A 30-year-old man with polyuria, polydipsia and an abnormal chest X-ray: what is your diagnosis?

ZIKA virus infection

IgG4 related disease

Refeeding syndrome

Splenic irradiation in frail patients with CLL
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Refeeding syndrome refers to biochemical and clinical symptoms as well as metabolic abnormalities among malnourished patients undergoing refeeding, irrespective of whether these consequences are induced by oral, enteral or parenteral feeding. Typically, low serum concentrations of predominately intracellular ions such as phosphate, magnesium and potassium are encountered; however, frequently also abnormalities in the glucose metabolism, including thiamine deficiency and levels of sodium and water balance have been described. Refeeding syndrome has been shown to be associated with considerable morbidity and mortality.

In the current issue of the journal, Kraaijenbrink and co-workers describe the incidence of refeeding syndrome among 178 patients acutely admitted to an internal medicine department of a teaching hospital in the Netherlands. Surprisingly, they observed that half of the patients were at risk for refeeding according to the NICE guideline definitions and actually 1 out of 12 patients developed refeeding syndrome defined as a positive refeeding risk score combined with new-onset hypophosphataemia during follow-up.

The incidence of refeeding syndrome has been rarely reported or varies markedly, most probably due to lack of a universally accepted definition. Among anorexia nervosa patients on the ICU, refeeding syndrome was encountered in 10%, a similar incidence as compared with the internal medicine population studied by Kraaijenbrink. This may be due to the fact that any patient with negligible food intake for more than five days or poor nutritional status is at risk of developing refeeding-associated problems. Internal medicine patients with oncological diagnoses are at enhanced risk for refeeding syndrome, possibly due to cancer cachexia, poor intake or other unknown associations. Unfortunately, nutritional risk assessment instruments such as the SNAQ score were proven not useful to predict the syndrome. No major differences in clinical outcome, such as mortality and handgrip strength, were observed comparing those patients with and without refeeding syndrome. The sharpest decline in phosphate levels was observed on days 2 and 3, with the nadir in patients with refeeding on day 5.

In my opinion, this should not lead to the assumption that diagnosing refeeding syndrome is not relevant for the following reasons: First, in this observational study, data on actual treatment of refeeding syndrome patients are lacking as this was not the objective of the study. Second, until recently recommendations that feeding should be commenced at maximally 50% of energy demands were only expert based. In contrast, some physicians believed that a strategy to prescribe full feeding while aggressively correcting electrolytes should be considered safe. Such a strategy may be possible in internal medicine departments, but may be more feasible in the setting of an ICU where patients have arterial lines and drawing blood and correcting electrolyte abnormalities and fluid status is routine. To shed light on these contradicting approaches, the first randomised controlled trial studying caloric restriction in adults was recently published. Doig and co-workers compared normal caloric intake during the management of refeeding syndrome with restricted intake up to a maximum of 480 kilocalories per day for two days among 339 adult mechanically ventilated ICU patients. The inclusion criteria were pragmatically designed focusing on ICU patients with new-onset hypophosphataemia (a drop in serum phosphate > 0.16 mmol/l from a previous reading to below 0.65 mmol/l within 72 hours after nutritional support commencement, similar to the criteria used by Kraaijenbrink and co-workers. Hypophosphataemia may have been caused by other reasons, however hypophosphataemia on admission was an exclusion criterion similar to the Kraaijenbrink study. The full caloric strategy induced higher mortality rates at hospital discharge (+9.2% (95% CI 0.7-17.7; p = 0.017)), and at 60 days (+12.3% (95% CI 3.9-20.7; p = 0.002)), and 90 days (+8.7% (95% CI 0.04-17.0; p = 0.041)). Furthermore, more major infections and airway or lung infections were encountered during full feeding.
Therefore, in my opinion it can be recommended to follow-up acutely admitted patients at risk for the development of refeeding syndrome-associated hypophosphataemia after the commencement of nutritional support in the hospital setting and to reduce caloric intake for 48 hours (caloric restriction) while aggressively correcting electrolytes, monitoring the fluid balance and administering thiamine. Subsequently caloric intake may be gradually increased to full nutritional support.

As refeeding syndrome may be frequently encountered in internal medicine wards, plasma phosphate monitoring on day 2-3 after resuming nutrition seems essential. Diagnosing the refeeding syndrome is very relevant, as it may be encountered frequently among acutely admitted medical and critically ill hospitalised patients and not optimally handling its consequences, including caloric restriction, may potentially confer worse outcomes.

DISCLOSURES

ARHvZ has received honoraria for advisory board meetings, lectures, and travel expenses from Abbott, Baxter, Danone-Nutricia, Fresenius Kabi, and Nestle-Novartis.

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Zika virus and the current outbreak: an overview

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ABSTRACT

Zika virus (ZIKV), a mosquito-borne flavivirus closely related to yellow fever virus and dengue virus, is currently causing a large outbreak in the Americas. Historically, ZIKV infection was considered a sporadic, relatively mild disease characterised by fever, maculopapular rash, conjunctivitis and often arthralgia. However, current observational studies suggest that ZIKV may cause more severe neurological sequelae such as Guillain-Barre syndrome, and birth defects, mainly microcephaly, in babies of whom the mother was infected with ZIKV during pregnancy. This article provides a clinically focussed overview of ZIKV, with emphasis on the current outbreak, clinical manifestations, diagnostic tools and caveats.

KEYWORDS

Zika virus, microcephaly, flavivirus, Aedes, outbreak, Americas

BACKGROUND

In May 2015, the Pan American Health Organization (PAHO) issued an alert about possible autochthonous transmission of Zika virus (ZIKV) in Brazil, South America. Since then, the virus has spread widely in Middle and South America, and the Caribbean, affecting 29 countries and resulting in ten-thousands of probable and confirmed cases as of 22 February 2016.¹ These include (former) European overseas countries and territories and due to intensive international travel, the risk of importing ZIKV to Europe has increased. On 11 December 2015 the first case of ZIKV imported from the New World was reported in the Netherlands.¹ Since then, 30 cases, imported from Suriname and some islands of the (former) overseas territories of the Netherlands, were diagnosed (as of 22 February 2016). Possible association of ZIKV with microcephaly in newborns and other neurological disorders urged the World Health Organization (WHO) to declare the outbreak of microcephaly-associated ZIKV a Public Health Emergency of International Concern on the 1 February.³ Co-circulation of dengue and chikungunya virus, which share overlapping clinical manifestations with ZIKV, complicates clinical diagnosis, while dengue virus, West Nile virus and yellow fever virus may cause cross-reactivity in serological diagnostic tests which severely hampers laboratory diagnosis of ZIKV infection in the outbreak region.⁵ Here, we briefly provide an overview of the current outbreak, and some characteristics of the virus, clinical manifestations and management of ZIKV infections, and finally the diagnostic tools which can be used.

EPIDEMIOLOGY

ZIKV is a member of the genus Flavivirus, family Flaviviridae. Other flaviviruses of importance to human health are dengue virus, West Nile virus, yellow fever virus, Japanese encephalitis virus and tick-borne encephalitis virus. ZIKV is most closely related to the New World flaviviruses St. Louis encephalitis virus, Rocio virus and Ilheus virus.²,⁶ ZIKV was first discovered in the Zika forest in Uganda in 1947 and incidental cases were reported for the next 60 years in both Africa and South-East Asia.⁶ In 2007, ZIKV caused an outbreak of mild disease in the Pacific, characterised by fever, rash, arthralgia and conjunctivitis in Micronesia. This was followed by an epidemic with an estimated 32,000 patients in French Polynesia in 2013-2014.⁷,⁸ Since then, the virus has extended its geographic distribution to
multiple countries in the Pacific Ocean and ZIKV emerged for the first time in the Americas on Easter Island, Chile in 2014. In May 2015, the authorities in Brazil confirmed autochthonous transmission in the northeast of the country and since then, the virus has spread rapidly in the region with ten-thousands of cases (figure 1). In addition, there is a ZIKV outbreak on the Cape Verde islands with approximately 7000 cases recorded since December 2015. The current outbreak in the Americas has led to an increase of travel-associated imported ZIKV cases to Europe with registered cases in Austria, Denmark, Finland, France, Germany, Ireland, Italy, Portugal, the Netherlands, Spain, Sweden, Switzerland and the United Kingdom.8 ZIKV is transmitted in a human-mosquito-human cycle involving Aedes mosquitoes. Ae. aegypti is the only species for which transmission outside Africa has been confirmed. Although competence for Ae. albopictus, a mosquito species established in large parts of Southern Europe and occasionally introduced into the Netherlands by trade of plants and used tires,11 has been demonstrated in laboratory circumstances for the African lineage of ZIKV, this mosquito species has never been implied in ZIKV epidemiology outside Africa.6,13-14 Blood transfusion mediated, perinatal and possible sexual transmission of ZIKV have been reported as well.6,15-20 The potential for transmission of ZIKV by other Aedes mosquitoes in Europe is under investigation, but is considered to be low.

VIROLOGY

Viruses of the genus flavivirus are positive-stranded, enveloped RNA viruses with a single genome of approximately 11 kb. The ZIKV genome encodes for three structural proteins C, M and E, and seven non-structural proteins, NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5.21-23 Because the RNA-dependent-RNA-polymerase (NS5) is very conserved among flaviviruses, this genomic region is often used as a target in pan-flavi molecular tests. ZIKV belongs to the Spondweni serogroup, together with Spondweni virus which circulates in Sub-Saharan Africa and Papua New Guinea. Two lineages of ZIKV are recognised: the African lineage and the Asian lineage.6 The African lineage has not (yet) disseminated outside Africa. ZIKV strains circulating in the Americas are of the Asian lineage with 99.9% identity with the ZIKV strains circulating in French Polynesia in 2013-2014.24

CLINICAL MANIFESTATIONS

Knowledge about the clinical course of ZIKV infection is based on a relatively small number of studies in comparison with other emerging pathogens. The first documented case of human ZIKV infection dates back to 1964 and describes a febrile illness that, without diagnostics proving ZIKV to be the causative agent, could easily have been caused by another arboviral infection, such as dengue or chikungunya.6,9 The majority of ZIKV infections seem to be asymptomatic, confirmed by data from outbreaks in Micronesia and French Polynesia in 2007 and 2013-2014, respectively, with symptoms in only 18% of patients with documented antibodies. However, overestimation of the number of asymptomatic infections may be considered, since serological cross reactivity may have occurred with other circulating flaviviruses such as dengue virus, West Nile virus and Japanese encephalitis virus.25 Other evidence for the occurrence of asymptomatic infections came from studies in blood donors that show a significant seroprevalence.24-35 After an incubation period of 3-12 days, symptomatic patients generally present with fever, arthralgia, myalgia, headache, non-purulent conjunctivitis, and maculopapular rash.26-27 The arthralgia is most often localised in the small joints of hands and feet and could be accompanied with joint swelling.6,10 Other manifestations include anorexia, nausea and vomiting, diarrhoea, abdominal pain, sore throat, retro-orbital pain, a burning sensation of the palms and soles and vertigo.6,7,9,23 In contrast to dengue virus infection, haemorrhagic complications seem rarely to be associated with ZIKV, and leukopenia and thrombocytopenia seem to only occur in a minority of ZIKV cases.23 Oedema of the extremities, noticed as swelling of especially the ankles, is considered to be quite specific for ZIKV in comparison with dengue and chikungunya virus.2,3 Although not much is known yet about the morbidity and mortality of the current ZIKV outbreak, it is assumed that in comparison with other arboviral infections, ZIKV is relatively mild and self-limiting. Currently, three deaths have been linked to ZIKV infection, although, the level of evidence for causality...
remains doubtful. In the current ZIKV outbreak, much attention has been drawn towards potential neurological complications of ZIKV infection, where the main concerns are the possible association of ZIKV infection with Guillain-Barré syndrome (GBS) and microcephaly as a neurological manifestations in newborns.

Both complications were observed in the outbreak in French Polynesia as well as in the current outbreak, with Brazil reporting more than 4700 suspected cases of microcephaly since May 2015. One should bear in mind that only a minority of these 4700 cases remained linked to ZIKV infection after correction for differing criteria for microcephaly, birth weight and potential other factors predisposing to microcephaly. ZIKV RNA was identified in the amniotic fluid of two women whose foetuses had microcephaly.

The potential causality is further supported by the full genome detection of the virus in the brain of a foetus with microcephaly. The potential causality is further supported by the full genome detection of the virus in the brain of a foetus with microcephaly.

Sequelae

- Possible link to GBS, encephalitis and microcephaly
- Long-term arthralgia up to 24 months
- Link to GBS, haemophagocytosis and encephalitis

Vaccination

- None
- None
- Experimental

Diagnostics available

- PCR urine and serum, serology under development
- PCR, serology
- PCR, serology, antigen tests

Based on references: 9, 23, 28-30. GBS = Guillain-Barre syndrome; PCR = polymerase chain reaction.
association between ZIKV infection and these complications.

**CLINICAL MANAGEMENT AND TREATMENT**

No specific antiviral treatment is available thus, if needed, care is supportive. However, the disease is self-limiting and mainly lasts no longer than seven days in the majority of cases. Since there is no evidence yet for haemorrhagic complications in ZIKV, the use of non-steroidal anti-inflammatory drugs (NSAIDs) in case of (severe) arthralgia is not strictly contraindicated. However, in case of uncertainty of the diagnosis and the possibility of a dengue virus infection pending the test results, NSAIDs should still be avoided. In daily practice, normal thrombocyte counts could favour the use of NSAIDs. Where possible acetaminophen, which does not alter platelet aggregation, could be used to supress milder symptoms.

In case of GBS, intravenous immunoglobulin might be effective, although severe GBS cases may require intensive care, including mechanical ventilation. Currently, the Centers for Disease Control (CDC) recommends monitoring of foetal development in pregnant women with evidence of ZIKV infection by 3-4 weeks ultrasounds. This strategy would increase the knowledge about causality of ZIKV-infected pregnant women and birth defects. However, the benefits for the mother and unborn child are limited due to the lack of treatment or intervention other than abortion.

Currently, the Dutch National Institute for Public Health and the Environment (RIVM), advises pregnant women, when possible, to postpone non-essential travel to ZIKV outbreak areas. If travel is necessary, mosquito repellents, long sleeved clothing and an impregnated bed net should be used. When a pregnant woman has a molecular proven ZIKV infection, follow-up in a specialised perinatal care centre during the pregnancy is recommended (http://www.rivm.nl/dsresource?objectid=rivmp:304780&type=org&disposition=inline&ns_nc=1).

**DIFFERENTIAL DIAGNOSIS**

Since the majority of symptomatic ZIKV patients present with arthralgia, fever and rash, the differential diagnosis of suspected ZIKV includes viruses with similar clinical manifestations, like chikungunya and dengue virus. Based on the geographical exposure, the differential diagnosis can be broadened. For the Americas the alphaviruses Mayaro virus, Oropouche virus and equine encephalitis virus, as well as West Nile virus and La Crosse encephalitis virus may be considered. Also, malaria and rickettsioses may be taken into account. The differential diagnosis can be broadened to other acute virus infections including influenza, rubella and measles, or non-viral diseases.

**DIAGNOSTICS**

Information on ZIKV infection kinetics is indispensable for proper interpretation of diagnostic results. The information available in literature is limited to Asian ZIKV and concerns only a few cases. Viraemia seems low and short. ZIKV shows a peak in viral load when symptoms appear and can be detected up to 3-5 days after onset of symptoms with reverse transcription polymerase chain reaction (RT-PCR). ZIKV RNA has been detected in saliva, nasopharyngeal swabs, urine and semen as well. A combination of blood, urine and saliva samples is advised to increase both the sensitivity of molecular detection and the detection window. The viral load in urine seems to be higher than in blood/serum, is observed to peak 5-7 days upon onset of symptoms and has a much longer detection window (detection > 28 days post-onset of symptoms have been described) than blood, although sensitivity of detection at these time points remains to be determined. A combination of blood and saliva sampling increased the ZIKV detection rate by 19% but did not increase the detection window.

ZIKV specific IgM seems to appear 3-5 days and IgG 10 days after onset of illness in patients without previous flavivirus infections. Typically in flavivirus infections IgM develops within a few days upon onset of symptoms and is generally detectable up to three months. IgG develops a few days later and is typically detectable for months to years. More studies are needed to validate these observations.

Multiple real-time and conventional RT-PCRs specific for ZIKV or pan-flavi, and serology tests have been described in the literature or are commercially available. All still need extensive validation in the context of both the outbreak region and areas were cases are imported. Patients in the current outbreak region will have a high level flavivirus background while travellers returning to Europe will generally have been exposed to these viruses to a far lesser extent. This is especially important for serology-based testing as extensive cross-reactivity between antibodies triggered by different flavivirus infections or vaccination exist. Furthermore, an acute ZIKV infection might boost cross-reactive antibodies due to prior flavivirus infection/vaccination. This will complicate diagnosis based on serology in the outbreak region and will require detailed knowledge on the vaccination history for Japanese encephalitis virus, tick-borne encephalitis virus and yellow fever virus when interpreting diagnostic results of returning travellers.

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discriminating ZIKV serology is especially important to identify asymptomatic ZIKV infections in pregnant women due to putative teratogenic effects.

CONCLUDING REMARKS

The current outbreak of ZIKV in the Americas, including Dutch (former) overseas territories, has direct implications for infectious disease specialists, obstetricians, midwives and microbiologists in the Netherlands. Besides dengue and chikungunya virus, clinicians should also include ZIKV in their differential diagnosis of fever with rash in travellers returning from Asia, Africa, the Pacific ocean area and the Americas. Although ZIKV infections usually manifest as asymptomatic or mild, infection of women during pregnancy requires intensive follow-up due to putative correlation with neurological defects in newborns, until the link between ZIKV and microcephaly has been substantiated or rejected. Determination of asymptomatic ZIKV infection during pregnancy is complicated due to extensive cross-reactivity in serology-based testing. For diagnosis in acutely infected patients a combination of blood, urine and saliva will increase the sensitivity and window of ZIKV detection. Current ongoing international collaborative studies might give insights in these issues on short notice.

DISCLOSURES

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An inflammatory condition with different faces: immunoglobulin G4-related disease

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ABSTRACT

Background: Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibro-inflammatory condition with involvement of different organs. The pathophysiological mechanism is unclear, but fibrosis is the hallmark of this disease. Early recognition is critical to avoid irreversible organ damage. Recently improved histological testing boosts the diagnostic yield. We present three cases of patients with IgG4-RD to emphasise the broad clinical presentation of this disease.

Case descriptions: Patient A, a 63-year-old male with bilateral orbital swelling due to IgG4-RD, was shown to suffer from IgG4-RD in a multifocal pattern as demonstrated by PET scanning. Patient B, a 53-year-old male with a long-standing abdominal mass of unknown origin, eventually proved to have IgG4-RD. Patient C was a 32-year-old male admitted with pleural effusion and pericardial tamponade. Histological diagnosis after pericardiectomy confirmed IgG4-RD.

Discussion: IgG4-RD has many faces and may mimic other conditions, such as malignancy and infectious diseases. Knowledge of this disease is needed to avoid unnecessary diagnostics and delay in treatment. IgG4-RD may be suspected based on specific clinical findings such as elevated serum IgG4 levels, but the diagnosis can only be established histologically. Although corticosteroids are an effective first choice of therapy, the relapse rate after this treatment remains high. The role of disease-modifying antirheumatic drugs in the treatment of IgG4-RD has not been outlined yet, but there is increasing evidence that rituximab might be an effective second-line therapy.

Conclusion: IgG4-RD is a disease with many faces requiring early recognition and therapy to avoid permanent damage of the organs.

KEYWORDS

Fibro-inflammatory disease, immunoglobulin G4, and IgG4-related disease

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibro-inflammatory condition with manifestations in almost all parts of the human body. It is characterised by tumour-like infiltration of IgG4-positive plasma cells in the tissues, mostly with fibrotic or sclerotic abnormalities, and often elevated serum IgG4 levels. IgG4-RD was initially described in patients with sclerosing pancreatitis, but from 2003 it is recognised as a systemic disease. The disease can manifest in one single organ, but it can also occur simultaneously in multiple organs. IgG4-RD usually occurs in the salivary and lacrimal glands, the orbit, pancreas and lymph nodes. Other preferential localisations include the lungs, kidneys, thyroid, peritoneum and prostate. Conditions previously called Mikulicz’s disease, sclerosing sialadenitis, inflammatory orbital pseudotumour, a subset of idiopathic retroperitoneal fibrosis and Riedel’s thyroiditis are now reclassified under the umbrella of IgG4-RD. IgG4-RD mimics many infectious, inflammatory and malignant disorders often leading to a delay in both diagnosis and treatment, potentially progressing into irreversible fibrosis. Awareness of this disease is important to avoid unnecessary delay. We therefore present three different cases of patients with IgG4-RD to emphasise the broad clinical presentation of this disease and present a review on the pathogenesis, diagnosis and treatment.

CASE PRESENTATIONS

We briefly present three different cases of IgG4-RD. The patient characteristics and the main clinical features are shown in table 1.
### Table 1. Characteristics and the main clinical features of the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Medical history</th>
<th>Symptoms and duration of symptoms</th>
<th>Diagnosis</th>
<th>Serum IgG4</th>
<th>Other relevant findings</th>
<th>Imaging</th>
<th>Histology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Male</td>
<td>63 years</td>
<td>- Suspected pulmonary sarcoidosis without histological confirmation 20 years ago – Hypothyroidism - Lower urinary tract symptoms – No asthma or allergies</td>
<td>Progressive bilateral painless periorbital swelling and diplopia for 4 months</td>
<td>Orbital IgG4-RD with multifocal disease manifestation on PET imaging</td>
<td>1.65 g/l</td>
<td>ESR and CRP normal. ACE normal. Anti-TSH receptor absent</td>
<td>MRI brain: bilateral enlarged and contrast-enhancing lacrimal glands; PET scan: multifocal increased activity in various organs, including the lacrimal glands, parotid gland, thyroid, prostate, right seminal vesicle, testis and multiple mediastinal and hilar lymph nodes</td>
<td>Surgical excision of lacrimal gland; - Lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, &gt;200 IgG4 positive plasma cells per HPF and IgG4/IgG ratio &gt;0.5</td>
<td>Prednisone 1 mg/kg, currently being tapered successfully. No maintenance therapy initiated, because of normalisation of symptoms, serum IgG4 and MRI</td>
</tr>
<tr>
<td>B</td>
<td>Male</td>
<td>53 years</td>
<td>- Unknown abdominal mass for the past 20 years – No asthma or allergies</td>
<td>Episodes of malaise, weight loss and an abdominal mass of unknown origin for the last 20 years</td>
<td>Mesenteric IgG4-RD</td>
<td>25 g/l</td>
<td>Elevated ESR and CRP, decreasing with therapy. Microcytic anaemia responding very well to iron supplements. Gastroscopy, colonoscopy and bone marrow survey normal</td>
<td>CT abdomen: mesenteric mass, decreasing in volume after treatment</td>
<td>Fine needle biopsy mesenteric mass: Lymphoplasmacytic infiltration, storiform fibrosis, &gt;50 IgG4 positive plasma cells per HPF and IgG4/IgG ratio &gt;0.5. No obliterative phlebitis</td>
<td>Prednisone 1 mg/kg and azathioprine 150 mg/day after tapering prednisone. Azathioprine was initiated because ESR and serum IgG4 were not normalised and persistence of abdominal mass</td>
</tr>
<tr>
<td>C</td>
<td>Male</td>
<td>32 years</td>
<td>- Unremarkable – No asthma or allergies</td>
<td>Malaise, dyspnoea, pleural and pericardial effusion for a couple of weeks. Four weeks after presentation pericardiectomy was performed. Afterwards, persistent pleural effusion in 3-month follow-up, for which prednisone was started</td>
<td>Pericardial and pleural IgG4-RD</td>
<td>5.5 g/l (after pericardiectomy)</td>
<td>Elevated CRP normalising after pericardiectomy. ESR not measured. ANCA, rheumatic factors, lupus anticoagulants absent, complement factors normal</td>
<td>CT thorax and abdomen: pleural and pericardial effusion; CT thorax: bilateral pleural effusion on both sides, vanishing after starting prednisone; PET: slight activity of the pleura without other abnormalities (after pericardiectomy)</td>
<td>Prednisone 30 mg daily, currently being tapered successfully. No maintenance therapy was initiated, because serum IgG4 almost normalised and pleural effusion disappeared</td>
<td></td>
</tr>
</tbody>
</table>

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ACE = angiotensin-converting enzyme; TSH = thyroid-stimulating hormone; ANCA = anti-neutrophil cytoplasmic antibodies; ANA = antinuclear antibodies; HPF = high power field.
Patient A
This 63-year-old male patient was referred to the ophthalmologist because of a painless bilateral periorbital swelling and diplopia suspected to be lymphoma or recurrence of sarcoidosis. Pulmonary sarcoidosis was diagnosed on the basis of the clinical symptoms and was not histologically confirmed, and this had been stable without medication for 20 years. His history also included levothyroxine for hypothyroidism and alpha-blockers for relapsing lower urinary tract symptoms. Bilateral periorbital swelling with slight proptosis was found on physical examination. Laboratory tests revealed elevated serum IgG4 without other abnormalities. Computed tomography (CT) of the thorax and abdomen was normal. MRI of the brain revealed only bilateral enlarged and contrast-enhancing lacrimal glands (figure 1A). On F-18 FDG PET/CT scan, multifocal increased activity was noted in various organs (table 1). Histology of the lacrimal gland was compatible with IgG4-RD (figure 1C+D). Prednisone 1 mg/kg/day significantly decreased the periorbital swelling, but also resulted in a complete recovery of the urinary tract symptoms within one week and recovery of thyroid dysfunction. After four weeks, the steroids could be tapered and levothyroxine was discontinued without recurrence after six months of follow-up.

Patient B
A 53-year-old male patient consulted several medical specialists over the past 20 years because of an abdominal mass. Extensive diagnostics including biopsies and bone marrow examination did not yield any diagnosis. The patient complained of slowly progressive malaise, weight loss and abdominal pain. After referral to our hospital, IgG4-RD was suspected, also because of the elevated serum IgG4 levels. Laboratory tests further revealed an elevated erythrocyte sedimentation rate (ESR), normal ferritin and microcytic anaemia, known to have existed for years. Gastroscopy and colonoscopy were without evidence of malignancy, intraepithelial lymphocytosis, IgG4-RD, villous atrophy, Giardia, Whipple’s disease or Helicobacter pylori infection. CT imaging demonstrated a progressively increasing mesenteric mass of 50 mm surrounded by mesenteric lymphadenopathy (figure 2A). Histology of the mesenteric mass confirmed the diagnosis of IgG4-RD (figure 2C). Prednisone 1 mg/kg/day was initiated. Hereafter, the symptoms eased, the serum IgG4 and ESR decreased and haemoglobin levels almost normalised. The abdominal mass and lymphadenopathy decreased (figure 2B) and serum IgG4 and ESR levels showed a downward trend. The steroids were tapered after four weeks and azathioprine 150 mg daily was started after two months since the mass had not totally regressed.

Patient C
This 32-year-old male patient was admitted to the department of cardiology because of cardiac tamponade. On a CT of the thorax and abdomen both pleural and pericardial effusions were seen (figure 3A). Laboratory tests showed elevated C-reactive protein (CRP), ESR was not measured at that moment. Because of persistent pericardial effusion with constrictive signs, a pericardiectomy was performed and diuretics were given. Hereafter, the CRP normalised and the ESR was normal. Detailed bacteriological and virological analyses (including serology or viral load determinations of HIV, hepatitis A/B/C, Borrelia burgdorferi, syphilis, mycoplasma, tuberculosis, parvovirus, Cytomegalovirus, Epstein-Barr, Coxiella burnetii, toxoplasmosis, Coxsackie virus and varicella-zoster) were unremarkable. Elevated

Figure 1. A+B: Transverse spin echo T1 weighted MRI of the orbit. A: Note the bilateral homogeneous enhancement of the enlarged lacrimal glands (yellow arrows). B: Normalisation of the size of the lacrimal gland and a dramatic decrease in enhancement after treatment with prednisone. C+D: Histology of the lacrimal gland of patient A. C: HE staining demonstrating lymphocytes, plasma cells and local fibrosis. Obliterative phlebitis was also observed. D: Immunohistochemical staining for IgG4 (brown colour) of the lacrimal gland of patient A showing widely scattered IgG4 positive plasma cells with an average of 240 per HPF out of 2 HPF with a ratio of 0.5 to total IgG plasma cells in the tissue. Figure C and D are at x200 magnification. MRI = magnetic resonance imaging; HE = haematoxylin and eosin; HPF = high-power field

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serum IgG4 and pericardial histology finally offered sufficient evidence for IgG4-RD (figure 3D+E). Cultures of the pericardial tissue ruled out bacterial pathogens including *Mycobacterium tuberculosis*. F-18 FDG PET/CT three months after pericardiectomy revealed slight activity of the pleura without other abnormalities. Prednisone 30 mg daily led to the disappearance of the pleural effusion (figure 3B+C) and almost normalisation of serum IgG4; diuretics were no longer required. Hereafter, the prednisone carefully was tapered to 20 mg in seven weeks without signs of recurrence.

**Figure 2.** A+B: CT image of the abdomen after intravenous contrast injection, venous phase. A: Pre-treatment: abdominal/mesenteric mass of 50 mm (red arrow) with enlarged mesenteric lymph nodes. B: Post-treatment: decrease in size of the mesenteric mass to 36 mm (blue arrow) and decrease in lymph nodes size. C: Immunohistochemical staining for IgG4 of mesenteric mass of patient B revealing widely scattered IgG4 plasma cells with an average of 421 per HPF out of 3 HPF with a ratio of 0.5 to total IgG plasma cells in the tumorous tissue. Unfortunately, no HE images were available, but lymphoplasmacytic infiltration and storiform fibrosis were seen and documented. Figure C is at x200 magnification

**Figure 3** A: CT scan of the thorax showing bilateral pleural effusion (red arrows) and pericardial effusion (yellow arrow). B: Pleural effusion was evident on plain film of the thorax as well. C: Disappearance of pleural effusion six weeks after starting prednisone. D: Histology of pericardium of patient C. HE-staining showing lymphocytes, plasma cells and fibrosis. Obliterative phlebitis was also observed. E: Immunohistochemical staining for IgG4 consists of IgG4 plasma cells with an average of 136 per HPF out of 3 HPF with a ratio of 0.7 to total IgG plasma cells in the tissue. Figures D and E are at x200 magnification
DISCUSSION

Here we present three cases of patients with unrecognised IgG4-RD, each presenting with a different clinical presentation. The courses of these patients reflect the broad spectrum of clinical faces of IgG4-RD. By demonstrating the variable presentation of IgG4-RD, we briefly provide an overview of the spectrum of symptoms and treatment options in this new disease entity.

IgG4-RD is a systemic disease that can be found in almost any organ, but with certain sites of preference (orbit, salivary tract, pancreas and lymph nodes) which may be guiding when considering this new disease entity. On the other hand, IgG4-RD mimics various benign and malignant disorders. Therefore, careful diagnostics should be applied before setting the diagnosis. The vast clinical manifestation range and potentially organ- and life-threatening situations emphasise that awareness of this relatively new entity is pivotal to swiftly set a diagnosis and prevent organ damage. This is highlighted by the histories of the presented patients. Patient A presented with a relatively short history, and lymphoma or recurrent sarcoidosis were suspected. Extensive diagnostics were conducted to rule out these entities. A typical FDG-uptake pattern led to the diagnosis of IgG4-RD by histology of a lacrimal gland. The abdominal mass resembling retroperitoneal fibrosis seen in patient B is remarkable and has rarely been described before. Multiple diagnostics including biopsies of the abdominal mass excluded conditions such as malignancy and infectious diseases. Eventually, after almost 20 years, attention towards IgG4 resulted in the diagnosis of IgG4-RD. Cardiac manifestations of IgG4-RD, such as in patient C, are rare. The patient presented with constrictive pericarditis and a pleural effusion. It remains a challenge to rule out infectious or malignant disease and consider IgG4-RD.

The diagnosis of IgG4-RD is based on the combination of clinical presentation, serological and histological findings, but histology is the gold standard. Although the disease is called IgG4-RD, about 30 to 50% of histologically proven cases show normal IgG4 levels leading to misinterpretation and erroneous rejection of the diagnosis. Furthermore, the specificity and positive predictive value of serum IgG4 concentrations are low, which make them poor disease markers. In our cases, serum IgG4 levels were elevated in all three patients, but with different ranges (1.65 to 25 g/l). Other, though unspecific, serological findings are ESR and CRP in patients with active disease, but these are elevated in 53% and 40%, respectively, of the cases. In this study 51% of these patients had elevated serum IgG4. In our patients, not all elevated IgG4 levels corresponded with an elevated ESR and CRP.

Only in patient A were the ESR and CRP both normal. Although speculative, longstanding active disease and high serum IgG could lead to elevated ESR and CRP, which applied in case B.

Measuring plasmablasts originating from CD20+ B cells is a superior alternative to measuring IgG4 concentrations in serum, but so far this technique has not been widely introduced for clinical application. So far, imaging studies play a crucial role in the diagnostics of IgG4-RD; however, imaging is not specific for this disease and several conditions such as malignancy should be excluded. Radionuclide imaging in patient A was more sensitive than conventional CT. Several studies have shown the usefulness of FDG-PET/CT scanning for diagnosis, staging and the degree of organ involvement and monitoring of therapy response, and this imaging method seems to detect more lesions than conventional methods such as ultrasonography and CT. This emphasises the utility of PET scanning in IgG4-RD. However, histology remains crucial for the diagnosis of IgG4-RD. The histological abnormalities should meet the Boston consensus on IgG4-RD. The characteristic histological features of IgG4-RD are dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterator phlebitis. The ratio of IgG4/IgG-positive plasma cells in tissues should be greater than 0.4 and the numbers of IgG4-positive plasma cells per high power field should be greater than the numbers agreed in the consensus. The absolute numbers of IgG4-positive plasma cells and the thresholds for disease differ for the diverse organs. Our patients had histologically confirmed IgG4-RD according to the criteria; however, in case B no obliterator phlebitis was seen.

The pathogenesis of IgG4-RD is unclear. Generally, the disease is characterised by a decreased T-helper cells 1/T-helper cells 2 ratio and increased numbers of regulatory T-cells, most probably as a result from a certain antigen triggering the immune system. Production of different cytokines such as interleukin (IL)-4, IL-5, IL-10, IL-13 and transforming growth factor (TGF)-beta leads to co-activations of B-cells, production of IgG4 expressing B-cells and fibrosis. Still, the role of IgG4 antibodies is unclear, but in the pathophysiology of IgG4-RD these antibodies most probably play an anti-inflammatory role as response to an unknown trigger. Patient C presented with constrictive pericarditis and pleural effusion. Plasma cell manifestation of the pericardium has also been described in multiple myeloma, whereby infiltration of plasma cells in the pericardium is suggested to be the reason. Maybe some viral infection led to IgG4-positive plasma cell infiltration in the serosal cavity leading to the clinical manifestation of this disease, but this remains a speculative hypothesis. The pleural effusion was most probably also because of infiltration by lymphoplasmacytic
cells, as it was slightly positive on PET and disappeared after starting prednisone. However, secondary pleural effusion because of restricted heart function due to constrictive pericarditis could also have contributed to the development of pleural effusion.

IgG4-RD can cause significant morbidity and even lead to organ damage. Aggressive treatment is therefore necessary, especially when vital organs are at risk. Glucocorticoids are the first choice of treatment for most types of IgG4-RD and are mostly effective at a prednisone dosage of 30-40 mg/day and should be adjusted according to body weight or in cases of aggressive disease. This treatment dose is, in most cases, rapidly effective, but should be maintained for two to four weeks after initiation. Thereafter, prednisone can be tapered according to clinical responses. The clinical response of prednisone is dependent upon the organ system involved and the degree of fibrosis. Pancreatic function and lacrimal gland function, for example, will respond better to this treatment than retroperitoneal disease or sclerosing mesenteritis. This phenomenon highlights the need for earlier treatment of this disease. About 25% of patients demonstrate relapse after tapering prednisone necessitating steroid-sparing agents. Patient A responded very well to prednisone. His symptoms, serum IgG4 and MRI imaging normalised and remained so during tapering. Patient C also responded very well to prednisone. His symptoms disappeared, serum IgG4 reached almost normal levels and a recent chest X-ray no longer demonstrated pleural effusion. Therefore, we decided not to initiate maintenance therapy in cases A and C. According to international consensus, a steroid-sparing agent is appropriate when the glucocorticoid dosage cannot be tapered due to persistently active disease. For this reason, azathioprine was initiated in case B. Conventional steroid-sparing agents such as mycophenolate mofetil, azathioprine and methotrexate have all been used in the treatment of IgG4-RD, but management of further immunosuppressive therapy with these disease-modifying antirheumatic drugs (DMARDs) has not been outlined and there are no studies confirming the superiority of one of these agents in the treatment of IgG4-RD. There is improving evidence for the efficacy of rituximab in the treatment of IgG4-RD, even as a single therapy. This B-cell ablative therapeutic agent has induced clinical remission in patients with various organ involvement of IgG4-RD. More case series or prospective studies with different DMARDs and rituximab are required in order to define the (long-term) effect of these agents in the treatment of IgG4-RD.

CONCLUSION

In conclusion, IgG4-RD is a rare and new clinical entity with many faces and manifestations in different parts of the body. Early recognition is critical to start treatment and to avoid permanent damage of the organs. Diagnosis is based on histology, while serum IgG4 could be supportive. Glucocorticoids are the first choice of treatment, but there is often a need for maintenance therapy. Several DMARDs as well as rituximab are used in the treatment of IgG4-RD, with growing evidence for the latter.

DISCLOSURES

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Karim et al. Immunoglobulin G4-related disease.
Incidence of refeeding syndrome in internal medicine patients

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ABSTRACT

Background: Refeeding syndrome is a potentially fatal shift of fluids and electrolytes that may occur after reintroducing nutrition in a malnourished patient. Its incidence in internal medicine patients is not known. We aimed at determining the incidence in a heterogeneous group of patients acutely admitted to a department of internal medicine.

Methods: All patients acutely admitted to the department of internal medicine of a teaching community hospital in Amsterdam, the Netherlands, between 22 February 2011 and 29 April 2011, were included. We applied the National Institute for Health and Care Excellence (NICE) criteria for determining people at risk of refeeding syndrome and took hypophosphataemia as the main indicator for the presence of this syndrome.

Results: Of 178 patients included in the study, 97 (54%) were considered to be at risk of developing refeeding syndrome and 14 patients actually developed the syndrome (14% of patients at risk and 8% of study population). Patients with a malignancy or previous malignancy were at increased risk of developing refeeding syndrome (p < 0.05). Measurement of muscle strength over time was not associated with the occurrence of refeeding syndrome. The Short Nutritional Assessment Questionnaire score had a positive and negative predictive value of 13% and 95% respectively.

Conclusion: The incidence of refeeding syndrome was relatively high in patients acutely admitted to the department of internal medicine. Oncology patients are at increased risk of developing refeeding syndrome. When taking the occurrence of hypophosphataemia as a hallmark, no other single clinical or composite parameter could be identified that accurately predicts the development of refeeding syndrome.

KEYWORDS

Incidence, internal medicine, malnutrition, refeeding, phosphate

INTRODUCTION

In the last decades, malnutrition and the institution of appropriate nutrition in malnourished patients are receiving increasing attention by clinicians. In parallel, alertness for the development of refeeding syndrome has been emphasised.1-2 Early detection is considered to be of utmost importance to prevent the development of its clinical sequelae.

Although there is no universally accepted definition of refeeding syndrome, it can be defined as a potentially fatal shift in fluids and electrolytes that may occur after reintroducing nutrition in malnourished patients.3 The pathophysiological mechanism relies on a transition from a catabolic state, in which fatty acid oxidation is the main source of energy, to an anabolic state, where mainly combustion of carbohydrates provides the energy. During this process, the metabolism of phosphate and thiamine increases and there is a shift of potassium and magnesium to the intracellular environment. Combined with the existing depleted state of electrolytes and enzymes due to malnutrition, low plasma levels of phosphate, potassium, magnesium and thiamine are likely to occur.4-6 Disorders of glucose metabolism have also been described.7 The clinical spectrum of refeeding syndrome is diverse and ranges from a paucity of signs and symptoms to a multisystem disorder.5-9 Muscle weakness is an aspecific symptom and is caused predominantly by hypophosphataemia. Besides, tachycardia can occur during the early stage of refeeding syndrome due to volume overload, which
is caused by renal sodium and fluid retention owing to high levels of insulin.
Several risk factors for the development of refeeding syndrome have been identified. These include acute or chronic malnutrition, alcohol abuse, old age, oncological diseases, and malabsorption. Patients taking antacids or diuretics, which is accompanied by a loss of electrolytes via the gastrointestinal tract or kidneys respectively, also have a higher risk of developing refeeding syndrome.

The incidence of refeeding syndrome varies in different studies, partially due to the lack of a universally accepted definition. Most studies were done in surgical or ICU patients. Marik & Bedigian found that 34% of intensive care patients experienced refeeding hypophosphataemia. Among all hospital patients started on artificial nutrition, Rio et al. found a 1% incidence of refeeding syndrome. Camp & Allon found a 10.4% incidence of hypophosphataemia among malnourished patients in a Veterans Administration Hospital. To our knowledge, no studies have been performed in a large group of internal medicine patients.

Since a practical definition and objective criteria for refeeding syndrome seem to be lacking, patient management is not supported by generally accepted guidelines.

The National Institute for Health and Care Excellence (NICE) criteria for identifying patients at high risk for the development of refeeding syndrome may provide clinicians a useful tool in daily practice (Table 1). Objectives

In this prospective observational study we aimed to determine the incidence of refeeding syndrome in patients acutely admitted to the department of internal medicine. We also aimed at defining risk factors for the development of refeeding syndrome and to measure the time between hospitalisation and its occurrence. We examined whether muscle strength, heart rate and a scoring system (Short Nutritional Assessment Questionnaire, SNAQ) are associated or predictive for its development.

Materials and Methods

This study was performed at the Department of Internal Medicine of the Sint Lucas Andreas Hospital in Amsterdam, the Netherlands. This is a general inner city teaching hospital. The local Medical Ethics Committee approved the study and patients gave their informed consent. Between 22 February 2011 and 29 April 2011, reasons for exclusion were: duration of stay less than 48 hours (36%), elective hospitalisation (21%), readmission during study period (87%), admission from another department or hospital (11%), hypophosphataemia at admission (8%) and insufficient laboratory data (7% patients).

Table 1. National Institute for Health and Care Excellence (NICE) criteria for determining patients at high risk of developing refeeding problems

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
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<tbody>
<tr>
<td>BMI &lt; 16 kg/m²</td>
<td>1</td>
</tr>
<tr>
<td>Unintentional weight loss &gt; 15% within the last 3-6 months</td>
<td>1</td>
</tr>
<tr>
<td>Little or no nutritional intake for more than 10 days</td>
<td>1</td>
</tr>
<tr>
<td>Low levels of phosphate, potassium or magnesium prior to feeding</td>
<td>1</td>
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Or patient has two or more of the following:

<table>
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<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>BMI &lt; 18.5 kg/m²</td>
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<tr>
<td>Unintentional weight loss &gt; 10% within the last 3-6 months</td>
<td>1</td>
</tr>
<tr>
<td>Little or no nutritional intake for more than 5 days</td>
<td>1</td>
</tr>
<tr>
<td>A history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics</td>
<td>1</td>
</tr>
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Low electrolyte levels are not used as one of the major criteria since this is used as a hallmark to identify the occurrence of refeeding syndrome.
all patients admitted to the department of internal medicine were included. Exclusion criteria were elective hospitalisation, readmission during study period, duration of stay less than 48 hours, admission from another department or hospital or the presence of hypophosphataemia at admission. Patients were followed during the first seven days of hospitalisation.

Refeeding syndrome was defined as follows: a syndrome of electrolyte shifts, hypophosphataemia being a fundamental condition, which might occur as a result of reintroduction of caloric intake after a period of malnutrition or fasting. We applied the NICE criteria for determining people at high risk of developing refeeding problems in all patients acutely admitted (table 1). We excluded patients with hypophosphataemia at admission since the occurrence of hypophosphataemia is used as a hallmark for the occurrence of refeeding syndrome. Refeeding syndrome was established in patients with a positive NICE score and normal phosphate levels at admission who developed severe hypophosphataemia during follow-up. Reference values for normal phosphate levels were 0.75-1.20 mmol/l in men and 0.90-1.30 mmol/l in women. Severe hypophosphataemia was defined as a phosphate level < 0.60 mmol/l.

The SNAQ is a validated screening tool and is frequently used in Dutch hospitals to determine people at risk of malnutrition (table 2). We investigated whether this score could also be used to identify patients at risk of refeeding syndrome.

To objectively evaluate possible clinical effects of refeeding syndrome, we measured muscle strength and heart rate. Handgrip strength was used as a measure of peripheral muscle strength, which is applied in a wide variety of studies. Handgrip strength was measured on the dominant side on days 1, 3 and 7 using the JAMAR hand dynamometer (Lafayette Instrument Company, UK). The JAMAR hand dynamometer has proven to be reliable in terms of test-retest and intra-tester reliability for the measurement of handgrip strength.20 Heart rate was recorded daily.

**Statistical analysis**
Statistical analysis was performed using SPSS Statistics version 20 (IBM Corporation, New York). Continuous variables are expressed by their mean (standard deviation). Categorical variables are expressed as n (%). Normally distributed data were compared by the independent-sample t test and not normally distributed data by the

<table>
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<th>Table 2. Short Nutritional Assessment Questionnaire (SNAQ)</th>
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<tbody>
<tr>
<td>Unintentional weight loss</td>
</tr>
<tr>
<td>• More than 6 kg within the last 6 months</td>
</tr>
<tr>
<td>• More than 3 kg within the last month</td>
</tr>
<tr>
<td>2 points</td>
</tr>
<tr>
<td>Little or no nutritional intake for the last 3 days, or less than normal for the last week</td>
</tr>
<tr>
<td>Use of tube feeding or nutritional drinks in the last month</td>
</tr>
<tr>
<td>Total of 0-1 points: no risk of malnutrition. 2 points: average risk of malnutrition. 3-5 points: high risk of malnutrition.</td>
</tr>
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Mann-Whitney U test. Categorical data were compared by the Chi square test or the Fisher’s exact test, as appropriate. A two-sided p < 0.05 was considered to be statistically significant.

RESULTS

A total of 399 patients were admitted to the Department of Internal Medicine of the Sint Lucas Andreas Hospital (figure 1). We included 178 patients who were acutely admitted; 221 patients were excluded due to duration of stay less than 48 hours (36%), elective hospitalisation (21%), readmission during the study period (17%), admission from another department or hospital (11%), hypophosphataemia at admission (8%) or insufficient laboratory data (7% patients).

The baseline characteristics of the 178 patients included in our study, assessed for the risk of developing refeeding syndrome, according to the NICE criteria, are shown in table 3. The mean age was 66.8 years (±17.4). The ratio of men to women was about equal. The mean body mass index (BMI) was 24.4 kg/m² (±6.4) and mean follow-up was 6.3 days (±1.3).

Of all 178 patients admitted to the internal medicine department, 97 (54%) were at risk of developing refeeding syndrome according to the NICE criteria. Of these patients, 14 (14%) actually developed hypophosphataemia and consequently refeeding syndrome. The incidence of refeeding syndrome in the total study population was 8%. Of the 81 patients not at risk, only one patient developed hypophosphataemia. In total two patients died during follow-up: neither had refeeding syndrome (p = 1.00).

Patients at risk of developing refeeding syndrome had a lower BMI at admission than patients not at risk, as expected considering our definition (p < 0.01). Furthermore, they tended to be older (p = 0.19). The SNAQ score, used in this study to identify patients at risk for the development of refeeding syndrome, had a positive and negative predictive value of 13% and 95% respectively. Table 4 shows the reason of admission and comorbidity of our population, assessed for the risk of developing refeeding syndrome according to the NICE criteria. As reason of admission, malignancy was more common in patients at risk of developing refeeding syndrome (p = 0.02). Patients with a previous malignancy (in the last 10 years) were also at increased risk of developing refeeding syndrome (p = 0.03). In contrast, patients

<table>
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<tr>
<th>Reason of admission</th>
<th>Total population (n = 178)</th>
<th>Refeeding risk* (n = 97)</th>
<th>No refeeding risk* (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infection / sepsis</td>
<td>49 (28%)</td>
<td>24 (25%)</td>
<td>25 (31%)</td>
</tr>
<tr>
<td>• Malignancy</td>
<td>19 (11%)</td>
<td>15 (16%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>• Diabetes mellitus (including ketoadidosis)</td>
<td>16 (9%)</td>
<td>8 (8%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>• Renal failure</td>
<td>15 (8%)</td>
<td>10 (10%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>• Pancreatitis</td>
<td>8 (5%)</td>
<td>4 (4%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>• Gastrointestinal bleedingi</td>
<td>7 (4%)</td>
<td>1 (1%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>• Weight loss</td>
<td>5 (3%)</td>
<td>5 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>• Miscellaneous reasons</td>
<td>59 (33%)</td>
<td>30 (31%)</td>
<td>29 (36%)</td>
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<tr>
<th>Comorbidity</th>
<th>Total population (n = 178)</th>
<th>Refeeding risk* (n = 97)</th>
<th>No refeeding risk* (n = 81)</th>
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<tbody>
<tr>
<td>• CVD</td>
<td>82 (46%)</td>
<td>46 (47%)</td>
<td>36 (44%)</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>36 (32%)</td>
<td>31 (32%)</td>
<td>25 (31%)</td>
</tr>
<tr>
<td>• Malignancy (in the past 10 years)ii</td>
<td>52 (29%)</td>
<td>35 (36%)</td>
<td>17 (21%)</td>
</tr>
<tr>
<td>• Chronic pulmonary disease</td>
<td>32 (18%)</td>
<td>19 (20%)</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>• Chronic renal failure</td>
<td>34 (19%)</td>
<td>20 (21%)</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>• Drugs or alcohol abuse</td>
<td>12 (7%)</td>
<td>6 (6%)</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>• Rheumatoid / autoimmune disease</td>
<td>7 (4%)</td>
<td>4 (4%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>• Hepatitis B/C</td>
<td>3 (2%)</td>
<td>1 (1%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>• IBD</td>
<td>3 (2%)</td>
<td>1 (1%)</td>
<td>3 (4%)</td>
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<tr>
<td>• HIV positivity</td>
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<tr>
<td>• Surgery (within last 2 months)</td>
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Reason of admission and comorbidity of 178 patients acutely admitted to the department of internal medicine. Data are n (%). CVD = cardiovascular disease; IBD = inflammatory bowel disease; HIV = human immunodeficiency virus. *According to NICE criteria for determining people at high risk of developing refeeding problems. iStatistically significant difference between patients at risk and not at risk (p = 0.02). iiStatistically significant difference between patients at risk and not at risk (p = 0.03). iiiStatistically significant difference between patients at risk and not at risk (p = 0.03).
admitted for gastrointestinal bleeding were not found to be at risk of developing refeeding syndrome (p = 0.05).

**Phosphate levels**

*Figure 2* shows phosphate levels during admission in all patients and according to risk stratification based on the NICE scores. A total of 15 patients developed severe hypophosphataemia during follow-up, of whom 14 had a positive NICE score and one had a negative NICE score at admission.

For all patients who developed refeeding syndrome during follow-up, the difference between baseline phosphate and the lowest measured value was a mean of 0.60 mmol/l (±0.23). The sharpest declines in phosphate levels were observed on days 2 and 3. The mean lowest measured value of phosphate was measured on day 5 (±1.8).

**Clinical parameters for refeeding syndrome**

No difference in handgrip strength was found between patients with and without refeeding syndrome during follow-up. Patients with refeeding syndrome tended to have lower muscle strength on days 3 (p = 0.35) and 7 (p = 0.28) compared with patients without refeeding syndrome.

Heart rate measured during hospital admission is shown in *Figure 3*. Patients with refeeding syndrome had a significantly higher heart rate on day 1, 2, and 7 than patients without refeeding syndrome (p < 0.05). The heart rate of the patients without refeeding syndrome remained stable during follow-up.

**DISCUSSION**

Refeeding syndrome is increasingly considered to be a frequently occurring and important clinical problem. Studies exploring the incidence of refeeding syndrome have shown various rates of occurrence, possibly due to differences in study design, patient population, and the definition used.

This is the first study to explore the incidence in patients acutely admitted to a department of internal medicine, using serum phosphate as a hallmark. In addition, we tried to identify risk factors for the development of refeeding syndrome, and examined the relevance of objective parameters before and during its development that might possibly help clinicians in identifying patients.

The incidence of refeeding syndrome in our patient group was 8%. Of all patients who were at risk of developing refeeding syndrome when applying the NICE criteria, 14% actually developed the syndrome. Our study demonstrates that patients who are admitted to hospital due to malignancy or with a history of malignancy deserve special attention in this respect. In addition, our study demonstrates that the difference between patients with and without refeeding syndrome regarding comorbidity and diagnosis at admission is relatively small, indicating that it is difficult for clinicians to identify patients at risk of refeeding syndrome at admission.

The previously reported development of hypophosphataemia in refeeding syndrome occurs between two and seven days after resuming nutrition. The sharpest decline in phosphate levels in this study was observed on days 2 and 3, with the nadir in patients with refeeding syndrome on day 5. This finding provides clinicians with a practical indication when to monitor patients at risk.

Since objective risk scores could be of importance in helping clinicians to identify at-risk patients at admission, we examined the relevance of the SNAQ score. The SNAQ had a low positive predictive value and a high negative predictive value, which makes this questionnaire useful in...
daily practice to waive the diagnosis of refeeding syndrome in patients with a low SNAQ score.
Other objective clinical signs during admission were also investigated. To this end we used muscle strength and heart rate. Muscle strength was not found to be significantly decreased in patients with refeeding syndrome. An increase in heart rate was found in patients with refeeding syndrome, most pronounced on days 1, 2 and 7. The increase in heart rate in patients with refeeding syndrome during follow-up is in line with the onset of the syndrome. Its cause may be multifactorial and was not investigated in the present study.
In this study, 55% of the patients were at risk of refeeding problems according to the NICE criteria. Elmahdawi et al. described 32% of cancer patients at high risk of refeeding problems. The relatively high age of our population, the acute setting, and exclusion of patients who were admitted electively may explain the high number of patients at risk of developing refeeding syndrome.

In conclusion, the incidence of refeeding syndrome is relatively high in patients acutely admitted to the department of internal medicine. Of all patients admitted to our internal medicine department, 8% developed refeeding syndrome. Patients with a malignancy or previous malignancy are at increased risk of developing refeeding syndrome. Clinicians should be aware of this risk when feeding these patients. When taking the occurrence of hypophosphataemia as a hallmark, no other objective parameters were identified in this study that may help to identify at risk patients at admission or during the hospital stay.

**DISCLOSURES**

The authors have no potential conflicts of interest to be disclosed. This study had no external funding source. The local Medical Ethics Committee approved the study protocol. All patients gave verbal informed consent.

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The beneficial local and abscopal effect of splenic irradiation in frail patients with chronic lymphocytic leukaemia

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ABSTRACT

Background: Chronic lymphocytic leukaemia (CLL) is a common haematological malignancy that mainly occurs in the elderly population. Patients frequently have comorbidities compromising the use of old and new systemic therapies.

Methods and results: We report the prevalence of comorbidities in patients with CLL as present in the southern region of the Netherlands Cancer Registry. Comorbid conditions were present in 67% of the male and 63% of the female patients, and became more common with increasing age. Furthermore, we describe the beneficial local and abscopal effects of splenic irradiation in four patients with CLL who were not suitable for systemic chemoimmunotherapy because of severe comorbidities, or who were unwilling to undergo systemic therapy.

Conclusion: Our results show that, although an old tool, splenic irradiation should not be forgotten as a potentially effective palliative treatment option in frail patients with symptomatic CLL.

KEYWORDS

Chronic lymphocytic leukaemia, comorbidity, spleen, radiotherapy, abscopal effect

INTRODUCTION

Chronic lymphocytic leukaemia (CLL), characterised by clonal proliferation and accumulation of mature B lymphocytes in blood, bone marrow, and lymphoid organs, is the most common type of leukaemia in the Western world.1 It mainly affects the elderly population, with a median age at diagnosis of about 70 years.2 Many elderly CLL patients have comorbidities,2 which negatively impact survival.3,4 Treatment indications for CLL are well defined by international and national guidelines.5,6 Asymptomatic patients do not need treatment. For symptomatic patients, depending on age and clinical condition, there is a dichotomy in first-line therapy: go go for young and fit patients and slow go for older and less fit patients.5 For the young and fit patients the standard chemoimmunotherapy consists of fludarabine, cyclophosphamide, and rituximab (FCR), while for the less fit the standard therapy consists of chlorambucil monotherapy or in combination with rituximab.5,7 In addition to these traditional agents, many new and promising drugs directly targeting the B-cell receptor signalling pathway, such as ofatumumab, ibrutinib, idelalisib, and obinutuzumab, are about to be added, or are already added, to the therapeutic armamentarium.8-11 All these therapeutic options are palliative, and not curative. Because of severe comorbidities, sometimes even mild chemoimmunotherapy is not an option to palliate symptomatic, mostly elderly, patients.

An older palliative therapy of CLL is radiotherapy, which was the primary treatment of CLL before the introduction of modern chemotherapy,12 but which is no longer included in the current CLL treatment guidelines.5,6 Local radiotherapy can be employed when lymphadenopathy is bothering a patient, and splenic irradiation can be useful when patients experience symptoms related to splenomegaly.13 Here, we report the high prevalence of comorbidities in elderly patients with CLL as registered in the southern region of the population-based Netherlands Cancer
Aalbers et al. Splenic irradiation in frail CLL patients. Registry. We also describe the beneficial local and abscopal effects of splenic irradiation in four CLL patients, diagnosed and treated in a large non-academic teaching hospital in Delft, the Netherlands, who were unfit and/or unwilling to undergo systemic therapy. In this exciting era for the treatment of CLL with many novel agents, we emphasise that the use of this old tool of splenic irradiation should not be forgotten as palliative treatment for elderly CLL patients with severe comorbidities.

METHODS

CLL patients registered at the Netherlands Cancer Registry
Clinical data of all cancer patients the Netherlands are registered at the Netherlands Cancer Registry, which is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL). The Cancer Registry in the Eindhoven region records the data from all cancer patients in the southern Netherlands, an area with approximately 2.4 million inhabitants (about 15% of the Dutch population); there are no academic hospitals in this area. All patients diagnosed with CLL (ICD-O-3 code 9823) in the period 2002-2011, aged 35 and over, and recorded in the Eindhoven region of the Netherlands Cancer Registry, were included in this study. For the classification of comorbidity, a slight modification of the Charlson Comorbidity Index was used. Patients were arbitrarily divided into three age groups (35-59 years, 60-74 years, 75 years and over). A chi-square test was used to test for differences in the prevalence of comorbidity in the different age groups.

CLL patients undergoing splenic irradiation
Four consecutive, symptomatic CLL patients (three male, one female, age at diagnosis ranging from 65-77 years), diagnosed and treated in a large non-academic teaching hospital in Delft, the Netherlands, were unfit and/or unwilling to undergo systemic therapy, and were treated with splenic irradiation from 2012 onwards. Last follow-up was in April 2015.

Splenic irradiation
Whole-spleen irradiation was performed with a linear accelerator (6 MV) using anterior/posterior parallel opposing fields after CT planning. A total dose of 6 Gy, 12 x 0.5 Gy, twice weekly, was given to all patients. The total dose and fractionation schedule was based on previous studies on splenic irradiation in CLL, reviewed by Weinmann et al.

Response criteria
CLL response criteria are defined by the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL). Complete remission according to these criteria requires the absolute lymphocyte count to decrease < 4 x 10⁹/L, lymph nodes to be < 1.5 cm, normalisation of liver and spleen size, constitutional symptoms to disappear, bone marrow to be free of CLL cells, and absolute neutrophil count to increase > 1.5 x 10⁹/L, thrombocyte count > 100 x 10⁹/L, and haemoglobin level > 6.8 mmol/L. In our patients, bone marrow biopsy was not performed after therapy for patient comfort and because of the absence of clinical consequences, and in most patients, a differential leukocyte count directly after therapy was not performed. Therefore, in our cohort, a complete response was defined when the leukocyte count normalised, thrombocyte count increased to > 100 x 10⁹/L, haemoglobin level increased to > 6.8 mmol/L, and no hepatomegaly/splenomegaly and lymphadenopathy were detected on physical examination. Partial response was defined when the leukocyte count decreased by at least 50%, liver and spleen and enlarged lymph nodes decreased in size by at least 50% on physical examination, and thrombocyte count increased to > 100 x 10⁹/L or haemoglobin level increased to > 6.8 mmol/L. Stable disease was defined when neither CLL remission nor progression occurred.

RESULTS
Elderly CLL patients frequently present with comorbid conditions
In the period 2002-2011, 919 CLL patients (588 male, 331 female) were registered in the Eindhoven region of the Netherlands Cancer Registry. The median age at diagnosis was 68 years (range, 36 to 97 years). Females were slightly older than males (median 71 vs. 67 years, respectively). Registered comorbid conditions were previous malignancies, cardiovascular disease, pulmonary disease, hypertension, and diabetes mellitus (table 1). In patients aged 60 to 75 years, one or more comorbidities were present in 67% of male patients, and in 63% of female patients. When hypertension was excluded, 55% of male patients, and 49% of female patients aged 60 to 75 years suffered from one or more comorbidities. The most frequently occurring comorbid condition in all age categories was cardiovascular disease (especially cardiac disease), which was present in 32% of male patients aged 60 to 75, and in 18% of female patients. Results are summarised in table 2.
Splenic irradiation in symptomatic CLL patients has beneficial local and abscopal effects

Case A
A then 65-year-old woman with a medical history of severe nicotine abuse and likely (although not documented) peripheral vascular disease, World Health Organisation (WHO) performance status 2, presented in 2012 with abdominal discomfort and tiredness. Physical examination revealed splenomegaly (19.4 x 7.4 cm by ultrasound) without lymphadenopathy, and laboratory results showed a leukocytosis of $54.8 \times 10^9/l$ and atypical lymphocytes consisting of a monoclonal B-cell population. She was diagnosed with B-CLL/small lymphocytic lymphoma (SLL) RAI stage III. A bone marrow biopsy showed leukaemic cell bone marrow infiltration with replacement of normal haematopoiesis. Cytogenetic analysis was unremarkable. Because of splenomegaly causing mechanical complaints, the patient received splenic irradiation in 2012, in a total dose of 6 Gy ($12 \times 0.5$ Gy, twice weekly). The patient’s spleen size normalised, lymph nodes remained undetectable, and a complete haematological response (based on normalisation of haemoglobin, thrombocyte and leukocyte levels) (figure 1A) with a very good clinical response was noted, without side effects. Two years later, in 2014, the patient again complained of tiredness, dyspnoea, and night sweats. Her splenomegaly had reappeared, blood counts had dropped, and her leukocyte count increased to $115.0 \times 10^9/l$. She received a second course of splenic irradiation ($12 \times 0.5$ Gy, twice weekly), after which her spleen size normalised rapidly, her leukocyte count dropped, and peripheral blood counts increased (figure 1A). Unfortunately, about ten days after radiotherapy had started, the patient died due to complications of massive cerebral infarction. Thrombocyte count two days prior to the infarction was $237 \times 10^9/l$. It seems unlikely that the infarction is directly related to the splenic irradiation.

Case B
A then 65-year-old man, with a medical history of severe chronic obstructive pulmonary disease, was diagnosed with B-CLL RAI stage 0 in 1996. A bone marrow aspirate showed infiltration of bone marrow with CLL cells. The

Table 1. Comorbidities grouped per disease category as registered by the Netherlands Cancer Registry in the Eindhoven region

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Comorbid conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other malignancy</td>
<td>Other malignancy, excluding: basal cell carcinoma and carcinoma in situ of the cervix</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Obstructive and restrictive pulmonary disease, lung fibrosis, lung transplantation</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Myocardial infarction, coronary artery bypass grafting, percutaneous transluminal</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>Coronary angioplasty of the heart, heart decompensation, angina pectoris, heart valve</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>DVT, lung embolus, generalised arterial atherosclerosis, peripheral arterial disease</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Systemic hypertension, portal hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Insulin dependent, oral medication dependent, diet</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>HIV, AIDS, tuberculosis</td>
</tr>
<tr>
<td>Digestive tract disease</td>
<td>Ulcer disease, reflux oesophagitis, (partial) stomach resection, chronic inflammatory</td>
</tr>
<tr>
<td>Genitourinary disease</td>
<td>Chronic glomerulonephritis, kidney failure, nephrotic syndrome, kidney transplantation, dialysis, pregnancy at time of diagnosis</td>
</tr>
<tr>
<td>Muscle, connective tissue and joint disease</td>
<td>Connective tissue disease, sarcoidosis, Wegener, periarthritis nodosa, systemic lupus erythematosus, rheumatoid arthritis</td>
</tr>
<tr>
<td>Central and peripheral nervous system</td>
<td>Dementia, Alzheimer, Parkinson, serious psychiatric disease (severe depression, admittance in a psychiatric unit, psychosis, schizophrenia)</td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis; TIA = transient ischaemic attack; HIV = human immunodeficiency virus; AIDS = acquired immune deficiency syndrome.
Aalbers et al. Splenic irradiation in frail CLL patients.

The patient was asymptomatic, and a watch-and-wait policy was followed. The patient withdrew from follow-up from 2010 to 2013, but was recently admitted again to our hospital with a lower airway infection. Despite adequate treatment of the airway infection his condition remained fragile, with a WHO performance status 4. He complained of invalidating night sweats, discomfort in the upper abdomen, and weight loss. Furthermore, he remained dyspnoeic, and had hepatosplenomegaly (craniocaudal size of liver 17.5 cm, spleen size 15.6 x 15.6 cm by CT scan) and lymphadenopathy on physical examination. His laboratory results showed a leukocytosis of 124.3 x 10^9/l, anaemia and thrombocytopenia. A CT scan showed bilateral pulmonary consolidations, bullous emphysema, mediastinal, axillar and para-aortic lymphadenopathy, and a severe hepatosplenomegaly. Due to his frail condition,
systemic chemotherapy, and even mild immunotherapy, were not options to treat his CLL-related symptoms. Because his splenomegaly caused abdominal discomfort and also compromised his pulmonary function, palliative splenic irradiation was given (12 x 0.5 Gy, twice weekly). After splenic irradiation, his clinical condition improved dramatically: night sweats and abdominal discomfort disappeared, his dyspnoea diminished, and on physical examination, the hepatosplenomegaly and lymphadenopathy disappeared. A partial haematological response was reached: his leukocyte count decreased, and haemoglobin and thrombocyte levels normalised (figure 1B). No significant side effects of splenic irradiation were noted. The patient was seen several times afterwards at our outpatient department with a markedly improved condition and without splenomegaly or lymphadenopathy. Unfortunately, 14 months after radiotherapy, the patient died unexpectedly at home, possibly due to pneumonia or pulmonary bleeding. At that time, his thrombocyte count and haemoglobin levels were normal, although his leukocyte count was slowly rising again.

**Case C**

A then 76-year-old man, with a medical history of low-risk prostate carcinoma, was diagnosed with symptomatic B-CLL RAI stage IV in 2012. At presentation, he was extremely tired, and he complained of discomfort in the upper abdomen. On physical examination, splenomegaly (19 x 8 cm by CT scan) was noted without lymphadenopathy. His leukocyte count was 79.9 x 10\(^9\)/l, and he was anaemic and thrombocytopenic. A bone marrow biopsy showed CLL bone marrow infiltration with significant replacement of normal haematopoiesis. Shortly after diagnosis, because of his symptomatic splenomegaly, palliative fractionated splenic irradiation was given (12 x 0.5 Gy, twice weekly). Hereafter, on physical examination, his spleen size decreased, lymph nodes remained undetectable, his clinical condition improved, and he showed a very good partial haematological response, based on haemoglobin, thrombocyte and leukocyte levels (figure 1C). No significant side effects were noted. One year later, the patient became tired again, his splenomegaly reappeared, while no lymphadenopathy was noted, and
his leukocyte count increased to 122.9 x 10⁹/l. The patient chose to undergo splenic irradiation again, with similar beneficial effects to his first course of radiotherapy. At the last follow-up, 14 months after the second round of splenic irradiation, the patient was well and asymptomatic.

Case D
A then 72-year-old man was diagnosed with asymptomatic B-CLL Rai stage 0 in 2010. His medical history consisted of prostate hypertrophy and renal insufficiency. In 2012, based on thrombocytopenia, his CLL progressed to an asymptomatic Rai stage IV, and a year later, he became symptomatic because of massive splenomegaly (spleen size one year earlier by ultrasound 17.5 x 8.4 cm). No lymphadenopathy was noted on physical examination. His leukocyte count had increased to 176.8 x 10⁹/l. Bone marrow biopsy was not performed. The patient refused therapy with chlorambucil and/or rituximab, and splenic irradiation was started (12 x 0.5 Gy, twice weekly). No significant side effects were noted. Hereafter, his clinical condition improved greatly, his splenomegaly disappeared, lymph nodes remained undetectable, and his blood counts improved, although partial response criteria were not met (figure 1D). The patient is well at last follow-up, approximately 14 months after start of radiotherapy. The patient characteristics are summarised in table 3.

DISCUSSION

CLL is a malignancy that frequently occurs in elderly patients, who often have comorbidities. In a large

<table>
<thead>
<tr>
<th>Table 3. Patient characteristics</th>
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<tbody>
<tr>
<td>Patient A</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Age at time of SI (years)</td>
</tr>
<tr>
<td>CLL stage at time of SI</td>
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<tr>
<td>Months since presentation for SI</td>
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<tr>
<td>Cytogenetics</td>
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<tr>
<td>Bone marrow infiltration</td>
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<tr>
<td>CLL pretreatment</td>
</tr>
<tr>
<td>Blood counts before SI*</td>
</tr>
<tr>
<td>Leukocytes (x 10⁹/l)</td>
</tr>
<tr>
<td>Thrombocytes (x 10⁹/l)</td>
</tr>
<tr>
<td>Haemoglobin (mmol/l)</td>
</tr>
<tr>
<td>Blood counts after SI*</td>
</tr>
<tr>
<td>Leukocytes (x 10⁹/l)</td>
</tr>
<tr>
<td>Thrombocytes (x 10⁹/l)</td>
</tr>
<tr>
<td>Haemoglobin (mmol/l)</td>
</tr>
<tr>
<td>Haematological response</td>
</tr>
<tr>
<td>Reduction in spleen size</td>
</tr>
<tr>
<td>Time to next treatment (months)</td>
</tr>
<tr>
<td>Time from presentation to last follow-up (months)</td>
</tr>
<tr>
<td>Last follow-up</td>
</tr>
</tbody>
</table>

*Displayed are last blood counts before start of splenic irradiation, and first blood counts after the last fraction of a radiotherapy course. SI = splenic irradiation; ND = not determined; CR = complete response; PR = partial response. SD = stable disease. For blood counts before and after the second course of splenic irradiation, please refer to figure 1.
prospective population-based cohort of 919 CLL patients, we report that more than half of the patients had one or more comorbid conditions. This is in line with the previously published frequency of 46% of newly diagnosed CLL patients with one or more major comorbidities (coronary artery disease, peripheral vascular disease, cerebrovascular disease, other cardiac disease, diabetes mellitus, COPD/respiratory disease or second malignancy, excluding non-melanomatous skin cancer).因为在这一人群中，大约一半的患者至少患有多种慢性病。这与之前报道的46%的初诊断CLL患者中至少有一种严重慢性病的结果一致（包括冠状动脉疾病、周围血管疾病、脑血管疾病、其他心脏病、糖尿病、COPD/呼吸系统疾病或另一种恶性肿瘤，不包括非黑色素瘤皮肤癌）。

Due to these frequently occurring comorbidities, the use of old and novel chemoimmunotherapy regimens is frequently not feasible or refused by the patient. We show in four elderly symptomatic CLL patients who were unfit or unwilling to undergo systemic treatment that splenic irradiation is a very effective palliative treatment. Apart from effectively treating splenomegaly, these patients also obtained complete or partial haematological responses of significant duration.总共有4名老年、症状明显的CLL患者，他们因身体条件差或不愿意接受全身治疗，我们显示了腹腔照射是有效的姑息治疗。除了有效地治疗脾大外，这些患者还获得了显著的血细胞学应答。

Total body, total lymph node, mediastinal, or extracorporeal irradiation have historically been used as primary treatment of CLL, but resulted in significant haematological and infectious complications. After the introduction of modern chemotherapy, it was demonstrated that these radiotherapy regimens had no superior effect compared with chemotherapy (reviewed by Paule et al.14). In contrast, in several historic studies, splenic irradiation was shown to not only be effective in resolving splenomegaly-related symptoms, but also to result in haematological responses with few side effects (reviewed by Weinmann et al.).25-28 The only larger historic trials directly comparing splenic irradiation with chemotherapy, the Medical Research Council (MRC) 1 and 2 trials, showed a similar survival in patients treated with splenic irradiation and those treated with chlorambucil.21 How exactly splenic irradiation exerts its beneficial effect in CLL is incompletely understood. Likely, there is a direct effect of irradiation by inducing apoptosis of malignant B lymphocytes (which are, like normal B lymphocytes, more radiosensitive than normal T lymphocytes) in the spleen, thereby reducing the CLL tumour burden.22-23 Improved haemoglobin and thrombocyte levels might be direct results of a reduction in spleen size, with consequent decrease in erythrocyte and thrombocyte degradation by the spleen. Splenic irradiation in CLL might also have more indirect, or abscopal, effects. The term ‘abscopal effect’ was first used by Mole in the 1950s to describe systemic effects after local radiotherapy.24 For example, factors released from irradiated B-CLL cells into their supernatants were shown to inhibit non-irradiated leukaemic cell growth in vitro.25 Furthermore, in the 1980s splenic irradiation was shown to induce shifts in lymphocyte subsets, which was hypothesised to augment anti-tumour responses in lymph nodes and bone marrow, and to have a beneficial effect on normal haematopoiesis, which might be suppressed by autoimmune phenomena.26 Experimental evidence supporting these hypotheses was indirect. From more recent studies it is becoming clear that the interaction between CLL cells and their tissue microenvironment (consisting of amongst others stromal cells, monocytederived nurse-like cells, and T lymphocytes), plays an important role in promoting the survival of CLL cells.25 Irradiation of the spleen could result in disruption of this beneficial microenvironment. To better characterise which mechanisms exactly contribute to the beneficial effects, abscopal or direct, of splenic irradiation, novel studies should be performed.

No significant side effects of splenic irradiation were observed in the four cases presented here. Solely based on our small case series no conclusions can be drawn on the safety of splenic irradiation in CLL. However, also in previous studies side effects were modest, and limited to tiredness, thrombocytopenia, and to a lesser extent neutropenia.19-21 Because of this low toxicity, multiple courses of splenic irradiation can be given. The effectiveness of splenic irradiation in frail CLL patients might be improved in the future by combining splenic irradiation with immunotherapeutic agents targeting the B-cell receptor signalling pathway, which might be better tolerated in frail patients than the combination of immunotherapy with chemotherapy. Alternatively, in the future splenic irradiation might be combined with checkpoint inhibition of PD-1 or PD-L1 (expressed by CLL cells),26 in analogy with the very promising combination of radiotherapy and checkpoint inhibition in the treatment of melanoma.29

In conclusion, although the application of splenic irradiation in CLL is nowadays mostly limited to treat splenomegaly-related symptoms, historic studies and the current results in four elderly CLL patients show that splenic irradiation might also result in prolonged periods of haematological remission and an improved wellbeing with low or no toxicity. We therefore emphasise that old tool should not be forgotten in the treatment of especially the elderly CLL patient, who frequently presents with multiple comorbidities.

DISCLOSURES

The authors have no competing interests to disclose.

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The atopic heart: a curious case of coronary hypersensitivity

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ABSTRACT

Kounis syndrome is a coronary hypersensitivity disorder involving coronary vasospasm secondary to inflammatory mediators released primarily from mast cells. We report a case of the type I variant of Kounis syndrome manifesting as angioedema with significant inferolateral ST elevation (2 mm) and raised cardiac biomarkers. Diagnosis requires a high index of suspicion and treatment is tactical. Caution should be exercised before using beta-blockers, morphine and epinephrine, which are empiric in cases of acute coronary syndrome and anaphylaxis, respectively. Our patient was treated with intravenous steroids and histamine blockers given the angioedema at presentation. The purpose of our case is to emphasise the importance of including Kounis syndrome in the differential diagnosis for acute coronary syndrome, and formulation of standard treatment guidelines for this under-recognised condition.

KEYWORDS

Kounis syndrome, coronary hypersensitivity, acute coronary syndrome, troponin, allergic reaction, ST-elevation

CASE REPORT

A 70-year-old woman presented to the emergency department with new-onset difficulty in breathing and worsening generalised pruritus. She had tachycardia with marked tongue swelling, generalised skin rash, laboured breathing and stridor. Hence, she was emergently intubated for significant upper airway oedema. Her medical history included asthma, hypertension with home medications notable for naproxen, ibuprofen, benazepril, folic acid, and hydroxyzine but no known allergies. We presumed angioedema, and started treatment with intravenous corticosteroids, histamine (H)1 and (H)2 receptor blockers. Complete blood count, blood chemistry, troponin-I and chest X-ray were normal. However, the post intubation electrocardiogram (ECG) revealed sinus tachycardia with 2 mm ST-segment elevation in the inferior and lateral leads (figure 1). Troponin-I was now 5 ng/ml (normal 0-0.045) with the maximum being 5.6 ng/ml, and the
Echocardiogram showed apical and septal wall hypokinesis suggestive of Takotsubo cardiomyopathy. The patient underwent emergent left heart catheterisation, which revealed normal coronary arteries, and an ejection fraction of 20%. The ECG changes returned to baseline after treatment (figure 2).

A diagnosis of type I Kounis syndrome was suggested based on concurrence of angioedema and ST-elevation myocardial infarction (STEMI) in the setting of normal coronary anatomy. Subsequent work up showed an IgE level of 221 IU/ml (normal < 114), and normal C1 esterase inhibitor, C3, C4 and tryptase. By day 4 of hospitalisation, she was weaned off mechanical ventilation and discharged.

**DISCUSSION**

First described in 1991, Kounis syndrome is the concurrence of acute coronary syndromes (ACS) (angina and/or myocardial infarction) with allergic reactions (hypersensitivity, anaphylaxis or anaphylactoid reaction) due to coronary artery vasospasm caused by inflammatory mediators released during the allergic insult. Kounis syndrome is a common, yet rarely diagnosed condition. Three variants are recognised: type I with normal or near-normal coronary arteries, type II with preexisting atheromatous disease, and type III with coronary stent thrombosis. Various drugs (beta-lactam antibiotics, analgesics, contrast media, anti-cancer agents, proton pump inhibitors, angiotensin-converting enzyme inhibitors, thrombolytics), conditions (angioedema, urticarial, asthma, mastocytosis), and environmental exposures (hymenoptera stings, latex, poison ivy) can cause Kounis syndrome with recent offenders including histamine fish poisoning and losartan. The aetiology in our case was likely multifactorial with predisposing asthma, medications including naproxen and benazepril, and succinylcholine used for intubation, and angioedema at presentation. Common adverse effects of the above medications include: NSAIDs causing gastrointestinal ulcer/bleeding, rash, nephrotoxicity, hepatotoxicity; benazepril causing cough, hyperkalaemia, azotaemia, angioedema; folic acid causing nausea, anorexia; and succinylcholine causing muscle paralysis, rhabdomyolysis and malignant hyperthermia.

Pathogenesis of Kounis syndrome involves mast cells, which release mediators such as histamine and leukotrienes that constrict coronary vessels, and tryptase/chymase that cause plaque rupture/erosion. Patients present with chest pain with or without elevation of troponins, along with dermatological and/or systemic manifestations of allergy. ECG changes range from ST elevation or depression to arrhythmias. Unlike ACS, the degree of ST elevation may not correlate with the troponin levels. In cases of Kounis syndrome with normal cardiac biomarkers and ECG, cardiac magnetic resonance imaging helps to confirm the diagnosis. Furthermore, signs of cardiac disease and/or hypersensitivity may be absent, making Kounis syndrome an easily overlooked diagnosis. The differential diagnosis includes hypersensitivity myocarditis and isolated eosinophilic arteritis. Hypersensitivity myocarditis is usually clinically indistinguishable from Kounis syndrome, however, it is characterised by the presence of eosinophils, atypical lymphocytes and giant cells on myocardial biopsy. While eosinophilic arteritis involves
eosinophilic infiltration in all layers of the vessel wall with diffusely distributed mast cells. Further, Kounis syndrome is commonly associated with Takotsubo cardiomyopathy, as seen in our case.

No biomarker accurately predicts the risk of Kounis syndrome, albeit recent reports link elevated serum tryptase levels to increased susceptibility to allergic reactions as well as asymptomatic ACS. Further, treatment is challenging with a lack of uniform consensus on therapy. Most recommendations are based on anecdotal case reports or case series. A 2009 review revealed intravenous steroids (76%), nitroglycerin (47%), H1-blockers (70%), and H2-blockers (35%) as the most commonly used treatment options. Both beta-blockers (commonly used in ACS) and epinephrine (commonly used in anaphylaxis) should be avoided as they exacerbate coronary spasm due to unopposed alpha-adrenergic activity. Further, data supporting the use of prophylactic medications such as H1-blockers to avoid recurrence is lacking.

The prognosis of Kounis syndrome depends upon the patient’s sensitivity, allergen concentration, number of allergens the patient is exposed to, magnitude of the initial allergic response as well as the syndrome’s variance, with type I Kounis syndrome having a better prognosis than type II and type III.

REFERENCES


DISCLOSURES

The authors declare no conflicts of interests. No funding or financial support was received.

Figure 2. Post treatment with steroids and histamine blockers, the ECG showed normal sinus rhythm with resolution of the ST elevation.
CASE REPORT

A 45-year-old woman with an anticholinergic toxidrome

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ABSTRACT

Intentional or accidental intoxications are common in the emergency department, but are not always sufficiently recognised. When intoxication is suspected, the causative agent or combination of agents often remain unclear, making these patients a diagnostic challenge. We present here a 45-year-old woman who was admitted due to altered consciousness. The clinical presentation fitted the anticholinergic toxidrome and an intoxication with venlafaxine (her known prescribed medication) was suspected. Plasma venlafaxine concentrations, however, were very low. After 24 hours the patient recovered completely. Further testing after discharge revealed high concentrations of promethazine, confirming the suspected diagnosis. This case illustrates the importance of knowledge of toxidromes and good collaboration with the hospital pharmacist. Because of the thorough testing the patient could receive proper treatment.

INTRODUCTION

Intentional or accidental intoxications are common in the emergency department, but they are not always sufficiently recognised. Approximately 11,000 patients with intentional intoxications are seen each year in Dutch emergency departments. Statistics concerning morbidity and mortality are incomplete. When intoxications are suspected, the causative agent or combination of agents often remains unclear, making these patients a diagnostic challenge.

CASE REPORT

A 45-year-old woman presented to the emergency department by ambulance because of altered consciousness. Medical history revealed hypertension, depression and alcohol abuse. Her known prescribed medications were venlafaxine 150 mg once daily, omeprazole 20 mg once daily and irbesartan 150 mg once daily. The patient also used approximately ten tablets of acetaminophen with caffeine 500/50 mg, and xylometazoline 1 mg/ml on a daily basis, which she acquired over the counter. Until recently, she had overused bisacodyl for weight loss.

The patient’s partner found her behaving abnormally. No signs of intentional intoxication were found. In the previous days she had no fever or illness. At physical examination the patient was confused and disoriented in time and place. Also, she spoke with slurred speech. Her blood pressure was 160/112 mmHg, pulse rate 110 beats/min, temperature 36.7 °C and oxygen saturation was 95% at ambient air. She had dilated pupils, a dry tongue, red skin, and urinary retention of more than 1 litre. The Glasgow Coma Score was E4M6V3 and the patient was suspected to have visual hallucinations, since she was talking to imaginary people. Further neurological examination was unremarkable.

What was known on this topic?
Intentional or accidental intoxications with antihistamines can cause an anticholinergic toxidrome.

What does this add?
This case is a reminder of an important clinical lesson in recognition of an anticholinergic toxidrome. Also, this case illustrates that an appropriate diagnostic work-up and good collaboration between the physician and hospital pharmacist is important and leads to the proper diagnosis and treatment for your patient.
Additional testing, including routine laboratory analysis, an electrocardiogram and a CT scan of the cerebrum showed no abnormalities.

The clinical presentation fitted the anticholinergic toxidrome. At that moment it was unclear what medication the patient could have taken and a possible co-intoxication with non-prescribed medication was expected. Therefore, we decided to measure plasma concentrations of drugs that we know were available to the patient (venlafaxine and acetaminophen), as well as to perform screening for drugs of abuse in the urine. Plasma venlafaxine concentrations were very low: < 25 µg/l venlafaxine and < 80 µg/l desvenlafaxine (the therapeutic range of the sum of venlafaxine and desvenlafaxine plasma levels is 250-750 µg/l). The acetaminophen plasma concentration was also low (< 2.8 mg/l). The test for drugs of abuse was negative for amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, methadone and opiates. The patient was admitted for observation and treated with intravenous fluids.

In 24 hours of observation the patient recovered without sequelae. She denied taking any drugs and was discharged, initially without follow-up. However, despite her denial of taking any medication, we performed further diagnostics to find a causative agent for her strongly suspected anticholinergic poisoning.

Further testing using liquid chromatography-mass spectrometry (LC-MS) (multiple reaction monitoring (MRM) and full-scan mass spectrometry (MS) data) revealed high concentrations of promethazine, confirming our suspected diagnosis. There was also a semi-quantitative high level of tramadol found, proving a co-intoxication. Both concentrations were above the therapeutic range. We informed the patient’s general practitioner, who confronted the patient and she admitted the intoxication was an attempted suicide. Subsequently, she was referred for psychiatric treatment. The tramadol she used belonged to her partner; the promethazine was prescribed six months previously by a locum general practitioner.

DISCUSSION

Anticholinergic poisoning can be the result of medication and plants, and more than 600 compounds with anticholinergic properties are known. These compounds competitively inhibit binding of acetylcholine to muscarinic acetylcholine receptors. These receptors are found on peripheral postganglionic cholinergic nerves in smooth muscle, the ciliary body of the eye, the central nervous system and secretory glands. Symptoms of an anticholinergic poisoning, therefore, include both central and peripheral effects. Central effects manifest as agitation, psychosis and seizures. Peripheral effects manifest as tachycardia, cutaneous vasodilation, leading to a red skin, mydriasis, anhidrosis, hyperthermia, urinary retention and gastrointestinal dysmotility. These symptoms are collectively described as ‘Blind as a bat, mad as a hatter, red as a beet, hot as Hades, dry as a bone, the bowel and bladder lose their tone, and the heart runs alone’.

In the Netherlands, 60% of reported intoxications concern medication. Antihistamines, such as promethazine, currently form the sixth most commonly reported drugs and the frequency of antihistamine abuse has increased. Treatment of antihistamine overdose is mainly supportive and consists of intravenous fluids and urinary catheterisation, and in some cases, gastrointestinal decontamination and administration of activated charcoal in combination with a laxative. Gastrointestinal decontamination is appropriate within two hours of ingestion. Severe agitation and seizures should be treated with benzodiazepines. Physostigmine, a short-acting anticholinesterase with a half-life of approximately 15 minutes, is the treatment of choice in case of a central anticholinergic syndrome. Dexmedetomidine, an alpha-2 agonist with sedative, analgesic, anxiolytic, and sympatholytic effects, is considered to be an adjunctive treatment option. Clonidine may be an equal and cheaper alternative for dexmedetomidine, but to our knowledge the use of clonidine in intoxications with antihistamines has not been described before. For our patient, we chose supportive care with fluids. Because the causative agent was unclear at the moment of presentation, no further treatment was given. Gastrointestinal decontamination was contraindicated because of the altered mental state of our patient. Besides, the time of ingestion was unclear. Agitation was mild and therefore the use of benzodiazepines was not necessary.

In our patient, the screening for drugs of abuse, including opiates, was negative and serum venlafaxine concentrations were low. After close collaboration with the patient’s physician and the hospital pharmacist, we decided to perform further testing with LC-MS (MRM and full-scan MS data) because proving an intoxication would have consequences for the further follow-up and psychiatric treatment of our patient. Additional testing should be considered per individual case. LC-MS revealed not only promethazine, but also high concentrations of tramadol. Tramadol does not have anticholinergic effects itself, but can lead to depression of the central nerve system and therefore probably contributed to the clinical presentation in this case. Tramadol is not detected by the general screening for opioids (the immunoassay analyser Architect Abbott; a particle enhanced turbidimetric inhibition
immunoassay). The intoxication was without long-term physical harm for the patient, but the diagnosis led to referral for psychiatric counselling.

In conclusion, we present a patient with an anticholinergic toxidrome, and where thorough additional diagnostic testing revealed the causative agent and led to additional psychiatric treatment of the patient. This case illustrates the importance of knowledge of toxidromes, and the value of good collaboration between physicians and hospital pharmacists for patient care.

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

REFERENCES
PHOTO QUIZ

A 39-year-old woman with a mushroom intoxication

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CASE REPORT

A 39-year-old Thai woman, living in the Netherlands, was seen at the emergency department with symptoms of nausea and vomiting for a few hours. She had no relevant medical history and was not taking any medications. She looked moderately ill, had a blood pressure of 91/53 mmHg and a regular pulse of 103 beats/min, with no fever. On admission, her blood tests showed a metabolic acidosis, most likely caused by enteral bicarbonate loss (table 1). Supportive care was started. The patient told us that one day prior to her presentation, she had eaten a homemade soup with mushrooms picked from a local forest. We performed a bedside test on such mushroom, by letting juice from the cap dry on a piece of newspaper and subsequently adding concentrated hydrochloric acid (25% HCl). After several minutes the stain changed colour from yellowish to pale blue, indicating a positive test. The test set-up and result are shown in figure 1.

Table 1. Lab results on admission

<table>
<thead>
<tr>
<th>Measurement (units)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/l)</td>
<td>136</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.1</td>
</tr>
<tr>
<td>Chloride (mmol/l)</td>
<td>109</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>8.0</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>42</td>
</tr>
<tr>
<td>Bilirubin (µmol/l)</td>
<td>21</td>
</tr>
<tr>
<td>ALAT (U/l)</td>
<td>22</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>173</td>
</tr>
<tr>
<td>PT (INR)</td>
<td>1.02</td>
</tr>
</tbody>
</table>

Arterial blood gas

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.29</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>29</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>13.4</td>
</tr>
<tr>
<td>Anion gap (mmol/l)</td>
<td>14</td>
</tr>
<tr>
<td>Urine anion gap (mmol/l)</td>
<td>-4</td>
</tr>
</tbody>
</table>

ALAT = alanine aminotransferase; LDH = lactate dehydrogenase; PT = prothrombin time; INR = international normalised ratio.

Figure 1. The bedside test

WHAT TYPE OF MUSHROOM DID OUR PATIENT INGEST AND WHAT IS THE NAME OF THE BEDSIDE TEST?

See page 137 for the answers to this photo quiz.
ANSWERS

*Amanita phalloides* (death cap) contains highly toxic amanitins. Dosages of 0.1-0.5 mg/kg may be lethal, whereas the average death cap contains 80 mg. Classically, the first symptoms of abdominal pain, (bloody) diarrhoea, nausea and vomiting emerge 6 to 24 hours after ingestion. With appropriate care the patient may soon improve. However, amanitins entering the hepatocyte will continue to inhibit RNA polymerase II, leading to a stop in protein synthesis and subsequent hepatic failure. This generally occurs 24 to 36 hours after ingestion and is accompanied by a rapid elevation of liver transaminases, often complicated by renal tubular necrosis.1 The reference standard test for detection of amanitin is ELISA urinalysis (sensitivity 60%, specificity 100%) performed 6 to 24 hours after intoxication.2 However, this test was not readily available and a bedside test, known as the Meixner test, was performed.3 Based on the history in combination with the positive test, we started treatment promptly with activated charcoal and N-acetylcysteine (150 mg/kg in the first 15 minutes followed by 150 mg/kg/day). Moreover, silibinin was urgently ordered and administered intravenously at 5 mg/kg during the first hour, followed by 20 mg/kg/day. Silibinin, derived from milk thistles, inhibits uptake of amanitin in human hepatocytes and was successfully used in several case reports.4,5 Two days later, the presence of amanitins was confirmed by urinalysis. During this period, the patient’s liver tests deteriorated rapidly. Fortunately, on day 3 all the tests improved (table 2) and our patient recovered well without the need of a liver transplantation.

The blue colour arises from a reaction with lignin (present in most poor-quality paper, such as newspaper); false-positives resulting from this reaction are reported to be rare. However, blue pigments in a mushroom may yield false-positive results. Therefore, a negative control test on lignin-free (office) paper may increase the specificity. Findings should always be confirmed with a urinary ELISA test.6,7 This case clearly illustrates how the Meixner test may expedite the diagnosis of *Amanita* intoxication; patients should be treated as soon as possible with N-acetylcysteine and activated charcoal, as well as silibinin.

**REFERENCES**


**Table 2. Progression of lab results**

<table>
<thead>
<tr>
<th>October 13 (2 days after ingestion)</th>
<th>October 15</th>
<th>October 18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilirubin (µmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:00</td>
<td>41</td>
<td>69</td>
</tr>
<tr>
<td>23:00</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td><strong>ASAT (U/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>881</td>
<td>3661</td>
</tr>
<tr>
<td><strong>ALAT U/l</strong></td>
<td>22</td>
<td>1015</td>
</tr>
<tr>
<td><strong>LDH (U/l)</strong></td>
<td>173</td>
<td>557</td>
</tr>
<tr>
<td><strong>PT (INR)</strong></td>
<td>1.02</td>
<td>1.8</td>
</tr>
</tbody>
</table>

ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; LDH = lactate dehydrogenase; PT = prothrombin time; INR = international normalised ratio.
PHOTO QUIZ

An unusual manifestation of diabetic ketoacidosis

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CASE REPORT

A 30-year-old male with no known medical history presented to the emergency department with a one-week history of polyuria, polydipsia, weakness, and weight loss. This was associated with a significantly decreased appetite and two episodes of vomiting over the two days prior to hospital presentation. On admission, he was obtunded, hypothermic at 34.2°C, with a blood pressure 90/53 mmHg, heart rate 116 beats/min and respiratory rate 33 breaths/min. He was lethargic, emaciated, and had dry mucous membranes. Physical examination was also significant for crepitus over the neck and shoulders. Laboratory studies were as follows: white blood cell 18.8 k/µl (3.8-10.6 k/µl), glucose 1182 mg/dl (50-140 mg/dl), beta hydroxybutyrate 14.79 mmol/l (0.00-0.30 mmol/l), blood urea nitrogen 53 mg/dl (10-25 mg/dl), creatinine 4.37 mg/dl (< 1.13 mg/dl), glycated haemoglobin 12.3% (< 5.7%), arterial pH 6.94 (7.35-7.45), and arterial bicarbonate 1.5 mmol/l (22-26 mmol/l).

The electrocardiogram demonstrated sinus tachycardia. Chest X-ray showed air tracking into the soft tissue of the lower neck and bilateral scapular regions without pneumothorax (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 139 for the answers to this photo quiz.
DIAGNOSIS

Computed tomography (CT) was performed, demonstrating extensive pneumomediastinum extending into the lower neck and bilateral supravacicular and subscapular regions (figure 2A and B), followed by contrast oesophagram, which was negative for perforation (figure 2C). The patient was diagnosed with diabetic ketoacidosis complicated by spontaneous pneumomediastinum and admitted to the intensive care unit for aggressive intravenous fluid resuscitation and glucose control. He recovered uneventfully following medical therapy and was discharged home four days later.

Spontaneous pneumomediastinum complicating diabetic ketoacidosis is a rare, but well-described entity first described by McNicholl in 1968.1 Although the precise pathophysiology remains elusive, some have postulated that it relates to the abnormal pattern of ketotic hyperventilation (Kussmaul respiration), which induces transalveolar pressure swings sufficient to cause alveolar rupture into the lung interstitium. This results in the dissection of air along the peribronchial and perivascular planes with extravasation into the mediastinum.2 Substernal chest pain with radiation to the back, dyspnoea and subcutaneous emphysema are the classic indicators of spontaneous pneumomediastinum, although it is not uncommon for patients in diabetic ketoacidosis to be ‘asymptomatic’ due to their symptoms being attributed to metabolic acidosis. The differential diagnosis in these patients includes spontaneous oesophageal perforation (Boerhaave’s syndrome), pneumothorax, pneumonia, pulmonary embolism, and cardiovascular events such as ischaemia, arrhythmia, pericarditis, or aortic dissection.3 Therefore, initial evaluation of spontaneous pneumomediastinum should always include chest X-ray and ECG. Given the gravity of a missed or delayed diagnosis of oesophageal perforation, any patient with spontaneous pneumomediastinum and a history of chest pain, vomiting, fever, leucocytosis, haemodynamic instability or pleural effusion on chest X-ray should undergo immediate oesophagram or CT of the neck and chest with a water soluble oral contrast.4

Negative imaging warrants a 24-hour period of observation, analgesia, oxygen therapy, and bed rest. A clear liquid diet can be initiated once the patient is able to tolerate oral intake, and advanced accordingly.4 Antibiotics and repeat swallow studies are not necessary, although daily chest X-ray can be followed for 1-2 days to ensure that there is no radiographic progression.5,6

DISCLOSURES

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REFERENCES

A rare complication of pneumonia

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CASE REPORT

A 62-year-old woman was admitted to the emergency department because of severe fatigue, coughing, and fever. Her blood pressure was 90/65 mmHg, pulse frequency 108 beats/min, oxygen saturation 99%, and body temperature 38.5 °C. Pulmonary auscultation revealed bilateral rhonchi. Blood examination showed leukocytes of 16.3 x 10⁹/l, predominantly segmented granulocytes, a C-reactive protein concentration of 288 mg/l, renal insufficiency, anaemia, hypoalbuminaemia, raised liver enzyme concentrations, and a lactate concentration of 4 mmol/l. Radiography of the thorax showed infiltrative changes in the right upper and middle lung lobes, with a rounded heart contour (figure 1). A routinely obtained electrocardiogram showed concave ST-segment elevation in leads I, II, III, aVF, V₄-₆, and ST-segment depression in leads aVR and V₁ (figure 2).

WHAT IS YOUR DIAGNOSIS?

See page 141 for the answer to this photo quiz.

Figure 1. Anteroposterior radiograph of the thorax showing infiltrative changes in the right upper and middle pulmonary lobes

Figure 2. Electrocardiogram showing concave ST-segment elevation in leads I, II, III, aVF, V₄-₆, and ST-segment depression in leads aVR and V₁
DIAGNOSIS

Initial ultrasound examination showed pericardial effusion without any signs of cardiac tamponade (figure 3). Blood cultures and urinary antigen tests suggested infection with *Streptococcus pneumoniae*. Pericardiocentesis revealed pericardial effusate with leukocyte counts > 10 x 10⁹/l and a lactate dehydrogenase concentration of 3516 U/l. Pneumonia, sepsis with multiple organ failure and purulent pericarditis, all due to *Streptococcus pneumoniae* infection, were diagnosed. Treatment was initially started with amoxicillin and ciprofloxacin and later converted to benzylpenicillin for two weeks when cultures became available. Mechanical ventilation was temporarily required because of respiratory insufficiency and pericardial drainage was performed because of signs of cardiac tamponade and inadequate infectious control. The patient was admitted to the intensive care unit for several days and then gradually recovered during a four-week hospitalisation. Six months later, fibrotic changes of the right lung remained, while the pericardial effusion had resolved completely.

The incidence of infectious purulent pericarditis has clearly decreased after antibiotics became available in the 1940s and is nowadays mainly observed in immunocompromised patients, after cardiothoracic surgery, and/or other predisposing conditions. In the pre-antibiotic era streptococcal pericarditis was relatively common, mostly preceded by pneumonia. In the current antibiotic era, infectious purulent pericarditis is more often caused by *Staphylococcus aureus* and Gram-negative micro-organisms. Other potentially causative infections are diverse and include tuberculosis and candidiasis.

All patients with purulent pericarditis are reported to demonstrate leucocytosis and tachycardia. Other signs, such as pericardial friction rubbing, pulsus paradoxus, and signs of right-sided heart failure, are not always present. Echocardiography appears to be an important instrument for making clinicians consider the diagnosis of purulent pericarditis.³

When left untreated, purulent pericarditis is uniformly fatal.²,³ Treatment includes systemic antibiotics, pericardiocentesis, and/or surgical pericardial drainage. The last two may be needed in cases of cardiac tamponade and inadequate infectious control with antibiotics alone. Intrapericardial instillation of antibiotics has been evaluated but appeared of no use.³

CONCLUSION

Purulent pericarditis is a rare complication of pneumonia caused by *Streptococcus pneumoniae*. Because of the high mortality, rapid recognition and treatment are required in order to prevent haemodynamic instability and achieve infectious control.

DISCLOSURES

The authors declare no conflicts of interest.

REFERENCES

PHOTO QUIZ

Reactions and complications to bites

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CASE REPORT

A 46-year-old female patient who lived alone, with a poor personal hygiene, was admitted to the emergency department because of cough, anorexia, weakness, bloody pituitary, and a wound on the ankle. It was learned that the patient had consulted physicians several times for the lesions and had been treated with topical medicines and oral antibiotics.

On physical examination, she was conscious, and cooperative. Her body temperature was 38.2 °C, pulse rate 81 beats/min, blood pressure 100/80 mmHg and respiration rate was 26 breaths/min. Her body had widespread excoriation related to itching, petechial bleeding and haemorrhagic papules on uncovered parts (figure 1). Crepitant rales were heard at the lower and centre zones of her right lung. There was a 10 x 8 cm necrotic wound on and around the lateral malleolus of her right ankle and the medial malleolus was uncovered (figure 2). Local warmth and oedema were observed on the back of foot. The laboratory results were as follows: haemoglobin 8.2 g/dl, haematocrit 25.9%, white-cell count 16 x 10⁹/µl, thrombocytes 67 x 10³/µl, prothrombin time 16.2 sec, activated partial thromboplastin time 42 sec, fibrinogen 78.7 mg/dl, d-dimer 4.7 mg/dl, creatinine 3.4 mg/dl, urea 91.8 mg/dl, sodium 129 mEq/l, chlorine 96.2 mEq/l, aspartate aminotransferase 472 U/l, alanine aminotransferase 163 U/l, creatine kinase 2599 U/l, creatine kinase-myocardial band 65.8 U/l, and amylase 82 U/l. Additionally, many erythrocytes were detected in the full examination of the urine, and the blood culture was positive on the second day (Staphylococcus aureus).

The whole abdomen ultrasound examination showed that the echogenicity of both kidneys had increased (grade II). However, bilateral pleural effusion and diffuse fluid in the whole abdomen was shown. Doppler ultrasound was applied bilaterally to the venous and arterial system in the sub-extremities, and evaluated as normal.

WHAT IS YOUR DIAGNOSIS?

See page 143 for the answer to this photo quiz.
DIAGNOSIS

These pictures demonstrate typical skin lesions developed due to bites from bedbugs, and a situation of disseminated intravascular coagulation originating from secondary bacterial infections. The bedbug, *Cimex lectularius*, is a worldwide parasite that feeds nocturnally on humans. Although economic progress and improved sanitation in developed countries have led to a steady decline in recent years, bedbugs continue to be a problem in tropical and subtropical regions of developing countries.

Bedbugs most frequently attack exposed areas of the skin on the face, neck, hands or arms, but bites may be generalised. The bites are painless, and these bloodsuckers are not usually noticed unless large numbers are present. They grasp and penetrate the skin, inject an anticoagulant as well as pharmacologically active substances, and withdrew blood and liquefied epidermal tissue. Reactions to the bites consist of wheals and papules with a small haemorrhagic puncture at the centre. Some patients show severe systemic hypersensitivity. Secondary bacterial infections such as impetigo, ecthyma, cellulitis and lymphangitis may occur due to scratching and excoriation. On the preparation of the treatment, the location of the bites, age, socioeconomic status and intellectual capacity of the patient have to be taken into account. The goals of pharmacotherapy are to reduce morbidity and to prevent complications. Minimal symptomatic treatment and good hygiene to prevent pruritus and secondary infection are sufficient in most cases. In the presence of a secondary infection, topical antiseptic lotion or antibiotic cream should be applied. Efficient prophylaxis of systemic infectious complications requires early diagnosis and prompts aetiological treatment of mucocutaneous infections.

REFERENCES