localisation is not limited to a few eggs, or to a single worm pair that has lost its way. Rather, it seems that a cluster of several worm pairs had settled in the seminal vasculature. In our case no eggs were found in urine and only a few in faeces, implying that no worms had reached the commonly inhabited perivesical venous plexus yet.

Schistosoma infections affecting the male genital tract have been described before, both in travellers and endemic patients.[4-8] One of the first cases was reported in 1949 when Claude Barlow infected himself with larvae of *S. haematobium* and observed the development of haematospermia and the appearance of *Schistosoma* eggs in his own semen.[9] Only a small number of case reports describe lesions of the male genital tract caused by the *Schistosoma* infection, some simulating malignancy or sexually transmitted disease.[10,11] Male infertility from such lesions seems rare, but has never been well defined.[12] Still, the presence of *Schistosoma* eggs in semen does cause inflammation and release of inflammatory cytokines. As a result, infected men constitute an additional risk factor for the transmission of HIV, which is a great burden in endemic areas.[7]

Being a medical student, our patient suggested schistosomiasis to his general practitioner, which led to the diagnosis. The microscopic observation of eggs in semen was supported by detection of high levels of *Schistosoma*-specific antibodies in this patient who had never visited an endemic area before. Persistently high antibody levels, despite clinical and parasitological improvement following praziquantel treatment, as seen in this patient, are a common finding in schistosomiasis.[3] *Schistosoma*-specific antigens such as CAA are a better indicator of actual worm burden and therefore a complementary tool in the assessment of cure. However, antigen levels are often undetectably low in travellers harbouring a recent and relatively mild infection.[3]

Cough is one of the symptoms commonly seen in *Schistosoma*-infected non-immune persons presenting with acute schistosomiasis (Katayama fever). It is most likely mediated by an immunological response, not by the schistosomal migration through the lungs.[13] Persistent bronchial hyperreactivity in our patient is probably a result of eosinophilic inflammation in the airway mucosa through hypereosinophilia, although histamine bronchial responsiveness was not tested.[14] A chest X-ray one year after treatment did not show any abnormalities and there were no signs of asthma.

CONCLUSION

Schistosoma infections should be considered in any traveller showing seminal abnormalities who visited an endemic area during the previous year. In our patient, settlement of *Schistosoma* adult worms in the seminal vasculature seems more likely than migration of *Schistosoma* eggs. The semen returned to normal within weeks, demonstrating the efficacy of praziquantel in this compartment.

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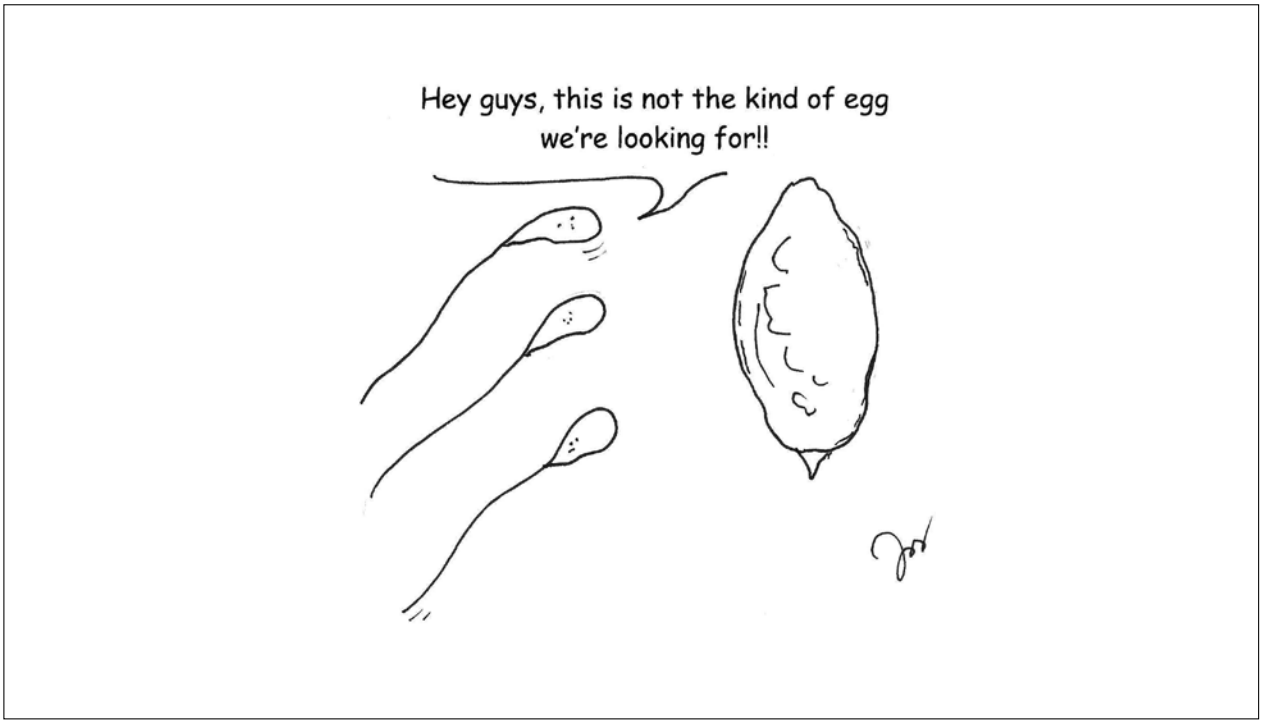

Van Delft, et al. Cough and alterations in semen.

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PHOTO QUIZ

A 65-year-old male patient with hoarseness of voice

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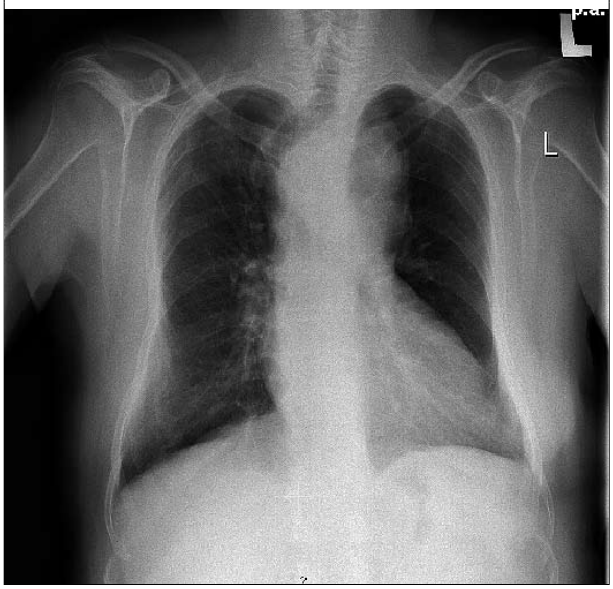
CASE REPORT

A 65-year-old male patient presented with hoarseness of voice lasting for several months. First he was examined by the otorhinolaryngologist of our hospital, who noticed cessation of movements of the left vocal cord. An X-ray of the chest was taken (*figure 1*) and the patient was referred to the pulmonologist. Bronchoscopy showed deviation of the trachea to the right, and small ostia with red swollen mucosa.

WHAT IS YOUR DIAGNOSIS?

See page 308 for the answer to this photo quiz.

Figure 1. *Trachea deviation to the right. Suspicion of a tumor in the mediastinum*



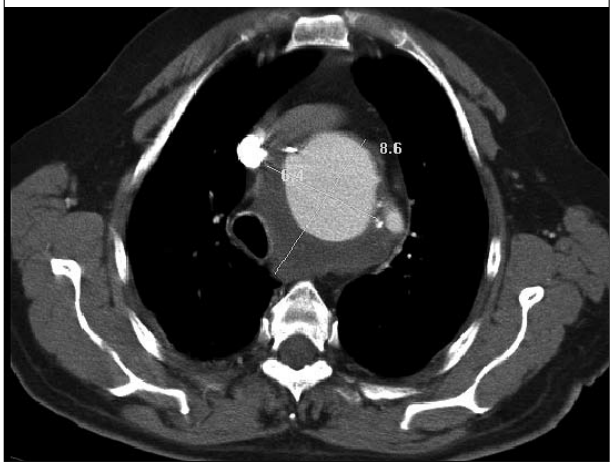
ANSWER TO PHOTO QUIZ (ON PAGE 307)

A 65-YEAR-OLD MALE PATIENT WITH HOARSENESS OF VOICE

DISCUSSION

The X-ray of the chest suggested a mass in the mediastinum. A mass in the mediastinum may be caused by lymphoma, teratoma, thyroid or thymoma. However, in our patient the diagnosis of a thoracic aneurysm was made (*figure 2*). The hoarseness of voice is due to paralysis of the left recurrent laryngeal nerve caused by the thoracic aneurysm. This is called Ortner's syndrome.[1]

Figure 2. *High thoracic level cross-section showing a large thoracic aneurysm*



DIAGNOSIS

The diagnosis in this patient is hoarseness of voice due to paralysis of the left recurrent laryngeal nerve caused by a thoracic aortic aneurysm. Ortner's syndrome (paralysis of the left recurrent laryngeal nerve) was first described as the result of atrial enlargement in mitral stenosis.[2]

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PHOTO QUIZ

Strange stripe

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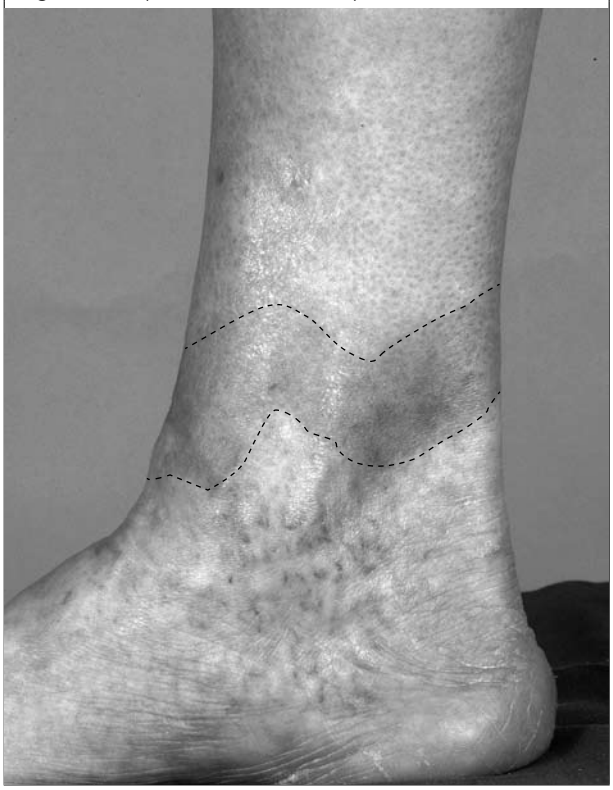
CASE REPORT

A 71-year-old woman with documented pernicious anaemia is examined before heart surgery. A circular, bracelet-like, brownish-coloured stripe on the skin above the right ankle is noticed (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 310 for the answer to this photo quiz.

Figure 1. *Circular, brownish-coloured stripe above the right ankle (between dotted line)*



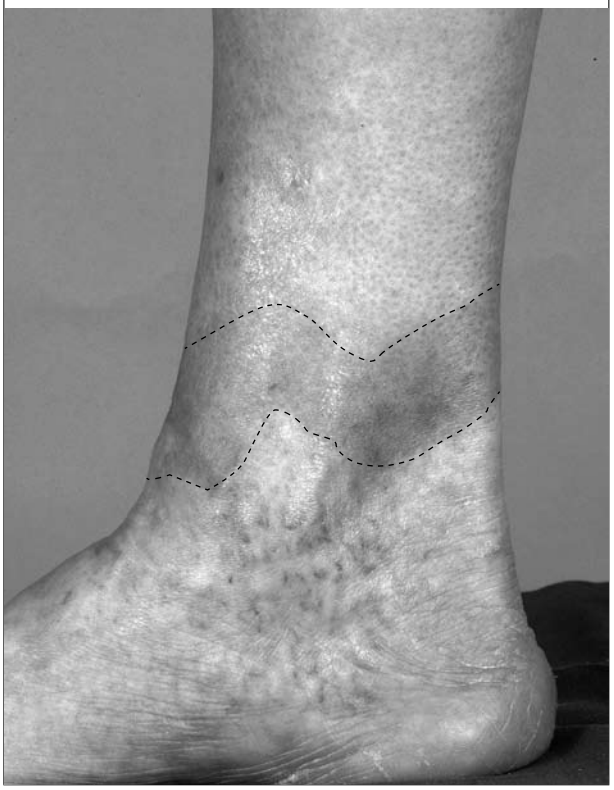
ANSWER TO PHOTO QUIZ (ON PAGE 309)

STRANGE STRIPE

DIAGNOSIS

Figure 2 showes a 71-year-old Caucasian woman who has been suffering from vitiligo since the age of 25, resulting in near total depigmentation (vitiligo universalis), leaving only one bracelet-like stripe of normal skin above her right ankle (*figure 1*). Her dark brown eyes contrast with her fair skin. During each of her (ten) pregnancies, the skin darkened and some repigmentation occurred but unfortunately the loss of her tan heralded spontaneous abortion, leaving her childless. Later in life pernicious anaemia was diagnosed. After a recent myocardial infarction, coronary artery bypass grafting was planned. Antiphospholipid antibodies are absent. She has neither thyroid disease nor diabetes mellitus. Her sister also has documented vitiligo and a history of miscarriages.

Figure 1. *Circular, brownish-coloured stripe above the right ankle (between dotted line)*



Autoimmunity directed against melanocytes is thought to be involved in the pathogenesis of vitiligo. Recently, autoantibodies against the melanin-concentrating hormone receptor 1 have been identified. Vitiligo is a component of the polyglandular autoimmune syndrome type II, which is characterised by the presence of endocrine disorders such as autoimmune thyroid disease, type 1 diabetes mellitus, primary adrenal insufficiency and hypopituitarism, and non-endocrine diseases including autoimmune hepatitis, alopecia areata and pernicious anaemia.

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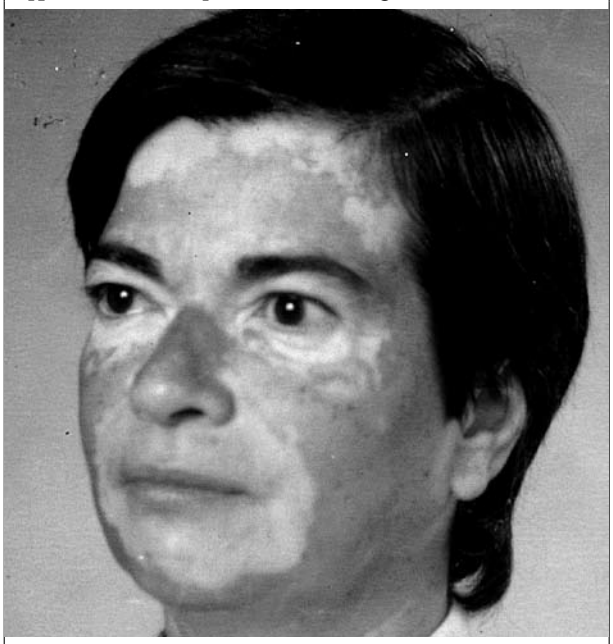
Figure 2. *Patient at a younger age, showing the typical bilateral symmetrical vitiligo*



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LETTER TO THE EDITOR

Yersinia enterocolitica O:3 mesenteric lymphadenopathy in an apparently healthy adult

Dear Sir,

Yersinia enterocolitica, a Gram-negative aerobic bacterium, is associated with various clinical manifestations, including acute gastroenteritis, abdominal pain, fever, weight loss, fatigue and, occasionally, mesenteric lymphadenopathy.[1,2] Important serotypes for human pathology are O:3, O:5, O:8, O:9 and O:27. These infections have usually been reported in patients with haematological diseases, such as thalassaemias, sickle cell disease and haemochromatosis.[1,3]

We recently observed a case of *Yersinia enterocolitica* infection, without gastrointestinal symptoms, in an apparently healthy 19-year-old female. The patient suffered from fever for 20 days, usually in the evening, and complained of fatigue, loss of appetite and significant weight loss. History and physical examination were unremarkable; laboratory investigation revealed anaemia, leucocytosis and elevated inflammatory indices. Blood and urine cultures were negative, as was serology for certain pathogens. Computed tomography (CT) of the abdomen revealed liver-spleen enlargement and mesenteric lymphadenopathy with 'sandwich sign', indicative for non-Hodgkin lymphoma (*figure 1*). Histopathology showed that lymphadenopathy was reactive, possibly due to infection with no signs of malignancy. Twenty days later, under second-generation cephalosporins, the patient presented with an acute abdomen; CT additionally revealed abscess formation in the right mesenteric region (*figure 2*). Repeated laparotomy was performed; histopathology showed infiltrates of neutrophils, histiocytes, eosinophils, plasma cells and giant cells indicating reactive lymphadenopathy, due to *Yersinia enterocolitica* or pseudotuberculosis. Serology confirmed *Yersinia enterocolitica* type O:3 infection. The patient was given ciprofloxacin 500 mg/twice daily for 20 days and recovered completely.

Yersinia enterocolitica is transmitted via the enteric route or by direct inoculation through blood transfusions.[1] Iron overload diseases and desferrioxamine favour *Yersinia* by providing the necessary iron for bacterial growth; these patients have a higher possibility of septicaemia.[4] Symptomatology may mimic acute appendicitis, Crohn's disease, ileum perforation or lymphoma. Further manifestations include reactive arthritis, especially in HLA-B27 positive individuals. Diagnosis is based on positive cultures of biological specimens. Serology may detect O:3 and O:9 serotypes, responsible for more than 90% of *Yersinia* infections in Europe; these serotypes have been proven resistant to penicillins and second-generation cephalosporins. Fluoroquinolones and third-generation cephalosporins are effective, while combinations with aminoglycosides or trimethoprim-sulfamethoxazole have

Figure 1. *Computed tomography of the abdomen revealed mesenteric lymphadenopathy with the 'sandwich sign', indicative of non-Hodgkin lymphoma (white arrow) and lymph nodes around the terminal ileum (black arrow)*

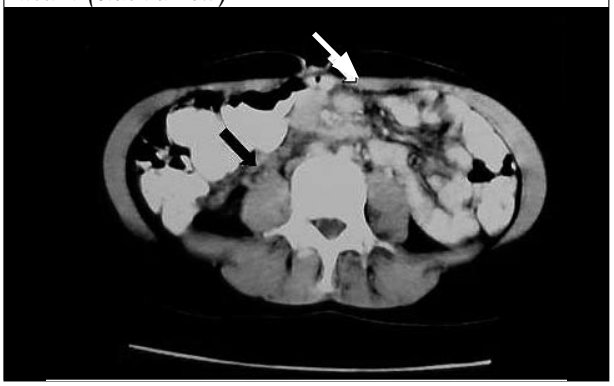
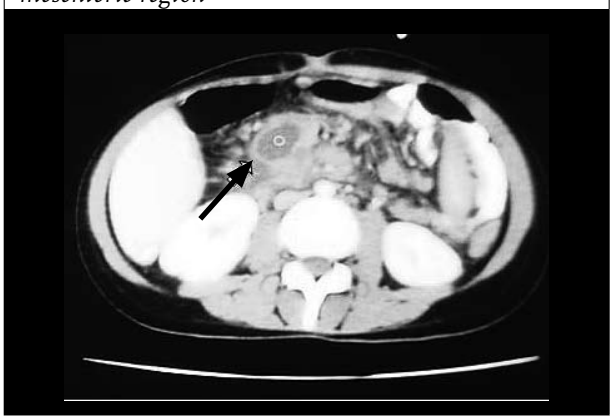


Figure 2. *Twenty days later, a block of pathological lymph nodes, hepatosplenomegaly and abscess formation (white arrow) were observed in the right mesenteric region*



been successfully used in septicaemia; surgical treatment is required for rare complications.[1,4]

Yersinia enterocolitica-related mesenteric lymphadenopathy with no gastrointestinal symptoms in this apparently healthy adult is considered to be extremely unusual. However, *Yersinia enterocolitica* should be included in the differential diagnosis of atypical abdominal symptoms combined with mesenteric lymphadenopathy.

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Terlipressin and tricyclic antidepressant intoxication

Dear sir,

Veris-van Dieren *et al*. report the importance of early ECG recordings in the diagnostic process of patients who are suspect for tricyclic antidepressant (TCA) intoxication.[1] The first case describes a clinical example of pulseless electrical activity (PEA), bradycardia and immeasurable pulse in a 66-year-old woman intoxicated with tricyclic antidepressants. The patient was treated with high-dose (quantity not mentioned) inotropics and vasopressors (epinephrine and norepinephrine). Since catecholamines compete with TCAs for α_1-adrenergic receptor binding, clinicians may be forced to infuse high doses of catecholamine in TCA-overdose patients in order to maintain an adequate organ perfusion pressure. *Tables 1* and *2* show the correlation between receptor affinity of TCAs and occurrence of side effects. However, high-dose catecholamines can have detrimental side effects.[2] Earlier this year we reported[3] a similar case in which the patient was treated with 1 mg terlipressin intravenously, with excellent haemodynamic and neurological outcome.[3] Terlipressin, a vasopressin analogue with a prolonged duration of action, acts as a selective V_1-receptor agonist. Stimulation of V_1 receptors

Table 1. *Common adverse effects of TCAs*

Generic name	Adverse effects				
Tertiary amines	**Hypotension**	**Sedation**	**Anticholinergica***	**Cardiac effects**	**Seizures**
Amitriptyline	+++	+++	+++	+++	++
Clomipramine	++	++	+++	+++	+++
Doxepine	+++	+++	++	++	++
Imipramine	++	++	++	+++	++
Trimipramine	++	+++	+++	+++	++
Secondary amines					
Amoxapine	++	+	+	++	++
Desipramine	+	o/+	+	++	+
Maprotiline	++	++	++	++	+++
Nortriptyline	+	+	+	++	+

*For example, tachycardia, dry mouth, urine retention, constipation.

Table 2. *Receptor affinity of TCAs*

Generic name	Receptor affinity				
Tertiary amines	α_1	H_1	M_1	D_2	α_2
Amitriptyline	+++	++++	++++	o	+/-
Clomipramine	++	+	++	++	o
Doxepine	+++	++++	++	o	o
Imipramine	++	+	++	o	o
Trimipramine	+++	++++	++	++	+/-
Secondary amines					
Amoxapine	++	+	o	++	o
Desipramine	+	+/-	+	o	o
Maprotiline	++	+++	+	+	o
Nortriptyline	++	+	++	o	o

α_1 = alpha-1 receptor; α_2 = alpha-2 receptor; H_1 = histamine-1 receptor; M_1 =muscarine-1 receptor; D_2 = dopamine-2 receptor.

results in elevation of intracellular calcium which, in turn, contracts smooth muscle cells resulting in an α_1-adrenergic receptor-independent vasoconstriction, and increase in systemic vascular resistance (SVR) and mean arterial pressure (MAP).[4] Since vasopressin analogues 'bypass' the hampered catecholamine system in TCA overdose, it may be an alternative strategy to manage hypotension that is refractory to catecholamines in TCA intoxication.

Furthermore, based upon old literature, the authors advise the reader to be cautious with the use of sodium bicarbonate ($NaHCO_3$) in TCA intoxication. Some case reports and animal studies suggest that cardiac arrhythmias and broad QRS complexes react to aggressive treatment with $NaHCO_3$. In spite of hard scientific evidence, Vrijlandt and colleagues recommend the use of $NaHCO_3$ in TCA-intoxicated patients.[5] As mentioned before, $NaHCO_3$ can diminish direct cardiac toxicity and facilitates binding of TCA to proteins which, in turn, lowers the free fraction of TCA.

In conclusion, we suggest that terlipressin may have a potential role as an adjunct vasopressor in a shock state refractory to catecholamines in TCA-intoxicated patients and recommend the use of $NaHCO_3$.

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The table lists online hits for all articles published in the May issue of the Netherlands Journal of Medicine, 2007 (available online on PubMed since 22 May 2007). This is based on the analysis of our user log file on 23 August 2007.

Article	Hits
EDITORIAL	
Do we need new drugs for the treatment of type 2 diabetes mellitus?	239
REVIEW	
Heterozygous alpha-1 antitrypsin deficiency as a co-factor in the development of chronic liver disease: a review	201
ORIGINAL ARTICLES	
Non-evidence-based variables affecting physicians' test-ordering tendencies: a systematic review	151
Single-centre experience with nonmyeloablative allogeneic stem cell transplantation in patients with multiple myeloma: prolonged remissions induced	137
CASE REPORTS	
Papillary thyroid carcinoma in a patient with sarcoidosis treated with minocycline	221
An itchy holiday	308
PHOTO QUIZ	
Rare localisation of air	173
SPECIAL REPORT	
Recurrent pericardial effusion with a common clinical disorder	214
MONTHLY NJM ONLINE HITLIST	
For all articles published in February 2007	116
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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
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